MAYO CLINIC
LABORATORIES

Rochester
2025 Interpretive Handbook

Sorted By Test Name

Current as of July 14, 2025 3:15 pm CDT

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Definition of Specimen "Minimum Volume"

Defines the amount of specimen required to perform an assay once, including instrument and container dead space. Submitting the minimum specimen volume makes it impossible to repeat the test or perform confirmatory or perform reflex testing. In some situations, a minimum specimen volume may result in a QNS (quantity not sufficient) result, requiring a second specimen to be collected.

Quality Framework Policies
Mayo Clinic Laboratories

PURPOSE

Mayo Clinic Laboratories is a reference laboratory operating within Mayo Clinic's Department of Laboratory Medicine and Pathology (DLMP). Mayo Clinic Laboratories specializes in providing esoteric laboratory testing services to customers across the United States and around the world. This document provides policy guidance on an expanse of topics for internal and external customers.

POLICY STATEMENTS

Animal Specimens

Mayo Clinic Laboratories does not accept animal specimens for laboratory testing.

Business Continuity and Contingency Planning

In the event of a local, regional, or national disaster, Mayo Clinic and Mayo Clinic Laboratories performing sites have comprehensive contingency plans in place in each location to ensure that the impact on laboratory practice is proactively addressed. With test standardization between our performing sites and medical practice locations throughout the country, we have worked to ensure that patient care will not be compromised.

Cancellation of Tests

Cancellations received prior to test setup will be honored at no charge. Requests received following test setup cannot be honored. A report will be issued automatically and charged appropriately.

Chain-of-Custody

Chain-of-custody, a record of disposition of a specimen to document the individuals who collected it, handled it, and performed the analysis, is necessary when results are to be used in a court of law. Mayo Clinic Laboratories has developed packaging and shipping materials that satisfy legal requirements for chain-of-custody. This service is only offered for drug testing.

Compliance Policies

Mayo Clinic Laboratories is committed to compliance with applicable laws and regulations such as the Clinical Laboratory Improvement Amendments (CLIA). Regulatory agencies that oversee our compliance include, but are not limited to, the Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), and the Department of Transportation (DOT). Mayo Clinic Laboratories develops, implements, and maintains policies, processes, and procedures throughout our organization which are designed to meet relevant requirements. We expect clients utilizing our services will ensure their compliance with patient confidentiality, diagnosis coding, anti-kick back statutes, professional courtesy, CPT-4 coding, CLIA-approved proficiency testing, and other similar regulatory requirements. Also see “Accreditation and Licensure,” “HIPAA Compliance,” and “Reportable Disease.”

Confidentiality of Results

Mayo Clinic Laboratories is committed to maintaining confidentiality of patient information. To ensure Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the College of American Pathologists (CAP) compliance for appropriate release of patient results, Mayo Clinic Laboratories has adopted the following policies:

Phone Inquiry Policy—One of the following unique identifiers will be required:

- Mayo Clinic Laboratories order ID number for specimen; **or**
- Client account number (assigned by Mayo Clinic Laboratories) along with patient name; **or**

- Client accession ID number interfaced to Mayo Clinic Laboratories; **or**
- Identification by individual that he or she is, in fact, "referring physician" identified on requisition form by Mayo Clinic Laboratories client.

Mayo Clinic Laboratories is authorized to release results to ordering physicians or other health care providers responsible for the individual patient's care. Patients or a patients' personal representative requesting results can do so via the following link: https://www.mayocliniclabs.com/customer-service/patient-reports.html.

Critical Values
The "Critical Values Policy" of the Department of Laboratory Medicine and Pathology (DLMP), Mayo Clinic, Rochester, Minnesota is described below. These values apply to Mayo Clinic patients as well as external clients of Mayo Clinic Laboratories. Clients should provide "Critical Value" contact information to Mayo Laboratory Inquiry (MLI) to facilitate call-backs. To standardize this process, a customized form is available at mayocliniclabs.com.

Definition of Critical Value—A critical value is defined as a value that represents a pathophysiological state at such variance with normal (expected values) as to be life-threatening unless something is done promptly and for which some corrective action could be taken.

Abnormals are Not Considered Critical Values— Most laboratory tests have established reference ranges, which represent results that are typically seen in a group of healthy individuals. While results outside these reference ranges may be considered abnormal, "abnormal" results and "critical values" are not synonymous. Analytes on the DLMP Critical Values List represent a subgroup of tests that meet the above definition.

Action Taken when a Result is Obtained that Exceeds the Limit Defined by the DLMP Critical Values List—In addition to the normal results reporting (e.g., fax, interface), Mayo Clinic Laboratories' staff telephone the ordering physician or the client-provided contact number within 60 minutes following laboratory release of the critical test result(s). In the event that contact is not made within the 60-minute period, we continue to telephone until the designated party is reached and the result is conveyed in compliance and adherence to the CAP.

Semi-Urgent Results— Semi-Urgent Results are defined by Mayo Clinic as those infectious disease-related results that are needed promptly to avoid potentially serious health consequences for the patient (or in the case of contagious diseases, potentially serious health consequences to other persons exposed to the patient) if not acknowledged and/or treated by the physician. While not included on the Critical Values List, this information is deemed important to patient care in compliance and adherence to the CAP.

To complement Mayo Clinic Laboratories normal reporting mechanisms (e.g., fax, interface), Mayo Clinic Laboratories' staff will telephone results identified as semi-urgent findings to the ordering facility within 2 hours following laboratory release of the result(s). In the event that contact is not made within the 2-hour period, we will continue to telephone until the responsible party is reached and the result is conveyed. In addition, in most instances, you will see the comment **SIGNIFICANT RESULT** appear on the final report.

For information regarding the Mayo Clinic Critical Value List, contact Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700 or visit mayocliniclabs.com.

Disclosures of Results
Under federal regulations, we are only authorized to release results to ordering physicians or other health care providers responsible for the individual patient's care. Third parties requesting results are directed to the ordering facility.

Mayo Clinic Laboratories is authorized to release results to ordering physicians or other health care providers responsible for the individual patient's care. Patients or a patients' personal representative requesting results can do so via the following link: https://www.mayocliniclabs.com/customer-service/patient-reports.html.

Environmental Specimens
Mayo Clinic Laboratories does not accept environmental specimens for laboratory testing.

Extracted Specimens
Mayo Clinic Laboratories will accept extracted nucleic acid for clinical testing, provided it is an acceptable specimen source for the ordered test **only** as listed in the Laboratory Test Catalog, and if the isolation was performed in a CLIA-certified laboratory or a laboratory meeting equivalent requirements as determined by the CAP and/or the CMS.

Framework for Quality
"Framework for Quality" is the foundation for the development and implementation of the quality program for Mayo Clinic Laboratories. Our framework builds upon the concepts of quality control and quality assurance providing an opportunity to deliver consistent, high-quality and cost-effective service to our clients. In addition, our quality program enhances our ability to meet and exceed the requirements of regulatory/ accreditation agencies and provide quality service to our customers.

A core principle at Mayo Clinic Laboratories is the continuous improvement of all processes and services that support the care of patients. Our continuous improvement process focuses on meeting the needs of you, our client, to help you serve your patients.

The Mayo Clinic Department of Laboratory Medicine and Pathology Quality Management System (DLMP QMS) is composed of twelve (12) "Quality System Essentials", or QSEs. The policies, processes, and procedures associated with the QSEs can be applied to all operations in the path of workflow (e.g., pre-analytical, analytical, and post-analytical). Performance is measured through active monitoring of activities in the path of workflow and comparing performance through benchmarking internal and external quality indicators and proficiency testing. The DLMP QMS is the basis for all that we do and is integrated into our daily work processes.

Data generated by quality indicators drives process improvement initiatives to seek resolutions to system-wide problems. Mayo Clinic Laboratories utilizes Failure Modes and Effects Analysis (FMEA), Plan Do Study Act (PDSA), LEAN, Root Cause Analysis, and Six Sigma quality improvement tools to determine appropriate remedial, corrective, and preventive actions.

Quality Indicators—Mayo Clinic Laboratories produces hundreds of Key Performance Indicators (KPI) for our business and operational areas, and we review them regularly to ensure that we continue to maintain our high standards. A sampling of these metrics includes:

- Pre-analytic performance indicators
  - Incoming defects*
  - Lost specimens*
  - MayoTrac™ compliance
  - On-time delivery
  - Specimen identification*

- Analytic performance indicators
  - Proficiency testing
  - Quality control
  - Turnaround (analytic) times
  - Quantity-not-sufficient (QNS) specimens*
- Post-analytic performance indicators
  - Revised reports*
  - Total Critical Results Notification Reports*
- Operational performance indicators
  - Incoming call resolution
  - Incoming call abandon rate
  - Call completion rate
  - Call in-queue monitoring
  - Customer complaints
  - Customer satisfaction surveys

*Measured using Six Sigma defects per million (dpm) method.

The system provides a planned, systematic program for defining, implementing, monitoring, and evaluating our services.

HIPAA Compliance
Mayo Clinic Laboratories is fully committed to compliance with all privacy, security, and electronic transaction code requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All services provided by Mayo Clinic Laboratories that involve joint efforts will be done in a manner which enables our clients to be HIPAA and the College of American Pathologists (CAP) compliant.

Informed Consent Certification
Submission of an order for any tests contained in this catalog constitutes certification to Mayo Clinic Laboratories by ordering physician that: (1) ordering physician has obtained "Informed Consent" of subject patient as required by any applicable state or federal laws with respect to each test ordered; and (2) ordering physician has obtained from subject patient authorization permitting Mayo Clinic Laboratories to report results of each test ordered directly to ordering physician.
On occasion, we forward a specimen to an outside reference laboratory. The laws of the state where the reference laboratory is located may require written informed consent for certain tests. Mayo Clinic Laboratories will request that ordering physician pursue and provide such consent. Test results may be delayed or denied if consent is not provided.

Non-Biologic Specimens
Due to the inherent exposure risk of non-biologic specimens, their containers, and the implied relationship to criminal, forensic, and medico-legal cases, Mayo Clinic Laboratories does not accept nor refer non-biologic specimen types. Example specimens include unknown solids and liquids in the forms of pills, powder, intravenous fluids, or syringe contents.

Patient Safety Goals
The Joint Commission National Patient Safety Goal #1 is to improve the accuracy of patient identification by using at least two (2) patient identifiers when providing care, treatment, or services.

Mayo Clinic Laboratories uses multiple patient identifiers to verify the correct patient is matched with the correct specimen and the correct order for the testing services. As a specimen is received at Mayo Clinic Laboratories, the client accession number, patient first and last name, and patient age and date of birth are verified by comparing the labels on the specimen tube or container with the electronic order and any paperwork (batch sheet or form) which may accompany the specimen to be tested. When discrepancies are identified, Mayo Laboratory Inquiry will call the client to verify discrepant information to assure Mayo Clinic Laboratories is performing the correct testing for the correct patient. When insufficient or inconsistent identification is submitted, Mayo Clinic Laboratories will recommend that a new specimen be obtained, if feasible. In cases where an irreplaceable specimen is mislabeled, additional conditions must be met prior to testing.

In addition, Anatomic Pathology consultation services require the Client Pathology Report. The pathology report is used to match the patient name, patient age and/or date of birth, and pathology case number. Since tissue blocks and slides have insufficient space to print the patient name on the block, the pathology report provides Mayo Clinic Laboratories another mechanism to confirm the patient identification with the client order and labels on tissue blocks and slides.

Parallel Testing (also called Comparison Testing)
Parallel testing may be appropriate in some cases to re-establish patient baseline results when converting to a new methodology at Mayo Clinic Laboratories. Contact your Hospital Account Executive at 800-533-1710 or 507-266-5700 for further information. Specific planning is required prior to implementation.

Proficiency Testing
Mayo Clinic Laboratories are College of American Pathologists (CAP)-accredited, CLIA-licensed laboratories that voluntarily participate in many diverse external and internal proficiency testing programs. It is Mayo Clinic Laboratories' expectation that clients utilizing our services will adhere to CLIA requirements for proficiency testing (42 CFR 493.801). This includes a prohibition of discussion about proficiency testing samples or results and sending of proficiency testing materials to Mayo Clinic Laboratories during the active survey period.

Mayo Clinic Laboratories' proficiency testing includes participation in CMS-approved programs. Mayo Clinic Laboratories also performs alternative assessment using independent state, national, and international programs when proficiency testing is not available. Mayo Clinic Laboratories also conducts comparability studies to ensure the accuracy and reliability of patient testing, when necessary. We comply with the regulations set forth in Clinical Laboratory Improvement Amendments (CLIA-88), the Occupational Safety and Health Administration (OSHA), or the Centers for Medicare & Medicaid Services (CMS).

It is Mayo Clinic Laboratories' expectation that clients utilizing our services will adhere to CLIA requirements for proficiency testing including a prohibition on discussion about samples or results and sharing of proficiency testing materials with Mayo Clinic Laboratories during the active survey period.

Radioactive Specimens
Specimens from patients receiving radioactive tracers or material should be labeled as such. All incoming shipments arriving at Mayo Clinic Laboratories are routed through a detection process in receiving to determine if the samples have any levels of radioactivity. If radioactive levels are detected, the samples are handled via an internal process that assures we do not impact patient care and the safety of our staff. This radioactivity may invalidate the results of radioimmunoassay (RIA).

Record Retention
Mayo Clinic Laboratories retains all test requisitions and patient test results at a minimum for the retention period required to comply with and adhere to the CAP, CLIA and New York State (NYS) requirements. A copy of the original report can be reconstructed including reference ranges, interpretive comments, flags, and footnotes with the source system as the Department of Laboratory Medicine's laboratory information system.

Referral of Tests to Another Laboratory
Mayo Clinic Laboratories forwards tests to other laboratories as a service to its clients. This service should in no way represent an endorsement of such test or referral laboratory or warrant any specific performance for such test.

We have established collaborative relationships with more than 140 laboratories within the United States. Outside vendors are selected on the basis of certifications, service, turnaround time, methodology, reference range and price. Laboratory qualifications are reviewed by our internal operations and quality teams. A recommendation is forwarded to our medical director for final consideration as to compliance with and adherence to College of American Pathologists (CAP) Laboratory General Checklist (GEN.41350). Once selected, each laboratory is monitored to ensure that turnaround time is prompt and certain customer service criteria are met. The referral laboratories must requalify every two years, or as their test offerings change.

Reflex Testing
Mayo Clinic Laboratories identifies tests that reflex when medically appropriate. In many cases, Mayo Clinic Laboratories offers components of reflex tests individually as well as together. Clients should familiarize themselves with the test offerings and make a decision whether to order a reflex test or an individual component and only order test offerings based on medical necessity. Clients, who order a reflex test, can request to receive an "Additional Testing Notification Report" which indicates the additional testing that has been performed. This report will be faxed to the client. Clients who wish to receive the "Additional Testing Notification Report" should contact their Hospital Account Executive or Regional Service Representative. Do not send reflex testing on proficiency testing samples to Mayo Clinic Laboratories before the Proficiency Testing submission deadline.

Reportable Disease
Mayo Clinic Laboratories, in compliance with and adherence to the College of American Pathologists (CAP Laboratory General Checklist (GEN. 41316) strives to comply with laboratory reporting requirements for each state health department regarding reportable disease conditions. We report by mail, fax, and/or electronically, depending upon the specific state health department regulations. Clients shall be responsible for compliance with any state specific statutes concerning reportable conditions, including, but not limited to, birth defects registries or chromosomal abnormality registries. This may also include providing patient address/demographic information. Mayo Clinic Laboratories' reporting does not replace the client or physician responsibility to report as per specific state statues.

Request for Physician Name and Number
Mayo Clinic Laboratories endeavors to provide high quality, timely results so patients are able to receive appropriate care as quickly as possible. While providing esoteric reference testing, there are times when we need to contact the ordering physician directly. The following are 2 examples:

- When necessary to the performance of a test, the ordering physician's name and phone number are requested as part of "Specimen Required." This information is needed to allow our physicians to make timely consultations or seek clarification of requested services. If this information is not provided at the time of specimen receipt, we will call you to obtain the information. By providing this information up front, delays in patient care are avoided.
- In some situations, additional information from ordering physician is necessary to clarify or interpret a test result. At that time, Mayo Clinic Laboratories will request physician's name and phone number so that one of our staff can consult with the physician.

We appreciate your rapid assistance in supplying us with the ordering physician's name and phone number when we are required to call. Working together, we can provide your patients with the highest quality testing services in the shortest possible time.

Special Handling
Mayo Clinic Laboratories serves as a reference laboratory for clients around the country and world. Our test information, including days and time assays are performed as well as analytic turnaround time, is included under each test listing in the Test Catalog on mayocliniclabs.com. Unique circumstances may arise with a patient resulting in a physician request that the specimen or results receive special handling. There are several options available. These options can only be initiated by contacting Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700 and providing patient demographic information.

There is a nominal charge associated with any special handling.

- **Hold:** If you would like to send us a specimen and hold that specimen for testing pending initial test results performed at your facility, please call Mayo Laboratory Inquiry. We will initiate a hold and stabilize the specimen until we hear from you.
- **Expedite:** If you would like us to expedite the specimen to the performing laboratory, you can call Mayo Laboratory Inquiry and request that your specimen be expedited. Once the shipment is received in our receiving area, we will deliver the specimen to the performing laboratory for the next scheduled analytic run. We will not set up a special run to accommodate an expedite request.
- **STAT:** In rare circumstances, STAT testing from the reference laboratory may be required for patients who need immediate treatment. These cases typically necessitate a special analytic run to turn results around as quickly as possible. To arrange STAT testing, please have your pathologist, physician, or laboratory director call Mayo Laboratory Inquiry. He/she will be connected with one of our medical directors to consult about the patient's case. Once mutually agreed upon that there is a need for a STAT, arrangements will be made to assign resources to run the testing on a STAT basis when the specimen is received.

Specimen Identification Policy
Mayo Clinic Laboratories uses a minimum of two patient-specific identifiers to verify the correct patient is matched with the correct specimen and the correct order for testing services. As a specimen is received at Mayo Clinic Laboratories, the patient's first and last name, date of birth, medical record number, and client accession number are verified by comparing the labels on the specimen tube or container with the electronic order and any paperwork (batch sheet or form) that may accompany the specimen to be tested. When discrepancies are identified, the Mayo Laboratory Inquiry Call Center will telephone the client to verify discrepant information to assure Mayo Clinic Laboratories is performing the correct testing for the correct patient. Specimens are considered mislabeled when there is a mismatch between the person-specific identifiers on the specimen and information accompanying the specimen (e.g. computer system, requisition form, additional paperwork). When insufficient or inconsistent identification is submitted, Mayo Clinic Laboratories will recommend that a new specimen be obtained.

In addition, Anatomic Pathology consultation services require the client pathology report. The pathology report is used to match patient name, patient age and/or date of birth and pathology case number. Since tissue blocks and slides have insufficient space to print the patient name on the block, the pathology report provides Mayo Clinic Laboratories another mechanism to confirm the patient identification with the client order and labels on tissue blocks and slides.

Specimen Rejection
All tests are unique in their testing requirements. To avoid specimen rejection or delayed turnaround times, please check the "Specimen Required" field within each test. You will be notified of rejected or problem specimens upon receipt.

Please review the following conditions prior to submitting a specimen to Mayo Clinic Laboratories:
- Full 24 hours for timed urine collection
- pH of urine
- Lack of hemolysis/lipemia

- Specimen type (plasma, serum, whole blood, etc.)
- Specimen volume
- Patient information requested
- Proper identification of patient/specimen
- Specimen container (metal-free, separation gel, appropriate preservative, etc.)
- Transport medium
- Temperature (ambient, frozen, refrigerated)

Specimen Volume
The "Specimen Required" section of each test includes the preferred volume, but the "Specimen Minimum Volume" is also provided. Preferred volume has been established to optimize testing and allows the laboratory to quickly process specimen containers, present containers to instruments, perform test, and repeat test, if necessary. Many of our testing processes are fully automated; and as a result, this volume allows hands-free testing and our quickest turnaround time (TAT). Since patient values are frequently abnormal, repeat testing, dilutions, or other specimen manipulations often are required to obtain a reliable, reportable result. Our preferred specimen requirements allow expeditious testing and reporting.

When venipuncture is technically difficult or the patient is at risk of complications from blood loss (e.g., pediatric or intensive care patients), smaller volumes may be necessary. Specimen minimum volume is the amount of sample necessary to provide a clinically relevant result as determined by the Testing Laboratory.

When patient conditions do not mandate reduced collection volumes, we ask that our clients submit preferred volume to facilitate rapid, cost-effective, reliable test results. Submitting less than preferred volume may negatively impact quality of care by slowing TAT, increasing the hands-on personnel time (and therefore cost) required to perform test.

Mayo Clinic Laboratories makes every possible effort to successfully test your patient's specimen. If you have concerns about submitting a specimen for testing, please call Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700. Our staff will discuss the test and specimen you have available. While in some cases specimens are inadequate for desired test, in other cases, testing can be performed using alternative techniques.

Supplies
Shipping boxes, specimen vials, special specimen collection containers, and request forms are supplied without charge. Supplies can be requested using one of the following methods: use the online ordering functionality available at mayocliniclabs.com/supplies or call Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700.

Test Classifications
Analytical tests offered by Mayo Clinic Laboratories are classified according to the FDA labeling of the test kit or reagents and their usage. Where appropriate, analytical test listings contain a statement regarding these classifications, test development, and performance characteristics.

Test Development Process
Mayo Clinic Laboratories is dedicated to providing clinically useful, cost-effective testing strategies for patient care. Development, validation and implementation of new and improved laboratory methods are major components of that commitment. We have launched a standardized test life cycle process (TLCP) which includes seven specific phases of the test life cycle process (test design, development, verification, validation, launch, maintenance and test retirement). This process streamlines all development operations and activities and aligns with FDA test development definitions. Assays utilized at Mayo Clinic, whether laboratory developed or FDA cleared/approved/exempt, undergo verification and validation before the test becomes available for clinical use, including (as applicable):
- Accuracy
- Precision
- Sensitivity

- Specificity and interferences
- Reportable range
- Linearity
- Specimen stability
- Specimen type comparisons
- Urine preservative stability studies
- Comparative evaluation
- Reference values*
- Workload recording
- Limitations of the assay
- Clinical utility and interpretation (written by Mayo Clinic medical experts, available electronically - MayoAccess™)

*Reference values provided by Mayo Clinic Laboratories are derived from studies performed in our laboratories. If reference values are obtained from other sources, the source is indicated in the "Reference Values" field.

Test Result Call-Backs
Results will be phoned to a client when requested from the client (either on Mayo Clinic Laboratories request form or from a phone call to Mayo Clinic Laboratories from the client). See also Critical Values.

Time-Sensitive Specimens
Please contact Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700 prior to sending a specimen for testing of a time-sensitive nature. Relay the following information: facility name, account number, patient name and/or Mayo Clinic Laboratories accession number, shipping information (i.e., courier service, FedEx®, etc.), date to be sent, and test to be performed. Place specimen in a separate Mayo Clinic Laboratories temperature appropriate bag. Please write “Expedite” in large print on outside of bag.

Turnaround Time (TAT)
Mayo Clinic Laboratories extensive test menu reflects the needs of our own health care practice. We are committed to providing the most expedient TAT possible to improve diagnosis and treatment. We consider laboratory services as part of the patient care continuum wherein the needs of the patient are paramount. In that context, we strive to fulfill our service obligations. Our history of service and our quality metrics will document our ability to deliver on all areas of service including TAT.

Mayo Clinic Laboratories defines TAT as the analytical test time (the time from which a specimen is received at the testing location to time of result) required and is listed for each test as “Report Available”. TAT is monitored continuously by each performing laboratory site within the Mayo Clinic Department of Laboratory Medicine and Pathology. For the most up-to-date information on TAT for individual tests, please visit us at mayocliniclabs.com or contact Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700.

Unlisted Tests
Mayo Clinic Laboratories does not list all available test offerings in the catalog. New procedures are developed throughout the year; therefore, some tests are not listed in this catalog. Although we do not usually accept referred tests of a more routine type, special arrangements may be made to provide your laboratory with temporary support during times of special need such as sustained instrumentation failure. For information about unlisted tests, please call Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700.

POLICY NOTE:
Review MCL Framework for Quality document simulatiously with this policy:
https://www.mayocliniclabs.com/it-mmfiles/quality-and-compliance.pdf.

DHVD
8822

1,25-Dihydroxyvitamin D, Serum

Clinical Information: Vitamin D is a generic designation for a group of fat-soluble, structurally similar sterols, which act as hormones. In the presence of renal disease or hypercalcemia, testing of 1,25-dihydroxy vitamin D (DHVD) may be needed to adequately assess vitamin D status. The 25-hydroxyvitamin D (25HDN) test (25HDN / 25-Hydroxyvitamin D2 and D3, Serum) in serum is otherwise the preferred initial test for assessing vitamin D status and most accurately reflects the body's vitamin D stores. Vitamin D compounds in the body are exogenously derived by dietary means from plants as 25-hydroxyvitamin D2 (ergocalciferol or calciferol) or from animal products as 25-hydroxyvitamin D3 (cholecalciferol or calcidiol). Vitamin D may also be endogenously derived by conversion of 7-dihydrocholesterol to 25-hydroxyvitamin D3 in the skin upon ultraviolet exposure. The 25-hydroxyvitamin D is subsequently formed by hydroxylation by CYP2R1 in the liver. 25HDN is a prohormone that represents the main reservoir and transport form of vitamin D, being stored in adipose tissue and tightly bound by a transport protein while in circulation. Biological activity is expressed in the form of DHVD, the active metabolite of 25HDN. 1-Alpha-hydroxylation by CYP27B1 occurs on demand, primarily in the kidneys, under the control of parathyroid hormone (PTH) before expressing biological activity. Like other steroid hormones, DHVD binds to a nuclear receptor, influencing gene transcription patterns in target organs. 25-hydroxyvitamin D may also be converted into the inactive metabolite 24,25-dihydroxyvitamin D (24,25D) by alternative hydroxylation by CYP24A1. This process, regulated by PTH, might increase DHVD synthesis at the expense of the alternative CYP24A1 hydroxylation product 24,25D. Inactivation of 25HDN and DHVD by CYP24A1 is a crucial process that prevents over production of DHVD and resultant vitamin D toxicity. 1,25-dihydroxy vitamin D stimulates calcium absorption in the intestine and its production is tightly regulated through concentrations of serum calcium, phosphorus, and PTH. DHVD promotes intestinal calcium absorption and, in concert with PTH, skeletal calcium deposition or, less commonly, calcium mobilization. Renal calcium and phosphate reabsorption are also promoted, while prepro-PTH mRNA expression in the parathyroid glands is downregulated. The net result is a positive calcium balance, increasing serum calcium and phosphate levels, and falling PTH concentrations. In addition to its effects on calcium and bone metabolism, DHVD regulates the expression of a multitude of genes in many other tissues including immune cells, muscle, vasculature, and reproductive organs. 1,25-dihydroxy vitamin D levels are decreased in hypoparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in physiologic hyperparathyroidism secondary to low calcium or vitamin D intake. Some patients with granulomatous diseases (eg, sarcoidosis) and malignancies containing nonregulated 1-alpha hydroxylase in the lesion might have hypercalcemia that appears vitamin D mediated with normal or high serum phosphate (hyperphosphatemia) and hypercalcemia (both of which might be severe) in addition to low PTH and absent parathyroid hormone-related peptide (PTHRP). Assessment of 24,25D might also be required in patients with hypercalcemia that does not appear to be driven by PTH or PTHRP and may be helpful in assessment of patients with loss of function inactivating CYP24A1 mutations. Differential diagnostic considerations include vitamin D intoxication and CYP24A1 deficiency.

Useful For: As a second-order test in the assessment of vitamin D status, especially in patients with renal disease Investigation of some patients with clinical evidence of vitamin D deficiency (eg, vitamin D-dependent rickets due to hereditary deficiency of renal 1-alpha hydroxylase or end-organ resistance to 1,25-dihydroxyvitamin D) Differential diagnosis of hypercalcemia

Interpretation: 1,25-Dihydroxyvitamin D (DVHD) concentrations are low in chronic renal failure and hypoparathyroidism. 1,25-Dihydroxyvitamin D concentrations are high in sarcoidosis and other granulomatous diseases, some malignancies, primary hyperparathyroidism, and physiologic hyperparathyroidism. 1,25-Dihydroxyvitamin D concentrations are not a reliable indicator of vitamin D toxicity; normal (or even low) results may be seen in such cases.

Reference Values:
Males:

<16 years: 24-86 pg/mL
> or =16 years: 18-64 pg/mL

Females:
<16 years: 24-86 pg/mL
> or =16 years: 18-78 pg/mL

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Endres DB, Rude RK. Vitamin D and its metabolites. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 3rd ed. WB Saunders Company, 1999:1417-1423 2. Bringhurst FR, Demay MB, Kronenberg HM. Vitamin D (calciferols): metabolism of vitamin D. In: Wilson JD, Foster DS, Kronenberg HM, Larsen PR, eds. Williams Textbook of Endocrinology. 9th ed. 1998:1166-1169 3. Laha TJ, Strathmann FG, Wang Z, de Boer IH, Thummel KE, Hoofnagle AN. Characterizing antibody cross-reactivity for immunoaffinity purification of analytes prior to multiplexed liquid chromatography-tandem mass spectrometry. Clin Chem. 2012;58(12):1711-1716. doi:10.1373/clinchem.2012.185827 4. Strathmann FG, Laha TJ, Hoofnagle AN. Quantification of 1a,25-dihydroxy vitamin D by immunoextraction and liquid chromatography-tandem mass spectrometry. Clin Chem. 2011;57(9):1279-1285. doi:10.1373/clinchem.2010.161174 5. Herrmann M. Assessing vitamin D metabolism - four decades of experience. Clin Chem Lab Med. 2023;61(5):880-894. doi:10.1515/cclm-2022-1267

SFUNG
604094

1,3-Beta-D-Glucan (Fungitell), Serum

Clinical Information: Invasive fungal infections (IFI) due to opportunistic fungal pathogens are a significant cause of morbidity and mortality, particularly among patients who are significantly immunosuppressed, including hematopoietic stem cell transplant recipients, solid organ transplant recipients, and those with hematologic or immune deficiencies. Patient recovery and survival following an IFI are directly related to the timely clinical recognition and prompt administration of antifungal therapy. Laboratory diagnosis of IFI is largely based on direct microscopic examination of patient specimens, histopathologic examination of tissue biopsies, isolation of fungi via culture, and, more recently, through molecular methods. However, these techniques commonly require invasive sample collection methods (eg, biopsy, bronchoalveolar lavage), which may be contraindicated in certain patients. Additionally, both microscopy and culture are frequently insensitive, with prior studies showing the sensitivity of culture for invasive Aspergillus infections ranges from 40% to 85%, and some fungi require prolonged incubation times, limiting the utility of culture in the acute patient setting. Due to these limitations, use of fungal biomarkers, including detection of (1,3)-beta-D-glucan (BDG), have emerged as useful adjunct tests available for detection of IFI. (1,3)-beta-D-glucan is found in the cell walls of most fungi (eg, Candida, Aspergillus, Fusarium, Pneumocystis jirovecii) with the notable exception of Cryptococcus species, Blastomyces species, and the Mucorales (eg, Lichtheimia, Mucor, Rhizopus), which either lack BDG entirely or produce it in very low amounts. Elevated serum BDG levels have been associated with the presence of a fungal infection. The BDG levels may be detected prior to the development of clinical symptoms and before isolation or identification of the fungal organism via routine methods. The sensitivity and specificity of BDG detection in patients with proven or probable IFI range from 64% to 93% and 87% to 100%, respectively, among different studies. Importantly, the BDG assay should not be used alone to diagnose an IFI but rather in conjunction with careful evaluation of patient risk factors for infection, other laboratory testing, and radiologic findings.

Useful For: Aiding in the diagnosis of invasive fungal infections caused by various fungi, including Aspergillus species, Fusarium species, Candida species, and Pneumocystis jirovecii, among others

Interpretation: The Fungitell assay should be used in conjunction with other diagnostic procedures, such as routine bacterial/fungal cultures, histologic examination of biopsy material, and radiologic studies. Positive: (1,3)-Beta-D-glucan detected. A single positive result should be interpreted with caution and correlated alongside consideration of patient risk for invasive fungal disease, results of routine laboratory tests (eg, bacterial and fungal culture, histopathologic evaluation), and radiologic findings. Repeat testing on a new sample (collected in 3-4 days) is recommended as serially positive samples are associated with a higher diagnostic odds ratio for invasive fungal infection compared to a single positive result. False-positive results may occur in patients who have recently (in the past 3-4 days) undergone hemodialysis, treatment with certain fractionated blood products (eg, serum albumin, immunoglobulins), or those who have had significant exposure to glucan-containing gauze during surgery. Indeterminate: Repeat testing on a new sample is recommended in patients at risk for an invasive fungal infection. Negative: No (1,3)-Beta-D-glucan detected. This assay does not detect certain fungi, including Cryptococcus species, which produce very low levels of (1,3)-beta-D-glucan (BDG) and the Mucorales (eg, Lichtheimia, Mucor, and Rhizopus), which are not known to produce BDG. Additionally, the yeast phase of Blastomyces dermatitidis produces little BDG and may not be detected by this assay.

Reference Values:

Fungitell quantitative value:
<60 pg/mL

Fungitell qualitative result:
Negative

Reference values apply to all ages.

Clinical References: Ramanan P, Wengenack NL, Theel ES. Laboratory diagnostics for fungal infections: a review of current and future diagnostic assays. Clin Chest Med. 2017;38(3):535-554

DOCS
46919

11-Deoxycorticosterone, Serum

Clinical Information: The adrenal glands, ovaries, testes, and placenta produce steroid hormones, which can be subdivided into 3 major groups: mineralocorticoids, glucocorticoids, and sex steroids. Synthesis proceeds from cholesterol along 3 parallel pathways, corresponding to these 3 major groups of steroids, through successive side-chain cleavage and hydroxylation reactions. At various levels of each pathway, intermediate products can move into the respective adjacent pathways via additional, enzymatically catalyzed reactions (see Steroid Pathways). 11-Deoxycorticosterone represents the last intermediate in the mineral corticoid pathway that has negligible mineralocorticoid activity. It is converted by 11-beta-hydroxylase 2 (CYP11B2) or by 11-beta-hydroxylase 1 (CYP11B1) to the first mineralocorticoids with significant activity, corticosterone. Corticosterone is in turn converted to 18-hydroxycorticosterone and ultimately to aldosterone, the most active mineralocorticoid. Both reactions are catalyzed by CYP11B2, which, unlike its sister enzyme CYP11B1, also possesses 18-hydroxylase and 18-methyloxidase activity. The major diagnostic utility of measurement of steroid synthesis intermediates is in diagnosing disorders of steroid synthesis, particularly congenital adrenal hyperplasia (CAH). All types of CAH are associated with cortisol deficiency except for CYP11B2 deficiency and isolated impairments of the 17-lyase activity of CYP17A1 (this enzyme also has 17-alpha-hydroxylase activity). In cases of severe illness or trauma, CAH predisposes patients to poor recovery or death. Patients with the most common form of CAH (21-hydroxylase deficiency, which accounts for >90% of cases), with the third most common form of CAH (3-beta-steroid dehydrogenase deficiency, which accounts for <3% of cases), or the extremely rare StAR (steroidogenic acute regulatory protein) or 20,22 desmolase deficiencies might also suffer mineralocorticoid deficiency, as the enzyme blocks in these disorders are proximal to potent mineral corticoids. These patients might suffer salt-wasting crises in infancy. By contrast, patients with the second most common form of CAH

(11-hydroxylase deficiency, which accounts for <5% of cases) are normotensive or hypertensive, as the block affects either CYP11B1 or CYP11B2, but rarely both, thus ensuring that at least corticosterone is still produced. In addition, patients with all forms of CAH might suffer the effects of substrate accumulation proximal to the enzyme block. In the 3 most common forms of CAH, the accumulating precursors spill over into the sex steroid pathway, resulting in virilization of female patients or, in milder cases, in hirsutism, polycystic ovarian syndrome, or infertility, as well as in possible premature adrenarche and pubarche in both sexes. Measurement of the various precursors of mature mineralocorticoids and glucocorticoids, in concert with the determination of sex steroid concentrations, allows diagnosis of CAH and its precise type and serves as an aid in monitoring steroid replacement therapy and other therapeutic interventions. Measurement of 11-deoxycorticosterone and its glucocorticoid pendant, 11-deoxycortisol (also known as compound S), is aimed at diagnosing: -CYP11B1 deficiency (associated with cortisol deficiency) -The rarer CYP11B2 deficiency (no cortisol deficiency) -The yet less common glucocorticoid-responsive hyperaldosteronism (where expression of the gene CYP11B2 is driven by the CYP11B1 promoter, thus making it responsive to corticotropin [previously adrenocorticotrophic hormone: ACTH] rather than renin) For other forms of CAH, the following tests might be relevant: 21-Hydroxylase deficiency: -OHPG / 17-Hydroxyprogesterone, Serum -ANST / Androstenedione, Serum -21DOC / 21-Deoxycortisol, Serum 11-Hydroxylase deficiency: -DOCS / 11-Deoxycorticosterone, Serum -CORTC / Corticosterone, Serum -PRA / Renin Activity, Plasma -ALDS / Aldosterone, Serum 3-Beta-steroid-dehydrogenase deficiency: -17PRN / Pregnenolone and 17-Hydroxypregnenolone, Serum 17-Hydroxylase deficiency or 17-lyase deficiency (CYP17A1 has both activities): -17PRN / Pregnenolone and 17-Hydroxypregnenolone, Serum -PGSN / Progesterone, Serum -OHPG / 17-Hydroxyprogesterone, Serum -DHEA_ / Dehydroepiandrosterone (DHEA), Serum -ANST / Androstenedione, Serum Cortisol should be measured in all cases of suspected CAH. In the diagnosis of suspected 11-hydroxylase deficiency and glucocorticoid-responsive hyperaldosteronism, this test should be used in conjunction with measurements of 11-deoxycortisol, corticosterone, 18-hydroxycorticosterone, cortisol, renin, and aldosterone.

Useful For: Diagnosis of suspected 11-hydroxylase deficiency, including the differential diagnosis of 11-beta-hydroxylase 1 (CYP11B1) versus 11-beta-hydroxylase 2 (CYP11B2) deficiency Diagnosis of glucocorticoid-responsive hyperaldosteronism Evaluating congenital adrenal hyperplasia newborn screen-positive children, when elevations of 17-hydroxyprogesterone are only moderate, suggesting possible 11-hydroxylase deficiency

Interpretation: In 11-beta-hydroxylase 1 (CYP11B1) deficiency, serum concentrations of cortisol will be low (usually <7 mcg/dL for a morning collection). 11-Deoxycortisol and 11-deoxycorticosterone are elevated, usually to at least 2 to 3 times (more typically 20-300 times) the upper limit of the normal reference range for a morning blood collection. Elevations in 11-deoxycortisol are usually relatively greater than those of 11-deoxycorticosterone, because of the presence of intact 11-beta-hydroxylase 2 (CYP11B2). For this reason, serum concentrations of all potent mineralocorticoids (corticosterone, 18-hydroxycorticosterone, and aldosterone) are typically increased above the normal reference range. Plasma renin activity is correspondingly low or completely suppressed. Caution needs to be exercised in interpreting the mineralocorticoid results in infants younger than 7 days; mineralocorticoid levels are often substantially elevated in healthy newborns in the first few hours of life and only decline to near-adult levels by week 1. Mild cases of CYP11B1 deficiency might require corticotropin (previously adrenocorticotrophic hormone: ACTH) 1-24 stimulation testing for definitive diagnosis. In affected individuals, the observed serum 11-deoxycortisol concentration 60 minutes after intravenous or intramuscular administration of 250 micrograms of ACTH1-24 will usually exceed 20 ng/mL or demonstrate at least a 4-fold rise. Such increments are rarely, if ever, observed in unaffected individuals. The corresponding cortisol response will be blunted (<18 ng/mL peak). In CYP11B2 deficiency, serum cortisol concentrations are usually normal, including a normal response to ACTH1-24. 11-Deoxycorticosterone will be elevated, often more profoundly than in CYP11B1 deficiency, while 11-deoxycortisol may or may not be significantly elevated. Serum corticosterone concentrations can be low, normal, or slightly elevated, while serum 18-hydroxycorticosterone and aldosterone concentrations will be low in the majority of cases. However, if the underlying genetic defect has selectively affected

18-hydroxylase activity, corticosterone concentrations will be substantially elevated. Conversely, if the deficit affects aldosterone synthase function primarily, 18-hydroxycorticosterone concentrations will be very high. Expression of the CYP11B2 gene is normally regulated by renin and not ACTH. In glucocorticoid-responsive hyperaldosteronism, the ACTH-responsive promoter of CYP11B1 exerts aberrant control over CYP11B2 gene expression. Consequently, corticosterone, 18-hydroxycorticosterone, and aldosterone are significantly elevated in these patients and their levels follow a diurnal pattern, governed by the rhythm of ACTH secretion. In addition, the high levels of CYP11B2 lead to 18-hydroxylation of 11-deoxycortisol (an event that is ordinarily rare, as CYP11B1, which has much greater activity in 11-deoxycortisol conversion than CYP11B2, lacks 18-hydroxylation activity). Consequently, significant levels of 18-hydroxycortisol, which normally is only present in trace amounts, might be detected in these patients. Ultimate diagnostic confirmation comes from showing direct responsiveness of mineral corticoid production to ACTH1-24 injection. Normally, this has little if any effect on corticosterone, 18-hydroxycorticosterone, and aldosterone levels. This testing may then be further supplemented by showing that mineralocorticoid levels fall after administration of dexamethasone. Sex steroid levels are moderately to significantly elevated in CYP11B1 deficiency and much less, or minimally, pronounced in CYP11B2 deficiency. Sex steroid levels in glucocorticoid-responsive hyperaldosteronism are usually normal. Most untreated patients with 21-hydroxylase deficiency have serum 17-hydroxyprogesterone concentrations well in excess of 1000 ng/dL. For the few patients with levels in the range of higher than 630 ng/dL (upper limit of reference range for newborns) to 2000 or 3000 ng/dL, it might be prudent to consider 11-hydroxylase deficiency as an alternative diagnosis. This is particularly true if serum androstenedione concentrations are also only mildly to modestly elevated, and if the phenotype is not salt wasting but either simple virilizing (female) or normal (female or male). 11-Hydroxylase deficiency, particularly if it affects CYP11B1, can be associated with modest elevations in serum 17-hydroxyprogesterone concentrations. In these cases, testing for CYP11B1 deficiency and CYB11B2 deficiency should be considered and interpreted as described above. Alternatively, measurement of 21-deoxycortisol might be useful. This minor pathway metabolite accumulates in CYP21A2 deficiency, as it requires 21-hydroxylaion to be converted to cortisol but is usually not elevated in CYP11B1 deficiency since its synthesis requires via 11-hydroxylation of 17-hydroxyprogesterone.

Reference Values:

< or =18 years: <30 ng/dL
>18 years: <10 ng/dL

Clinical References: 1. Von Schnakenburg K, Bidlingmaier F, Knorr D. 17-hydroxyprogesterone, androstenedione, and testosterone in normal children and in prepubertal patients with congenital adrenal hyperplasia. Eur J Pediatr. 1980;133(3):259-267 2. Therrell BL. Newborn screening for congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. 2001;30(1):15-30 3. Collett-Solberg PF. Congenital adrenal hyperplasia: from genetics and biochemistry to clinical practice, part I. Clin Pediatr. 2001;40:1-16 4. Forest MG. Recent advances in the diagnosis and management of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Hum Reprod Update. 2004;10:469-485 5. Tonetto-Fernandes V, Lemos-Marini SH, Kuperman H, Ribeiro-Neto LM, Verreschi JTN, Kater CE. Serum 21-deoxycortisol, 17-hydroxyprogesterone, and 11-deoxycortisol in classic congenital adrenal hyperplasia: clinical and hormonal correlations and identification of patients with 11 beta-hydroxylase deficiency among a large group with alleged 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2006;91:2179-2184 6. Lashanske G, Sainger P, Fishman K, et al. Normative data for adrenal steroidogenesis in a healthy pediatric population: age-and sex-related changes after adrenocorticotropin stimulation. J Clin Endocrinol Metab. 1991;73:674-686 7. Holst JP, Soldin SJ, Tractenberg RE, et al. Use of steroid profiles in determining the cause of adrenal insufficiency. Steroids. 2007;72:71-84 8. Berneis K, Staub JJ, Gessler A, Meier C, Girard J, Muller B. Combined stimulation of adrenocorticotropin and compound-S by single dose metyrapone test as an outpatient procedure to assess hypothalamic-pituitary-adrenal function. J Clin Endocrinol Metab. 2002;87(12):5470-5475 9. Sciarra F, Tosti-Croce C, Toscano V. Androgen-secreting adrenal tumors. Minerva Endocrinol. 1995;20:63-68 10. Speiser PW, Arlt W, Auchus RJ, et al. Congenital adrenal hyperplasia due to steroid

21-hydroxylase deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(11):4043-4088. doi:10.1210/jc.2018-01865 Correction in: J Clin Endocrinol Metab. 2019;104(1):39-40 11. Khattab A, Haider S, Kumar A, et al. Clinical, genetic, and structural basis of congenital adrenal hyperplasia due to 11beta-hydroxylase deficiency. Proc Natl Acad Sci U S A. 2017;114(10):E1933-E1940 doi:10.1073/pnas.1621082114

DCORT
46920

11-Deoxycortisol, Serum

Clinical Information: 11-Deoxycortisol (compound S) is the immediate precursor of cortisol: 11 beta-hydroxylase 11-deoxycortisol---------->cortisol Compound S is typically increased when corticotropin (previously adrenocorticotropic hormone: ACTH) levels are increased (eg, Cushing disease, ACTH-producing tumors) or in 11-beta-hydroxylase deficiency, a rare subform of congenital adrenal hyperplasia (CAH). In CAH due to 11-beta-hydroxylase deficiency, cortisol levels are low, resulting in increased pituitary ACTH production and increased serum and urine 11-deoxycortisol levels. Pharmacological blockade of 11-beta-hydroxylase with metyrapone can be used to assess the function of the hypothalamic-pituitary-adrenal axis (HPA). In this procedure, metyrapone is administered to patients, and serum 11-deoxycortisol levels or urinary 17-hydroxy steroid levels are measured either at baseline (midnight) and 8 hours later (overnight test), or at baseline and once per day during a 2-day metyrapone test (4-times a day metyrapone administration over 2 days). Two-day metyrapone testing has been largely abandoned because of the logistical problems of multiple timed urine and blood collections and the fact that overnight testing provides very similar results. In either case, the normal response to metyrapone administration is a fall in serum cortisol levels, triggering a rise in pituitary ACTH secretion, which, in turn, leads to a rise in 11-deoxycortisol levels due to the ongoing 11-deoxycortisol-to-cortisol conversion block. In the diagnostic workup of suspected adrenal insufficiency, the results of overnight metyrapone testing correlate closely with the gold standard of HPA-axis assessment, insulin hypoglycemia testing. Combining 11-deoxycortisol measurements with ACTH measurements during metyrapone testing further enhances the performance of the test. Impairment of any component of the HPA-axis results in a subnormal rise in 11-deoxycortisol levels. By contrast, standard-dose or low-dose ACTH(1-24) (cosyntropin)-stimulation testing, which forms the backbone for diagnosis of primary adrenal failure (Addison disease), only assess the ability of the adrenal cells to respond to ACTH stimulation. While this allows unequivocal diagnosis of primary adrenal failure, in the setting of secondary or tertiary adrenal insufficiency, metyrapone testing is more sensitive and specific than either standard-dose or low-dose ACTH(1-24)-stimulation testing. Metyrapone testing is also sometimes employed in the differential diagnosis of Cushing syndrome. In Cushing disease (pituitary-dependent ACTH overproduction), the ACTH-hypersecreting pituitary tissue remains responsive to the usual feedback stimuli, just at a higher "set-point" than in the normal state, resulting in increased ACTH secretion and 11-deoxycortisol production after metyrapone administration. By contrast, in Cushing syndrome due to primary adrenal corticosteroid oversecretion or ectopic ACTH secretion, pituitary ACTH production is appropriately shut down, and there is usually no further rise in ACTH and, hence 11-deoxycortisol, after metyrapone administration. The metyrapone test has similar sensitivity and specificity to the high-dose dexamethasone suppression test in the differential diagnosis of Cushing disease but is less widely used because of the lack of availability of an easy, automated 11-deoxycortisol assay. In recent years, both tests have been supplanted to some degree by corticotropin-releasing hormone-stimulation testing with petrosal sinus serum ACTH sampling. For more information see Steroid Pathways.

Useful For: Diagnostic workup of patients with congenital adrenal hyperplasia Part of metyrapone testing in the workup of suspected secondary or tertiary adrenal insufficiency Part of metyrapone testing in the differential diagnostic workup of Cushing syndrome

Interpretation: In a patient suspected of having congenital adrenal hyperplasia (CAH), elevated serum 11-deoxycortisol levels indicate possible 11-beta-hydroxylase deficiency. However, not all patients will show baseline elevations in serum 11-deoxycortisol levels. In a significant proportion of cases, increases in 11-deoxycortisol levels are only apparent after corticotropin (previously adrenocorticotropic

hormone)(1-24) stimulation.(1) Serum 11-deoxycortisol levels below 1700 ng/dL when measured 8 hours after metyrapone administration is indicative of probable adrenal insufficiency. The test cannot reliably distinguish between primary and secondary or tertiary causes of adrenal failure, as neither patients with pituitary failure, nor those with primary adrenocortical failure, tend to show an increase of 11-deoxycortisol levels after metyrapone is administered. For more information see Steroid Pathways.

Reference Values:

< or =18 years: <344 ng/dL
>18 years: 10-79 ng/dL

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Tonetto-Fernandes V, Lemos-Marini SH, Kuperman H, Ribeiro-Neto LM, Verreschi IT, Kater CE. Serum 21-deoxycortisol, 17-hydroxyprogesterone, and 11-deoxycortisol in classic congenital adrenal hyperplasia: clinical and hormonal correlations and identification of patients with 11 beta-hydroxylase deficiency among a large group with alleged 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2006;91(6):2179-2184 2. Lashansky G, Saenger P, Fishman K, et al. Normative data for adrenal steroidogenesis in a healthy pediatric population: age- and sex-related changes after adrenocorticotropin stimulation. J Clin Endocrinol Metab. 1991;73(3):674-686 3. Holst JP, Soldin SJ, Tractenberg RE, et al. Use of steroid profiles in determining the cause of adrenal insufficiency. Steroids. 2007;72(1):71-84 4. Berneis K, Staub JJ, Gessler A, Meier C, Girard J, Muller B. Combined stimulation of adrenocorticotropin and compound-S by single dose metyrapone test as an outpatient procedure to assess hypothalamic-pituitary-adrenal function. J Clin Endocrinol Metab. 2002;87(12):5470-5475 5. Idkowiak, J, Cragun, D, Hopkin RJ, Arlt W. Cytochrome P450 oxidoreductase deficiency. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. Gene Reviews [Internet]. University of Washington, Seattle; 2005. Updated August 3, 2017. Accessed March 3, 2025. Available at www.ncbi.nlm.nih.gov/sites/books/NBK1419/ 6. Held PK, Bird IM, Heather NL. Newborn screening for congenital adrenal hyperplasia: review of factors affecting screening accuracy. Int J Neonatal Screen. 2020;6(3):67. doi:10.3390/ijns6030067

F11DX
75673

11-Desoxycortisol

Reference Values:

Age	Range (ng/dL)
Premature (26 - 28 weeks) Day 4	110-1376
Premature (31 - 35 weeks) Day 4	48-579
Newborn Day 3	13-147
Newborn 1 to 11 months	
Prepubertal 8 AM	20-155
Prepubertal Children and Adults 8 AM	12-158

THCMX
62744

11-nor-Delta-9-Tetrahydrocannabinol-9-Carboxylic Acid (Carboxy-THC) Confirmation, Chain of Custody, Meconium

Clinical Information: Marijuana and other psychoactive products obtained from the plant Cannabis sativa are the most widely used illicit drugs in the world.(1) Marijuana has unique behavioral effects that include feelings of euphoria and relaxation, altered time perception, impaired learning and memory, lack of concentration, and mood changes (eg, panic reactions and paranoia). Cannabis sativa produces numerous compounds collectively known as cannabinoids, including delta-9-tetrahydrocannabinol (THC), which is the most prevalent and produces most of the characteristic pharmacological effects of smoked marijuana.(2) THC undergoes rapid hydroxylation by the cytochrome enzyme system to form the active metabolite 11-hydroxy-THC. Subsequent oxidation of 11-hydroxy-THC produces the inactive metabolite 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH; carboxy-THC). THC-COOH and its glucuronide conjugate have been identified as the major end-products of metabolism. THC is highly lipid soluble, resulting in its concentration and prolonged retention in fat tissue.(3) Cannabinoids cross the placenta, but a dose-response relationship or correlation has not been established between the amount of marijuana use during pregnancy and the levels of cannabinoids found in meconium, the first fecal matter passed by the neonate.(4,5) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing amniotic fluid.(5) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and it slowly moves into the colon by the 16th week of gestation.(6) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(5) Chain of custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting in utero drug exposure to marijuana (tetrahydrocannabinol) up to 5 months before birth Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

Interpretation: The presence of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid at 5 ng/g or greater is indicative of in utero drug exposure up to 5 months before birth.

Reference Values:

Negative

Positives are reported with a quantitative liquid chromatography tandem mass spectrometry result.

Cutoff concentration: 5 ng/g

Clinical References: 1. Huestis MA. Marijuana. In: Levine B, ed. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:229-264 2. O'Brein CP. Drug addiction and drug abuse. In: Burton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill; 2006 3. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020 4. Ostrea EM Jr, Knapp DK, Tannenbaum L, et al. Estimates of illicit drug use during pregnancy by maternal interview, hair analysis, and meconium analysis. J Pediatr. 2001;138(3):344-348 5. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989;115(3):474-477 6. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero: mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-74 7. Langman LJ,

Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

THCM
84284

11-nor-Delta-9-Tetrahydrocannabinol-9-Carboxylic Acid (Carboxy-THC) Confirmation, Meconium

Clinical Information: Marijuana and other psychoactive products obtained from the plant Cannabis sativa are the most widely used illicit drugs in the world.(1) Marijuana has unique behavioral effects that include feelings of euphoria and relaxation, altered time perception, impaired learning and memory, lack of concentration, and mood changes (eg, panic reactions and paranoia). Cannabis sativa produces numerous compounds collectively known as cannabinoids, including delta-9-tetrahydrocannabinol (THC), which is the most prevalent and produces most of the characteristic pharmacological effects of smoked marijuana.(2) THC undergoes rapid hydroxylation by the cytochrome enzyme system to form the active metabolite 11-hydroxy-THC. Subsequent oxidation of 11-hydroxy-THC produces the inactive metabolite 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH; carboxy-THC). THC-COOH and its glucuronide conjugate have been identified as the major end-products of metabolism. THC is highly lipid soluble, resulting in its concentration and prolonged retention in fat tissue.(3) Cannabinoids cross the placenta, but a dose-response relationship or correlation has not been established between the amount of marijuana use during pregnancy and the levels of cannabinoids found in meconium, the first fecal matter passed by the neonate.(4,5) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing amniotic fluid.(5) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and it slowly moves into the colon by the 16th week of gestation.(6) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(5)

Useful For: Detecting in utero drug exposure to marijuana (tetrahydrocannabinol) up to 5 months before birth

Interpretation: The presence of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid at 5 ng/g or greater is indicative of in utero drug exposure up to 5 months before birth.

Reference Values:
Negative

Positive results are reported with a quantitative liquid chromatography tandem mass spectrometry result.

Cutoff concentration: 5 ng/g

Clinical References: 1. Huestis MA. Marijuana. In: Levine B, ed. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:229-264 2. O'Brein CP. Drug addiction and drug abuse. In: Burton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill; 2006 3. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020 4. Ostrea EM Jr, Knapp DK, Tannenbaum L, et al. Estimates of illicit drug use during pregnancy by maternal interview, hair analysis, and meconium analysis. J Pediatr. 2001;138(3):344-348 5. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989;115(3):474-477 6. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero: mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-74 7. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham

C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

17OHP
81151

17-Hydroxypregnenolone, Serum

Clinical Information: Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. Deficiencies in several enzymes can cause CAH, including 21-hydroxylase (CYP21A2 variants; 90% of cases), 11-hydroxylase (CYP11A1 variants; 5%-8%), 3-beta-hydroxysteroid dehydrogenase (3-beta-HSD) (HSD3B2 variants; <5%), and 17-alpha-hydroxylase (CYP17A1 variants; <1%). The resulting hormone imbalances (reduced glucocorticoids and mineralocorticoids; elevated steroid intermediates and androgens) can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. The adrenal glands, ovaries, testes, and placenta produce steroid intermediates, which are hydroxylated at the position 21 (by 21-hydroxylase) and position 11 (by 11-hydroxylase) to produce cortisol. Deficiency of either 21-hydroxylase or 11-hydroxylase results in decreased cortisol synthesis and loss of feedback inhibition of adrenocorticotropic hormone (ACTH) secretion. The consequent increased pituitary release of ACTH drives increased production of steroid intermediates. The steroid intermediates are oxidized at position 3 by 3-beta-HSD. The 3-beta-HSD enzyme allows formation of 17-hydroxyprogesterone (17-OHPG) from 17-hydroxypregnenolone and progesterone from pregnenolone. When 3-beta-HSD is deficient, cortisol is decreased, 17-hydroxypregnenolone and pregnenolone levels may increase, and 17-OHPG and progesterone levels are low. Dehydroepiandrosterone is also converted to androstenedione by 3-beta-HSD and may be elevated in patients affected with 3-beta-HSD deficiency. The best screening test for CAH, most often caused by either 21- or 11-hydroxylase deficiency, is the analysis of 17-OHPG, along with cortisol and androstenedione. CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency, Serum allows the simultaneous determination of these 3 analytes. Alternatively, these tests may be ordered individually: OHPG / 17-Hydroxyprogesterone, Serum; CINP / Cortisol, Mass Spectrometry, Serum; and ANST / Androstenedione, Serum. If both 21- and 11-hydroxylase deficiency have been ruled out, analysis of 17-hydroxypregnenolone and pregnenolone may be used to confirm the diagnosis of 3-beta-HSD or 17-alpha-hydroxylase deficiency. For more information see Steroid Pathways.

Useful For: As an ancillary test for congenital adrenal hyperplasia (CAH), particularly in situations in which a diagnosis of both 21- and 11-hydroxylase deficiency have been ruled out Confirming a diagnosis of 3-beta-hydroxysteroid dehydrogenase deficiency As part of a battery of tests to evaluate women with hirsutism or infertility; both can result from adult-onset CAH

Interpretation: The diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always require the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) variants usually have very high levels of androstenedione, often 5-fold to 10-fold elevations. 17-Hydroxyprogesterone (17-OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. For the HSD3B2 variant, cortisol, 17-OHPG, and progesterone levels will be decreased; 17-hydroxypregnenolone, pregnenolone, and dehydroepiandrosterone (DHEA) levels will be increased. In the much less common CYP11A1 variant, androstenedione levels are elevated to a similar extent as in CYP21A2 variant, and cortisol is also low, but OHPG is only mildly, if at all, elevated. In the very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors (particularly pregnenolone, 11-dexycorticosterone, corticosterone, and 18-hydroxycorticosterone) are increased. For more information see Steroid Pathways.

Reference Values:
CHILDREN/ADOLESCENTS*
Males

Premature (26-28 weeks): 1,219-9,799 ng/dL
Premature (29-36 weeks): 346-8,911 ng/dL
Full term (1-5 months): 229-3,104 ng/dL
6 months-364 days: 221-1,981 ng/dL
1-2 years: 35-712 ng/dL
3-6 years: <277 ng/dL
7-9 years: <188 ng/dL
10-12 years: <393 ng/dL
13-15 years: 35-465 ng/dL
16-17 years: 32-478 ng/dL

Tanner Stages
Stage I: <209 ng/dL
Stage II: <356 ng/dL
Stage III: <451 ng/dL
Stage IV-V: 35-478 ng/dL

Females
Premature (26-28 weeks): 1,219-9,799 ng/dL
Premature (29-36 weeks): 346-8,911 ng/dL
Full term (1-5 months): 229-3,104 ng/dL
6 months-364 days: 221-1,981 ng/dL
1-2 years: 35-712 ng/dL
3-6 years: <277 ng/dL
7-9 years: <213 ng/dL
10-12 years: <399 ng/dL
13-15 years: <408 ng/dL
16-17 years: <424 ng/dL

Tanner Stages
Stage I: <236 ng/dL
Stage II: <368 ng/dL
Stage III: <431 ng/dL
Stage IV-V: <413 ng/dL

*Kushnir MM, Rockwood AL, Roberts WL, et al. Development and performance evaluation of a tandem mass spectrometry assay for 4 adrenal steroids. Clin Chem. 2006;52(8):1559-1567

ADULTS
Males
> or =18 years: 55-455 ng/dL
Females
> or =18 years: 31-455 ng/dL

To convert to nmol/L, multiply the value in ng/dL by 0.03159757.

Clinical References: 1. Wudy SA, Harmann M, Swoboda M. Determination of 17-hydroxypregnenolone in plasma by stabile isotope dilution/bechtop liquid chromatography-tandem mass spectrometry. Horm Res 2000;53(2):68-71 2. Therrell BL. Newborn screening for congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. 2001;30(1):15-30 3. Bachega TA, Billerbeck AE, Marcondes JA, et al. Influence of different genotypes on 17-hydroxyprogesterone levels in patients with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Clin Endocrinol. 2000;52(5):601-607 4. Kao P, Machacek DA, Magera MJ, Lacey JM, Rinaldo P. Diagnosis of adrenal cortical dysfunction by liquid chromatography-tandem mass spectrometry. Ann Clin. Lab. Sci.

2001;31:199-204 5.. Collett-Solberg PF. Congenital adrenal hyperplasia: from genetics and biochemistry to clinical practice, part I. Clin Pediatr (Phila). 2001:40(1):1-16 6. Kushnir MA, Rockwood AL, Roberts WL, Pattison EG, et al. Development and performance evaluation of a tandem mass spectrometry assay for 4 adrenal steroids. Clinical Chemistry 2006;52(8):1559-1567 7. Siklar Z, Camtosun E, Bolu S, et al. 17 alpha hydroxylase/17,20 lyase deficiency: clinical features and genetic insights from a large Turkey cohort. Endocrine. 2024;85(3):1407-1416. doi:10.1007/s12020-024-03962-6 8. Duskova M, Kolatorova L, Simkova M, et al. Steroid diagnostics of 21st century in the light of their new roles and analytical tools. Physiol Res. 2020;69(Suppl 2):S193-S203. doi:10.33549/physiolres.934517

OHPG
9231

17-Hydroxyprogesterone, Serum

Clinical Information: Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. The resulting hormone imbalances with reduced glucocorticoids and mineralocorticoids and elevated 17-hydroxyprogesterone (OHPG) and androgens can lead to life-threatening, salt-wasting crisis in the newborn period and incorrect gender assignment of virtualized female patients. Adult-onset CAH may result in hirsutism or infertility in women. The adrenal glands, ovaries, testes, and placenta produce OHPG. It is hydroxylated at the 11 and 21 position to produce cortisol. Deficiency of either 11- or 21-hydroxylase results in decreased cortisol synthesis, and feedback inhibition of adrenocorticotropic hormone (ACTH) secretion is lost. Consequent increased pituitary release of ACTH increases production of OHPG. But, if 17-alpha-hydroxylase (which allows formation of OHPG from progesterone) or 3-beta-hydroxysteroid dehydrogenase type 2 (which allows formation of 17-hydroxyprogesterone formation from 17-hydroxypregnenolone) are deficient, OHPG levels are low with possible increase in progesterone or pregnenolone respectively. OHPG is bound to both corticosteroid binding globulin and albumin, and total OHPG is measured in this assay. OHPG is converted to pregnanetriol, which is conjugated and excreted in the urine. In all instances, more specific tests are available to diagnose disorders or steroid metabolism than pregnanetriol measurement. Most (90%) cases of CAH are due to variants in the steroid 21-hydroxylase gene (CYP21A2). CAH due to 21-hydroxylase deficiency is diagnosed by confirming elevations of OHPG and androstenedione (ANST / Androstenedione, Serum) with decreased cortisol (CINP / Cortisol, Mass Spectrometry, Serum). By contrast, in 2 less common forms of CAH, due to 17-hydroxylase or 11-hydroxylase deficiency, OHPG and androstenedione levels are not significantly elevated and measurement of progesterone (PGSN / Progesterone, Serum) and deoxycorticosterone (DOCS / 11-Deoxycorticosterone, Serum), respectively, are necessary for diagnosis. For more information see Steroid Pathways

Useful For: Screening test for congenital adrenal hyperplasia (CAH), caused by either 11- or 21-hydroxylase deficiency, when used in combination with testing for cortisol and androstenedione As part of a battery of tests to evaluate women with hirsutism or infertility

Interpretation: Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) variants usually have very high levels of androstenedione, often 5- to 10-fold elevations. 17-hydroxyprogesterone (OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. In the much less common CYP11A1 variant, androstenedione levels are elevated to a similar extent as in CYP21A2 variant, and cortisol is also low, but OHPG is only mildly, if at all, elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors, in particular progesterone, 11-deoxycorticosterone, and 18-hydroxycorticosterone, are increased. The goal of CAH treatment is normalization of cortisol levels and, ideally, also of sex-steroid levels. Traditionally, OHPG and urinary pregnanetriol or total ketosteroid excretion are measured to guide treatment, but these tests correlate only modestly with androgen levels. Therefore, androstenedione and testosterone should also be measured and used to guide treatment modifications. Normal prepubertal levels may be difficult to achieve, but if testosterone levels are within

the reference range, androstenedione levels of up to 100 ng/dL are usually regarded as acceptable. For more information see Steroid Pathways .

Reference Values:

Children:

Preterm infants

Preterm infants may exceed 630 ng/dL, however, it is uncommon to see levels reach 1,000 ng/dL.

Term infants

0-28 days: <630 ng/dL

Levels fall from newborn (<630 ng/dL) to prepubertal gradually within 6 months.

Prepubertal males: <110 ng/dL

Prepubertal females: <100 ng/dL

Adults:

Males: <220 ng/dL

Females

Follicular: <80 ng/dL

Luteal: <285 ng/dL

Postmenopausal: <51 ng/dL

Note: For pregnancy reference ranges, see: Soldin OP, Guo T, Weiderpass E, et al. Steroid hormone levels in pregnancy and 1 year postpartum using isotope dilution tandem mass spectrometry. Fertil Steril. 2005;84(3):701-710

Clinical References: 1. Von Schnakenburg K, Bidlingmaier F, Knorr D. 17-hydroxyprogesterone, androstenedione, and testosterone in normal children and in prepubertal patients with congenital adrenal hyperplasia. Eur J Pediatr. 1980;133(3):259-267 2. Sciarra F, Tosti-Croce C, Toscano V. Androgen-secreting adrenal tumors. Minerva Endocrinol. 1995;20(1):63-68 3. Collett-Solberg P. Congenital adrenal hyperplasia: from genetics and biochemistry to clinical practice, part I. Clin Pediatr. 2001;40(1):1-16 4. Speiser PW, Azziz R, Baskin LS, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2010;95(9):4133-4160 5. Nordenstrom A, Falhammar H. Management of Endocrine Disease: Diagnosis and management of the patient with non-classic CAH due to 21-hydroxylase deficiency. Eur J Endocrinol. 2019;180(3):R127-R14 6. Young WF Jr. Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev. 1999;7(4):207-214 7. Young WF Jr. Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am. 1997;26(4):801-827 8. Wudy SA, Hartmann M, Svoboda M. Determination of 17-hydroxypregnenolone in plasma by stabile isotope dilution/benchtop liquid chromatography-tandem mass spectrometry. Horm Res. 2000;53(2):68-71 9. Therrell BL. Newborn screening for congenital adrenal hyperplasia Endocrinol Metab Clin North Am. 2001;30(1):15-30 10. Bachega TA, Billerbeck AE, Marcondes JA, Madureira G, Arnhold IJ, Mendonca BB. Influence of different genotypes on 17-hydroxyprogesterone levels in patients with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Clin Endocrinol. 2000;52(5):601-607 11. Kao P, Machacek DA, Magera MJ, Lacey JM, Rinaldo P. Diagnosis of adrenal cortical dysfunction by liquid chromatography-tandem mass spectrometry. Ann Clin Lab Sci. 2001;31(2):199-204 12. Young WF Jr. Management approaches to adrenal incidentalomas-a view from Rochester, Minnesota. Endocrinol Metab Clin North Am. 2000;29(1):159-185 13. Ibanez L, DiMartino-Nardi J, Potau N, Saenger P. Premature adrenarche-normal variant or forerunner of adult disease? Endocr Rev. 2000;21(6):671-696 14. Allolio B, Arlt W. DHEA treatment: myth or reality? Trends Endocrinol Metab 2002;13(7):288-294 15. Lin CL, Wu TJ, Machacek DA, Jiang NS, Kao PC. Urinary free cortisol and cortisone determined by high-performance liquid chromatography in the diagnosis of Cushing's syndrome. J Clin Endocrinol Metab. 1997;82(1):151-155 16. Findling JW, Raff H. Diagnosis and differential diagnosis of Cushing's syndrome. Endocrinol Metab Clin North Am 2001;30(3):729-747 17. Buchman Al. Side effects of corticosteroid therapy. J Clin Gastroenterol. 2001;33(4):289-297 18. Dodds HM, Taylor PJ, Cannell GR, Pond SM. A high-performance liquid

chromatography-electrospray-tandem mass spectrometry analysis of cortisol and metabolites in placental perfusate. Anal Biochem. 1997;247(2):342-347 19. Cengiz H, Demirci T, Varim C, Cetin S. Establishing a new screening 17 hydroxyprogesterone cut-off value and evaluation of the reliability of the long intramuscular ACTH stimulation test in the diagnosis of nonclassical congenital adrenal hyperplasia. Eur Rev Med Pharmacol Sci. 2021;25(16):5235-5240. doi:10.26355/eurrev_202108_26537

FHC18
75675

18-Hydroxycorticosterone, Serum

Reference Values:

Age	Range (ng/dL)
Premature (26-28 weeks) Day 4	10-670
Premature (31-35 weeks) Day 4	57-410
Full-term Day 3	31-546
31 days to 11 months	5-220
12-23 months	18-155
24 months to 9 years	6-85
10-14 years	10-72
Adults	9-58
Adults 8:00 AM Supine	4-21
Adults 8:00 AM Upright	5-46

GLIOF
35272

1p/19q Deletion in Gliomas, FISH, Tissue

Clinical Information: Astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas are the major histologic types of human gliomas; histologic differentiation among these tumors can be difficult. It has been shown that specific genetic alterations are highly associated with specific morphologic types of gliomas. In addition, specific genetic alterations seem to predict prognosis (survival), as well as response to specific chemotherapeutic and radiotherapeutic regimens, irrespective of tumor morphology. Deletions of the short arm of chromosome 1(1p) and long arm of chromosome 19 (19q), are strongly correlated with gliomas of oligodendroglial morphology. Approximately 70%, 50%, and 50% of oligodendrogliomas have deletions of 19q, 1p, and of both 19q and 1p, respectively. Combined 1p and 19q loss is infrequent in gliomas of astrocytic origin. Thus, the presence of combined 1p/19q loss is strongly suggestive that a glioma is of oligodendroglioma lineage. Gains of chromosome 19 and of the 19 q-arm are associated with gliomas of astrocytic origin. Deletions of 1p and of both 1p and 19q also have been associated with response to various chemotherapeutic and radiotherapeutic regimens. These responses have been especially associated with high-grade oligodendrogliomas (anaplastic oligodendrogliomas). Chromosomal microarray (CMAPT / Chromosomal Microarray, Tumor, Formalin-Fixed Paraffin-Embedded), rather than fluorescence in situ hybridization, may be of benefit to evaluate for acquired alterations associated with the molecular classification of glioma.(1) For more information and frequently asked questions, see Clarity on Reason for and Benefits of Chromosomal Microarray.

Useful For: Aids in diagnosing oligodendroglioma tumors and predicting the response of an oligodendroglioma to therapy May be useful in tumors with a complex "hybrid" morphology requiring differentiation from pure astrocytomas to support the presence of oligodendroglial differentiation/lineage Indicated when a diagnosis of oligodendroglioma, both low-grade World Health Organization (WHO, grade II) and anaplastic (WHO, grade III) is rendered Strongly recommended when a diagnosis of mixed oligoastrocytomas is rendered

Interpretation: The presence of short arm of chromosome 1(1p) deletion and combined 1p and long arm of chromosome 19 deletion supports a diagnosis of oligodendroglioma may indicate that the patient may respond to chemotherapy and radiation therapy. The presence of gain of chromosome 19 supports a diagnosis of high-grade astrocytoma (glioblastoma multiforme). A negative result does not exclude a diagnosis of oligodendroglioma or high-grade astrocytoma.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board. Central Nervous System Tumours: WHO Classification of Tumours. Vol 6. 5th ed. IARC Press; 2022:19-55 2. Ball MK, Kollmeyer TM, Praska CE, et al. Frequency of false-positive FISH 1p/19q codeletion in adult diffuse astrocytic gliomas. Neurooncol Adv. 2020 Aug 27;2(1):vdaa109. doi: 10.1093/noajnl/vdaa109

JGLIF
615002

1p/19q Glioma Deletions, FISH, Tissue

Clinical Information: Chromosome 1p/19q co-deletion is a diagnostic and prognostic marker of oligodendroglioma. Studies have shown that the co-deletion of these 2 chromosomal arms is due to a balanced whole arm translocation between chromosomes 1 and 19 and subsequent loss of the 1p and 19q arms. Detection of 1p/19q co-deletion along with molecular testing of other genes including MGMT promotor methylation, IDH1/2 variant, TERT promotor variants, as well as TP53 variants, will assist glioma classification and predicting prognosis and providing a guidance for treatment. Variants in many other genes may occur and detection of these by next generation sequencing may provide useful information for classification and therapeutic consideration. 1p/19q co-deletion is determined by fluorescence in situ hybridization (FISH) in this test. Interpretation of the clinical significance of the FISH result should be correlated with the results of other molecular testing for disease subclassification and therapy selection. While IDH1/2 variants with co-deletion of 1p and 19q define oligodendrogliomas, isolated 19q loss is common in astrocytomas and focal loss of 1p frequently is seen in IDH-wild-type glioblastoma. Rarely, a 1p/19q co-deletion detected by FISH may not represent loss of the whole chromosome 1p and 19q arms. If a positive FISH result is not consistent with the disease subclassification, additional tests such as chromosome microarray should be considered to confirm presence of 1p/19q whole arm loss.

Useful For: Glioma subclassification, prognosis and selection of therapies

Interpretation: While IDH1/2 variantss with co-deletion of 1p and 19q define oligodendrogliomas, isolated 19q loss is common in astrocytomas and focal loss of 1p frequently is seen in IDH wildtype glioblastoma. Interpretation of the fluorescence in situ hybridization result must be correlated with other molecular testing results.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Eckel Passow JE, Lachance DH, Molinaro AM, et al: Glioma Groups Based on 1p/19q, IDH, and TERT Promoter Mutations in Tumors. N Engl J Med.

2015;372(26):2499-2508 2. Weller M, Wick W, Aldape K, et al. Glioma. Nat Rev Dis Primers. 2015;1:15017 3. Reifenberger G, Wirsching HG, Knobbe-Thomsen CB, Weller M. Advances in the molecular genetics of gliomas implications for classification and therapy. Nat Rev Clin Oncol. 2017;14(7):434-452 4. Chen R, Smith-Cohn M, Cohen AL, Colman H. Glioma Subclassifications and Their Clinical Significance. Neurotherapeutics 2017;14(2):284-297 5. Nicholson JG, Fine HA. Diffuse Glioma Heterogeneity and Its Therapeutic Implications. Cancer Discov. 2021;11(3):575-590 6. Galbraith K, Snuderl M. Molecular Pathology of Gliomas. Surg Pathol Clin. 2021;14(3):379-386

BPGMM
63208

2,3-Bisphosphoglycerate Mutase, Full Gene Sequencing Analysis, Varies

Clinical Information: Erythrocytosis (ie, increased red blood cell mass and elevated hemoglobin and hematocrit) may be primary, due to an intrinsic defect of bone marrow stem cells as in polycythemia vera (PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide, cyanotic heart disease, high-altitude living, kidney cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanism may be suspected. Unlike PV, hereditary erythrocytosis is not associated with the risk of clonal evolution and most commonly presents as isolated erythrocytosis that has been present since childhood. Hereditary erythrocytosis may be caused by alterations in one of several genes and inherited in either an autosomal dominant or autosomal recessive manner. Genetic variants causing hereditary erythrocytosis have been found in genes coding for alpha and beta hemoglobins, hemoglobin stabilization proteins (eg, 2,3-bisphosphoglycerate mutase: BPGM), the erythropoietin receptor (EPOR), and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF, prolyl hydroxylase domain: PHD, and von Hippel Lindau: VHL), see Table. The true prevalence of variants causing hereditary erythrocytosis is unknown; however, very few cases of 2,3-BPG deficiency-associated hereditary erythrocytosis have been identified, and this disorder is thought to be rare. Table. Erythrocytosis Testing Gene Inheritance Serum EPO JAK2 V617F Acquired Decreased JAK2 exon 12 Acquired Decreased EPOR Dominant Decreased PHD2/EGLN1 Dominant Normal BPGM Recessive Normal Beta globin Dominant Normal to increased Alpha globin Dominant Normal to increased HIF2A/EPAS1 Dominant Normal to increased VHL Recessive Normal to increased

Useful For: Diagnosing 2,3-bisphosphoglycerate mutase deficiency in individuals with lifelong, unexplained erythrocytosis Identifying genetic variant carriers in family members of an affected individual for the purposes of preconception genetic counseling This test is not intended for prenatal diagnosis.

Interpretation: An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any variations in the gene. If positive, the alteration will be correlated with clinical significance, if known.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Petousi N, Copley RR, Lappin TR, et al: Erythrocytosis associated with a novel missense mutation in the BPGM gene. Haematologica. 2014 Oct;99(10):e201-e204 2. Hoyer JD, Allen SL, Beutler E, Kubik K, West C, Fairbanks VF: Erythrocytosis due to bisphosphoglycerate mutase deficiency with concurrent glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Am J Hematol. 2004 Apr;75(4):205-208 3. Rosa R, Prehu MO, Beuzard Y, Rosa J: The first case of a complete deficiency of diphosphoglycerate mutase in human erythrocytes. J Clin Invest. 1978 Nov;62(5):907-915

23BPT
606357

2,3-Dinor 11 Beta-Prostaglandin F2 Alpha, 24 Hour, Urine

Clinical Information: 2,3-Dinor-11beta-prostaglandin F2 alpha (2,3 BPG) is the most abundant metabolic product of prostaglandins released by activated mast cells. Systemic mastocytosis (SM) is a disease in which clonally derived mast cells accumulate in peripheral tissues. Degranulation of these mast cells releases large amounts of histamines, prostaglandins, leukotrienes, and tryptase. The World Health Organization diagnostic criteria for SM require the presence of elevated mast cell counts on a bone marrow biopsy and one of the following minor criteria: -Abnormal mast cell morphology -KIT Asp816Val variant -CD25-positive mast cells -Serum tryptase greater than 20 ng/mL Alternatively, SM diagnosis can be made with the presence of 3 minor criteria in the absence of abnormal bone marrow studies. Measurement of mast cell mediators in blood or urine is less invasive and is advised for the initial evaluation of suspected cases. Elevated levels of serum tryptase, urinary N-methylhistamine, 2,3 BPG, or leukotriene E4 are consistent with the diagnosis of systemic mast cell disease.

Useful For: Screening for mast cell activation disorders including systemic mastocytosis using 24-hour urine specimens

Interpretation: Elevated urinary 2,3-dinor-11beta-prostaglandin F2 alpha (2,3 BPG) concentrations greater than 1820 pg/mg creatinine are consistent with the diagnosis of systemic mast cell disease when combined with clinical signs and symptoms. Pharmacological treatment with aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) has been shown to decrease production of 2,3 BPG. Urinary 2,3 BPG has been shown to improve sensitivity in the screening of mastocytosis when used in conjunction with urinary leukotriene E4, and urinary N-methylhistamine. An internal study showed when all three urine markers are measured; sensitivity for systemic mastocytosis detection is 90%.

Reference Values:
<1802 pg/mg creatinine

Clinical References: 1. Gotlib J, Pardanani A, Akin C, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. Blood. 2013;121(13):2393-2401. doi:10.1182/blood-2012-09-458521 2. Butterfield JH. Increased leukotriene E4 excretion in systemic mastocytosis. Prostaglandins Other Lipid Mediat. 2010;92(1-4):73-76. doi:10.1016/j.prostaglandins.2010.03.003 3. Roberts LJ 2nd, Sweetman BJ, Lewis RA, Austen KF, Oates JA. Increased production of prostaglandin D2 in patients with systemic mastocytosis. N Engl J Med. 1980;303(24):1400-1404. doi:10.1056/NEJM198012113032405 4. Metcalfe DD. Mastocytosis syndromes. In: Middleton E Jr, Reed CE, Ellis EF, et al. eds. Allergy Principles and Practice. Vol II. 4th ed. Mosby Yearbook Inc; 1993:1537-1551 5. Butterfield J, Weiler CR. The utility of measuring urinary metabolites of mast cell mediators in systemic mastocytosis and mast cell activation syndrome. J Allergy Clin Immunol Pract. 2020;8(8):2533-2541

23BPR
606356

2,3-Dinor 11 Beta-Prostaglandin F2 Alpha, Random, Urine

Clinical Information: 2,3-Dinor-11beta-prostaglandin F2 alpha (2,3 BPG) is the most abundant metabolic product of prostaglandins released by activated mast cells. Systemic mastocytosis (SM) is a disease in which clonally derived mast cells accumulate in peripheral tissues. Degranulation of these mast cells releases large amounts of histamines, prostaglandins, leukotrienes, and tryptase. The World Health Organization diagnostic criteria for SM require the presence of elevated mast cell counts on a bone marrow biopsy and one of the following minor criteria: -Abnormal mast cell morphology -KIT Asp816Val variant -CD25-positive mast cells -Serum tryptase greater than 20 ng/mL Alternatively, SM diagnosis can be made with the presence of 3 minor criteria in the absence of abnormal bone marrow studies. Measurement of mast cell mediators in blood or urine is less invasive and is advised for the

initial evaluation of suspected cases. Elevated levels of serum tryptase, urinary N-methylhistamine, 2,3 BPG, or leukotriene E4 are consistent with the diagnosis of systemic mast cell disease.

Useful For: Screening for mast cell activation disorders including systemic mastocytosis using random urine specimens

Interpretation: Elevated urinary 2,3-dinor-11beta-prostaglandin F2 alpha (2,3 BPG) concentrations greater than 1820 pg/mg creatinine are consistent with the diagnosis of systemic mast cell disease when combined with clinical signs and symptoms. Pharmacological treatment with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) has been shown to decrease production of 2,3 BPG. Urinary 2,3 BPG has been shown to improve sensitivity in the screening of mastocytosis when used in conjunction with urinary leukotriene E4 and urinary N-methylhistamine. An internal study showed when all three urine markers are measured; sensitivity for systemic mastocytosis detection is 90%.

Reference Values:
<1802 pg/mg creatinine

Clinical References: 1. Gotlib J, Pardanani A, Akin C, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. Blood. 2013 Mar 28;121(13):2393-2401. doi: 10.1182/blood-2012-09-458521 2. Butterfield JH. Increased leukotriene E4 excretion in systemic mastocytosis. Prostaglandins Other Lipid Mediat. 2010 Jun;92(1-4):73-76. doi: 10.1016/j.prostaglandins.2010.03.003 3. Roberts LJ 2nd, Sweetman BJ, Lewis RA, Austen KF, Oates JA. Increased production of prostaglandin D2 in patients with systemic mastocytosis. N Engl J Med. 1980;303(24):1400-1404. doi:10.1056/NEJM198012113032405 4. Metcalfe DD. Mastocytosis syndromes. In: Middleton E Jr, Reed CE, Ellis EF, et al. eds. Allergy Principles and Practice. Vol II. 4th ed. Mosby Yearbook Inc; 1993:1537-1551 5. Butterfield J, Weiler CR. The utility of measuring urinary metabolites of mast cell mediators in systemic mastocytosis and mast cell activation syndrome. J Allergy Clin Immunol Pract. 2020;8(8):2533-2541

2HGA
614603

2-Hydroxyglutaric Acid Chiral Analysis, Quantitative, Random, Urine

Clinical Information: 2-Hydroxyglutaric aciduria disorders are a group of cerebral organic acidurias that present biochemically with an elevation of 2-hydroxyglutaric acid (2-HGA) in the urine. There are 2 enantiomers of 2-HGA, the D-form and the L-form. Depending on the genetic defect, individuals may have an elevation of one or both forms of 2-HGA. Routine organic acid analysis (OAU / Organic Acids Screen, Random, Urine), while able to detect 2-HGA, is unable to distinguish between the 2 enantiomers; however, they can be separated with this more specialized biochemical test. L-2-hydroxyglutaric aciduria (L-2-HGA) is caused by defects in L2HGDH and is characterized by progressive cerebellar ataxia and intellectual disability, seizures, and macrocephaly beginning in infancy or early childhood. Symptoms worsen over time, leading to severe disability by early adulthood. Magnetic resonance imaging (MRI) findings include subcortical leukoencephalopathy, generalized cerebellar and cerebral atrophy, and atrophy of the corpus callosum. D-2-hydroxylglutaric aciduria (D-2-HGA) is characterized by elevated levels of D-2-hydroxyglutaric acid (D-2-HG) and typically manifests with developmental delay, seizures, and hypotonia, though can vary widely from asymptomatic to severe. There are 2 types of D-2-HGA depending on the genetic cause. D-2-HGA can either be autosomal recessive, resulting from variants in D2HGDH causing reduced enzymatic activity (type I), or autosomal dominant, with gain-of-function variants in IDH2 causing overproduction of D-2-HG (type II). Combined D,L-2-hydroxylglutaric aciduria (D,L-2-HGA) is the most severe of the 3 types and is caused by defects in SLC25A1, which encodes the mitochondrial citrate carrier. It is characterized by neonatal-onset encephalopathy with severe muscular weakness, intractable seizures, respiratory distress, and lack of psychomotor development resulting in

early death. Molecular genetic testing is available (2OHGP / 2-Hydroxyglutaric Aciduria Gene Panel, Varies), which includes analysis of D2HGDH, L2HGDH, IDH2, and SLC25A1 and can be used to confirm abnormal urine results.

Useful For: Determining type of 2-hydroxyglutaric aciduria by chiral analysis of urine

Interpretation: The values for the D-2-hydroxyglutaric acid and L-2-hydroxyglutaric acid concentrations are reported. The interpretation of the result must be correlated with clinical and other laboratory findings.

Reference Values:

Age	D-2-hydroxyglutaric acid (mmol/mol creatinine)	L-2-hydroxyglutaric acid (mmol/mol creatinine)
0-11 months	< or =14.11	< or =17.38
12-23 months	< or =13.76	< or =17.03
24-35 months	< or =13.38	< or =16.63
3 years	< or =12.96	< or =16.18
4 years	< or =12.20	< or =15.35
5 years	< or =11.40	< or =14.44
6 years	< or =10.56	< or =13.46
7 years	< or =9.71	< or =12.43
8 years	< or =8.93	< or =11.44
9 years	< or =8.21	< or =10.50
10 years	< or =7.56	< or =9.66
11 years	< or =6.99	< or =8.94
12 years	< or =6.47	< or =8.33
13 years	< or =6.01	< or =7.83
14 years	< or =5.60	< or =7.44
15 years	< or =5.23	< or =7.14
16 years	< or =4.91	< or =6.93
17 years	< or =4.63	< or =6.78
18 years	< or =4.40	< or =6.69
19 years	< or =4.21	< or =6.63
20 years	< or =4.07	< or =6.60
21 years	< or =3.96	< or =6.59
22 years	< or =3.88	< or =6.58
23 years	< or =3.81	< or =6.56
24 years	< or =3.76	< or =6.54
25 years	< or =3.71	< or =6.50

26 years	< or =3.67	< or =6.44
27 years	< or =3.63	< or =6.37
28 years	< or =3.59	< or =6.27
29 years	< or =3.56	< or =6.15
30 years	< or =3.54	< or =6.02
31 years	< or =3.52	< or =5.87
32 years	< or =3.50	< or =5.72
33 years	< or =3.49	< or =5.57
34 years	< or =3.48	< or =5.41
35 years	< or =3.46	< or =5.26
36 years	< or =3.45	< or =5.13
37 years	< or =3.43	< or =5.00
38 years	< or =3.42	< or =4.88
39 years	< or =3.40	< or =4.78
40 years	< or =3.39	< or =4.70
41 years	< or =3.37	< or =4.62
42 years	< or =3.35	< or =4.55
43 years	< or =3.33	< or =4.50
44 years	< or =3.30	< or =4.44
45 years	< or =3.28	< or =4.40
46 years	< or =3.24	< or =4.35
47 years	< or =3.21	< or =4.31
48 years	< or =3.17	< or =4.27
49 years	< or =3.13	< or =4.23
50 years	< or =3.10	< or =4.19
51 years	< or =3.07	< or =4.16
52 years	< or =3.04	< or =4.12
53 years	< or =3.01	< or =4.10
54 years	< or =2.99	< or =4.07
55 years	< or =2.97	< or =4.04
56 years	< or =2.95	< or =4.01
57 years	< or =2.93	< or =3.98
58 years	< or =2.91	< or =3.94
59 years	< or =2.89	< or =3.91
60 years	< or =2.87	< or =3.87
61 years	< or =2.85	< or =3.84
62 years	< or =2.83	< or =3.80

63 years	< or =2.79	< or =3.78
64 years	< or =2.76	< or =3.75
65 years	< or =2.71	< or =3.73
66 years	< or =2.67	< or =3.72
67 years	< or =2.61	< or =3.71
68 years	< or =2.56	< or =3.69
69 years	< or =2.50	< or =3.68
70 years	< or =2.44	< or =3.66
71 years	< or =2.38	< or =3.64
72 years	< or =2.32	< or =3.61
73 years	< or =2.26	< or =3.56
74 years	< or =2.21	< or =3.50
75 years	< or =2.16	< or =3.43
76 years	< or =2.10	< or =3.35
77 years	< or =2.05	< or =3.26
78 years	< or =2.00	< or =3.17
79 years	< or =1.94	< or =3.08
80 years	< or =1.89	< or =2.99
81 years	< or =1.84	< or =2.91
82 years	< or =1.80	< or =2.84
83 years	< or =1.75	< or =2.78
84 years	< or =1.71	< or =2.73
85 years	< or =1.68	< or =2.69
86 years	< or =1.65	< or =2.67
87 years	< or =1.64	< or =2.65
88 years	< or =1.63	< or =2.64
> or =89 years	< or =1.62	< or =2.64

Clinical References: 1. Kranendijk M, Struys EA, Salomons GS, Van der Knaap MS, Jakobs C. Progress in understanding 2-hydroxyglutaric acidurias. J Inherit Metab Dis. 2012;35(4):571-587. doi:10.1007/s10545-012-9462-5 2. Muhlhausen C, Salomons GS, Lukacs Z, et al. Combined D2-/L2-hydroxyglutaric aciduria (SLC25A1 deficiency): clinical course and effects of citrate treatment. J Inherit Metab Dis. 2014;37(5):775-781. doi:10.1007/s10545-014-9702-y 3. Struys EA. D-2-Hydroxyglutaric aciduria: unravelling the biochemical pathway and the genetic defect. J Inherit Metab Dis. 2006;29(1):21-29. doi:10.1007/s10545-006-0317-9 4. Perales-Clemente E, Hewitt AL, Studinski AL, et al. Bilateral subdural hematomas and retinal hemorrhages mimicking nonaccidental trauma in a patient with D-2-hydroxyglutaric aciduria. JIMD Rep. 2020;58(1):21-28. doi:10.1002/jmd2.12188

2OHGP 608030 2-Hydroxyglutaric Aciduria Gene Panel, Varies

Clinical Information: The 2-hydroxyglutaric aciduria disorders are a group of cerebral organic acidurias that present biochemically with an elevation of 2-hydroxyglutaric acid (2-HG) in the urine. There are two enantiomers or forms of 2-hydroxyglutaric acid, the D-form and the L-form. Depending on the genetic defect, individuals may have an elevation of one or both forms of 2-HG. Routine organic acid analysis (OAU / Organic Acids Screen, Random, Urine), while able to detect 2-HG, is unable to distinguish between the two enantiomers; however, they can be separated with more specialized biochemical testing. L-2-hydroxyglutaric aciduria (L-2-HGA) is caused by defects in L2HGDH and is characterized by progressive cerebellar ataxia and intellectual disability, seizures, and macrocephaly beginning in infancy or early childhood. Symptoms worsen over time leading to severe disability by early adulthood. Magnetic resonance imaging findings include subcortical leukoencephalopathy, generalized cerebellar and cerebral atrophy, and atrophy of the corpus callosum. D-2-hydroxylglutaric aciduria (D-2-HGA) is characterized by elevated levels of D-2-hydroxyglutaric acid and typically manifests with developmental delay, seizures, and hypotonia, though can vary widely from asymptomatic to severe. There are 2 types of D-2-HGA depending on the genetic cause. D-2-HGA can either be autosomal recessive, resulting from variants in D2HGDH causing reduced enzymatic activity (Type I) or autosomal dominant gain-of-function variants in IDH2 causing overproduction of D-2-HG (Type II). D,L-2-hydroxylglutaric aciduria is the most severe of the 3 and caused by defects in SLC25A1, which encodes the mitochondrial citrate carrier. It is characterized by neonatal-onset encephalopathy with severe muscular weakness, intractable seizures, respiratory distress, and lack of psychomotor development resulting in early death. Because of the genetic heterogeneity of the 2-hydroxyglutaric acidurias and the specialized biochemical testing needed to distinguish among the conditions, this genetic panel, which includes D2HGDH, L2HGDH, IDH2, and SLC25A1, is an efficient way to diagnose these conditions.

21DOC
89477

21-Deoxycortisol, Serum

Clinical Information: The adrenal glands, ovaries, testes, and placenta produce steroid hormones, which can be subdivided into 3 major groups: mineralocorticoids, glucocorticoids, and sex steroids. Synthesis proceeds from cholesterol along 3 parallel pathways, corresponding to these 3 major groups of steroids, through successive side-chain cleavage and hydroxylation reactions. At various levels of each pathway, intermediate products can move into the respective adjacent pathways via additional, enzymatically-catalyzed reactions (see Steroid Pathways). 21-Deoxycortisol is an intermediate steroid in the glucocorticoid pathway. While the main substrate flow in glucocorticoid synthesis proceeds from 17-hydroxyprogesterone via 21-hydroxylation to 11-deoxycortisol and then, ultimately, to cortisol, a small proportion of 17-hydroxyprogesterone is also hydroxylated at carbon number 11 by 11-beta-hydroxylase 1 (CYP11B1), yielding 21-deoxycortisol. This in turn can also serve as a substrate for 21-hydroxylase (CYP21A2), resulting in formation of cortisol. The major diagnostic utility of measurements of steroid synthesis intermediates lies in the diagnosis of disorders of steroid synthesis, particularly congenital adrenal hyperplasia (CAH). All types of CAH are associated with cortisol deficiency except for CYP11B2 deficiency and isolated impairments of the 17-lyase activity of CYP17A1 (this enzyme also has 17-alpha-hydroxylase activity). In case of severe illness or trauma, CAH predisposes patients to poor recovery or death. Patients with the most common form of CAH (21-hydroxylase deficiency, which accounts for >90% of cases), the third most common form of CAH (3-beta-steroid dehydrogenase deficiency, which accounts for <3% of cases), or the extremely rare StAR (steroidogenic acute regulatory protein) or 20,22 desmolase deficiencies might also suffer mineralocorticoid deficiency, as the enzyme blocks in these disorders are proximal to potent mineral corticoids. These patients might suffer salt-wasting crises in infancy. By contrast, patients with the second most common form of CAH (11-hydroxylase deficiency, which accounts for <5% of cases) are normotensive or hypertensive, as the block affects either CYP11B1 or CYP11B2, but rarely both, thus ensuring that at least corticosterone is still produced. In addition, patients with all forms of CAH might suffer the effects of substrate accumulation proximal to the enzyme block. In the 3 most common forms of CAH, the accumulating precursors spill over into the sex steroid pathway, resulting in virilization of female patients or, in milder cases, in hirsutism, polycystic ovarian syndrome, or infertility, as well as in possible premature adrenarche and pubarche in both sexes. Measurement of the various precursors of mature mineralocorticoids and glucocorticoids, in concert with the determination of sex steroid concentrations, allows diagnosis of CAH and its precise type and serves as an aid in monitoring steroid replacement therapy and other therapeutic interventions. Measurement of 21-deoxycortisol can

supplement or confirm 17-hydroxyprogesterone and androstenedione measurements in the diagnosis of difficult cases of CAH presumed to be due to CYP21A2 deficiency. 11-Hydroxylation remains intact in such patients. However, since the CYP21A2 enzyme block prevents formation of 11-deoxycortisol while simultaneously increasing the concentrations of the precursor, 17-hydroxyprogesterone, unoccupied CYP11B1 starts to hydroxylate the abundant 17-hydroxyprogesterone substrate into 21-deoxycortisol. The 21-deoxycortisol accumulates, as the diminished or absent CYP21A2 activity slows or prevents its conversion into cortisol. For other forms of CAH, the following tests may be relevant: 21-Hydroxylase deficiency: -OHPG / 17-Hydroxyprogesterone, Serum -ANST / Androstenedione, Serum -21DOC / 21-Deoxycortisol, Serum 11-Hydroxylase deficiency: -DOCS / 11-Deoxycorticosterone, Serum -CORTC / Corticosterone, Serum -PRA / Renin Activity, Plasma -ALDS / Aldosterone, Serum 3-Beta-steroid-dehydrogenase deficiency: -17PRN / Pregnenolone and 17-Hydroxypregnenolone, Serum 17-Hydroxylase deficiency or 17-lyase deficiency (CYP17A1 has both activities): -17PRN / Pregnenolone and 17-Hydroxypregnenolone, Serum -PGSN / Progesterone, Serum -OHPG / 17-Hydroxyprogesterone, Serum -DHEA_ / Dehydroepiandrosterone (DHEA), Serum -ANST / Androstenedione, Serum Cortisol should be measured in all cases of suspected CAH. It has been suggested that in the pubertal patient with 21-hydroxylase deficiency, 21-deoxycortisol may be useful and better than 17-hydroxyprogesterone for therapeutic decisions.

Useful For: As an adjunct to measurement of 17-hydroxyprogesterone, androstenedione, and cortisol in the diagnosis of difficult cases of suspected 21-hydroxylase (CYP21A2) deficiency Identifying heterozygote CYP21A2 deficiency carriers As an adjunct to measurements of 17-hydroxyprogesterone, androstenedione, testosterone, and, in female patients, estradiol in the follow-up of children with CYP21A2 deficiency

Interpretation: In untreated 21-hydroxylase (CYP21A2) deficiency, 21-deoxycortisol serum concentrations on average exceed the upper limit of the reference range 30-fold to 40-fold. 21-Hydroxycortisol measurements are particularly useful in equivocal cases of suspected 21-hydroxylase deficiency. Most untreated patients with 21-hydroxylase deficiency have serum 17-hydroxyprogesterone concentrations well in excess of 1000 ng/dL. For the few patients with levels in the range of greater than 630 ng/dL (upper limit of reference range for newborns) to 2000 ng/dL or 3000 ng/dL, it might be prudent to consider 11-hydroxylase deficiency as an alternative diagnosis. This is particularly true if serum androstenedione concentrations are also only mildly-to-modestly elevated and if the phenotype is not salt wasting but either simple virilizing (female) or normal (female or male). 11-Hydroxylase deficiency, particularly if it affects 11 beta-hydroxylase 1 (CYP11B1), can be associated with modest elevations in serum 17-hydroxyprogesterone concentrations. In these cases, testing for CYP11B1 deficiency and 11 beta-hydroxylase 2 (CYP11B2) deficiency should be considered and interpreted as described above. Alternatively, measurement of 21-deoxycortisol might be useful in such cases. This minor pathway metabolite accumulates in CYP21A2 deficiency, as it requires 21-hydroxylation to be converted to cortisol but is usually not elevated in CYP11B1 deficiency since its synthesis requires via 11-hydroxylation of 17-hydroxyprogesterone. For genetic counseling purposes, identification of asymptomatic carriers of CYP21A2 variants and deletions is sometimes required. The gold-standard is full DNA sequencing of CYP21A2, its pseudogene CYP21A1P, and, if possible, recombinants of gene and pseudogene, along with deletion detection. Such a procedure may be costly and complex and often has a slow turnaround time. Therefore, many laboratories perform less complex, but also less complete, variant and deletion assessments, which may miss a significant minority of heterozygote carriers. Biochemical testing using corticotropin (previously adrenocorticotropic hormone: ACTH) 1-24 adrenal stimulation represents an alternative. However, for 17-hydroxyprogesterone and androstenedione measurements, there is significant overlap between poststimulation results in normal patients and in heterozygote carriers. By contrast, poststimulation 21-deoxycortisol concentrations of 55 ng/dL identify virtually all heterozygote carriers, with minimal overlap with normal individuals. The goal of congenital adrenal hyperplasia (CAH) treatment is normalization of cortisol levels and, ideally, sex steroid levels. Serum 17-hydroxyprogesterone, androstenedione, and testosterone should be measured and used to guide treatment modifications. Normal prepubertal androgen levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels up

to 100 ng/dL are usually regarded as acceptable. 17-Hydroxyprogesterone levels should not significantly exceed the normal reference range at any time of the day. However, during puberty, the changing levels of sex steroid production may make 17-hydroxyprogesterone measurements less reliable. Since 21-deoxycortisol is not a sex-steroid precursor, its levels appear more reliable during the pubertal period; again, the aim being not to exceed the reference range significantly.

Reference Values:
<5.0 ng/dL
Reference values apply to all ages.

Clinical References: 1. Von Schnakenburg K, Bidlingmaier F, Knorr D. 17-hydroxyprogesterone, androstenedione, and testosterone in normal children and in prepubertal patients with congenital adrenal hyperplasia. Eur J Pediatr. 1980;133(3):259-267 2. Tonetto-Fernandes V, Lemos-Marini SH, Kuperman H, et al. Serum 21-deoxycortisol, 17-hydroxyprogesterone, and 11-deoxycortisol in classic congenital adrenal hyperplasia: clinical and hormonal correlations and identification of patients with 11beta-hydroxylase deficiency among a large group with alleged 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2006;91:2179-2184 3. Idkowiak, J, Cragun, D, Hopkin RJ, and Arlt W. Cytochrome P450 oxidoreductase deficiency. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. Gene Reviews [Internet]. University of Washington, Seattle; 2005. Updated August 3, 2017. Accessed May 2, 2024. Available at www.ncbi.nlm.nih.gov/sites/books/NBK1419/ 4. Held PK, Bird IM, Heather NL. Newborn screening for congenital adrenal hyperplasia: review of factors affecting screening accuracy. Int J Neonatal Screen. 2020;6(3):67. doi:10.3390/ijns6030067

21OH
607788

21-Hydroxylase Antibodies, Serum

Clinical Information: Adrenal insufficiency is caused by failure of the adrenal cortex to produce cortisol. This failure can result from loss of function of the adrenal glands (ie, primary adrenal insufficiency). This is most frequently caused by autoimmune adrenalitis or Addison disease accounting for 68% to 94% of cases. It can occur sporadically or in combination with other autoimmune endocrine diseases that together comprise type I or II autoimmune polyglandular syndrome (APS). Antibodies that react with several steroidogenic enzymes (most often 21-hydroxylase) are present in the serum of up to 86% of patients with autoimmune primary adrenal insufficiency but only rarely in patients with other causes of adrenal insufficiency. Therefore, 21-hydroxylase autoantibodies are markers of autoimmune Addison disease, whether present alone or as part of type I or II APS. The measurement of 21-hydroxylase autoantibodies is an important step in the investigation of adrenal insufficiency and may aid in the detection of those at risk of developing autoimmune adrenal failure in the future.

Useful For: Investigating adrenal insufficiency Aiding in the detection of those at risk of developing autoimmune adrenal failure in the future

Interpretation: This is a qualitative test. A positive result indicates the presence of autoantibodies to 21-hydroxylase and is consistent with Addison disease. Utilizing an index value of <45 as a negative cutoff, this assay has a clinical sensitivity and specificity of 87.0% (95% CI: 79.4%-92.2%) and 99.3% (95% CI: 97.5%-99.8%), respectively.

Reference Values:
Negative

Clinical References: 1. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet. 2014;383(9935):2152-2167 2. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol. 2015;3(3):216-226 3. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: An Endocrine Society

CYPZ
37445

21-Hydroxylase Gene, CYP21A2, Full Gene Analysis, Varies

Clinical Information: Congenital adrenal hyperplasia (CAH), with a worldwide incidence rate of 1 in 14,000 to 1 in 18,000 live births, is one of the most common inherited conditions. It is characterized by impaired cortisol production due to inherited defects in steroid biosynthesis. The clinical consequences of CAH, besides diminished cortisol production, depend on which enzyme is affected and whether the loss of function is partial or complete. In greater than 90% of CAH cases, the affected enzyme is 21-steroid hydroxylase, encoded by the CYP21A2 gene located on chromosome 6. 21-hydroxylase deficient CAH (21-OHD CAH) is inherited in an autosomal recessive pattern and has a spectrum of clinical symptoms depending upon residual enzyme activity. Excessive adrenal androgen biosynthesis results in varying degrees of virilization. If there is approximately 20% to 50% residual enzyme activity a non-classic phenotype results, with signs of hyperandrogenism typically starting in later childhood or adolescence. Individuals with severe enzyme deficiency have the classic form of CAH, with prenatal onset of virilization. Classic CAH is further subdivided into simple-virilizing (generally between 1% to 5% residual enzyme activity) and salt-wasting (<1% residual enzyme activity) forms. Patients with salt-wasting CAH have both cortisol and mineral corticosteroid deficiency and are at risk for life-threatening salt-wasting crises if untreated. Because of its high incidence rate, 21-hydroxylase deficiency is included in most US newborn screening programs, typically by measuring 17-hydroxyprogesterone concentrations in blood spots by immunoassay. Confirmation by other testing strategies (eg, liquid chromatography tandem mass spectrometry [LC-MS/MS], CAH2T / Congenital Adrenal Hyperplasia Newborn Screen, Blood Spot), or retesting after several weeks, is required for most positive screens because of the high false-positive rates of the immunoassays (due to physiological elevations of 17-hydroxyprogesterone in premature babies and immunoassay cross-reactivity with other steroids). In a small percentage of cases, additional testing will fail to provide a definitive diagnosis. In addition, screening strategies can miss non-classic CAH cases, which may present later in childhood or adolescence and require more extensive steroid hormone profiling, including testing before and after adrenal stimulation with corticotropin (previously adrenocorticotropic hormone: ACTH)-1-24. In some non-classic CAH cases individuals may not come to medical attention until adulthood. Rare instances of cases of classic CAH being missed by newborn screening have also been reported. For these reasons, molecular genetic testing plays an important role in both classic and non-classic CAH cases. In addition, the high carrier frequency (approximately 1 in 50) for CYP21A2 variants makes genetic diagnosis important for genetic counseling and risk assessment. Genetic testing can also play a role in prenatal diagnosis of 21-hydroxylase deficiency. However, accurate genetic diagnosis continues to be a challenge because most of the variants arise from recombination events between CYP21A2 and its highly homologous pseudogene, CYP21A1P (transcriptionally inactive). In particular, unequal crossovers and gene conversion events result in large structural rearrangements, copy number changes, and sequence transfers between CPY21A2 and CYP21A1P. Approximately, 90% of individuals with 21-OHD CAH have one or more common pseudogene derived pathogenic variants. The high likelihood of an affected individual having a common variant means that some laboratories may offer genotyping assays, particularly in the setting of carrier screening, which may miss disease causing variants, or be unable to determine cis/trans status of detected variants. Full gene sequencing and copy number assessment of CYP21A2 is the best approach to exclude or confirm a diagnosis of 21-OHD CAH. However, the high homology between CYP21A2 and its pseudogene, the high probability of hybrid or chimera alleles, and frequent copy number gains and losses, present diagnostic challenges, including for most short-read next generation sequencing technologies. Therefore, comprehensive genetic testing strategies should consider all of the above challenges when assessing CYP21A2 for disease causing variants. Testing of additional family members may be necessary to clarify the phase of identified reportable variants (i.e. whether the variants are in cis in the same copy of CYP21A2 or in trans on different copies). In addition, recent years have seen an uptick in literature focusing on CAH-X syndrome, which presents when an unequal crossover event results in a full gene CYP21A2 deletion and a TNXA::TNXB hybrid. It is estimated that approximately 6% to15% of individuals with a

diagnosis of 21-OHD CAH have CAH-X and these individuals are more likely to have hypermobile Ehlers Danlos syndrome features in addition to classic CAH features. These additional symptoms may include joint hypermobility, chronic joint pain, joint dislocations, and cardiac valve abnormalities. There are 3 CAH-X TNXA::TNXB hybrids that have been reported in the literature: CH-1, CH-2 and CH-3; all of these hybrids are associated with a full gene deletion of CYP21A2.

Useful For: Carrier screening and diagnosis of 21-hydroxylase deficient congenital adrenal hyperplasia (CAH) in individuals with a personal or family history of 21-hydroxylase deficiency, or as follow-up to positive CAH newborn screens and/or measurement of basal and adrenocorticotropic hormone- 1-24 stimulated 17-hydroxyprogesterone, androstenedione, and other adrenal steroid levels May identify CYP21A2 variants in individuals with a suspected diagnosis of 21-hydroxylase deficient CAH when a common variant panel is negative or only identifies 1 variant May identify the CH-1 TNXA::TNXB hybrid associated with CAH-X. Note that the CH-2 and CH-3 TNXA::TNXB hybrids will not be detected by current methodologies. Evaluation of 21-hydroxlase deficiency in prenatal cases with suspected differences of sex development (such as clitoromegaly) detected by ultrasound, particularly when the fetus is confirmed XX female by chromosome analysis Due to the complexity of the CYP21A2 locus, site specific testing for known/familial CYP21A2 variants is not offered.

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Collett-Solberg PF. Congenital adrenal hyperplasias: from clinical genetics and biochemistry to clinical practice, part I. Clin Pediatr. 2001;40:1-16 3. Mercke DP, Bornstein SR, Avila NA, Chrousos GP. NIH conference: future directions in the study and management of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Ann Intern Med. 2002;136:320-334 4. Speiser PW, White PC. Medical progress: congenital adrenal hyperplasia. N Engl J Med. 2003;349:776-788 5. Sarafoglou K, Banks K, Kyllo J, Pittock S, Thomas W. Cases of congenital adrenal hyperplasia missed by newborn screening in Minnesota. JAMA. 2012;307(22):2371-2374 6. Lao Q, Brookner B, Merke DP. High-Throughput Screening for CYP21A1P-TNXA/TNXB Chimeric Genes Responsible for Ehlers-Danlos Syndrome in Patients with Congenital Adrenal Hyperplasia. J Mol Diagn. 2019;21(5):924-931 7. Baumgartner-Parzer S, Witsch-Baumgartner M, Hoeppner W. EMQN best practice guidelines for molecular genetic testing and reporting of 21-hydroxylase deficiency. Eur J Hum Genet. 2020;28(10):1341-1367 8. Concolino P, Falhammar H. CAH-X Syndrome: Genetic and Clinical Profile. Mol Diagn Ther. 2022;26(3):293-300 9. Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, et al. Congenital Adrenal Hyperplasia-Current Insights in Pathophysiology, Diagnostics, and Management. Endocr Rev. 2022;43(1):91-159

DD22F
35246

22q11.2 Deletion/Duplication, FISH, Varies

Clinical Information: The 22q deletion syndrome and 22q duplication syndrome have overlapping phenotypes. Deletions of 22q are associated with DiGeorge and velocardiofacial syndrome. These syndromes are manifested by the presence of growth deficiency, global developmental delay, heart defect, and hearing loss. The major birth defects include palatal clefting or insufficiency and thymus aplasia. Prominent facial features are widely spread eyes, superior placement of eyebrows, downward slanting

palpebral fissures with or without ptosis (droopy upper eyelid), mild micrognathia (small jaw), and a long, narrow face. Fluorescence in situ hybridization studies are highly specific and do not exclude other chromosome abnormalities.

Useful For: Establishing a diagnosis of 22q deletion/duplication syndromes Detecting cryptic rearrangements involving 22q11.2 or 22q11.3 that are not demonstrated by conventional chromosome studies

Interpretation: Any individual with a normal signal pattern in each metaphase is considered negative for this probe. Any patient with a fluorescence in situ hybridization (FISH) signal pattern indicating loss of the critical region (1 signal) will be reported as having a deletion of the region tested by this probe. This is consistent with a diagnosis of 22q deletion syndrome. Any patient with a FISH signal pattern indicating duplication of the critical region (3 signals) will be reported as having a duplication of the region tested by this probe. This is consistent with a diagnosis 22q duplication syndrome

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Ensenauer RE, Adeyinka A, Flynn HC, et al. Microduplication 22q11.2 an emerging syndrome: clinical, cytogenetic, and molecular analysis of thirteen patients. Am J Hum Genet. 2003;73(5):1027-1040 2. Yobb TM, Sommerville MJ, Willatt L, et al. Microduplication and triplication of 22q11.2: a highly variable syndrome. Am J Hum Genet. 2005;76(5):865-876 3. Bassett AS, Chow EWC, Husted J, et al. Clinical features of 78 adults with 22q11 deletion syndrome. Am J Med Genet. 2005;138(4):307-313 4. Manji A, Roberson JR, Wiktor A, et al. Prenatal diagnosis of 22q11.2 deletion when ultrasound examination reveals a heart defect. Genet Med. 2001;3(1):65-66 5. McDonald-McGinn DM, Emanuel BS, Zackai EH: 22q11.2 Deletion Syndrome. GeneReviews. Updated May 9, 2024. Accessed June 13, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1523/

25HDN
83670

25-Hydroxyvitamin D2 and D3, Serum

Clinical Information: Vitamin D is a generic designation for a group of fat-soluble, structurally similar sterols that act as hormones. This test is the preferred initial test for assessing vitamin D status and most accurately reflects the body's vitamin D stores. In the presence of kidney disease, testing 1,25-dihydroxyvitamin D (DHVD) levels may be needed to adequately assess vitamin D status. DHVD testing alone may not clearly indicate deficiencies of vitamin D stores. 25-Hydroxyvitamin D2 and D3 (25-OH-VitD) are equipotent steroid hormones that require 1-alpha-hydroxylation before expressing biological activity. Vitamin D compounds are derived from dietary ergocalciferol (from plants, VitD2), cholecalciferol (from animals, VitD3), or by conversion of 7-dihydrocholesterol to VitD3 in the skin upon UV exposure. VitD2 and VitD3 are subsequently 25-hydroxylated in the liver to 25-OH-VitD. 25-OH-VitD represents the main body reservoir and transport form of vitamin D, being stored in adipose tissue and tightly bound by a transport protein while in circulation. A fraction of circulating 25-OH-VitD is converted to its active metabolites 1,25-dihydroxy vitamin D2 and D3 (1,25-OH-VitD), mainly by the kidneys. This process is regulated by parathyroid hormone (PTH), which increases 1,25-OH-VitD synthesis at the expense of the alternative, biologically inactive hydroxylation product 24,25-OH-VitD. Like other steroid hormones, 1,25-OH-VitD binds to a nuclear receptor, influencing gene transcription patterns in target organs. 1,25-OH-VitD plays a primary role in the maintenance of calcium homeostasis. It promotes intestinal calcium absorption and, in concert with PTH, skeletal calcium deposition, or less commonly, calcium mobilization. Renal calcium and phosphate reabsorption are also promoted, while prepro-PTH messenger RNA expression in the parathyroid glands is downregulated. The net result is a positive calcium balance, increasing serum calcium and phosphate levels, and falling PTH concentrations. In addition to its effects on calcium and bone metabolism,

1,25-OH-VitD regulates the expression of a multitude of genes in many other tissues, including immune cells, muscle, vasculature, and reproductive organs. The exact 25-OH-VitD level reflecting optimal body stores remains unknown. Mild-to-modest deficiency can be associated with osteoporosis or secondary hyperparathyroidism. Severe deficiency may lead to failure to mineralize newly formed osteoid in bone, resulting in rickets in children and osteomalacia in adults. The consequences of vitamin D deficiency on organs other than bone are not fully known but may include increased susceptibility to infections, muscular discomfort, and an increased risk of colon, breast, and prostate cancer. Modest 25-OH-VitD deficiency is common; in institutionalized older adults, its prevalence may be >50%. Although much less common, severe deficiency is not rare either. Reasons for suboptimal 25-OH-VitD levels include lack of sunshine exposure, a particular problem in Northern latitudes during winter; inadequate intake; malabsorption (eg, due to Celiac disease); depressed hepatic vitamin D 25-hydroxylase activity, secondary to advanced liver disease; and enzyme-inducing drugs, particularly many antiepileptic drugs, including phenytoin, phenobarbital, and carbamazepine, that increase 25-OH-VitD metabolism. In contrast to the high prevalence of 25-OH-VitD deficiency, hypervitaminosis D is rare and is only seen after prolonged exposure to extremely high doses of vitamin D. When it occurs, it can result in severe hypercalcemia and hyperphosphatemia.

Useful For: Diagnosis of vitamin D deficiency Differential diagnosis of causes of rickets and osteomalacia Monitoring vitamin D replacement therapy Diagnosis of hypervitaminosis D

Interpretation: Based on animal studies and large human epidemiological studies, 25-hydroxyvitamin D2 and D3 (25-OH-VitD) levels below 25 ng/mL are associated with an increased risk of secondary hyperparathyroidism, reduced bone mineral density, and fractures, particularly in the elderly. Intervention studies support this clinical cutoff, showing a reduction of fracture risk with 25-OH-VitD replacement. Levels less than 10 ng/mL may be associated with more severe abnormalities and can lead to inadequate mineralization of newly formed osteoid, resulting in rickets in children and osteomalacia in adults. In these individuals, serum calcium levels may be marginally low, and parathyroid hormone (PTH) and serum alkaline phosphatase are usually elevated. Definitive diagnosis rests on the typical radiographic findings or bone biopsy/histomorphometry. Baseline biochemical work-up of suspected cases of rickets and osteomalacia should include measurement of serum calcium, phosphorus, PTH, and 25-OH-VitD. In patients where testing is not completely consistent with the suspected diagnosis, particularly if serum 25-OH-VitD levels are greater than 10 ng/mL, an alternative cause for impaired mineralization should be considered. Possible differential diagnosis includes partly treated vitamin D deficiency, extremely poor calcium intake, vitamin D resistant rickets, renal failure, renal tubular mineral loss with or without renal tubular acidosis, hypophosphatemic disorders (eg, X-linked or autosomal dominant hypophosphatemic rickets), congenital hypoparathyroidism, activating calcium sensing receptor mutations, and osteopetrosis. Measurement of serum urea, creatinine, magnesium, and 1,25-dihydroxyvitamin D (DHVD) is recommended as a minimal additional workup for these patients. 25-OH-VitD replacement in the United States typically consists of vitamin D2. Lack of clinical improvement and no reduction in PTH or alkaline phosphatase may indicate patient noncompliance, malabsorption, resistance to 25-OH-VitD, or additional factors contributing to the clinical disease. Measurement of serum 25-OH-VitD levels can assist in further evaluation, particularly as the liquid chromatography tandem mass spectrometry methodology allows separate measurement of 25-OH-VitD3 and of 25-OH-VitD2, which is derived entirely from dietary sources or supplements. Patients who present with hypercalcemia, hyperphosphatemia, and low PTH may suffer either from ectopic, unregulated conversion of 25-OH-VitD to 1,25-OH-VitD, as can occur in granulomatous diseases, particular sarcoid, or from nutritionally-induced hypervitaminosis D. Serum 1,25-OH-VitD levels will be high in both groups, but only patients with hypervitaminosis D will have serum 25-OH-VitD concentrations of greater than 80 ng/mL, typically greater than 150 ng/mL.

Reference Values:

TOTAL 25-HYDROXYVITAMIN D2 AND D3 (25-OH-VitD)

<10 ng/mL (severe deficiency)*

10-19 ng/mL (mild to moderate deficiency)**

20-50 ng/mL (optimum levels)***

51-80 ng/mL (increased risk of hypercalciuria)****
>80 ng/mL (toxicity possible)*****

*Could be associated with osteomalacia or rickets
**Might be associated with increased risk of osteoporosis or secondary hyperparathyroidism
***Optimum levels in the healthy population
****Sustained levels >50 ng/mL 25OH-VitD along with prolonged calcium supplementation may lead to hypercalciuria and decreased kidney function
*****80 ng/mL is the lowest reported level associated with toxicity in patients without primary hyperparathyroidism who have normal kidney function. Most patients with toxicity have levels >150 ng/mL. Patients with kidney failure can have very high 25-OH-VitD levels without any signs of toxicity, as renal conversion to the active hormone 1,25-OH-VitD is impaired or absent.

These reference ranges represent clinical decision values, based on the 2011 Institute of Medicine report, that apply to males and females of all ages, rather than population-based reference values. Population reference ranges for 25-OH-VitD vary widely depending on ethnic background, age, geographic location of the studied populations, and the sampling season. Population-based ranges correlate poorly with serum 25-OH-VitD concentrations that are associated with biologically and clinically relevant vitamin D effects and are therefore of limited clinical value.

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Jones G, Strugnell SA, DeLuca HF. Current understanding of the molecular actions of vitamin D. Physiol Rev. 1998;78(4):1193-1231 2. Miller WL, Portale AA. Genetic causes of rickets. Curr Opin Pediatr. 1999;11(4):333-339 3. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr. 1999;69(5):842-856 4. Vieth R, Ladak Y, Walfish PG. Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. J Clin Endocrinol Metab. 2003;88(1):185-191 5. Wharton B, Bishop N. Rickets. Lancet. 2003;362(9393):1389-1400 6. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. Dietary Reference Intakes for Calcium and Vitamin D. National Academies Press: 2011. Available at www.ncbi.nlm.nih.gov/books/NBK56070 7. Su Z, Narla SN, Zhu Y. 25-Hydroxyvitamin D: Analysis and clinical application. Clinica Chimica Acta. 2014;433:200-205 8. LeFevre ML. US Preventative Services Task Force: Screening for vitamin D deficiency in adults: US Preventative Services Task Force recommendation statement. Ann Intern Med. 2015;162(2):133-140

2425D
63416

25-Hydroxyvitamin D:24,25-Dihydroxyvitamin D Ratio, Serum

Clinical Information:

Useful For: As a screening test for inactivating CYP24A1 variants in patients with symptoms, signs, or biochemical findings of parathyroid hormone-independent hypercalcemia or hypercalciuria

Interpretation: Results should be interpreted in the context of other biochemical findings including serum calcium, parathyroid hormone (PTH), and 1,25 dihydroxyvitamin D (DHVD) concentrations. If 25-hydroxyvitamin D (25HDN) result is less than 20 ng/mL, the ratio of 25HDN to 24,25-dihydroxyvitamin D (24,25D) will be falsely elevated since there is no inactivation of 25HDN to 24,25D. 24,25-Dihydroxyvitamin D formation by CYP24A1 is dependent on CYP24A1 activity and the concentrations of its substrate, 25HDN. The ratio of 25HDN to 24,25D, therefore, allows the most reliable estimation of CYP24A1 activity. Ratios of 25HDN to 24,25D less than 25 may be interpreted as

normal, although ratios less than 25 may also be observed in heterozygous carriers of CYP24A1 variants. Ratios of 25HDN to 24,25D between the 25 and 80 range may be seen in patients with low vitamin D or having heterozygous CYP24A1 variants. Confirmation with molecular testing is recommended. Confirmation with molecular testing is also recommended for ratios of 25HDN to 24,25D greater than 80, as this may indicate a probable biallelic CYP24A1 variants or deletion.

Reference Values:

Interpretative commentary provided based on 25-hydroxyvitamin D (25HDN) to 24,25-dihydroxyvitamin D (24,25D) ratio result.

25HDN to 24,25D Ratio
<25: Normal; also be observed in heterozygous carriers of CYP24A1 variants
25-80: Seen in patients with low vitamin D or heterozygous CYP24A1 variants
>80: Indicate probable biallelic CYP24A1 variant or deletion

Clinical References: 1. Kaufmann M, Gallagher JC, Peacock M, et al. Clinical utility of simultaneous quantitation of 25-hydroxyvitamin D and 24,25-dihydroxyvitamin D by LC-MS/MS involving derivatization with DMEQ-TAD. J Clin Endocrinol Metab. 2014;99(7):2567-2574. doi:10.1210/jc.2013-4388 2. Ketha H, Kumar R, Singh RJ. LC-MS/MS for identifying patients with CYP24A1 mutations. Clin Chem. 2016;62(1):236-242

HMGCR 607414 3-Hydroxy-3-Methylglutaryl Coenzyme-A (HMG-CoA) Reductase, Serum

Clinical Information: Necrotizing autoimmune myopathy (NAM) is a serious but rare muscle disease strongly associated with autoantibodies to either signal recognition protein (SRP) or 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR).(1) NAM typically manifests with subacute proximal limb muscle weakness and persistently elevated serum creatine kinase (CK) concentrations, but slower onset can occur and complicate diagnosis. Muscle biopsies in affected patients can demonstrate necrotic and regenerating myofibers without inflammatory infiltrates, suggesting the diagnosis.(2) However, sampling issues and lack of access to persons having expertise in obtaining, preparing, and interpreting muscle biopsy specimens may delay a diagnosis.(3) Early identification of NAM and subsequent aggressive immune-modulating therapy is critical.(1,3) Discovery of SRP- or HMGCR-IgG autoantibodies can aid in establishing an earlier diagnosis and treatment initiation. In addition, the discovery of SRP or HMGCR autoantibodies should prompt a search for an underlying malignancy.(4) Serial testing for these autoantibodies can delay diagnosis with the discovery of either antibody aiding in establishing an earlier diagnosis and treatment initiation.(1,3) The clinical onsets are not specific to NAM, consisting of proximal limb weakness in association with an elevated serum creatinine kinase, with or without exposure to lipid-lowering statin medications.(1,3-9) The clinical presentation can be confused with forms of inflammatory (dermatomyositis, polymyositis), toxic, metabolic, or even neurodegeneration (ie, muscular dystrophy) and the diagnosis delayed without serological testing by SRP- or HMGCR-autoantibody testing. Panel testing of both HMGCR and SRP autoantibodies is the preferred strategy for the best patient care.

Useful For: Evaluating patients with suspected necrotizing autoimmune myopathy Measuring 3-hydroxy-3-methylglutaryl-CoA reductase antibodies

Interpretation: Seropositivity for 3-hydroxy-3-methylglutaryl-CoA reductase autoantibodies supports the clinical diagnosis of necrotizing autoimmune myopathy (NAM). Confirmation with muscle biopsy is recommended. A paraneoplastic basis should be considered, according to age, sex, and other risk factors.(4) In cases of NAM, immune therapy is required and often multiple simultaneously utilized immunotherapies are needed to successfully treat patients.

Reference Values:
<20.0 CU

Clinical References: 1. Kassardjian CD, Lennon VA, Alfugham NB, Mahler M, Milone M. Clinical features and treatment outcomes of necrotizing autoimmune myopathy. JAMA Neurol. 2015;72(9):996-1003 2. Emslie-Smith AM, Engel AG. Necrotizing myopathy with pipestem capillaries, microvascular deposition of the complement membrane attack complex (MAC), and minimal cellular infiltration. Neurology. 1991;41(6):936-939 3. Ramanathan S, Langguth D, Hardy T, et al. Clinical course and treatment of anti-HMGCR antibody-associated necrotizing autoimmune myopathy. Neurol Neuroimmunol Neuroinflamm. 2015;2(3):e96 4. Allenbach Y, Keraen J, Bouvier AM, et al. High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. Brain. 2016;139(Pt 8):2131-2135 5. Christopher-Stine L, Casciola-Rosen L, Hong G, Chung T, Corse AM, Mammen AL. A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy. Arthritis Rheum. 2010;62(9):2757-2766 6. Mammen AL, Chung T, Christopher-Stine L, et al. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum. 2011;63(3):713-721 7. Hengstman GJ, ter Laak HJ, Vree Egberts WT, et al. Anti-signal recognition particle autoantibodies: marker of a necrotising myopathy. Ann Rheum Dis. 2006;65(12):1635-1638 8. Miller T, Al-Lozi MT, Lopate G, Pestronk A. Myopathy with antibodies to the signal recognition particle: clinical and pathological features. J Neurol Neurosurg Psychiatry. 2002;73(4):420-428 9. Watanabe Y, Uruha A, Suzuki S, et al. Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy. J Neurol Neurosurg Psychiatry. 2016;87(10):1038-1044

3MT
65157

3-Methoxytyramine, 24 Hour, Urine

Clinical Information: Pheochromocytomas and paragangliomas (Pheo/PGL) are rare, usually benign, tumors of chromaffin cells in the adrenal medulla or paragangliomas (estimated population prevalence rates of 1 in 200,000 with a yearly incidence rate of 1-2/1000), that are potentially lethal, because they secrete excessive, uncontrolled amounts of catecholamines (dopamine, epinephrine, and norepinephrine) resulting in often severe hypertension and many cardiac abnormalities. A subgroup of these patients will also suffer tumor recurrence and sometimes malignant behavior. Untreated, these tumors have substantial morbidity and mortality. Key symptoms are episodes of hypertension with palpitations, severe headaches, and sweating (spells). However, some patients might be asymptomatic, have mild symptoms that might be missed, or have sustained hypertension, which is frequently observed in these patients. Finally, due to the high frequency of medical imaging for unrelated ailments, increasing numbers of occult small adrenal tumors are often incidentally discovered, some of which might be Pheo/PGLs. 3-Methoxytyramine (3MT), metanephrine, and normetanephrine are the metabolites of dopamine, epinephrine, and norepinephrine, respectively. These metabolites are further metabolized to vanillylmandelic acid. Pheochromocytoma cells also have the ability to oxymethylate catecholamines into metanephrines, which are secreted into circulation and urine. 3-MT is only elevated in a small proportion of patients with Pheo/PGL. Because of its low levels, testing is performed using only 24-hour urine specimens at this time, while epinephrine, and norepinephrine can be measured in plasma or 24-hour urine specimens. An early childhood malignancy that arises from immature neuroendocrines in the adrenals, called neuroblastoma, shares many features of Pheo/PGL but has the added threat of a high malignancy rate; however, there are also frequent spontaneous remissions, particular in very young infants. Biochemical testing for neuroblastoma differs from Pheo/PGL because of many specific issues in testing infants and young children, using urine tests rather than blood tests. For all Pheo/PGL, the preferred initial testing is by plasma metanephrine testing, as it has the highest clinical sensitivity thus facilitating ruling out Pheo/PGL if the test results are within the healthy population reference range. However, in potentially familial cases or monitoring of treated patients, some additional and repeated testing may be required. Testing for 24-hour urine metanephrine plus urinary catecholamine levels may be used as a confirmatory study in patients with less than a 2-fold elevation in plasma free fractionated catecholamines. This is highly desirable, as the very low

population incidence rate of Pheo/PGL (<1:200,000 population per year) will otherwise result in large numbers of unnecessary, costly, and sometimes risky imaging procedures. Finally, familial Pheo/PGL probably accounts for a higher proportion of cases than previously thought; at least 30% are now believed to be familial. The corollary of this is that about 20 to 30 seemingly sporadic cases are likely familial. Given these statistics, genetic testing for index cases and family members should be considered. Treatment consists of surgical tumor removal after pharmaceutical alpha-adrenergic blockade, which may be supplemented with beta blockade once the alpha blockade has been established. This preparation is aimed to prevent massive catecholamine surges during surgery.

Useful For: A first- and second-tier screening test for the presumptive diagnosis of catecholamine-secreting pheochromocytomas and paragangliomas Testing in conjunction or as an alternative to plasma metanephrines (PMET / Metanephrines, Fractionated, Free, Plasma) or plasma catecholamine (CATP / Catecholamine Fractionation, Free, Plasma) testing

Interpretation: Further clinical investigation (eg, radiographic studies) and genetic studies might be warranted in patients whose 3-methoxytyramine (3MT), metanephrine, or normetanephrine are elevated or when there is a very high clinical index of suspicion. Increased 3MT levels are found in patients with pheochromocytoma and dopamine-secreting tumors. 3MT levels of 306 mcg/24 h or less in male patients and 242 mcg/24 h or less in female patients can be detected in non-pheochromocytoma hypertensive patients.

Reference Values:
Males: < or =306 mcg/24 h

Females: < or =242 mcg/24 h

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Muskiet FA, Thomasson CG, Gerding AM, Fremouw-Ottevangers DC, Nagel GT, Wolthers BG. Determination of catecholamines and their 3-O-methylated metabolites in urine by mass fragmentography with use of deuterated internal standards. Clin Chem. 1979;25(3):453-460 2. Taylor RL, Singh RJ: Validation of liquid chromatography-tandem mass spectrometry method for analysis of urinary conjugated metanephrine and normetanephrine for screening of pheochromocytoma. Clin Chem 2002;48:533-539 3. Roden M, Raffesberg W, Raber W, et al. Quantification of unconjugated metanephrines in human plasma without interference by acetaminophen. Clin Chem. 2001;47(6):1061-1067 4. Sawka AM, Singh RJ, Young WF. False positive biochemical testing for pheochromocytoma caused by surreptitious catecholamine addition to urine. The Endocrinologist. 2001;421-423 5. van Duinen N, Steenvoorden D, Kema IP, et al. Increased urinary excretion of 3-methoxytyramine in patients with head and neck paragangliomas. J Clin Endocrinol Metab. 2010;95(1):209-214 doi:10.1210/jc.2009-1632 6. Le Jacques A, Abalain JH, Le Saos F, Carre JL. Interet du dosage urinaire de la 3-methoxytyramine dans le diagnostic des pheochromocytomes et paragangliomes: a propos de 28 cas [Significance of 3-methoxytyramine urine measurement in the diagnosis of pheochromocytomas and paragangliomas: about 28 patients]. Ann Biol Clin (Paris). 2011;69(5):555-559. doi:10.1684/abc.2011.0612 7. Lam L, Woollard, GA Teague L, Davidson, JS. Clinical validation of urine 3-methoxytyramine as a biomarker of neuroblastoma and comparison with other catecholamine-related biomarkers. Ann Clin Biochem. 2017;54(2) 264-272 8. Hirsch, D, Grossman, A, Nadler, V, Alboim, S, Tsvetov, G. Pheochromocytoma: Positive predictive values of mildly elevated urinary fractionated metanephrines in a large cohort of community-dwelling patients. J Clin Hypertens (Greenwich). 2019; 21(10): 1527-1533. doi:10.1111/jch.13657 9. Gupta PK, Marwaha B. Pheochromocytoma. In: StatPearls [Internet]. StatPearls Publishing; 2024. Updated March 5, 2023. Accessed April 22, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK589700 10. Mubarik A, Adeddula NR. Chromaffin Cell Cancer. In: StatPearls [Internet]. StatPearls Publishing; May 8, 2023. Accessed April 22, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK535360/

3MGAP
608034

3-Methylglutaconic Aciduria Panel, Varies

Clinical Information: The 3-methylglutaconic acidurias (3-MGA) are a heterogeneous group of metabolic conditions characterized by increased urinary excretion of 3-MGA. Primary 3-MGA type I is an organic aciduria caused by defective leucine catabolism due to variants in 3-methylglutaconyl-CoA hydratase. Four more types of 3-MGA have been described where 3-MGA is a consistent feature. These are characterized by various degrees of mitochondrial dysfunction, very remotely, if at all, linked to leucine degradation and include Barth syndrome (type II), Costeff syndrome (type III), and type V or dilated cardiomyopathy with ataxia) syndrome. The remaining cases (type IV) with increased 3-MGA encompass a variety of disorders affecting mitochondrial function. Genes known to be associated with elevations of 3-MGA are included on this panel.

Useful For: Follow up for abnormal biochemical results suggestive of 3-methylglutaconic aciduria (3-MGA) Establishing a molecular diagnosis for patients with 3-MGA Identifying variants within genes known to be associated with3-MGA, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Wortmann SB, Kluijtmans LA, Engelke UF, Wevers RA, Morava E. The 3-methylglutaconic acidurias: what's new?. J Inherit Metab Dis. 2012;35(1):13-22. doi:10.1007/s10545-010-9210-7 3. Manoli I, Venditti CP. Disorders of branched chain amino acid metabolism. Transl Sci Rare Dis. 2016;1(2):91-110. doi:10.3233/TRD-160009 4. Wortmann SB, Duran M, Anikster Y, et al. Inborn errors of metabolism with 3-methylglutaconic aciduria as discriminative feature: proper classification and nomenclature. J Inherit Metab Dis. 2013;36:923-928. doi:10.1007/s10545-012-9580-0

F5NUL
57285

5'Nucleotidase

Useful For:

Reference Values:
0 - 15 U/L

FLUC
82741

5-Flucytosine, Serum

Clinical Information: Flucytosine is a broad-spectrum antifungal agent generally used in combined therapy (often with amphotericin B) for treatment of fungal infections such as cryptococcal meningitis. Concerns with toxicity (ie, bone marrow suppression, hepatic dysfunction) and development of fungal resistance limit the use of flucytosine, particularly as a monotherapy. The drug is well-absorbed orally but can also be administered intravenously (available outside of the United States). There is good correlation between serum concentrations of flucytosine with both efficacy and risk for toxicity.

Because of the drug's short half-life (3-6 hours), therapeutic monitoring is typically performed at peak levels approximately 2 hours after an oral dose or 30 minutes after an intravenous administration. Flucytosine is eliminated primarily as unmetabolized drug in urine. Patients with kidney dysfunction may require dose adjustments or more frequent monitoring to ensure that serum concentrations do not accumulate to excessive levels. Nephrotoxicity associated with use of amphotericin B can affect elimination of flucytosine when the drugs are coadministered.

Useful For: Monitoring serum concentration during therapy Evaluating potential toxicity May aid in evaluating patient compliance

Interpretation: Most individuals display optimal response to flucytosine when peak serum levels (1-2 hours after oral dosing) are greater than 25.0 mcg/mL. Some infections may require higher concentrations for efficacy. Toxicity is more likely when peak serum concentrations are greater than 100.0 mcg/mL

Reference Values:
Therapeutic concentration:
Peak >25.0 mcg/mL (difficult infections may require higher concentrations)
Toxic concentration:
Peak >100.0 mcg/mL

Clinical References: 1. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453 2. Goodwin ML, Drew RH. Antifungal serum concentration monitoring: an update. J Antimicrob Chemother. 2008;61(1):17-25. doi:10.1093/jac/dkm389 3. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother. 2009;53(1):24-34. doi:10.1128/AAC.00705-08

HIAA
9248

5-Hydroxyindoleacetic Acid, 24 Hour, Urine

Clinical Information: 5-Hydroxyindoleacetic acid (5-HIAA) is the major metabolite of serotonin and is excreted in the urine. Intestinal carcinoid tumors, along with neuroendocrine tumors, can produce excess amounts of 5-HIAA and serotonin, especially in individuals with carcinoid syndrome. Carcinoid syndrome is characterized by carcinoid tumors, flushing, heart disease, and hepatomegaly. Measurement of 5-HIAA in a 24-hour urine specimen can diagnose carcinoid disease with a high specificity.

Useful For: Biochemical diagnosis and monitoring of intestinal carcinoid syndrome using 24-hour urine specimens

Interpretation: If pharmacological and dietary artifacts have been ruled out, an elevated excretion of 5-hydroxyindoleacetic acid is a probable indicator of the presence of a serotonin-producing tumor.

Reference Values:

	5-HIAA, mg/24 hour 99th percentile cutoff
Age	Female
< or =23 months	< or =2.7
24-35 months	< or =3.0
3 years	< or =3.2

4 years	< or =3.4
5 years	< or =3.6
6 years	< or =3.8
7 years	< or =4.0
8 years	< or =4.2
9 years	< or =4.5
10 years	< or =4.7
11 years	< or =4.9
12 years	< or =5.2
13 years	< or =5.4
14 years	< or =5.6
15 years	< or =5.7
16 years	< or =5.9
17 years	< or =6.0
18 years	< or =6.0
19 years	< or =6.1
20 years	< or =6.1
21 years	< or =6.2
22 years	< or =6.2
23 years	< or =6.2
24 years	< or =6.3
25 years	< or =6.3
26 years	< or =6.3
27 years	< or =6.4
28 years	< or =6.4
29 years	< or =6.5
30 years	< or =6.6
31 years	< or =6.6
32 years	< or =6.7
33 years	< or =6.8
34 years	< or =6.8
35 years	< or =6.9
36 years	< or =6.9
37 years	< or =7.0
38 years	< or =7.0
39 years	< or =7.0
40 years	< or =7.1

41 years	< or =7.1
42 years	< or =7.2
43 years	< or =7.3
44 years	< or =7.4
45 years	< or =7.4
46 years	< or =7.5
47 years	< or =7.6
48 years	< or =7.6
49 years	< or =7.7
50 years	< or =7.7
51 years	< or =7.8
52 years	< or =7.8
53 years	< or =7.9
54 years	< or =8.0
55 years	< or =8.1
56 years	< or =8.1
57 years	< or =8.2
58 years	< or =8.3
59 years	< or =8.3
60 years	< or =8.3
61 years	< or =8.3
62 years	< or =8.4
63 years	< or =8.4
64 years	< or =8.4
65 years	< or =8.4
66 years	< or =8.5
67 years	< or =8.5
68 years	< or =8.5
69 years	< or =8.5
70 years	< or =8.5
71 years	< or =8.6
72 years	< or =8.6
73 years	< or =8.5
74 years	< or =8.5
75 years	< or =8.6
76 years	< or =8.6
77 years	< or =8.6

78 years	< or =8.6
79 years	< or =8.6
80 years	< or =8.7
81 years	< or =8.7
82 years	< or =8.7
83 years	< or =8.7
84 years	< or =8.7
85 years	< or =8.6
86 years	< or =8.5
87 years	< or =8.4
88 years	< or =8.3
89 years	< or =8.1
90 years	< or =7.9
91 years	< or =7.6
92 years	< or =7.4
93 years	< or =7.1
94 years	< or =7.0
= 95 years	< or =6.9

Clinical References: 1. Grimaldi F, Fazio N, Attanasio R, et al. Italian Association of Clinical Endocrinologists (AME) position statement: a stepwise clinical approach to the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. J Endocrinol Invest. 2014;37(9):875-909. doi:10.1007/s40618-014-0119-0 2. Vinik A, Hughes MS. Feliberti E, et al. Carcinoid tumors. In: Feingold KR, Anawalt B, Boyce A, et al, eds. Endotext [Internet]. MDText.com, Inc; 2000. Updated August 25, 2023. Accessed April 1, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK279162/ 3. Shah D, Mandot A, Cerejo C, Amarapurkar D, Pal A. The outcome of primary hepatic neuroendocrine tumors: A single-center experience. J Clin Exp Hepatol. 2019;9(6):710-715. doi:10.1016/j.jceh.2019.08.002 4. Perry D, Hayek SS. Carcinoid heart disease: A guide for clinicians. Cardiol Clin. 2019;37(4):497-503. doi:10.1016/j.ccl.2019.07.014 5. Degnan AJ, Tocchio S, Kurtom W, Tadros SS. Pediatric neuroendocrine carcinoid tumors: Management, pathology, and imaging findings in a pediatric referral center. Pediatr Blood Cancer. 2017;64(9). doi:10.1002/pbc.26477 6. Corcuff JB, Chardon L, El Hajji Ridah I, Brossaud J. Urinary sampling for 5HIAA and metanephrines determination: revisiting the recommendations. Endocr Connect. 2017;6(6):R87-R98. doi:10.1530/EC-17-0071

HIAAP
619735

5-Hydroxyindoleacetic Acid, Plasma

Clinical Information: Intestinal carcinoid and neuroendocrine tumors can produce excess amounts of serotonin and its degradation product, 5-hydroxyindoleacetic acid (5-HIAA). Determination of 5-HIAA in urine or plasma is used to diagnose and monitor patients with carcinoid syndrome. Carcinoid syndrome is characterized by a constellation of hormonal symptoms such as abdominal pain, increased bowel movements, episodic facial flushing, bronchoconstriction, venous telangiectasia, niacin deficiency-related symptoms, and long-term complications, such as mesenteric fibrosis and carcinoid heart disease.(1) Measurement of 5-HIAA in a plasma specimen can diagnose carcinoid disease and produces comparable results to urinary 5-HIAA testing.

Useful For: Biochemical diagnosis and monitoring of intestinal carcinoid syndrome using a plasma specimen

Interpretation: If pharmacological and dietary artifacts have been ruled out, an elevated concentration of 5-hydroxyindoleacetic acid is a probable indicator of the presence of a serotonin-producing tumor.

Reference Values:
< or =6 months: < or =130 ng/mL
>6 months: < or =30 ng/mL

Clinical References: 1. Oleinikov K, Avniel-Polak S, Gross DJ, Grozinsky-Glasberg S. Carcinoid syndrome: Updates and review of current therapy. Curr Treat Options Oncol. 2019 9;20(9):70. doi:10.1007/s11864-019-0671-0 2. Adaway JE, Dobson R, Walsh J, et al. Serum and plasma 5-hydroxyindoleacetic acid as an alternative to 24-h urine 5-hydroxyindoleacetic acid measurement. Ann Clin Biochem. 2016;53(Pt 5):554-560. doi:10.1177/0004563215613109 3. Tohmola N, Johansson A, Sane T, Renkonen R, Hamalainen E, Itkonen O. Transient elevation of serum 5-HIAA by dietary serotonin and distribution of 5-HIAA in serum protein fractions. Ann Clin Biochem. 2015;52(Pt 4):428-433. doi:10.1177/0004563214554842 4. Tellez MR, Mamikunian G, O'Dorisio TM, Vinik AI, Woltering EA. A single fasting plasma 5-HIAA value correlates with 24-hour urinary 5-HIAA values and other biomarkers in midgut neuroendocrine tumors (NETs). Pancreas. 2013;42(3):405-410. doi:10.1097/MPA.0b013e318271c0d5

HIAAR
616090

5-Hydroxyindoleacetic Acid, Random, Urine

Clinical Information: 5-Hydroxyindoleacetic acid (5-HIAA) is the major metabolite of serotonin and is excreted in the urine. Intestinal carcinoid tumors, along with neuroendocrine tumors, can produce excess amounts of 5-HIAA and serotonin, especially in individuals with carcinoid syndrome. Carcinoid syndrome is characterized by carcinoid tumors, flushing, heart disease, and hepatomegaly. Measurement of 5-HIAA in a random urine specimen can diagnose carcinoid disease with a high specificity.

Useful For: Biochemical diagnosis and monitoring of intestinal carcinoid syndrome using random urine specimens

Interpretation: If pharmacological and dietary artifacts have been ruled out, an elevated excretion of 5-hydroxyindoleacetic acid is a probable indicator of the presence of a serotonin-producing tumor.

Reference Values:

	5-HIAA, mg/g creatinine 99th percentile cutoff
Age	Female
< or =23 months	< or =17.53
24-35 months	< or =17.07
3 years	< or =16.70
4 years	< or =16.03
5 years	< or =15.26
6 years	< or =14.40

7 years	< or =13.47
8 years	< or =12.52
9 years	< or =11.58
10 years	< or =10.67
11 years	< or =9.81
12 years	< or =9.02
13 years	< or =8.32
14 years	< or =7.70
15 years	< or =7.16
16 years	< or =6.72
17 years	< or =6.36
18 years	< or =6.08
19 years	< or =5.88
20 years	< or =5.73
21 years	< or =5.64
22 years	< or =5.59
23 years	< or =5.57
24 years	< or =5.57
25 years	< or =5.58
26 years	< or =5.61
27 years	< or =5.64
28 years	< or =5.67
29 years	< or =5.70
30 years	< or =5.72
31 years	< or =5.75
32 years	< or =5.77
33 years	< or =5.78
34 years	< or =5.79
35 years	< or =5.80
36 years	< or =5.80
37 years	< or =5.80
38 years	< or =5.80
39 years	< or =5.81
40 years	< or =5.82
41 years	< or =5.85
42 years	< or =5.89
43 years	< or =5.95

44 years	< or =6.04
45 years	< or =6.14
46 years	< or =6.26
47 years	< or =6.40
48 years	< or =6.55
49 years	< or =6.71
50 years	< or =6.86
51 years	< or =7.01
52 years	< or =7.15
53 years	< or =7.29
54 years	< or =7.41
55 years	< or =7.52
56 years	< or =7.62
57 years	< or =7.71
58 years	< or =7.80
59 years	< or =7.88
60 years	< or =7.95
61 years	< or =8.02
62 years	< or =8.09
63 years	< or =8.15
64 years	< or =8.21
65 years	< or =8.28
66 years	< or =8.34
67 years	< or =8.40
68 years	< or =8.46
69 years	< or =8.52
70 years	< or =8.58
71 years	< or =8.65
72 years	< or =8.71
73 years	< or =8.77
74 years	< or =8.82
75 years	< or =8.86
76 years	< or =8.90
77 years	< or =8.92
78 years	< or =8.93
79 years	< or =8.93
80 years	< or =8.92

81 years	< or =8.90
82 years	< or =8.88
83 years	< or =8.86
84 years	< or =8.85
85 years	< or =8.84
86 years	< or =8.84
87 years	< or =8.84
88 years	< or =8.84
>or= 89 years	< or =8.85

Clinical References: 1. Grimaldi F, Fazio N, Attanasio R, et al. Italian Association of Clinical Endocrinologists (AME) position statement: a stepwise clinical approach to the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. J Endocrinol Invest. 2014;37(9):875-909. doi:10.1007/s40618-014-0119-0 2. Vinik A, Hughes MS. Feliberti E, et al. Carcinoid tumors. In: Feingold KR, Anawalt B, Boyce A, et al, eds. Endotext [Internet]. MDText.com, Inc; 2000. Updated August 25, 2023. Accessed April 1, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK279162/ 3. Shah D, Mandot A, Cerejo C, Amarapurkar D, Pal A: The outcome of primary hepatic neuroendocrine tumors: A single-center experience. J Clin Exp Hepatol. 2019;9(6):710-715. doi:10.1016/j.jceh.2019.08.002 4. Perry D, Hayek SS. Carcinoid heart disease. A guide for clinicians. Cardiol Clin. 2019;37(4):497-503. doi:10.1016/j.ccl.2019.07.014 5. Degnan AJ, Tocchio S, Kurtom W, Tadros SS. Pediatric neuroendocrine carcinoid tumors: Management, pathology, and imaging findings in a pediatric referral center. Pediatr Blood Cancer. 2017;64(9). doi:10.1002/pbc.26477 6. Corcuff JB, Chardon L, El Hajji Ridah I, Brossaud J. Urinary sampling for 5HIAA and metanephrines determination: revisiting the recommendations. Endocr Connect. 2017;6(6):R87-R98. doi:10.1530/EC-17-0071

F5M
57101

5-Methyltetrahydrofolate

Clinical Information: CSF 5-Methyltetrahydrofolate (NC01) is useful for determining a deficiency of folate in the central nervous system. CSF 5-Methyltetrahydrofolate (NC01) may also be used for assessment of Variants of Uncertain Significance (VUS) identified during genetic testing (e.g. Next Generation Sequencing or Capillary Sequencing Testing). CLINICAL 5-Methyltetrahydrofolate (5-MTHF) is the predominant form of folate in cerebrospinal fluid (CSF). Low CSF 5-MTHF levels are associated with inborn errors of metabolism affecting folate metabolism , dietary deficiency of folate, cerebral folate syndromes and Kearns-Sayre syndrome. Symptoms may include, anemia, developmental delay, seizures, depression and dementia.

Reference Values:

5-Methyltetrahydrofolate

Age (years)	5MTHF (nmol/L)
0-0.2	40-240
0.2-0.5	40-240
0.5-2.0	40-187
2.0-5.0	40-150
5.0-10	40-128
10-15	40-120
Adults	40-120

Note: If test results are inconsistent with the clinical presentation, please call our laboratory to discuss the case and/or submit a second sample for confirmatory testing.

DISCLAIMER required by the FDA for high complexity clinical laboratories: HPLC testing was developed and its performance characteristics determined by Medical Neurogenetics. These HPLC tests have not been cleared or approved by the U.S. FDA.

MAMMX 62732 6-Monoacetylmorphine (6-MAM) Confirmation, Chain of Custody, Meconium

Clinical Information: Heroin (diacetylmorphine) is a semisynthetic opiate that is closely related to morphine. It is no longer used clinically in the United States, although it is used elsewhere for rapid relief of pain.(1) Like morphine and other opiates, its relaxing and euphoric qualities make heroin a popular drug of abuse. Heroin is commonly injected intravenously but can be administered by other means, such as snorting, smoking, or inhaling vapors. Heroin shares the core structure of morphine with the addition of 2 acetyl groups, which are thought to enhance its permeation into the central nervous system.(2,3) Heroin is metabolized by sequential removal of these acetyl groups; loss of the first acetyl converts heroin into 6-monoacetylmorphine (6-MAM).(2,3) Heroin is rarely found in meconium since only 0.1% of a dose is excreted unchanged. 6-MAM is a unique metabolite of heroin, and its presence is a definitive indication of heroin use. Like heroin, 6-MAM has a very short half-life; however, its detection time in meconium, the first fecal material passed by the neonate, is uncharacterized. 6-MAM is further metabolized into morphine, the dominant metabolite of heroin, and morphine will typically be found in a specimen containing 6-MAM. Opiates, including heroin, have been shown to readily cross the placenta and distribute widely into many fetal tissues.(4) Opiate use by the mother during pregnancy increases the risk of prematurity and being small for gestational age. Furthermore, infants who have been exposed to heroin exhibit an early onset of withdrawal symptoms compared with infants who have been exposed to methadone. Infants exposed to heroin demonstrate a variety of symptoms including irritability, hypertonia, wakefulness, diarrhea, yawning, sneezing, increased hiccups, excessive sucking, and seizures. Long-term intrauterine drug exposure may lead to abnormal neurocognitive and behavioral development as well as an increased risk of sudden infant death syndrome.(5) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes the drug into bile and amniotic fluid. The drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(6) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and it slowly moves into the colon by the 16th week of gestation.(7) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(6) Chain of custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting in utero heroin exposure up to 5 months before birth Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

Interpretation: The presence of 6-monoacetylmorphine (6-MAM) in meconium is definitive for heroin use by the mother. However, the absence of 6-MAM does not rule-out heroin use because of its

short half-life.

Reference Values:
Negative

Positive results are reported with a quantitative liquid chromatography tandem mass spectrometry result.
Cutoff concentration: 5 ng/g

Clinical References: 1. Giovannelli M, Bedforth N, Aitkenhead A. Survey of intrathecal opioid usage in the UK. Eur J Anaesthesiol. 2008;25(2):118-122 2. Levine B, ed. Principles of Forensic Toxicology. 4th ed. AACC Press; 2013 3. Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. McGraw-Hill; 2018 4. Szeto HH. Kinetics of drug transfer to the fetus. Clin Obstet Gynecol. 1993;36(2):246-254 5. Kwong TC, Ryan RM. Detection of intrauterine illicit drug exposure by newborn drug testing. Clin Chem. 1997;43(1):235-242 6. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989;115(3):474-477 7. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-56; quiz 73-74 8. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 9. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020

6MAMM
89659

6-Monoacetylmorphine (6-MAM), Confirmation, Meconium

Clinical Information: Heroin (diacetylmorphine) is a semisynthetic opiate that is closely related to morphine. It is no longer used clinically in the United States, though it is used elsewhere for rapid relief of pain.(1) Like morphine and other opiates, its relaxing and euphoric qualities make heroin a popular drug of abuse. Heroin is commonly injected intravenously, although it can be administered by other means such as snorting, smoking, or inhaling vapors. Heroin shares the core structure of morphine with the addition of 2 acetyl groups, which are thought to enhance its permeation into the central nervous system.(2,3) Heroin is metabolized by sequential removal of these acetyl groups; loss of the first acetyl converts heroin into 6-monoacetylmorphine (6-MAM).(2,3) Heroin is rarely found in meconium since only 0.1% of a dose is excreted unchanged. 6-MAM is a unique metabolite of heroin, and its presence is a definitive indication of heroin use. Like heroin, 6-MAM has a very short half-life; however, its detection time in meconium, the first fecal material passed by the neonate, is uncharacterized. 6-MAM is further metabolized into morphine, the dominant metabolite of heroin, and morphine will typically be found in a specimen containing 6-MAM. Opiates, including heroin, have been shown to readily cross the placenta and distribute widely into many fetal tissues.(4) Opiate use by the mother during pregnancy increases the risk of prematurity and being small for gestational age. Furthermore, infants who have been exposed to heroin exhibit an early onset of withdrawal symptoms compared with infants who have been exposed to methadone. Infants exposed to heroin demonstrate a variety of symptoms including irritability, hypertonia, wakefulness, diarrhea, yawning, sneezing, increased hiccups, excessive sucking, and seizures. Long-term intrauterine drug exposure may lead to abnormal neurocognitive and behavioral development as well as an increased risk of sudden infant death syndrome.(5) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes the drug into bile and amniotic fluid. The drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(6) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and it slowly moves into the colon by the 16th week of gestation.(7) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(6)

Useful For: Detection of in utero heroin exposure up to 5 months before birth

Interpretation: The presence of 6-monoacetylmorphine (6-MAM) in meconium is definitive for heroin use by the mother. However, the absence of 6-MAM does not rule-out heroin use because of its short half-life and stability.

Reference Values:
Negative
Positive results are reported with a quantitative liquid chromatography tandem mass spectrometry result.
Cutoff concentration: 5 ng/g

Clinical References: 1. Giovannelli M, Bedforth N, Aitkenhead A. Survey of intrathecal opioid usage in the UK. Eur J Anaesthesiol. 2008;25:118-122 2. Levine B, ed. Principles of Forensic Toxicology. 4th ed. AACC Press; 2013 3. Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. McGraw-Hill; 2018 4. Szeto HH. Kinetics of drug transfer to the fetus. Clin Obstet Gynecol. 1993;36:246-254 5. Kwong TC, Ryan RM. Detection of intrauterine illicit drug exposure by newborn drug testing. Clin Chem. 1997;43(1):235-242 6. Ostrea EM Jr, Brady MJ, Parks PM, et al. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989;115(3):474-477 7. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-56; quiz 73-74 8. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 9. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020

6MAMU
89605

6-Monoacetylmorphine Confirmation, Random, Urine

Clinical Information: Heroin (diacetylmorphine) is a semisynthetic opiate that is closely related to morphine. It is no longer used clinically in the United States, though elsewhere it is used for rapid relief of pain.(1) Like morphine and other opiates, its relaxing and euphoric qualities make heroin a popular drug of abuse. Heroin is commonly injected intravenously, although it can be administered by other means, such as snorting, smoking, or inhaling vapors. Heroin shares the core structure of morphine, with the addition of 2 acetyl groups, which are thought to enhance its permeation into the central nervous system.(2,3) Heroin is metabolized by sequential removal of these acetyl groups; loss of first acetyl group converts heroin into 6-monoacetylmorphine (6-MAM) and loss of the second acetyl group converts 6-MAM to morphine, the dominant metabolite of heroin.(2,3) Heroin is rarely found in urine due to its rapid metabolism. 6-MAM is a unique metabolite of heroin, and its presence is a definitive indication of recent heroin use. Like heroin, 6-MAM has a very short half-life and detection window.

Useful For: Determination of heroin use

Interpretation: The presence of 6-monoacetylmorphine (6-MAM) in urine is definitive for recent heroin use. However, the absence of 6-MAM does not rule-out heroin use because of its short half-life. 6-MAM is typically only detectable within 24 hours of heroin use. 6-MAM is further metabolized into morphine, which may be detected 1 to 2 days after 6-MAM is no longer measurable. Morphine will typically be found in a specimen containing 6-MAM.(2,3)

Reference Values:
Negative (Positive result is reported with a quantitative result)

Cutoff concentration by gas chromatography mass spectrometry:
6-Monoacetylmorphine: 5 ng/mL

Clinical References: 1. Giovannelli M, Bedforth N, Aitkenhead A. Survey of intrathecal opioid usage in the UK. Eur J Anaesthesiol. 2008;25(2):118-122 2. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:187-205 3. Hardman JG, Limbird LE, Gilman AG. Goodman and Gilman's. The Pharmacological Basis of Therapeutics. 10th ed. McGraw-Hill Book Company; 2001:590-592 4. Levine BS, Kerrigan S, eds. Principles of Forensic Toxicology. 5th ed. Springer; 2020 5. Brunton LL, Knollmann BC, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 14th ed. McGraw Hill LLC; 2023 6. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:Chapter 43

6MAMX
62708

6-Monoacetylmorphine, Chain of Custody, Random, Urine

Clinical Information:

Useful For: Determination of heroin use Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that, it is always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of 6-monoacetylmorphine (6-MAM) in urine is definitive for recent heroin use. However, the absence of 6-MAM does not rule out heroin use because of its short half-life. 6-MAM is typically only detectable within 24 hours of heroin use. 6-MAM is further metabolized into morphine, which may be detected 1 to 2 days after 6-MAM is no longer measurable. Morphine will also typically be found in a specimen containing 6-MAM.(2,3)

Reference Values:
Negative (Positive result is reported with a quantitative result)

Cutoff concentration by gas chromatography mass spectrometry:
6-Monoacetylmorphine cutoff concentration: 5 ng/mL

Clinical References: 1. Giovannelli M, Bedforth N, Aitkenhead A. Survey of intrathecal opioid usage in the UK. Eur J Anaesthesiol. 2008;25(2):118-122 2. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:187-205 3. Hardman JG, Limbird LE, Gilman AG. Goodman and Gilman's. The Pharmacological Basis of Therapeutics. 10th ed. McGraw-Hill Book Company; 2001:590-592 4. Levine BS, Kerrigan S, eds. Principles of Forensic Toxicology. 5th ed. Springer; 2020 5. Brunton LL, Knollmann BC, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 14th ed. McGraw Hill LLC; 2023 6. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:Chapter 43

F68KD
91494

68kD (hsp-70) antibodies by Line Blot

Interpretation: Antibodies to inner ear antigen (68kDa) occur in approximately 70% of patients with autoimmune hearing loss. The antibody tests to this 68kDa antigen parallel with disease activity. In addition, a majority of patients positive for antibodies to 68kDa are responsive to corticosteroid treatment.(Hirose et al. The Laryngoscope. 109:1769-1999)

Reference Values:
Qualitative test - Positive or Negative

7AC4
607699

7AC4, Bile Acid Synthesis, Serum

Clinical Information: Bile acids are synthesized from cholesterol in the liver and released into the digestive tract where they function to emulsify dietary fats and facilitate lipid absorption in the small intestine. More than 95% of bile acids are then reabsorbed primarily by active uptake in the distal ileum, while less than 5% are excreted in stool. The synthesis of bile acids in the liver is regulated by a negative feedback mechanism from the bile acids reabsorbed from the intestine. 7 Alpha-hydroxy-4-cholesten-3-one (7aC4) is an intermediate in the biosynthesis pathway of cholesterol to bile acids. The concentration of 7aC4 in serum is a surrogate for the amount of bile acid synthesis in the liver. There is some diurnal variation in 7aC4 serum concentrations, so measurement should be performed on a fasting morning sample. Patients with increased bile acid in their stool suffer from chronic diarrhea termed bile acid diarrhea (BAD). Approximately 10% to 33% of patients with irritable bowel syndrome with diarrhea have BAD. Additionally, BAD has been identified as a contributor of diarrhea in other conditions such as irritable bowel disease (IBD), Celiac disease, microscopic colitis, and neuroendocrine tumors.(1) Identifying patients with BAD can be done by measuring total and fractionated bile acids in stool. The increased bile acids in feces can be caused by an inability to reabsorb bile acids in the terminal ileum (bile acid malabsorption: BAM). If the intestinal reabsorption if BA is decreased, this leads to increase synthesis of bile acids in the liver. Recent studies have shown that serum concentrations of 7aC4 are elevated in patients with BAD. Several intestinal diseases or functional abnormalities can lead to BAD. The definitive test in the United States for BAD is the 48-hour stool bile acids test (BA48F / Bile Acids, Bowel Dysfunction, 48 Hour, Feces). However, given the challenge of a 48-hour specimen collection, a random stool collection can be used in combination with the results from serum 7aC4 testing. From a random stool collection, only the percentage of primary bile acids can be reported. Internal studies have shown that a combination of serum 7aC4 result above 52.5 ng/mL and primary fecal bile acid result above 10% is 66% sensitive and 95% specific for BAD.(2) Identification of these patients can influence treatment decisions that could include the use of bile acid sequestrants. Conversely, patients with irritable bowel syndrome with constipation may have lower circulating 7aC4 as compared to healthy individuals.

Useful For: Screening for bile acid malabsorption in patients with irritable bowel syndrome with diarrhea

Interpretation: In patients with irritable bowel syndrome with diarrhea, elevated 7alpha-hydroxy-4-cholesten-3-one (7aC4) is consistent with bile acid diarrhea (BAD). A result of 17.6 ng/mL or greater is 83% sensitive and 53% specific for BAD. In these cases, a confirmatory 48-hour fecal bile acid test could be considered. A result above 52.5 ng/mL is 40% sensitive and 85% specific for BAD. Interpretation of 7aC4 results in patients with chronic diarrhea (bile acid malabsorption: BAM): Below 17.6 17.6 or above Above 52.5 BAM unlikely, consider other conditions BAM indeterminate, consider confirmatory fecal bile acids test or trial of bile acid sequestrant BAM likely, consider bile acid sequestrant therapy Serum 7aC4 can be used in combination with a random (single collection) stool bile acid assessment for increased sensitivity and specificity for BAM detection. See BAMRP / Bile Acids Malborption Panel, Serum and Feces.

Reference Values:
> or =18 years: 2.5-63.2 ng/mL
Reference values have not been established for patients who are <18 years of age.

Clinical References: 1. Vijayvargiya P, Gonzalez Izundegui D, Calderon G, et al: Increased fecal bile acid excretion in a significant subset of patients with other inflammatory diarrheal diseases. Dig Dis Sci. 2022 Jun;67(6):2413-2419 2. Camilleri M, Nadeau A, Tremaine WJ, et al: Measurement of serum 7 alpha-hydroxy-4-cholesten-3-one (or 7AC4), a surrogate test for bile acid malabsorption in health, ileal disease and irritable bowel syndrome using liquid chromatography-tandem mass spectrometry. Neurogastroenterol Motil. 2009;21(7):734-743 3. Vijayvargiya P, Camilleri M, Carlson P, et al: Performance characteristics of serum C4 and FGF19 measurements to exclude the diagnosis of bile acid diarrhoea in IBS-diarrhoea and functional diarrhoea. Aliment Pharmacol Ther. 2017;46(6):581-588. doi:

10.1111/apt.14214 4. Vijayvargiya P, Camilleri M, Shin A, et al: Methods for diagnosis of bile acid malabsorption in clinical practice. Clin Gastroenterol Hepatol. 2013;11(10):1232-1239 5. Vijayvargiya P, Camilleri M, Taylor A, et al: Combined fasting serum C4 and primary bile acids from a single stool sample to diagnose bile acid diarrhea. Gastroenterology. 2020 Nov;159(5):1952-1954.e23. 6. Wong BS, Camilleri M, Carlson P, et al: Increased bile acid biosynthesis is associated with irritable bowel syndrome with diarrhea. Clin Gastroenterol Hepatol. 2012 Sep;10(9):1009-1015.e3

A1R
113437

A1 Antigen Subtype, Blood

Clinical Information: The presence or absence of a cellular antigen is an inherited trait. Generally, individuals will not make antibody directed against an antigen present on their own red blood cells.

Useful For: Additional proof of alloantibody specificity Assessment of solid organ transplantation donor compatibility This test is not useful for the purpose of establishing paternity.

Interpretation: The A1 antigen type will be resulted as "pos," indicating that the antigen is present, or "neg," indicating that the antigen is absent.

Reference Values:
Reported as Negative or Positive

Clinical References: Cohn CS, Delaney M, Johnson ST, Katz LM, Schwartz J, eds. Technical Manual. 21st ed. AABB; 2023

RTQPC
620307

Abnormal Prion Protein, Real-Time Quaking Induced Conversion, Spinal Fluid

Clinical Information: This evaluation is intended for use in patients with suspected Creutzfeldt-Jakob disease (CJD) and other human prion diseases. CJD is a rare and fatal neurodegenerative disorder that predominantly affects the brain and is caused by misfolded prion proteins (PrP[Sc]). CJD accounts for more than 90% of human prion diseases. Initial symptom onset is heterogenous but commonly includes rapidly progressive dementia, cerebellar ataxia, and myoclonus. The timeline of symptom progression and the pattern of symptom evolution can be divergent across patients and CJD subtypes, making an accurate diagnosis based on clinical presentation alone challenging. The inclusion of biomarkers with high diagnostic accuracy has improved the differentiation of CJD and related prion diseases from treatable neurological conditions with overlapping phenotypes. The real-time quaking-induced conversion (RT-QuIC) assay has been established to have strong clinical utility for early and accurate diagnosis of CJD through numerous independent studies in cerebrospinal fluid (CSF). Furthermore, the robustness and reproducibility of the RT-QuIC assay for CJD across laboratories has been demonstrated through international ring trials. The clinical sensitivity and specificity of second-generation RT-QuIC assays in CSF have been consistently reported to be greater than or equal to 92% and greater than or equal to 99%, respectively. Despite the high diagnostic accuracy of the assay, RT-QuIC results should be interpreted in the appropriate clinical context along with other clinical and paraclinical findings. A definitive diagnosis of sporadic prion disease can be established only through neuropathological assessment of brain tissue. Unexpectedly negative RT-QuIC test results should prompt careful consideration of the differential diagnosis. If there is high suspicion of prion disease, repeat testing with RT-QuIC may be warranted. A small subset of cases initially negative by RT-QuIC may become positive as the disease progresses. However, RT-QuIC may be persistently negative in a small proportion of patients with definitive prion disease. False-negative RT-QuIC results are most often encountered in cases of genetic prion disease (eg, fatal familial insomnia and Gerstmann-

Straussler-Scheinker disease) and in atypical sporadic prion disease subtypes (eg, MM2 cortical subtype) that have slower indolent disease progression. Other CSF biomarkers have been utilized to support the diagnosis of CJD, including 14-3-3, total Tau measurement, and the ratio of total Tau to phosphorylated Tau at threonine 181. Recent studies have indicated that the Tau ratio (total Tau to pT181-Tau or vice versa) has a very high diagnostic accuracy that exceeds that provided by total Tau or 14-3-3 enzyme-linked immunosorbent assays (ELISA). In a cohort of probable/definite CJD cases and controls tested utilizing the Roche Total-Tau and p-Tau (threonine 181) Elecsys assays, the optimized cut-off value for total Tau (>393 ng/L) had a clinical sensitivity and specificity of 92.3% and 88.3% for CJD, respectively, and the optimized cut-off value for the total Tau to p-Tau ratio (>18) has a clinical sensitivity and specificity of 97.4% and 95.9% for CJD, respectively. Importantly, total Tau or total Tau to p-Tau ratios utilize assay-dependent cut-off values, and cut-off values from one assay are not transferable to different assay platforms. The National Prion Disease Pathology Surveillance Center (NPDPSC) coordinates autopsies and neuropathologic examinations on suspected prion disease cases. More information about services available at the NPDPSC can be found at https://case.edu/medicine/pathology/divisions/prion-center.

Useful For: Aiding in diagnosing sporadic Creutzfeldt-Jakob disease or other prion disease in patients with a rapidly progressive dementia

Interpretation: A positive real-time quaking-induced conversion (RT-QuIC) assay result is supportive of prion disease and, in the correct clinical context, fulfills the Centers of Disease Control and Prevention diagnostic criteria of probable prion disease.(1) Negative results do not exclude the possibility of prion disease.

Reference Values:
Only orderable as part of a profile. For more information see:
CJDE / Creutzfeldt-Jakob Disease Evaluation, Spinal Fluid
RPDE / Rapidly Progressive Dementia Evaluation, Spinal Fluid

Negative

Clinical References: 1. Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of High-Consequence Pathogens and Pathology (DHCPP). Diagnostic criteria: CDC's diagnostic criteria for Creutzfeldt-Jakob disease (CJD), 2018. CDC; Updated October 18, 2021. Accessed July 17, 2024. Available at www.cdc.gov/creutzfeldt-jakob/hcp/clinical-overview/diagnosis.html 2. Hermann P, Appleby B, Brandel JP, et al. Biomarkers and diagnostic guidelines for sporadic Creutzfeldt-Jakob disease. Lancet Neurol. 2021;20(3):235-46 3. Rhoads DD, Wrona A, Foutz A, et al. Diagnosis of prion diseases by RT-QuIC results in improved surveillance. Neurology. 2020;95(8):e1017-e1026 4. Hamlin C, Puoti G, Berri S, et al. A comparison of tau and 14-3-3 protein in the diagnosis of Creutzfeldt-Jakob disease. Neurology. 2012;79(6):547-552 5. Shir D, Lazar EB, Graff-Radford J, et al. Analysis of clinical features, diagnostic tests, and biomarkers in patients with suspected Creutzfeldt-Jakob disease, 2014-2021. JAMA Netw Open. 2022;5(8):e2225098

ABONR
113498

ABO/Rh Newborn, Blood

Clinical Information: The ABO and Rh typing indicates the presence of 2 of the various blood group systems. The identification of antigens in the ABO and Rh system has its major application in the selection of blood and blood products of the appropriate ABO/Rh type for transfusion therapy and in the determination of the mother's candidacy for Rh immune globulin therapy. Weak D testing will be performed on all Rh-negative babies.

Useful For: Selecting compatible blood products for transfusion therapy Determining the need for Rh

immune globulin in mother of baby

Interpretation: Agglutination of red cells with an antiserum represents the presence of the corresponding antigen on the red cells.

Reference Values:
ABO and Rh blood group antigens identified

Clinical References: Cohn CS, Delaney DO, Johnson ST, Katz LM, Schwartz J, eds. Technical Manual. 21st ed. AABB; 2023

ABOMR
113490

ABO/Rh, Blood

Clinical Information: This ABO and Rh blood typing test identifies the presence of specific red cell antigens and antibodies to determine the ABO/Rh type.

Useful For: Determining blood group ABO and Rh only

Interpretation: Standard ABO/Rh type will be reported. Routine types include: O pos, O neg, A pos, A neg, B pos, B neg, AB pos and AB neg. Any relevant discrepancies will be noted.

Reference Values:
ABO and Rh blood group antigens identified

Clinical References: Cohn CS, Delaney DO, Johnson ST, Katz LM, Schwartz J, eds. Technical Manual. 21st ed. AABB; 2023

ACAC
82757

Acacia, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to acacia Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased

likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ACARP
64717

Acanthamoeba species Molecular Detection, PCR, Ocular

Clinical Information: Acanthamoeba are ubiquitous, free-living, microscopic amebae that cause rare, but severe, infections of the eye, skin, lungs, and central nervous system (CNS). They are found worldwide in water and soil and may enter the body through inhalation, contamination of wounds, and contact lens use. As many as 24 species comprising 22 genotypes (T1-T22) have been described using 18S ribosomal RNA sequence analysis, although most human infections are due to genotype T4. Given their widespread distribution in the environment, many people will be exposed to Acanthamoeba during their lifetime, but very few will become sick from this exposure. The most common form of Acanthamoeba infection is amebic keratitis (AK). Infection occurs primarily in contact lens wearers due to contamination of lenses, cleaning solutions, or storage cases. Amebae can also enter the cornea following trauma. AK is a painful, subacute corneal infection associated with extensive scarring and blindness if untreated. Cases generally respond to treatment, but relapse is common. Compared to corneal infection, involvement of the CNS is rare and seen primarily in severely immunocompromised individuals, such as organ transplant recipients and patients with AIDS. CNS infection may also be caused by a related ameba, Balamuthia mandrillaris. Amebic keratitis is usually clinically suspected based on symptoms and confocal ophthalmologic examination. Confirmation of infection is classically identified by microscopic examination and culture of corneal tissue and contact lenses or equipment using tap water agar plate overlain with bacteria as a food source for the amebae. Unfortunately, it must be held and examined for 7 days for maximum sensitivity. A polymerase chain reaction assay provides a more rapid result with similar sensitivity to culture and is, therefore, the preferred method for confirming the clinical diagnosis of AK.

Useful For: Aids in the diagnosis of amebic keratitis in conjunction with clinical findings

Interpretation: A positive result indicates the presence of Acanthamoeba species DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with symptoms, clinical findings, radiologic features, or confocal ophthalmologic examination.

Reference Values:
Negative

Clinical References: 1. Cope JR, Ali KM, Visvesvara GS. Pathogenic and opportunistic free-living amebae. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th Ed. ASM Press; 2019:chap142 2. Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED): Parasites - Acanthamoeba - Granulomatous Amebic Encephalitis (GAE); Keratitis. CDC; Updated March 27, 2025. Accessed May 6, 2025. Available at www.cdc.gov/acanthamoeba/about/index.html?CDC_AAref_Val

ACAR
82850

Acarus siro, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to Acarus siro (flour mites) Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive

3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ACMA
37030

Acetaminophen, Serum

Clinical Information: Acetaminophen (found in Anacin-3, Comtrex, Contac, Datril, Dristan, Excedrin, Nyquil, Sinutab, Tempera, Tylenol, Vanquish, and many others) is an analgesic, antipyretic drug lacking significant anti-inflammatory activity. It is metabolized by the liver with a normal elimination half-life of less than 4 hours. In normal therapeutic doses, a minor metabolite, possessing electrophilic alkylating activity, readily reacts with glutathione in the liver to yield a detoxified product. In overdose situations, liver glutathione is consumed and the toxic metabolite (postulated metabolite: benzoquinone) reacts with cellular proteins resulting in hepatotoxicity, characterized by centrilobular necrosis and possible death if untreated. N-acetylcysteine can substitute for glutathione and serves as an antidote. Serum concentration and half-life are the only way to assess degree of intoxication in early stages since other liver function studies (eg, bilirubin, liver function enzymes) will not show clinically significant increases until after tissue damage has occurred, at which point therapy is ineffective.

Useful For: Monitoring toxicity in overdose cases

Interpretation: The normal half-life is less than 4 hours, while the toxic half-life is greater than 4 hours. The toxic level is dependent on half-life. When the half-life is 4 hours, hepatotoxicity generally will not occur unless the concentration is above 150 mcg/mL. The level at which toxicity occurs decreases with increasing half-life until it is encountered at values as low as 50 mcg/mL when the half-life reaches 12 hours. For half-life determination, draw 2 specimens at least 4 hours apart and note the exact time of each draw. Half-life can be calculated from the concentrations and the time interval.

Clinical References: Rumack BH, Peterson RG: Acetaminophen overdose: incidence, diagnosis, and management in 416 patients. Pediatrics Nov 1978;62:898-903

FACES
75388

Acetoacetate, Serum

Reference Values:
Reporting limit determined each analysis.

Acetoacetate: None Detected mcg/mL
-Normal range for adults: 5-30 mcg/mL

FCDU3
75778

Acetyl Fentanyl, Umbilical Cord Tissue

Reference Values:

Reporting limit determined each analysis.

Units: ng/g

Only orderable as part of a profile-see FCDSU.

ARBI 8338 Acetylcholine Receptor (Muscle AChR) Binding Antibody, Serum

Clinical Information: Fatigable weakness due to impaired postsynaptic transmission at the neuromuscular junction is characteristic of myasthenia gravis (MG). A clinical diagnosis should be supported by electrodiagnostic testing (ie, clinical-electrodiagnosis [EDX]). Positive autoimmune serology increases certainty of MG diagnosis but needs to be interpreted in the proper clinical-EDX context with response to anticholinesterase medications supporting the diagnosis. Most cases are autoimmune and are caused by IgG autoantibodies binding to critical postsynaptic membrane molecules (nicotinic muscle acetylcholine receptor [AChR] or its interacting proteins, such as muscle-specific kinase). Serologically, the detection of AChR binding antibody provides the best diagnostic sensitivity. However, the presence of both AChR binding and modulating activity improves diagnostic accuracy. Autoantibody detection frequency is lowest in patients with weakness confined to extraocular muscles (approximately 70% are positive for AChR binding antibodies) and highest in patients with generalized weakness due to MG (approximately 90% are positive for AChR binding antibodies). In adults with MG and AChR antibodies, approximately 20% will have thymoma and, very rarely (<1%), extrathymic cancers. Computed tomography imaging of the chest is considered the standard of care to evaluate for thymoma. These results should only be interpreted in the appropriate clinical and electrophysiological context and are not diagnostic in isolation. Note: Single antibody tests may be requested in the follow-up of patients with positive results previously documented in this laboratory.

Useful For: Supporting the diagnosis of autoimmune myasthenia gravis (MG) in adults and children Distinguishing autoimmune from congenital MG in adults and children or other acquired forms of neuromuscular junction transmission disorders An adjunct to the test for P/Q-type calcium channel binding antibodies as a diagnostic aid for Lambert-Eaton myasthenic syndrome

Interpretation: Positive results (>0.02 nmol/L) are indicative of autoimmune myasthenia gravis (MG). These results should be interpreted in the appropriate clinical and electrophysiological context. With a diagnosis of MG, a paraneoplastic basis should be considered with thymoma being the most frequently associated tumor with MG. The clinical sensitivity of this assay is approximately 90% in nonimmunosuppressed patients with generalized MG. The frequency of antibody detection is lower in MG patients with weakness clinically restricted to ocular muscles (71%), and antibody titers are generally low in ocular MG (eg, 0.03-1.0 nmol/L). Negative results do not exclude the diagnosis of MG. If clinical suspicion remains and symptoms persist or worsen consider retesting. Results may be negative in the first 12 months after symptoms of MG appear or during immunosuppressant therapy. Note: In follow up of seronegative patients with adult-acquired generalized MG, 17.4% seroconvert to positive at 12 months (ie, seronegativity rate at 12 months is 8.4%). A subset of MG patients that are persistently negative for acetylcholine receptor binding antibodies will have muscle-specific kinase (MuSK) antibodies, and therefore, it is recommended to test for MuSK antibodies in seronegative patients with high clinical suspicion of MG. In general, there is not a close correlation between antibody titer and severity of weakness, but in individual patients, clinical improvement may be accompanied by a decrease in titer.

Reference Values:
< or =0.02 nmol/L

Clinical References: 1. Lennon VA. Serological profile of myasthenia gravis and distinction from the Lambert-Eaton myasthenic syndrome. Neurology. 1997;48(Suppl 5):S23-S27. doi:10.1212/WNL.48.Suppl_5.23S 2. Lachance DH, Lennon VA. Paraneoplastic neurological autoimmunity. In: Kalman B, Brannagan III T, eds. Neuroimmunology in Clinical Practice. Blackwell Publishing Ltd; 2008:210-217 3. Gilhus NE. Myasthenia gravis. N Engl J Med. 2016;375(26):2570-2581. doi:10.1056/NEJMra1602678 4. Nicolle MW. Myasthenia gravis and Lambert-Eaton myasthenic syndrome. Continuum (Minneap Minn). 2016;22(6, Muscle and Neuromuscular Junction Disorders):1978-2005. doi:10.1212/CON.0000000000000415 5. Shelly S, Paul P, Bi H, et al. Improving accuracy of myasthenia gravis autoantibody testing by reflex algorithm. Neurology. 2020;95(22):e3002-e3011. doi:10.1212/WNL.0000000000010910

ACMFS 610029 Acetylcholine Receptor Modulating Antibody, Flow Cytometry Assay, Serum

Clinical Information: Fatigable weakness due to impaired postsynaptic transmission at the neuromuscular junction is characteristic of myasthenia gravis (MG). A clinical diagnosis should be supported by electrodiagnostic testing, ie, clinical-electrodiagnosis (EDX). Positive autoimmune serology increases certainty of MG diagnosis but needs to be interpreted in the proper clinical-EDX context with response to anticholinesterase medications supporting the diagnosis. Most cases are autoimmune and are caused by IgG autoantibodies binding to critical postsynaptic membrane molecules (nicotinic muscle acetylcholine receptor [AChR] or its interacting proteins, such as muscle-specific kinase [MuSK]). Serologically, the detection of AChR binding antibody provides the best diagnostic sensitivity. However, the presence of both AChR binding and modulating activity improves diagnostic accuracy. Autoantibody detection frequency is lowest in patients with weakness confined to extraocular muscles (72% are positive for AChR binding antibodies) and highest in patients with generalized weakness due to MG (92% are positive for AChR binding antibodies). In adults with MG and AChR antibodies, approximately 20% will have thymoma and very rarely (<1%) extrathymic cancers. Computed tomography (CT) imaging of the chest is considered the standard of care to evaluate for thymoma. These results should only be interpreted in the appropriate clinical and electrophysiological context and are not diagnostic in isolation. Note: Single antibody tests may be requested in the follow-up of patients with positive results previously documented in this laboratory.

Useful For: Diagnosis for autoimmune myasthenia gravis (MG) in adults and children Distinguishing autoimmune from congenital MG in adults and children or other acquired forms of neuromuscular junction transmission disorders. This test is a qualitative assay and should not be used for monitoring purposes.

Interpretation: This assay shows strong qualitative concordance with the previous modulating assay. Positive results in this antibody evaluation are indicative of autoimmune myasthenia gravis (MG). These results should be interpreted in the appropriate clinical and electrophysiological context. The presence of acetylcholine receptor (AChR) modulating antibodies along with AChR binding antibodies as compared to AChR binding antibodies alone, improves the diagnostic accuracy for MG. In the presence of AChR modulating antibodies, a paraneoplastic basis should be considered with thymoma being the most commonly associated tumor with MG. Negative results do not exclude the diagnosis of MG. If clinical suspicion remains and symptoms persistent or worsen consider re-testing.

Reference Values:

Only orderable as part of a profile. For more information see:

MGLE / Myasthenia Gravis/Lambert-Eaton Myasthenic Syndrome Evaluation, Serum

MGMR / Myasthenia Gravis Evaluation with Muscle-Specific Kinase (MuSK) Reflex, Serum

PAVAL / Paraneoplastic, Autoantibody Evaluation, Serum

Negative

Clinical References: 1. Lozier BK, Haven TR, Astill ME, Hill HR: Detection of acetylcholine receptor modulating antibodies by flow cytometry. Am J Clin Pathol. 2015 Feb;143(2):186-192 2. Keefe D, Hess D, Bosco J, et al: A rapid, fluorescence-based assay for detecting antigenic modulation of the acetylcholine receptor on human cell lines. Cytometry B Clin Cytom. 2009 May;76(3):206-212

ACHE_
9287

Acetylcholinesterase, Amniotic Fluid

Clinical Information: Neural tube defects (NTD) are a type of birth defect involving openings along the brain and spine. They develop in the early embryonic period when the neural tube fails to close completely. NTD can vary widely in severity. Anencephaly represents the most severe type of NTD, which occurs when the cranial end fails to develop properly, resulting in an absence of the forebrain, the area of the skull that covers the brain, and the skin. Most infants with anencephaly are stillborn or die shortly after birth. NTD along the spine are referred to as spina bifida. Individuals with spina bifida may experience hydrocephalus, urinary and bowel dysfunction, club foot, lower body weakness, and loss of feeling or paralysis. Severity varies depending upon whether the NTD is covered by skin, whether herniation of the meninges and spinal cord are present, and the location of the lesion. NTD not covered by skin are referred to as open NTD and are typically more severe than closed NTD. Likewise, those presenting with herniation and higher on the spinal column are typically more severe. Most NTD occur as isolated birth defects with an incidence of approximately 1 to 2 in 1000 live births in the United States. Rates vary by geographic region with lower rates being observed in the North and West than in the South and East. A fetus is at higher risk when the pregnancy is complicated by maternal diabetes, exposed to certain anticonvulsants, or there is a family history of NTD. Studies have shown a dramatic decrease in risk as a result of maternal dietary supplementation with folic acid. The March of Dimes currently recommends all women of childbearing age take 400 mcg of folic acid daily, increasing the amount to 600 mcg/day during pregnancy. For women who have had a prior pregnancy affected by an NTD, the recommended dose is at least 4000 mcg/day starting at least 1-month preconception and continuing through the first trimester. When an NTD is suspected based upon maternal serum alpha-fetoprotein (AFP) screening results or diagnosed via ultrasound, analysis of AFP and acetylcholinesterase (AChE) in amniotic fluid are useful diagnostic tools. AChE is primarily active in the central nervous system with small amounts of enzyme found in red blood cells, skeletal muscle, and fetal serum. Normal amniotic fluid does not contain AChE, unless contributed by the fetus as a result of an open NTD.

Useful For: Diagnosing open neural tube defects and, to a lesser degree, ventral wall defects

Interpretation: The presence of acetylcholinesterase in amniotic fluid is consistent with open neural tube defects and, to a lesser degree, ventral wall defects.

Reference Values:
Negative (reported as negative [normal] or positive [abnormal] for inhibitable acetylcholinesterase)

Reference values were established in conjunction with alpha-fetoprotein testing and include only amniotic fluids from pregnancies between 14- and 21-weeks gestation.

Clinical References: 1. Douglas Wilson R, Van Mieghem T, Langlois S, Church P. Guideline No. 410: Prevention, Screening, Diagnosis, and Pregnancy Management for Fetal Neural Tube Defects. J Obstet Gynaecol Can. 2021;43(1):124-139.e8. doi:10.1016/j.jogc.2020.11.003 2. Palomaki GE, Bupp C, Gregg AR, Norton ME, Oglesbee D. Laboratory screening and diagnosis of open neural tube defects, 2019 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22(3):462-474

ASCL1
71355

Achaete-Scute Homolog 1 (ASCL1) Immunostain, Technical Component Only

Clinical Information: Achaete-scute homolog 1 (ACSL1), alternatively titled hASH1 or MASH1, is a member of the basic helix-loop-helix family of transcription factors. ACSL1 may play a role at early stages of development of specific neural lineages in most regions of the central nervous system and of several lineages in the peripheral nervous system. The protein has been shown to be highly expressed in medullary thyroid cancer and small cell lung cancer and may be a useful marker for these cancers.

Useful For: Identification of the presence of achaete-scute homolog 1 (ASCL1)

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Au NH, Cheang M, Huntsman DG, et al. Evaluation of immunohistochemical markers in non-small cell lung cancer by unsupervised hierarchical clustering analysis: a tissue microarray study of 284 cases and 18 markers. J Pathol. 2004;204:101-109 2. Kosari F, Ida CM, Aubry M-C, et al. ASCL1 and RET expression defines a clinically relevant subgroup of lung adenocarcinoma characterized by neuroendocrine differentiation. Oncogene. 2014;33:3776-3783 3. Ralston J, Chiriboga L, Nonaka D. MASH1: a useful marker in differentiating pulmonary small cell carcinoma from merkel cell carcinoma. Mod Pathol. 2008;21(11):1357-1362 4. Somasundaram K, Reddy SP, Vinnakota K, et al. Upregulation of ASCL1 and inhibition of Notch signaling pathway characterize progressive astrocytoma. Oncogene. 2005;24:7073-7083 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

GAAWR
606281

Acid Alpha-Glucosidase Reflex, Leukocytes

Clinical Information: Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to variants in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and eventually, death. Individuals with Pompe disease, especially those with infantile, childhood, and juvenile onset, can have elevations of serum enzymes (eg, creatine kinase) secondary to cellular dysfunction. The clinical phenotype of Pompe disease lies on a spectrum dependent on age of onset and residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life when left untreated. Juvenile and adult-onset forms, as the names suggest, are characterized by later onset and longer survival. All disease variants are eventually associated with progressive muscle weakness and respiratory insufficiency. Cardiomyopathy is associated almost exclusively with the infantile form. Treatment with enzyme replacement therapy is available, making early diagnosis of Pompe disease desirable, as early initiation of treatment may improve prognosis. Newborn screening can identify individuals with all forms of Pompe disease, even before onset of symptoms. Unaffected individuals with GAA pseudodeficiency alleles and carriers may also be identified by newborn screening. Determination of GAA enzyme activity in leukocytes can help distinguish between infantile and later onset Pompe disease, but it may also be deficient in individuals with pseudodeficiency alleles and in some carriers. Urine glucotetrasaccharides (HEX4 / Glucotetrasaccharides, Random, Urine) have been shown to be elevated in some individuals, particularly those with infantile onset, and may aid in the initial diagnosis and treatment monitoring. Molecular

genetic analysis of the GAA gene (GAAZ / Pompe Disease, Full Gene Analysis, Varies) is necessary for differentiating alterations from disease-causing variants in affected individuals and for carrier detection in family members.

Useful For: Diagnosis of Pompe disease as a confirmatory reflex of the 6-enzyme panel

Interpretation: When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro, confirmatory studies (enzyme assay, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
Only orderable as a reflex. For more information see LSD6W / Lysosomal Storage Disorders, Six-Enzyme Panel, Leukocytes.

> or =1.50 nmol/hour/mg protein

Clinical References: 1. Elliott S, Buroker N, Cournoyer JJ, et al: Pilot study of newborn screening for six lysosomal storage diseases using tandem mass spectrometry. Mol Genet Metab. 2016 Aug;118(4):304-309. doi: 10.1016/j.ymgme.2016.05.015 2. Matern D, Gavrilov D, Oglesbee D, Raymond K, Rinaldo P, Tortorelli S: Newborn screening for lysosomal storage disorders. Semin Perinatol. 2015 Apr;39(3):206-216. doi: 10.1053/j.semperi.2015.03.005 3. Reuser AJ, Hirschhorn R, Kroos MA: Pompe disease: Glycogen storage disease type II, acid a-glucosidase (acid maltase) deficiency. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed June 30, 2020. Available at: https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225890450 4. Lin N, Huang J, Violante S, et al: Liquid chromatography-tandem mass spectrometry assay of leukocyte acid alpha-glucosidase for post-newborn screening evaluation of Pompe disease. Clin Chem. 2017 Apr;63(4):842-851. doi: 10.1373/clinchem.2016.259036 5. Leslie N, Bailey L: Pompe disease. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2007. Updated May 11, 2017. Accessed March 23, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1261/

GAAW
606267

Acid Alpha-Glucosidase, Leukocytes

Clinical Information: Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to variants in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and, eventually, death. Individuals with Pompe disease, especially those with infantile, childhood, and juvenile onset, can have elevations of serum enzymes (eg, creatine kinase) secondary to cellular dysfunction. The clinical phenotype of Pompe disease lies on a spectrum dependent on age of onset and residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life when left untreated. Juvenile and adult-onset forms, as the names suggest, are characterized by later onset and longer survival. All disease variants are eventually associated with progressive muscle weakness and respiratory insufficiency. Cardiomyopathy is associated almost exclusively with the infantile form. Treatment with enzyme replacement therapy is available, making early diagnosis of Pompe disease desirable, as early initiation of treatment may improve prognosis. Newborn screening can identify individuals with all forms of Pompe disease, even before onset of symptoms. Unaffected individuals with GAA pseudodeficiency

alleles and carriers may also be identified by newborn screening. Determination of GAA enzyme activity in leukocytes can help distinguish between infantile and later onset Pompe disease, but it may also be deficient in individuals with pseudodeficiency alleles and in some carriers. Urine glucotetrasaccharides (HEX4 / Glucotetrasaccharides, Random, Urine) have been shown to be elevated in some individuals, particularly those with infantile onset, and may aid in the initial diagnosis and treatment monitoring. Molecular genetic analysis of the GAA gene (GAAZ / Pompe Disease, Full Gene Analysis, Varies) is necessary for differentiating alterations from disease-causing variants in affected individuals and for carrier detection in family members.

Useful For: Diagnosis of Pompe disease

Interpretation: When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro, confirmatory studies (enzyme assay, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
> or =1.50 nmol/hour/mg protein
An interpretive report is provided.

Clinical References: 1. Elliott S, Buroker N, Cournoyer JJ, et al: Pilot study of newborn screening for six lysosomal storage diseases using tandem mass spectrometry. Mol Genet Metab. 2016 Aug;118(4):304-309. doi: 10.1016/j.ymgme.2016.05.015 2. Matern D, Gavrilov D, Oglesbee D, Raymond K, Rinaldo P, Tortorelli S: Newborn screening for lysosomal storage disorders. Semin Perinatol. 2015 Apr;39(3):206-216. doi: 10.1053/j.semperi.2015.03.005 3. Reuser AJJ, Hirschhorn R, Kroos MA: Pompe disease: Glycogen storage disease type II, acid a-glucosidase (acid maltase) deficiency. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed June 30, 2020. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225890450 4. Lin N, Huang J, Violante S, et al: Liquid chromatography-tandem mass spectrometry assay of leukocyte acid alpha-glucosidase for post-newborn screening evaluation of Pompe disease. Clin Chem. 2017 Apr;63(4):842-851. doi: 10.1373/clinchem.2016.259036 5. Leslie N, Bailey L: Pompe disease. In: Adam MP, Ardinger HH, Pagon RA, et al. GeneReviews [Internet]. University of Washington, Seattle; 2007. Updated May 11, 2017. Accessed March 23, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1261/

ASMW
606264

Acid Sphingomyelinase, Leukocytes

Clinical Information: Niemann-Pick disease (NPD) types A (NPA) and B (NPB) are autosomal recessive lysosomal storage disorders affecting metabolism of specific lipids within cells. NPA and NPB are caused by a deficiency of sphingomyelinase, which results in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. NPA disease is more severe than NPB and is characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness, leading to death by age 3. NPB disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Large lipid-laden foam cells are characteristic of the disease. Approximately 50% of cases have cherry-red spots in the macula. The combined prevalence of NPA and NPB is estimated to be 1 in 250,000. NPA and NPB are inherited in an autosomal recessive manner and are caused by variants in the SMPD1 gene. Although there is a higher frequency of type A among the Ashkenazi Jewish population, both types are panethnic. Individuals with NPD types A and B typically have elevations of lyso-sphingomyelin and lyso-sphingomyelin 509 combined with elevations of the oxysterols cholestane-3 beta, 5 alpha, 6 beta-triol (COT) and 7-ketocholesterol (7-KC). (OXNP /

Oxysterols, Plasma; OXYWB / Oxysterols, Blood; OXYBS / Oxysterols, Blood Spot). Molecular genetic testing for NPA and NPB disease is also available (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specifcy SMPD1 Gene List ID: IEMCP-W6S9XD).

Useful For: Investigation of possible diagnosis of Niemann-Pick disease types A and B This test is not recommended for carrier detection because of the wide range of enzymatic activities observed in carriers and noncarriers.

Interpretation: Values below the reference range are consistent with a diagnosis for Niemann-Pick types A and B. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
> or =0.32 nmol/hour/mg protein
An interpretative report will be provided.

Clinical References:

SAFB
8213

Acid-Fast Smear for Mycobacterium, Varies

Clinical Information: Mycobacterium tuberculosis is a leading infectious disease cause of death worldwide. The Centers for Disease Control and Prevention has reported a rise in the incidence of tuberculosis associated with AIDS, foreign-born cases, and increased transmission in high-risk populations. There has also been a rise in the number of M tuberculosis strains that exhibit resistance to one or more antituberculosis drugs. The public health implications of these facts are considerable. Because M tuberculosis is readily spread by airborne particles, rapid diagnosis and isolation of infected persons is important. Nontuberculous mycobacteria infections also cause significant morbidity and mortality in humans, particularly in immunocompromised persons. Detection of acid-fast bacilli in sputum and other specimens allows rapid identification of individuals who are likely to be infected with mycobacteria while definitive diagnosis and treatment are pursued.

Useful For: Detection of acid-fast bacilli in clinical samples

Interpretation: Patients whose sputum samples are identified as acid-fast positive should be considered potentially infected with Mycobacterium tuberculosis, pending definitive diagnosis by molecular methods or mycobacterial culture.

Reference Values:
Negative (reported as positive or negative)

Clinical References: 1. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: An official ATS/ERS/ESCMID/IDSA clinical practice guideline [published correction appears in Clin Infect Dis. 2020 Dec 31;71(11):3023. doi:10.1093/cid/ciaa1062]. Clin Infect Dis. 2020;71(4):e1-e36. doi:10.1093/cid/ciaa241 2. Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline [published correction appears in Am J Respir Crit Care Med. 2020 Feb 15;201(4):500-501. doi:10.1164/rccm.v201erratum2]. Am J Respir Crit Care Med. 2019;200(10):e93-e142.

doi:10.1164/rccm.201909-1874ST

SMACN 70551 Actin, Smooth Muscle (SMActin) Immunostain, Technical Component Only

Clinical Information: Smooth muscle actin reacts with the alpha-smooth muscle isoform of actin, and labels the smooth muscle cells of vessels, myoepithelial cells, pericytes, some stromal cells in the intestine, testis, and ovary, and tumors derived from smooth muscle cells. The antibody does not react with actin from fibroblasts, striated muscle, and myocardium. This immunostain is a useful tool in the identification of leiomyomas, leiomyosarcomas, and pleomorphic adenomas.

Useful For: Identification of cells expressing the alpha-smooth muscle isoform of actin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Arora G, Girdhar M, Gaghla A, et al. Comparing the expression of myoepithelial cell markers CD10 and smooth muscle actin with the estrogen receptor status in the invasive carcinoma breast: An immunohistochemical study. Clin Cancer Invest J. 2013;2:20-24 2. Nishio J, Iwasaki H, Skashita N, et al. Undifferentiated (embryonal) sarcoma of the liver in middle-aged adults: smooth muscle differentiation determined by immunohistochemistry and electron microscopy. Hum Pathol. 2003;34(3):246-252. 3. Tse GM, Tan PH, Lui PC, et al. The role of immunohistochemistry for smooth-muscle actin, p63, CD10 and cytokeratin 14 in the differential diagnosis of papillary lesions of the breast. J Clin Pathol. 2007;60(3):315-320 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

ACT 8221 Actinomyces Culture, Varies

Clinical Information: Anaerobic Actinomyces are nonsporeforming, thin branching, gram-positive bacilli that are part of the normal microbiota of the human oral cavity and may also colonize the gastrointestinal and female genital tracts. Their presence is important in preserving the usual bacterial populations of the mouth and in preventing infection with disease-causing bacteria. Actinomyces are generally of low pathogenicity but may be an important factor in the development of periodontal disease and may cause soft tissue infections in colonized areas of the body following trauma (surgical or otherwise). The typical lesion consists of an outer zone of granulation around central purulent loculations containing masses of tangled organisms ("sulfur granule"). Chronic burrowing sinus tracts develop. Typical actinomycotic infections occur around the head and neck, in the lung and chest wall, and in the peritoneal cavity and abdominal wall. Actinomycosis of the female genital tract occurs in association with the use of intrauterine contraceptive devices. Purulent collections containing "sulfur granules" may drain from some sinus tracts opening to the skin.

Useful For: Diagnosing anaerobic Actinomyces involved in infections

Interpretation: Isolation of anaerobic Actinomyces in significant numbers from well-collected specimens, including blood, other normally sterile body fluids, or closed collections of purulent fluid, indicates infection with the identified organism.

Reference Values:
No growth
Identification of probable pathogens

Clinical References: 1. Summanen P, Baron EJ, Citron DM, et al. Wadsworth Anaerobic Bacteriology Manual. 6th ed. Star Publishing Co; 2002 2. Butler-Wu SM, She RC. Actinomyces, Lactobacillus, Cutibacterium, and other non-spore-forming anaerobic gram-positive rods. In: Carroll KC, Pfaller MA, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:938-967 3. Hall GS. Anaerobic gram-positive bacilli. In: Leber AL, ed. Clinical Microbiology Procedures Handbook. 4th ed. Vol 1. ASM Press; 2016

APMSC
602182

Activated Partial Thromboplastin Time (APTT) Mix 1:1, Plasma

Clinical Information: The activated partial thromboplastin time (APTT) mixing test is only performed to evaluate a prolonged APTT test result, especially when mixing test results are combined with results of other coagulation tests and clinical information, to assist in differentiating coagulation factor deficiencies from coagulation inhibitors. The APTT measures the integrity of the intrinsic (factors VIII, IX, XI, and XII) and common (factors II, V, X, and I [fibrinogen]) pathway coagulation factors as well as contact factors, prekallikrein (PK) and high-molecular-weight kininogen (HMWK). The APTT assay depends on the phospholipid (a partial thromboplastin), contact activator (eg, silica), and ionic calcium supplied in the reagents. A prolonged APTT may be caused by congenital or acquired coagulation factor deficiencies, anticoagulant effect such as heparin anticoagulation therapy, and inhibition due to lupus anticoagulants as well as other nonspecific coagulation inhibitors (eg, monoclonal immunoglobulins). Although the APTT is commonly used as an initial test for detecting coagulation factor deficiencies, various reagents differ considerably in their sensitivity to deficiencies of coagulation factor proteins. The reagents are generally most sensitive to deficiencies of "contact factors" (XII, PK, and HMWK) and factor XI, less sensitive to deficiencies of factors VIII and IX (the "antihemophilic factors"), and least sensitive to deficiencies of common procoagulant pathway factors (X, V, II, I). The APTT prolongs typically when the activities of factors XI and XII are below the hemostatically adequate level of 40% to 50%. Although factor XII deficiency does not cause bleeding, it is a relatively common cause of APTT prolongation. Nevertheless, an APTT may still be normal when the factor VIII level is as low as 25% to 35%; factor IX as low as 20% to 30%, as seen in some patients with mild hemophilia A or B, respectively a shortened APTT due to increased factor VIII activity secondary to inflammation, pregnancy, or estrogen use, or other conditions may masquerade deficiencies of other factors. The APTT also has divergent sensitivity to nonspecific inhibitors of the intrinsic and common coagulation pathways, such as lupus anticoagulant (LAC) and specific coagulation factor inhibitors. LAC's are antibodies directed towards neoepitopes presented by complexes of phospholipid and proteins, such as prothrombin (factor II) or beta 2 glycoprotein I, instead of coagulation factors. They interfere with the in vitro phospholipid component of APTT assay, and result in a prolonged clotting time. Clinically, lupus anticoagulant represents an important marker of thrombotic tendency. In contrast, patients with specific coagulation inhibitors, such as factor VIII inhibitor antibodies, have a significant risk of hemorrhage and often require specific treatment for effective management.

Useful For: Screening for certain coagulation factor deficiencies and abnormalities (eg, factor VIII, IX, XI, or XII). Detection of coagulation inhibitors such as lupus anticoagulant, antiphospholipid antibodies, specific factor inhibitors, and nonspecific inhibitors

Interpretation: Prolongation of the activated partial thromboplastin time (APTT) can occur as a result of deficiency of 1 or more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a "nonspecific" inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. The APTT mixing study, using

equal volumes of patient and normal pool plasma, may be performed on specimens with a prolonged APTT to assist in differentiating coagulation factor deficiencies from coagulation inhibitors of all types. Correction of the APTT mix to within the normal reference range usually indicates a coagulation factor deficiency (normal plasma in the mixture ensures at least 50% activity of all coagulation factors). If the prolonged APTT is due to an inhibitor (eg, specific coagulation factor inhibitor, lupus anticoagulant, heparin), the APTT mix typically fails to correct a prolonged APTT. However, the presence of a weak inhibitor may be missed by the APTT mixing study. Accurate interpretation of both APTT and APTT mixing study results may often require additional testing. For example, the thrombin time test is helpful for identifying or excluding the presence of heparin, the platelet neutralization procedure (using a modified APTT method) for identifying or excluding lupus anticoagulant, the prothrombin time and dilute Russell's viper venom time for further assessment of the common procoagulant pathway, and coagulation factor assays to detect and identify deficient or abnormal factors. These assays are available as components of reflexive and interpretive testing panels in the Special Coagulation Laboratory (eg, APROL / Prolonged Clot Time Profile, Plasma). Shortening of the APTT usually reflects either elevation of factor VIII activity secondary to acute or chronic illness or inflammation, or spurious results from suboptimal venipuncture, specimen collection or processing. A normal or shortened APTT result does not exclude a hemostatic defect; and specific clotting factor assays should be performed despite a normal APTT when there is clinical impression of bleeding diathesis.

Reference Values:

Only orderable as a reflex. For more information see:
ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
AATHR / Thrombophilia Profile, Plasma and Whole Blood
APROL / Prolonged Clot Time Profile, Plasma
ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

25-37 seconds

Clinical References: Favaloro EJ, Lippi G. eds. Hemostasis and Thrombosis: Methods and Protocols. 1st ed. Humana Press; 2017

APTSC
602172

Activated Partial Thromboplastin Time (APTT), Plasma

Clinical Information: The activated partial thromboplastin time (APTT) measures the integrity of the intrinsic (factors VIII, IX, XI, and XII) and common (factors II, V, X, and I [fibrinogen]) pathway coagulation factors as well as contact factors, prekallikrein (PK) and high-molecular-weight kininogen (HMWK). The APTT assay depends on the phospholipid (a partial thromboplastin), contact activator (eg, silica), and ionic calcium supplied in the reagents. A prolonged APTT may be caused by congenital or acquired coagulation factor deficiencies, anticoagulant effect such as heparin anticoagulation therapy, and inhibition due to lupus anticoagulants as well as other nonspecific coagulation inhibitors (eg, monoclonal immunoglobulins). Although the APTT is commonly used as an initial test for detecting coagulation factor deficiencies, various reagents differ considerably in their sensitivity to deficiencies of coagulation factor proteins. The reagents are generally most sensitive to deficiencies of "contact factors" (XII, PK, and HMWK) and factor XI, less sensitive to deficiencies of factors VIII and IX (the "antihemophilic factors"), and least sensitive to deficiencies of common procoagulant pathway factors (X, V, II, I). The APTT prolongs typically when the activities of factors XI and XII are below the hemostatically adequate level of 40% to 50%. Although factor XII deficiency does not cause bleeding, it is a relatively common cause of APTT prolongation. Nevertheless, an APTT may still be normal when the factor VIII level is as low as 25% to 35%; factor IX as low as 20% to 30%, as seen in some patients with mild hemophilia A or B, respectively a shortened APTT due to increased factor VIII activity secondary to inflammation, pregnancy, or estrogen use, or other conditions may masquerade deficiencies of other factors. The APTT

also has divergent sensitivity to nonspecific inhibitors of the intrinsic and common coagulation pathways, such as lupus anticoagulant (LAC) and specific coagulation factor inhibitors. LAC's are antibodies directed towards neoepitopes presented by complexes of phospholipid and proteins, such as prothrombin (factor II) or beta 2 glycoprotein I, instead of coagulation factors. They interfere with the in vitro phospholipid component of APTT assay, and result in a prolonged clotting time. Clinically, lupus anticoagulant represents an important marker of thrombotic tendency. In contrast, patients with specific coagulation inhibitors, such as factor VIII inhibitor antibodies, have a significant risk of hemorrhage and often require specific treatment for effective management.

Useful For: Screening for certain coagulation factor deficiencies and abnormalities (eg, factor VIII, IX, XI, or XII) Detecting coagulation inhibitors such as lupus anticoagulant, antiphospholipid antibodies, specific factor inhibitors, and nonspecific inhibitors Evaluating a prolonged activated partial thromboplastin time (APTT) test result to assist in differentiating coagulation factor deficiencies from coagulation inhibitors, especially when the APTT mixing test results are combined with results of other coagulation tests and clinical information Monitoring heparin (unfractionated) therapy

Interpretation: Prolongation of the activated partial thromboplastin time (APTT) can occur as a result of deficiency of 1 or more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a "nonspecific" inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. The APTT mixing study, which uses equal volumes of patient and normal pool plasma, may be performed on specimens with a prolonged APTT to assist in differentiating coagulation factor deficiencies from coagulation inhibitors of all types. Correction of the APTT mix to within the normal reference range usually indicates a coagulation factor deficiency (normal plasma in the mixture ensures at least 50% activity of all coagulation factors). If the prolonged APTT is due to an inhibitor (eg, specific coagulation factor inhibitor, lupus anticoagulant, heparin), the APTT mix typically fails to correct a prolonged APTT. However, the presence of a weak inhibitor may be missed by the APTT mixing study. Accurate interpretation of both APTT and APTT mixing study results may often require additional testing. For example, the thrombin time test is helpful for identifying or excluding the presence of heparin, the platelet neutralization procedure (using a modified APTT method) for identifying or excluding lupus anticoagulant, the prothrombin time and dilute Russell's viper venom time for further assessment of the common procoagulant pathway, and coagulation factor assays to detect and identify deficient or abnormal factors. These assays are available as components of reflexive and interpretive testing panels in the Special Coagulation Laboratory (eg, APROL / Prolonged Clot Time Profile, Plasma). The APTT test is frequently used to monitor therapy with unfractionated heparin (UFH). Since APTT reagents can vary greatly in their sensitivity to UFH, it is important to establish a relationship between APTT response and heparin concentration.(1) The therapeutic APTT range in seconds should correspond with a UFH concentration of 0.3 to 0.7 U/mL as assessed by a heparin assay (inhibition of factor Xa activity with detection by a chromogenic substrate [1]). We have established the therapeutic APTT range to be approximately 70 to 120 seconds. Shortening of the APTT usually reflects either elevation of factor VIII activity secondary to acute or chronic illness or inflammation, or spurious results from suboptimal venipuncture, specimen collection or processing. A normal or shortened APTT result does not exclude a hemostatic defect; and specific clotting factor assays should be performed despite a normal APTT when there is clinical impression of bleeding diathesis.

Reference Values:

Clinical References: Favaloro EJ, Lippi G. eds. Hemostasis and Thrombosis: Methods and Protocols. 1st ed. Humana Press; 2017

APTTP 40935 Activated Partial Thromboplastin Time, Plasma

Clinical Information: The activated partial thromboplastin time (APTT) assay is used as a screening test to evaluate the overall integrity of the intrinsic/common coagulation pathway and to monitor patients on heparin therapy. This test reflects the activities of most of the coagulation factors in the intrinsic and common procoagulant pathway, but not the extrinsic procoagulant pathway, which includes factor VII and tissue factor, nor the activity of factor XIII (fibrin stabilizing factor).

Useful For: Monitoring heparin therapy (unfractionated heparin) Screening for certain coagulation factor deficiencies Detection of coagulation inhibitors such as lupus anticoagulant, specific factor inhibitors, and nonspecific inhibitors

Interpretation: Prolongation of the activated partial thromboplastin time (APTT) can occur as a result of deficiency of one or more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a nonspecific inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. Prolonged clotting times may also be observed in cases of fibrinogen deficiency, liver disease, and vitamin K deficiency. Shortening of the APTT usually reflects either elevation of factor VIII activity in vivo that most often occurs in association with acute or chronic illness or inflammation, or spurious results associated with either difficult venipuncture and specimen collection or suboptimal specimen processing.

Reference Values:
25-37 seconds

Clinical References: 1. Clinical and Laboratory Standards Institute (CLSI). One-stage PT and APTT test; Approved Guideline Second Edition. H47-A2, 2008 2. Greaves M, Preston FE: Approach to the bleeding patient. In Hemostasis and Thrombosis: Basic Principles and Clinical Practice. Fourth edition. Edited by RW Colman, J Hirsh, VJ Marder, et al. Philadelphia, JB Lippincott Co, 2001, pp 1197-1234 3. Boender J, Kruip MJ, Leebeek FW: A Diagnostic Approach to Mild Bleeding Disorders. J Thromb Haemost 2016;Aug;14(8):1507-1516. doi: 10.1111/jth.13368

APCRV
81967

Activated Protein C Resistance V (APCRV), Plasma

Clinical Information: Protein C, a part of the natural anticoagulant system, is a vitamin K-dependent protein zymogen (molecular weight=62,000 da) that is synthesized in the liver and circulates at a plasma concentration of approximately 5 mcg/mL. Protein C is activated to activated protein C (APC) via proteolytic cleavage by thrombin bound to thrombomodulin, an endothelial cell surface membrane protein. APC downregulates the procoagulant system by proteolytically inactivating procoagulant factors Va and VIIIa. Protein S, another vitamin K-dependent coagulation protein, catalyzes APC inactivation of factors Va and VIIIa. APC interacts with and proteolyses factors V/Va and VIII/VIIIa at specific APC binding and cleavage sites, respectively. Resistance to activated protein C (APC resistance) is a term used to describe abnormal resistance of human plasma to the anticoagulant effects of human APC. APC resistance is characterized by a reduced anticoagulant response of patient plasma after adding a standard amount of APC. For this assay, the activated partial thromboplastin time clotting test fails to prolong significantly after the addition of APC. The vast majority of individuals with familial APC resistance have a specific point mutation in the procoagulant factor V gene (1691G-A, factor V Leiden) encoding for a glutamine (Q) substitution for arginine (R)-506 in the heavy chain of factor V (factor V R506Q). This amino acid change alters an APC cleavage site on factor V such that factor V/Va is partially resistant to inactivation by APC. The carrier frequency for the factor V Leiden mutation varies depending on the population. Approximately 5% of asymptomatic white Americans of non-Hispanic ancestry are heterozygous carriers, while the carrier frequency among African Americans, Asian Americans, and Native Americans is less than 1%, and the carrier frequency for Hispanics is intermediate (2.5%). The carrier frequency can be especially high (up to 14%) among whites of Northern European or Scandinavian ancestry. Homozygosity for factor V Leiden is much less common but may confer a substantially

increased risk for thrombosis. The degree of abnormality of the APC-resistance assay correlates with heterozygosity or homozygosity for the factor V Leiden mutation; homozygous carriers have a very low APC-resistance ratio (eg, 1.1-1.4), while the ratio for heterozygous carriers is usually 1.5 to 1.8.

Useful For: Evaluation of patients with incident or recurrent venous thromboembolism (VTE)
Evaluation of individuals with a family history of VTE

Interpretation: An activated protein C (APC) resistance ratio of less than 2.3 suggests abnormal resistance to APC of hereditary origin. If the APC resistance test is abnormal, DNA-based testing for the factor V Leiden mutation (F5DNA / Factor V Leiden [R506Q] Mutation, Blood) may be helpful in confirming or excluding hereditary APC resistance.

Reference Values:
APCRV RATIO
> or =2.3
Pediatric reference range has neither been established nor is available in scientific literature. The adult reference range likely would be applicable to children older than 6 months.

Clinical References: 1. Nichols WL, Heit JA. Activated protein C resistance and thrombosis. Mayo Clin Proc. 1996;71(9):897-898 2. Dahlback B. Resistance to activated protein C as risk factor for thrombosis: molecular mechanisms, laboratory investigation, and clinical management. Semin Hematol. 1997;34(3):217-234 3. Rodeghiero F, Tosetto A. Activated protein C resistance and Factor V Leiden mutation are independent risk factors for venous thromboembolism. Ann Intern Med. 1999;130(8):643-650 4. Grody WW, Griffin JH, Taylor AK, Korf BR, Heit JA; ACMG Factor V. Leiden Working Group. American College of Medical Genetics consensus statement on factor V Leiden mutation testing. Genet Med. 2001;3(2):139-148 5. Press RD, Bauer KA, Kujovich JL, Heit JA. Clinical utility of factor V Leiden (R506Q) testing for the diagnosis and management of thromboembolic disorders. Arch Pathol Lab Med. 2002;126(11):1304-1318 6. Favaloro EJ and Lippi G. eds. Hemostasis and Thrombosis: Methods and Protocols. 1st ed. Humana Press; 2017

APCRR
60547

Activated Protein C Resistance V, with Reflex to Factor V Leiden, Blood and Plasma

Clinical Information: Protein C, a part of the natural anticoagulant system, is a vitamin K-dependent protein zymogen (molecular weight = 62,000 Da) that is synthesized in the liver and circulates at a plasma concentration of approximately 5 mcg/mL. Protein C is activated to activated protein C (APC) via proteolytic cleavage by thrombin bound to thrombomodulin, an endothelial cell surface membrane protein. APC downregulates the procoagulant system by proteolytically inactivating procoagulant factors Va and VIIIa. Protein S, another vitamin K-dependent coagulation protein, catalyzes APC inactivation of factors Va and VIIIa. APC interacts with and proteolyzes factors V/Va and VIII/VIIIa at specific APC binding and cleavage sites, respectively. Resistance to activated protein C (APC resistance) is a term used to describe abnormal resistance of human plasma to the anticoagulant effects of human APC. APC resistance is characterized by a reduced anticoagulant response of patient plasma after adding a standard amount of APC. For this assay, the activated partial thromboplastin time fails to prolong significantly after the addition of APC. The vast majority of individuals with familial APC resistance have a specific alteration in the procoagulant factor V gene (F5) encoding for a p.Arg534Gln substitution in the heavy chain of factor V (formerly R506Q). This glutamine to arginine amino acid change alters an APC cleavage site on factor V such that factor V/Va is partially resistant to inactivation by APC. The carrier frequency for the factor V Leiden variant varies depending on the population. Approximately 5% of asymptomatic White Americans of non-Hispanic ancestry are heterozygous carriers. In contrast, the carrier frequency among African Americans, Asian Americans, and Native Americans is less than 1%, and the carrier frequency for Hispanics is intermediate (2.5%).

The carrier frequency can be especially high (up to 14%) among White individuals of Northern European or Scandinavian ancestry. Homozygosity for factor V Leiden is much less common but may confer a substantially increased risk for thrombosis. The degree of abnormality of the APC-resistance assay correlates with heterozygosity or homozygosity for the factor V Leiden variant; homozygous carriers have a very low APC-resistance ratio (eg, 1.1-1.4), while the ratio for heterozygous carriers is usually 1.5 to 1.8.

Useful For: Evaluating patients with incident or recurrent venous thromboembolism (VTE) Evaluating individuals with a family history of VTE

Interpretation: An activated protein C (APC) resistance ratio below 2.3 suggests abnormal resistance to APC of hereditary origin. If the screening APC resistance test is abnormal, DNA-based testing for the factor V Leiden variant (p.Arg534Gln, formerly R506Q) is performed to confirm or exclude hereditary APC-resistance.

Reference Values:
ACTIVATED PROTEIN C RESISTANCE V RATIO
> or =2.3
Pediatric reference range has neither been established nor is available in scientific literature. The adult reference range likely would be applicable to children older than 6 months.

Clinical References: 1. Nichols WL, Heit JA. Activated protein C resistance and thrombosis. Mayo Clin Proc. 1996;71(9):897-898 2. Dahlback B. Resistance to activated protein C as risk factor for thrombosis: molecular mechanisms, laboratory investigation, and clinical management. Semin Hematol. 1997;34(3):217-234 3. Rodeghiero F, Tosetto A. Activated protein C resistance and factor V Leiden mutation are independent risk factors for venous thromboembolism. Ann Intern Med. 1999;130(8):643-650. doi:10.7326/0003-4819-130-8-199904200-00004 4. Grody WW, Griffin JH, Taylor AK, Korf BR, Heit JA; ACMG Factor V. Leiden Working Group. American College of Medical Genetics consensus statement on factor V Leiden mutation testing [published correction appears in Genet Med. 2021 Dec;23(12):2463]. Genet Med. 2001;3(2):139-148. doi:10.1097/00125817-200103000-00009 5. Press RD, Bauer KA, Kujovich JL, Heit JA. Clinical utility of factor V Leiden (R506Q) testing for the diagnosis and management of thromboembolic disorders. Arch Pathol Lab Med. 2002;126(11):1304-1318. doi:10.5858/2002-126-1304-CUOFVL 6. Yohe S, Olson J: Thrombophilia: Assays and interpretation. In: Kottke-Marchant K, Davis B, eds. Laboratory Hematology Practice. Blackwell Publishing; 2012:492-508

COGMF 113528 Acute Myeloid Leukemia (AML), Children's Oncology Group Enrollment Testing, FISH, Varies

Clinical Information: Acute myeloid leukemia (AML) is one of the most common adult leukemias, with almost 10,000 new cases diagnosed per year. AML also comprises 15% of pediatric acute leukemia and accounts for the majority of infant (<1 year old) leukemia. Several recurrent chromosomal abnormalities have been identified in AML. The most common chromosome abnormalities associated with AML include t(8;21), t(15;17), inv(16), and abnormalities of the MLL (KMT2A) gene at 11q23. The most common genes juxtaposed with MLL through translocation events in AML include MLTT4(AFDN)- t(6;11), MLLT3- t(9;11), MLLT10- t(10;11), and ELL- t(11;19p13.1). AML can also evolve from myelodysplasia (MDS). Thus, the common chromosome abnormalities associated with MDS can also be identified in AML, which include: inv(3), -5/5q-, -7/7q-, and 17p. Overall, the recurrent chromosome abnormalities identified in patients with AML are observed in approximately 60% of diagnostic AML cases. Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities in AML. However, some of the subtle rearrangements can be missed by karyotype, including inv(16) and MLL rearrangements. Fluorescence in situ hybridization

(FISH) analysis of nonproliferating (interphase) cells can be used to detect the common chromosome abnormalities observed in patients with AML. The abnormalities have diagnostic and prognostic relevance, and FISH testing can also be used to track response to therapy. Metaphase FISH confirmation of classic translocations that are cryptic and not visually detectable by chromosome analysis [ie, t(6;11) associated with KMT2A/MLLT4(AFDN) fusion] is performed as required by Children's Oncology Group (COG) and is included as part of the electronic case submission by the Mayo Clinic Genomics Laboratory to COG for central review. Additional cytogenetic techniques such as chromosomal microarray (CMAH / Chromosomal Microarray, Hematologic Disorders, Varies) may be helpful to resolve questions related to ploidy (hyperdiploid clone vs doubled hypodiploid clone).

Useful For: Evaluation of pediatric bone marrow and peripheral blood specimens by fluorescence in situ hybridization (FISH) probe analysis for classic rearrangements and chromosomal copy number changes associated with acute myeloid leukemia (AML) in patients being considered for enrolment in Children's Oncology Group (COG) clinical trials and research protocols As an adjunct to conventional chromosome studies in performed in pediatric patients with AML being considered for enrollment in COG protocols

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Grimwade D, Hills RK, Moorman AV, et al: Refinement of cytogenetics classification in acute myeloid leukemia: determination of prognostic significance or rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Research Council trials. Blood. 2010 Jul 22;116(3):354-365 2. Swerdlow SH, Campo E, Harris NL, et al. eds: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press; 2017 3. Dohner H, Estey E, Grimwade D, et al: Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017 Jan 26;129(4):424-447. doi: 10.1182/blood-2016-08-733196

AMLAF 609517 Acute Myeloid Leukemia (AML), FISH, Adult, Varies

Clinical Information: Acute myeloid leukemia (AML) is one of the most common adult leukemias, with almost 10,000 new cases diagnosed per year. AML also comprises 15% of pediatric acute leukemia and accounts for the majority of infant (<1 year old) leukemia. Several recurrent chromosomal abnormalities have been identified in AML with associated clinical significance. The most common chromosome abnormalities associated with AML include t(8;21), t(15;17), inv(16) or t(16;16), and abnormalities of the MLL (KMT2A) gene at 11q23. The most common genes juxtaposed with MLL through translocation events in AML include MLLT3- t(9;11), MLLT4- t(6;11), MLLT10- t(10;11), and ELL- t(11;19p13.1). Other recurrent chromosome abnormalities associated with AML include inv(3) or t(3;3), t(6;9) and t(9;22). In addition, AML can also evolve from myelodysplasia (MDS). Thus, the common chromosome abnormalities associated with MDS can also be identified in AML, which include: -5/5q-, -7/7q-, and 17p-. Overall, the recurrent chromosome abnormalities identified in patients with AML are observed in approximately 60% of diagnostic AML cases. Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities in AML. However, some of the subtle rearrangements can be missed by karyotype, including inv(16) or t(16;16) and MLL rearrangements. Fluorescence in situ hybridization analysis of nonproliferating (interphase) cells can be used to detect the common diagnostic and prognostic chromosome abnormalities observed in patients with AML.

Useful For: This test should not be used to screen for residual acute myeloid leukemia (AML). Useful at diagnosis for detecting recurrent common chromosome abnormalities in adult patients with AML An adjunct to chromosome studies in patients with AML Evaluating specimens in which chromosome studies are unsuccessful

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. The absence of an abnormal clone does not rule out the presence of an acute myeloid leukemia clone or another neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumour of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017 2. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447. doi:10.1182/blood-2016-08-733196 3. Pollyea DA, Bixby D, Perl A, et al. Acute Myeloid Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(1):17-27. doi:10.6004/jnccn.2021.0002

JAMLM
620194

Acute Myeloid Leukemia (AML), FISH, Bone Marrow

Clinical Information: Acute myeloid leukemia (AML) has been defined by genetic abnormalities and differentiation in the 5th edition of World Health Organization classification of hematolymphoid tumors.(1) The subtypes of AML defined by genetic abnormalities include: Acute promyelocytic leukemia with PML::RARA fusion AML with RUNX1::RUNXT1 fusion AML with CBFB::MYH11 fusion AML with DEK::NUP214 fusion AML with RBM15::MRTFA fusion AML with BCR::ABL1 fusion AML with KMT2A rearrangement AML with MECOM rearrangement AML with NUP98 rearrangement AML with NPM1 mutation AML with CEBPA mutation AML myelodysplasia-related AML with other defined genetic alterations Fluorescence in situ hybridization (FISH) testing detects specific gene fusions associated with AML. Fluorescence in situ hybridization testing will not detect gene variants associated with AML. RBM15::MRTFA fusion and NUP98 rearrangement will not be detected in this FISH test. These two abnormalities are rare and can be detected by next-generation sequencing. FISH testing for these two abnormalities may be added to this test at later date.

Useful For: Diagnosing and classifying acute myeloid leukemia using bone marrow specimens Providing guidance for clinical management of patients Confirming a gene fusion detected by next-generation sequencing Tracking response to therapy

Interpretation: Detection of a specific fusion or a rearrangement confirms a clinical diagnosis of acute myeloid leukemia (AML) and defines an AML classification. Absence of a specific gene fusion or rearrangement will not rule out presence of AML.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Khoury JD, Solary E, Abla O et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-1719. doi:10.1038/s41375-022-01613-1 2. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447

AMLPF
609527

Acute Myeloid Leukemia (AML), FISH, Pediatric, Varies

Clinical Information: Acute myeloid leukemia (AML) is one of the most common adult leukemias, with almost 10,000 new cases diagnosed per year. AML also comprises 15% of pediatric acute leukemia and accounts for the majority of infant (<1 year old) leukemia. Several recurrent chromosomal abnormalities have been identified in AML with associated clinical significance. The most common chromosome abnormalities associated with AML include t(8;21), t(15;17), inv(16) or t(16;16), and abnormalities of the MLL (KMT2A) gene at 11q23. The most common genes juxtaposed with MLL through translocation events in AML include MLTT4(MLLT4)- t(6;11), MLLT3- t(9;11), MLLT10- t(10;11), and ELL- t(11;19p13.1). AML can also evolve from myelodysplasia (MDS). Thus, the common chromosome abnormalities associated with MDS can also be identified in AML, which include: inv(3) or t(3;3), -5/5q-, -7/7q-. Overall, the recurrent chromosome abnormalities identified in patients with AML are observed in approximately 60% of diagnostic AML cases. Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities in AML. However, some of the subtle rearrangements can be missed by karyotype, including inv(16) or t(16;16) and MLL rearrangements. Fluorescence in situ hybridization analysis of nonproliferating (interphase) cells can be used to detect the common diagnostic and prognostic chromosome abnormalities observed in patients with AML.

Useful For: This test should not be used to screen for residual acute myeloid leukemia (AML). Useful at diagnosis for detecting recurrent common chromosome abnormalities in pediatric patients with AML An adjunct to chromosome studies in patients with AML Evaluating specimens in which chromosome studies are unsuccessful

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. The absence of an abnormal clone does not rule out the presence of an acute myeloid leukemia clone or another neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetics classification in acute myeloid leukemia: determination of prognostic significance or rare recurring chromosomal abnormalities among 5879 younger adult patients treated in the United Kingdom Research Council trials. Blood. 2010;116(3):354-365 2. Swerdlow SH, Campo E, Harris NL, et al. eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017 3. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447. doi:10.1182/blood-2016-08-733196 4. Pollyea DA, Bixby D, Perl A, et al. Acute Myeloid Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(1):17-27. doi:10.6004/jnccn.2021.0002

AMLMF
614202

Acute Myeloid Leukemia (AML), Specified FISH, Varies

Clinical Information: Acute myeloid leukemia (AML) is one of the most common adult leukemias, with almost 10,000 new cases diagnosed per year. AML also comprises 15% of pediatric acute leukemia and accounts for the majority of infant (<1 year old) leukemia. Several recurrent chromosomal abnormalities have been identified in AML with associated clinical significance. The most common chromosome abnormalities associated with AML include t(8;21), t(15;17), inv(16) or t(16;16), and abnormalities of the MLL (KMT2A) gene at 11q23. The most common genes juxtaposed with MLL through translocation events in AML include MLLT3- t(9;11), MLLT4- t(6;11), MLLT10- t(10;11), and ELL- t(11;19p13.1). Other recurrent chromosome abnormalities associated with AML include inv(3) or

t(3;3), t(6;9) and t(9;22). In addition, AML can also evolve from myelodysplasia (MDS). Thus, the common chromosome abnormalities associated with MDS can also be identified in AML, which include: inv(3) or t(3;3), -5/5q-, -7/7q-, and 17p. Overall, the recurrent chromosome abnormalities identified in patients with AML are observed in approximately 60% of diagnostic AML cases. Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities in AML. However, some of the subtle rearrangements can be missed by karyotype, including inv(16) or t(16;16) and MLL rearrangements. Fluorescence in situ hybridization analysis of nonproliferating (interphase) cells can be used to detect the common diagnostic and prognostic chromosome abnormalities observed in patients with AML.

Useful For: Detecting recurrent common chromosome abnormalities seen in patients with acute myeloid leukemia (AML) using a client-specified probe set An adjunct to chromosome studies in patients with AML Evaluating specimens in which chromosome studies are unsuccessful

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. The absence of an abnormal clone does not rule out the presence of an acute myeloid leukemia clone or another neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetics classification in acute myeloid leukemia: determination of prognostic significance or rare recurring chromosomal abnormalities among 5879 younger adult patients treated in the United Kingdom Research Council trials. Blood. 2010;116(3):354-365 2. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumour of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017 3. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447. doi:10.1182/blood-2016-08-733196 4. Pollyea DA, Bixby D, Perl A, et al. Acute Myeloid Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(1):17-27. doi: 10.6004/jnccn.2021.0002

APGP
608015

Acute Porphyria Gene Panel, Varies

Clinical Information: Acute porphyria is caused by variants in 1 of 4 genes: -HMBS is associated with acute intermittent porphyria (AIP) -CPOX is associated with hereditary coproporphyria (HCP) -PPOX is associated with variegate porphyria (VP) -ALAD is associated with aminolevulinic acid dehydratase deficiency porphyria Variants in these genes show incomplete penetrance, and patients with a confirmed deleterious variant may be asymptomatic. Clinical manifestations of acute porphyria include attacks of neurologic dysfunction, commonly characterized as abdominal pain. However, these acute attacks are variable and can include vomiting, diarrhea, constipation, urinary retention, acute episodes of neuropathic symptoms, psychiatric symptoms, seizures, respiratory paralysis, tachycardia, and hypertension. Respiratory paralysis can progress to coma and death. HCP and VP are also associated with cutaneous manifestations, including edema, sun-induced erythema, acute painful photodermatitis, and urticaria. In some cases, patients present with isolated photosensitivity. Acute attacks may be prevented by avoiding both endogenous and exogenous triggers. These triggers include porphyrogenic drugs, hormonal contraceptives, fasting, alcohol, tobacco, and cannabis. Fecal porphyrins and quantitative urinary porphyrins analyses are helpful in establishing a diagnosis of acute porphyria.

Useful For: Establishing a molecular diagnosis for patients with acute porphyria Identifying variants within genes known to be associated with acute porphyria, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Siegesmund M, van Tuyll van Serooskerken AM, Poblete-Gutierrez P, Frank J. The acute hepatic porphyrias: current status and future challenges. Best Pract Res Clin Gastroenterol. 2010;24(5):593-605 3. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment of the acute porphyrias. Ann Intern Med. 2005;142(6):439-450

AHEP
56105

Acute Viral Hepatitis Profile, Serum

Clinical Information: Hepatitis A: Hepatitis A virus (HAV) is an RNA virus that accounts for 20% to 25% of acute viral hepatitis in adults in the United States. Hepatitis A is spread by the oral/fecal route and produces acute hepatitis, which follows a benign, self-limited course. Spread of the disease is usually associated with contaminated food or water caused by poor sanitary conditions. Outbreaks frequently occur in overcrowded situations and institutions or high-density centers such as prisons and healthcare centers. Epidemics may occur following floods or other disaster situations. Chronic carriers of HAV have never been observed. Hepatitis B: Hepatitis B virus (HBV) is an endemic DNA virus throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles among injection drug users). The virus is also found in virtually every human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some chronic carriers are asymptomatic; others develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus that is a significant cause of morbidity and mortality worldwide. The infection is transmitted through contaminated blood or blood products or other close, personal contacts. It is recognized as the cause of most cases of posttransfusion hepatitis. Hepatitis C shows a high rate of progression (~75%) to chronic infection and disease and accounts for the majority of chronic viral hepatitis In the United States. Cirrhosis and hepatocellular carcinoma are sequelae of chronic infection with this virus.

Useful For: Differential diagnosis of recent acute viral hepatitis

Interpretation: Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles Hepatitis A Virus (HAV): HAV-specific antibodies are usually detectable by the onset of symptoms (usually 15 to 45 days after exposure). The initial antibody consists almost entirely of IgM subclass antibody. Anti-HAV IgM usually falls to undetectable levels 3 to 6 months after infection. Hepatitis B Virus (HBV): HBsAg is the first serologic marker appearing in the serum 6 to 8 weeks following HBV infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Anti-HBs appears with the resolution of HBV infection after the disappearance of HBsAg. Anti-HBs also appear as the immune response following a course of inoculation with the hepatitis B vaccine. During acute hepatitis B in symptomatic individuals, detectable anti-HBc consists almost entirely of the IgM subclass. Anti-HBc IgM can be detected shortly after the onset of symptoms and usually remains detectable for 6 months. Anti-HBc IgM and Anti-HBc total may be the only serologic markers of a recent HBV infection detectable in the "window period", during which HBsAg has declined to become

undetectable and anti-HBs has not yet become detectable. Hepatitis C Virus (HCV): In immunocompetent individuals, HCV-specific IgG and IgM antibodies are usually not detectable in the first 2 months after exposure to HCV, and this "window period: may be as long as 6 months in immunocompromised individuals. HCV antibodies are not neutralizing and does not provide immunity against subsequent HCV infection. If HBsAg, anti-HAV IgM, and anti-HCV are negative and patient's condition warrants, consider testing for Epstein-Barr virus or cytomegalovirus. The following algorithms are available: -Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management -Hepatitis C: Testing Algorithm for Screening and Diagnosis

Reference Values:

HEPATITIS B SURFACE ANTIGEN
Negative

HEPATITIS B SURFACE ANTIGEN CONFIRMATION
Negative

HEPATITIS B CORE IgM ANTIBODY
Negative

HEPATITIS A IgM ANTIBODY
Negative

HEPATITIS C ANTIBODY
Negative

HEPATITIS C VIRUS RNA DETECTION AND QUANTIFICATION BY REAL-TIME RT-PCR
Undetected

Clinical References: 1. LeFevre ML, et al. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 2. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis (Hoboken). 2018;12(1):5-11. doi:10.1002/cld.729 3. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019;156(2):355-368.e3. doi:10.1053/j.gastro.2018.11.037 4. World Health Organization. Guidelines on hepatitis B and C testing. World Health Organization; 2017. Accessed October 8, 2024. Available at www.who.int/hepatitis/publications/i/item/9789241549981 5. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. Published 2023 Mar 10. doi:10.15585/mmwr.rr7201a1

FACYS
75396

Acyclovir, Plasma

Reference Values:

Reporting limit determined each analysis.

For using Acyclovir:
Usual therapeutic range (vs. Genital Herpes) during chronic oral daily divided dosages of 1200 - 2400 mg:
Peak: 0.40 - 2.0 mcg/mL plasma
Trough: 0.14 - 1.2 mcg/mL plasma

For using Valacyclovir as a metabolite:

Mean steady-state (+/- 1 SD) peak plasma levels following a 500 mg twice daily regimen of Valacyclovir:
2.0-4.0 mcg Acyclovir/mL

ACRN
82413

Acylcarnitines, Quantitative, Plasma

Clinical Information: Acylcarnitine analysis enables the diagnosis of many disorders of fatty acid oxidation and several organic acidurias, as relevant enzyme deficiencies cause the accumulation of specific acyl-CoAs.(1) Fatty acid oxidation (FAO) plays a major role in energy production during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue, taken up by the liver and muscles, and oxidized to acetyl-CoA. In the liver, acetyl-CoA is the building block for the synthesis of ketone bodies, which enter the blood stream and provide an alternative substrate for production of energy in other tissues when the supply of glucose is insufficient to maintain a normal level of energy. The acyl groups are conjugated with carnitine to form acylcarnitines, which can be measured by tandem mass spectrometry. Diagnostic results are usually characterized by a pattern of significantly elevated acylcarnitine species compared to normal and disease controls. In general, more than 20 inborn errors of metabolism can be identified using this method, including FAO disorders and organic acidurias. The major clinical manifestations associated with individual FAO disorders include hypoketotic hypoglycemia, variable degrees of liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden or unexpected death. Organic acidurias also present as acute life-threatening events early in life with metabolic acidosis, increased anion gap, and neurologic distress. Patients with any of these disorders are at risk of developing fatal metabolic decompensations following the acquisition of even common infections. Once diagnosed, these disorders can be treated by avoidance of fasting, special diets, and cofactor and vitamin supplementation. Additional confirmatory testing is recommended. The diagnosis of an underlying FAO disorder or organic aciduria allows genetic counseling of the family, including the possible option of future prenatal diagnosis, and testing of at-risk family members of any age. The following disorders are detectable by acylcarnitine analysis. However, further confirmatory testing is required for most of these conditions because an acylcarnitine profile can be suggestive of more than one condition. Fatty Acid Oxidation Disorders: -Carnitine palmitoyltransferase I deficiency -Medium-chain 3-ketoacyl-CoA thiolase deficiency -Dienoyl-CoA reductase deficiency -Short-chain acyl-CoA dehydrogenase deficiency -Medium/Short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency -Medium-chain acyl-CoA dehydrogenase deficiency -Long-chain 3-hydroxyacyl-CoA dehydrogenase) deficiency and trifunctional protein deficiency -Very long-chain acyl-CoA dehydrogenase deficiency -Carnitine palmitoyl transferase type II deficiency -Carnitine-acylcarnitine translocase deficiency -Electron transfer flavoprotein (ETF) deficiency, ETF-dehydrogenase deficiency (multiple acyl-CoA dehydrogenase deficiency; glutaric acidemia type II) Organic Acid Disorders: -Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia type I) -Propionic acidemia -Methylmalonic acidemia -Isovaleric acidemia -3-Hydroxy-3-methylglutaryl-CoA carboxylase deficiency -3-Methylcrotonyl carboxylase deficiency -Biotinidase deficiency -Multiple carboxylase deficiency -Isobutyryl-CoA dehydrogenase deficiency -2-Methylbutyryl-CoA dehydrogenase deficiency -Beta-ketothiolase deficiency -Malonic aciduria -Ethylmalonic encephalopathy -Glutamate formiminotransferase deficiency (formiminoglutamic aciduria)

Useful For: Diagnosis of fatty acid oxidation disorders and several organic acidurias using plasma specimens Evaluating treatment during follow-up of patients with fatty acid beta-oxidation disorders and several organic acidurias

Interpretation: An interpretive report is provided. The individual quantitative results support the interpretation of the acylcarnitine profile but are not diagnostic by themselves. The interpretation is based on pattern recognition. Abnormal results are typically not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on an acylcarnitine analysis, independent biochemical or molecular genetic analyses are required.

Reference Values:

	< or =7 days (nmol/mL)	8 days-7 years (nmol/mL)	> or =8 years (nmol/mL)
Acetylcarnitine, C2	2.14-15.89	2.00-27.57	2.00-17.83
Acrylylcarnitine, C3:1			
Propionylcarnitine, C3			
Formiminoglutamate, FIGLU			
Iso-/Butyrylcarnitine, C4			
Tiglylcarnitine, C5:1			
Isovaleryl-/2-Methylbutyrylcarn C5			
3-OH-iso-/butyrylcarnitine, C4-OH			
Hexenoylcarnitine, C6:1			
Hexanoylcarnitine, C6			
3-OH-isovalerylcarnitine, C5-OH			
Benzoylcarnitine			
Heptanoylcarnitine, C7			
3-OH-hexanoylcarnitine, C6-OH			
Phenylacetylcarnitine			
Salicylcarnitine			
Octenoylcarnitine, C8:1			
Octanoylcarnitine, C8			
Malonylcarnitine, C3-DC			
Decadienoylcarnitine, C10:2			
Decenoylcarnitine, C10:1			
Decanoylcarnitine, C10			
Methylmalonyl-/succinylcarn, C4-DC			
3-OH-decenoylcarnitine, C10:1-OH			
Glutarylcarnitine, C5-DC			
Dodecenoylcarnitine, C12:1			

Dodecanoylcarnitine, C12
3-Methylglutarylcarnitine, C6-DC
3-OH-dodecenoylcarnitine, C12:1-OH
3-OH-dodecanoylcarnitine, C12-OH
Tetradecadienoylcarnitine, C14:2
Tetradecenoylcarnitine, C14:1
Tetradecanoylcarnitine, C14
Octanedioylcarnitine, C8-DC
3-OH-tetradecenoylcarnitine C14:1OH
3-OH-tetradecanoylcarnitine, C14-OH
Hexadecenoylcarnitine, C16:1
Hexadecanoylcarnitine, C16
3-OH-hexadecenoylcarnitine,C16:1-OH
3-OH-hexadecanoylcarnitine, C16-OH
Octadecadienoylcarnitine, C18:2
Octadecenoylcarnitine, C18:1
Octadecanoylcarnitine, C18
Dodecanedioylcarnitine, C12-DC
3-OH-octadecadienoylcarn, C18:2-OH
3-OH-

	octadecenoylcarnitine C18:1-OH
3-OH-octadecanoylcarnitine, C18-OH	

Clinical References: 1. Miller MJ, Cusmano-Ozog K, Oglesbee D, Young S; ACMG Laboratory Quality Assurance Committee. Laboratory analysis of acylcarnitines, 2020 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(2):249-258 2. Matern D. Acylcarnitines, including in vitro loading tests. In: Blau N, Duran M, Gibson KM, eds. Laboratory Guide to the Methods in Biochemical Genetics. Springer Verlag; 2008:171-206 3. Rinaldo P, Cowan TM, Matern D. Acylcarnitine profile analysis. Genet Med. 2008;10(2):151-156 4. Smith EH, Matern D. Acylcarnitine analysis by tandem mass spectrometry. Curr Protoc Hum Genet. 2010;Chap 17:Unit 17.8.1-20 5. Elizondo G, Matern D, Vockley J, Harding CO, Gillingham MB. Effects of fasting, feeding and exercise on plasma acylcarnitines among subjects with CPT2D, VLCADD and LCHADD/TFPD. Mol Genet Metab. 2020;131(1-2):90-97

ACRNS
60644

Acylcarnitines, Quantitative, Serum

Clinical Information: Acylcarnitine analysis enables the diagnosis of many disorders of fatty acid oxidation and several organic acidurias, as relevant enzyme deficiencies cause the accumulation of specific acyl-CoAs.(1) Fatty acid oxidation (FAO) plays a major role in energy production during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue, taken up by the liver and muscles, and oxidized to acetyl-CoA. In the liver, acetyl-CoA is the building block for the synthesis of ketone bodies, which enter the blood stream and provide an alternative substrate for production of energy in other tissues when the supply of glucose is insufficient to maintain a normal level of energy. The acyl groups are conjugated with carnitine to form acylcarnitines, which can be measured by tandem mass spectrometry. Diagnostic results are usually characterized by a pattern of significantly elevated acylcarnitine species compared to normal and disease controls. In general, more than 20 inborn errors of metabolism can be identified using this method including FAO disorders and organic acidurias. The major clinical manifestations associated with individual FAO disorders include hypoketotic hypoglycemia, variable degrees of liver disease or failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden or unexpected death. Organic acidurias also present as acute life-threatening events early in life with metabolic acidosis, increased anion gap, and neurologic distress. Patients with any of these disorders are at risk of developing fatal metabolic decompensations following the acquisition of even common infections. Once diagnosed, these disorders can be treated by avoidance of fasting, special diets, and cofactor/vitamin supplementation. Additional confirmatory testing is recommended. The diagnosis of an underlying FAO disorder or organic aciduria allows genetic counseling of the family, including the possible option of future prenatal diagnosis, and testing of at-risk family members of any age. The following disorders are detectable by acylcarnitine analysis. However, further confirmatory testing is required for most of these conditions because an acylcarnitine profile can be suggestive of more than one condition. Fatty Acid Oxidation Disorders: -Carnitine palmitoyltransferase I deficiency -Medium-chain 3-ketoacyl-CoA thiolase deficiency -Dienoyl-CoA reductase deficiency -Short-chain acyl-CoA dehydrogenase deficiency -Medium/Short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency -Medium-chain acyl-CoA dehydrogenase) deficiency -Long-chain 3-hydroxyacyl-CoA dehydrogenase) deficiency and trifunctional protein deficiency -Very long-chain acyl-CoA dehydrogenase deficiency -Carnitine palmitoyl transferase type II deficiency -Carnitine-acylcarnitine translocase deficiency -Electron transfer flavoprotein (ETF) deficiency, ETF-dehydrogenase deficiency (multiple acyl-CoA dehydrogenase deficiency; glutaric acidemia type II) Organic Acid Disorders: -Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia type I) -Propionic acidemia -Methylmalonic acidemia -Isovaleric acidemia -3-Hydroxy-3-methylglutaryl-CoA carboxylase deficiency -3-Methylcrotonyl carboxylase deficiency -Biotinidase deficiency -Multiple carboxylase deficiency -Isobutyryl-CoA dehydrogenase deficiency -2-Methylbutyryl-CoA dehydrogenase deficiency

-Beta-ketothiolase deficiency -Malonic aciduria -Ethylmalonic encephalopathy -Glutamate formiminotransferase deficiency (formiminoglutamic aciduria)

Useful For: Diagnosis of fatty acid oxidation disorders and several organic acidurias using serum specimens Evaluating treatment during follow-up of patients with fatty acid beta-oxidation disorders and several organic acidurias

Interpretation: An interpretive report will be provided. The individual quantitative results support the interpretation of the acylcarnitine profile but are not diagnostic by themselves. The interpretation is based on pattern recognition. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on an acylcarnitine analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required.

Reference Values:

	< or =7 days (nmol/mL)	8 days-7 years (nmol/mL)	> or =8 years (nmol/mL)
Acetylcarnitine, C2	2.14-15.89	2.00-27.57	2.00-17.83
Acrylylcarnitine, C3:1			
Propionylcarnitine, C3			
Formiminoglutamate, FIGLU			
Iso-/Butyrylcarnitine, C4			
Tiglylcarnitine, C5:1			
Isovaleryl-/2-Methylbutyrylcarn C5			
3-OH-iso-/butyrylcarnitine, C4-OH			
Hexenoylcarnitine, C6:1			
Hexanoylcarnitine, C6			
3-OH-isovalerylcarnitine, C5-OH			
Benzoylcarnitine			
Heptanoylcarnitine, C7			
3-OH-hexanoylcarnitine, C6-OH			
Phenylacetylcarnitine			
Salicylcarnitine			
Octenoylcarnitine, C8:1			
Octanoylcarnitine, C8			
Malonylcarnitine, C3-DC			
Decadienoylcarnitine,			

C10:2
Decenoylcarnitine, C10:1
Decanoylcarnitine, C10
Methylmalonyl-/succinylcarn, C4-DC
3-OH-decenoylcarnitine, C10:1-OH
Glutarylcarnitine, C5-DC
Dodecenoylcarnitine, C12:1
Dodecanoylcarnitine, C12
3-Methylglutarylcarnitine, C6-DC
3-OH-dodecenoylcarnitine, C12:1-OH
3-OH-dodecanoylcarnitine, C12-OH
Tetradecadienoylcarnitine, C14:2
Tetradecenoylcarnitine, C14:1
Tetradecanoylcarnitine, C14
Octanedioylcarnitine, C8-DC
3-OH-tetradecenoylcarnitine C14:1OH
3-OH-tetradecanoylcarnitine, C14-OH
Hexadecenoylcarnitine, C16:1
Hexadecanoylcarnitine, C16
3-OH-hexadecenoylcarnitine,C16:1-OH
3-OH-hexadecanoylcarnitine, C16-OH

Octadecadienoylcarnitine, C18:2
Octadecenoylcarnitine, C18:1
Octadecanoylcarnitine, C18
Dodecanedioylcarnitine, C12-DC
3-OH-octadecadienoylcarn, C18:2-OH
3-OH-octadecenoylcarnitine C18:1-OH
3-OH-octadecanoylcarnitine, C18-OH

Clinical References: 1. Miller MJ, Cusmano-Ozog K, Oglesbee D, Young S; ACMG Laboratory Quality Assurance Committee. Laboratory analysis of acylcarnitines, 2020 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(2):249-258 2. Matern D. Acylcarnitines, including in vitro loading tests. In: Blau N, Duran M, Gibson KM, eds. Laboratory Guide to the Methods in Biochemical Genetics. Springer Verlag; 2008:171-206 3. Rinaldo P, Cowan TM, Matern D. Acylcarnitine profile analysis. Genet Med. 2008;10(2):151-156 4. Smith EH, Matern D. Acylcarnitine analysis by tandem mass spectrometry. Curr Protoc Hum Genet. 2010;Chap 17:Unit 17.8.1-20 5. Elizondo G, Matern D, Vockley J, Harding CO, Gillingham MB. Effects of fasting, feeding and exercise on plasma acylcarnitines in obese subjects with CPT2D, VLCADD, and LCHADD/TFPD. Mol Genet Metab. 2020;131(1-2):90-97

AGU20
608909

Acylglycines, Quantitative, Random, Urine

Clinical Information: Acylglycines are glycine conjugates of acyl-coenzyme A species, which occur as normal intermediates of amino acid and fatty acid metabolism. In abnormal concentrations, acylglycines are biochemical markers of selected inborn errors of metabolism. Analysis of acylglycines is useful for the diagnosis and monitoring for specific fatty acid oxidation disorders and organic acidurias; however, it is recommended to use this testing in conjunction with urine organic acids and plasma acylcarnitines testing in order to establish a diagnosis. In particular, acylglycine analysis is more sensitive and specific for the identification of asymptomatic patients and those who may experience mild or intermittent biochemical phenotypes that could be missed by organic acid analysis alone.

Useful For: Diagnosis and monitoring for patients affected with one of the following inborn errors of metabolism: Fatty Acid Oxidation Disorders: -Glutaric acidemia type II -Medium-chain 3-ketoacyl-coenzyme A (CoA) thiolase (MCKAT) deficiency -Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency -Short chain acyl-CoA dehydrogenase (SCAD) deficiency Organic Acidurias: -2-Methyl-3-hydroxybutyryl-CoA dehydrogenase (2M3HBD) deficiency -2-Methylbutyryl-CoA dehydrogenase deficiency -3-Methylcrotonyl-CoA carboxylase deficiency -3-Methylglutaconyl-CoA-hydratase deficiency -Aminoacylase 1 deficiency -Beta-ketothiolase deficiency -Ethylmalonic encephalopathy -Glutaryl-CoA dehydrogenase deficiency -Isobutyryl-CoA dehydrogenase deficiency -Isovaleryl-CoA dehydrogenase deficiency -Multiple carboxylase deficiency -Propionic acidemia

Interpretation: When abnormal results are detected, a detailed interpretation is given including an overview of the results and of their significance; a correlation to available clinical information; elements

of differential diagnosis; recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis); name and phone number of key contacts who may provide these studies at Mayo Clinic or elsewhere; and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

n-Acetylglycine:< or =3.50 mg/g Creatinine
n-Propionylglycine:< or =2.25 mg/g Creatinine
Isobutyrylglycine:< or =3.00 mg/g Creatinine
Ethylmalonic acid:< or =25.00 mg/g Creatinine
n-Butyrylglycine:< or =2.50 mg/g Creatinine
2-Methylsuccinic acid:< or =9.00 mg/g Creatinine
2-Methylbutyrylglycine:< or =2.00 mg/g Creatinine
Isovalerylglycine:< or =8.00 mg/g Creatinine
Glutaric acid:< or =8.00 mg/g Creatinine
3-Methylcrotonylglycine:< or =2.25 mg/g Creatinine
n-Tiglylglycine:< or =9.00 mg/g Creatinine
3-Methylglutaconic acid:< or =25.00 mg/g Creatinine
n-Hexanoylglycine:< or =2.00 mg/g Creatinine
n-Octanoylglycine:< or =2.00 mg/g Creatinine
3-Phenylpropionylglycine:< or =2.00 mg/g Creatinine
trans-Cinnamoylglycine:< or =5.50 mg/g Creatinine
Suberylglycine:< or =5.00 mg/g Creatinine
Dodecanedioic acid:< or =0.50 mg/g Creatinine
Tetradecanedioic acid:< or =0.50 mg/g Creatinine
Hexadecanedioic acid:< or =0.50 mg/g Creatinine

Clinical References: 1. Rinaldo P, Hahn SH, Matern D. Inborn errors of amino acid, organic acid, and fatty acid metabolism. In: Burtis CA, Ashwood ER, Bruns DE eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 4th ed. WB Saunders Company; 2005:2207-2247 2. Roe CR, Ding J. Mitochondrial fatty acid oxidation disorders. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed March 21, 2024. http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225087274 3. Kolker S, Cazorla AG, Valayannopoulos V, et al. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 1: the initial presentation. J Inherit Metab Dis. 2015;38(6):1041-1057. doi:10.1007/s10545-015-9839-3 4. Tuncel AT, Boy N, Morath MA, Horster F, Mutze U, Kolker S. Organic acidurias in adults: late complications and management. J Inherit Metab Dis. 2018;41(5):765-776. doi:10.1007/s10545-017-0135-2 5. Pasquali M, Longo N. Newborn screening and inborn errors of metabolism. In: Rifai N, Chiu, RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 60

ABADL
620311

Adalimumab Antibody, Serum

Clinical Information: Adalimumab, sold under the brand names Amjevita and Humira, is a medication used to treat rheumatoid arthritis, psoriatic arthritis, Crohn disease, ulcerative colitis, and chronic psoriasis, among others. Adalimumab is a tumor necrosis factor (TNF)-inhibiting, antiinflammatory, biologic medication. TNF-alpha binds to TNF-alpha receptors, leading to the inflammatory response of autoimmune diseases. By binding to TNF-alpha, adalimumab can reduce the inflammatory response. Because TNF-alpha is also a part of the immune system that protects the body from infection, treatment with adalimumab may increase the risk of infections. Treatment with adalimumab is effective in reducing disease activity, offers significant benefits in quality of life, and may have the potential to slow or halt the progression of the disease when given early. However, over 30% of

patients fail to respond to anti-TNF-alpha therapy and approximately 60% of patients who responded initially lose the response over time and require either drug dose-escalation or a switch to an alternative therapy in order to maintain response.(1) This assay has been verified to measure the reference product adalimumab (Humira, AbbVie) and the biosimilar adalimumab-atto (Amjevita, Amgen) with no analytical differences in the quantitation of the medications. Humira and Amjevita have the same primary amino acid sequence. Therefore, adalimumab will be used to refer to both the reference product and the biosimilar product interchangeably. This test cannot distinguish between Humira and the adalimumab biosimilar product. Reasons for primary loss of response may include disease processes mediated by proinflammatory molecules other than TNF. Secondary loss of response, on the other hand, is associated with low serum albumin, high body-mass index, the degree of systemic inflammation and development of an immune response to therapy, or immunogenicity.(2,3) Antidrug antibody formation may increase drug clearance in treated patients or neutralize the drug effect, thereby potentially contributing to the loss of response. Antidrug antibodies could also cause adverse events such as serum sickness and hypersensitivity reactions.(4) Currently, adalimumab quantitation is commonly performed in conjunction with immunogenicity assessment for antibodies to adalimumab (ATA). Most often, this testing is ordered in patients on therapy who are experiencing partial or complete loss of response but can also be performed in any stage during therapy, when patients are responding well to the therapy or not. TNF inhibitor therapies are expensive and adverse events include greater risk for infections, such as reactivation of latent tuberculosis or hepatitis B, infusion or injection site reactions, cutaneous reactions, and reports of hepatoxicity, demyelinating disease, and higher incidence of mortality and hospitalization in heart failure patients have been documented.

Useful For: Therapeutic drug monitoring of adalimumab antibody levels

Interpretation:

Reference Values:
Only orderable as part of profile. For more information see ADALP / Adalimumab Quantitative with Antibody, Serum.

ADALIMUMAB ANTIBODY:
<14.0 AU/mL

Clinical References: 1. Willrich MAV, Murray DL, Snyder MR.Tumor necrosis factor inhibitors: clinical utility in autoimmune diseases. Transl Res. 2015;165(2):270-282 2. Ordas I, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther. 2012;91(4):635-646 3. Ordas I, Feagan BG, Sandborn WJ. Therapeutic drug monitoring of tumor necrosis factor antagonists in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2012;10(10):1079-1087; quiz e85-86 4. Restellini S, Chao CY, Lakatos PL, et al. Therapeutic drug monitoring guides the management of Crohn's patients with secondary loss of response to adalimumab. Inflamm Bowel Dis. 2018;24(7):1531-1538 5. American Gastroenterological Association: Therapeutic drug monitoring in inflammatory bowel disease: Clinical decision support tool. Gastroenterology. 2017;153(3):858-859. doi:10.1053/j.gastro.2017.07.039 6. D'Haens GR, Sandborn WJ, Loftus EV Jr, et al: Higher vs standard adalimumab induction dosing regimens and two maintenance strategies: Randomized SERENE CD trial results. Gastroenterology. 2022;162(7):1876-1890. doi:10.1053/j.gastro.2022.01.044 7. Yao J, Jiang X, You JHS. Proactive therapeutic drug monitoring of adalimumab for pediatric Crohn's disease patients: a cost-effectiveness analysis. J Gastroenterol Hepatol. 2021;36(9):2397-2407. doi:10.1111/jgh.15373 8. Kato M, Sugimoto K, Ikeya K, et al. Therapeutic monitoring of adalimumab at non-trough levels in patients with inflammatory bowel disease. PLoS One. 2021;16(7):e0254548 9. Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. Gastroenterology. 2017;153(3):835-857.e6. doi:10.1053/j.gastro.2017.07.031 10. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute Guideline on Therapeutic

Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology. 2017;153(3):827-834. doi:10.1053/j.gastro.2017.07.032 11. Sejournet L, Kerever S, Mathis T, Kodjikian L, Jamilloux Y, Seve P. Therapeutic drug monitoring guides the management of patients with chronic non-infectious uveitis treated with adalimumab: a retrospective study. Br J Ophthalmol. 2022;106(10):1380-1386. doi:10.1136/bjophthalmol-2021-319072 12. Gomez-Arango C, Gorostiza I, Ucar E, et al. Cost-effectiveness of therapeutic drug monitoring-guided adalimumab therapy in rheumatic diseases: A Prospective, Pragmatic Trial. Rheumatol Ther. 2021;8(3):1323-1339. doi:10.1007/s40744-021-00345-5 13. Abdalla T, Mansour M, Bouazzi D, Lowes MA, Jemec GBE, Alavi A. Therapeutic drug monitoring in patients with suboptimal response to adalimumab for hidradenitis suppurativa: A retrospective case series. Am J Clin Dermatol. 2021;22(2):275-283. doi:10.1007/s40257-020-00575-3

INTAD
620312

Adalimumab Panel, Interpretation

Clinical Information:

Useful For: Interpretation of therapeutic drug monitoring of adalimumab concentration and antibody levels

Interpretation: Adalimumab quantitation is generally performed in conjunction with immunogenicity assessment for antibodies to adalimumab (ATA). Most often, this testing is ordered for patients with inflammatory bowel disease (IBD) who are on adalimumab therapy and who are experiencing loss of response (reactive monitoring),(5) but the testing may be ordered for anyone on adalimumab-even when treatment is going well (proactive monitoring).(6-8) Results from adalimumab and ATA testing play an important role in patient management. In the setting of loss of response to adalimumab therapy for adults with active IBD, a clinical decision tool from the American Gastroenterology Association(9,10) suggests the following scenarios for a blood draw that occurred at trough, immediately before the next injection dose: -For patients who have undetectable or low concentrations of adalimumab (<8 mcg/mL) but no detectable ATA, the patient care team may choose to increase the dose of adalimumab in an attempt to increase the amount of the drug in circulation. -If the patient has subtherapeutic adalimumab concentrations (<8 mcg/mL) in the presence of an ATA, the patient care team may switch the patient to another TNF inhibitor. -For patients with increased trough concentrations of adalimumab (therapeutic or greater), whether an ATA is present or not, it may be necessary to switch the patient to a therapy with a different mechanism of action such as the anti-alpha 4-beta-7-integrin antibody vedolizumab or the IL12/IL23 antibody ustekinumab. -Low trough concentrations may be correlated with loss of response to adalimumab. Adalimumab concentration results above 35 mcg/mL are suggestive of a blood draw at a time-point in treatment other than trough. Test interpretation relies on clinical presentation and may differ from the statements above, which were designed for adults with IBD experiencing loss of response. For individuals on adalimumab therapy for other conditions such as rheumatoid arthritis, or pediatric patient populations or proactive monitoring, drug concentration therapeutic targets and patient management decision may be individualized. When both the drug quantitation and anti-drug-antibodies are ordered, an interpretive guide is offered below. Adalimumab quantitation, mcg/mL ATA, AU/mL Comment <8 Negative Absence of detectable antibody-to-adalimumab (ATA). Low concentration of adalimumab (ADL) may be attributable to other parameters related to adalimumab clearance. <8 Positive Presence of antibody-to-adalimumab (ATA) detected, which correlates with low concentration of adalimumab (ADL). ATAs may be associated with increased clearance and lower circulating concentrations of ADL. 8.1-15 Negative Absence of detectable antibody-to-adalimumab (ATA). At this concentration of adalimumab (ADL), a low-titer (50-150 AU/mL) or moderate titer (150-500 AU/mL) ATA cannot be excluded. However, the presence of a high-titer ATA (> or =500 U/mL) is unlikely. If there is clinical suspicion for a low-titer ATA, suggest submission of a new sample obtained at trough. This test has demonstrated drug tolerance up to 40 mcg/mL for ATAs > or =500 AU/mL, up to 15 mcg/mL for ATAs between 150-500 and up to 8 mcg/mL ADL for ATAs between 50-150 AU/mL. Low or moderate positive (14-499) Presence of antibody-to-adalimumab (ATA) detected. At this concentration of adalimumab (ADL), the detected titer of the ATA may be modestly underestimated. This test has demonstrated drug tolerance up

to 40 mcg/mL for ATAs > or =500 AU/mL, up to 15 mcg/mL for ATAs between 150-500 and up to 8 mcg/mL ADL for ATAs between 50-150 AU/mL. High positive (> or =500) Presence of antibody-to-adalimumab (ATA) detected. This test has demonstrated drug tolerance up to 40 mcg/mL for ATAs > or =500 AU/mL, up to 15 mcg/mL for ATAs between 150-500 and up to 8 mcg/mL ADL for ATAs between 50-150 AU/mL. >15 Negative At this concentration of adalimumab (ADL), a low (50-150 AU/mL) or moderate titer (150-500 AU/mL) ATA cannot be excluded. The presence of a high-titer ATA (> or =500 U/mL) is unlikely but also cannot be completely excluded. If there is clinical suspicion for an ATA, suggest submission of a new sample obtained at trough, preferably during the maintenance phase of therapy. This test has demonstrated drug tolerance up to 40 mcg/mL for ATAs > or =500 AU/mL, up to 15 mcg/mL for ATAs between 150-500 and up to 8 mcg/mL ADL for ATAs between 50-150 AU/mL. Low positive (14-149) Presence of antibody-to-adalimumab (ATA) detected. At this concentration of adalimumab (ADL), the detected titer of the ATA is likely underestimated. Suggest submission of a new sample obtained at trough, preferably during the maintenance phase of therapy. This test has demonstrated drug tolerance up to 40 mcg/mL for ATAs > or =500 AU/mL, up to 15 mcg/mL for ATAs between 150-500 and up to 8 mcg/mL ADL for ATAs between 50-150 AU/mL. Moderate positive (150-499 U/mL) Presence of antibody-to-adalimumab (ATA) detected. At this concentration of adalimumab (ADL), the detected titer of the ATA may be underestimated. Suggest submission of a new sample obtained at trough, preferably during the maintenance phase of therapy. This test has demonstrated drug tolerance up to 40 mcg/mL for ATAs > or =500 AU/mL, up to 15 mcg/mL for ATAs between 150-500 and up to 8 mcg/mL ADL for ATAs between 50-150 AU/mL. High positive (> or =500) Presence of antibody-to-adalimumab (ATA) detected. This test has demonstrated drug tolerance up to 40 mcg/mL for ATAs > or =500 AU/mL, up to 15 mcg/mL for ATAs between 150-500 and up to 8 mcg/mL ADL for ATAs between 50-150 AU/mL.

Reference Values:

Only orderable as part of a profile. For more information see ADALP / Adalimumab Quantitative with Antibody, Serum.

Clinical References: 1. Willrich MAV, Murray DL, Snyder MR. Tumor necrosis factor inhibitors: clinical utility in autoimmune diseases. Transl Res. 2015;165(2):270-282 2. Ordas I, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther. 2012;91(4):635-646 3. Ordas I, Feagan BG, Sandborn WJ. Therapeutic drug monitoring of tumor necrosis factor antagonists in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2012;10(10):1079-e86 4. Restellini S, Chao CY, Lakatos PL, et al. Therapeutic drug monitoring guides the management of Crohn's patients with secondary loss of response to adalimumab. Inflamm Bowel Dis. 2018;24(7):1531-1538 5. Syversen SW, Jahnsen J, Haavardsholm EA. Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy and Control of Immune-Mediated Inflammatory Diseases-Reply. JAMA. 2022;327(15):1506-1507. doi:10.1001/jama.2022.2938 6. American Gastroenterological Association. Therapeutic drug monitoring in inflammatory bowel disease: Clinical decision support tool. Gastroenterology. 2017;153(3):858-859. doi: 10.1053/j.gastro.2017.07.039 7. D'Haens GR, Sandborn WJ, Loftus EV Jr, et al. Higher vs standard adalimumab induction dosing regimens and two maintenance strategies: Randomized SERENE CD trial results. Gastroenterology. 2022;162(7):1876-1890. doi:10.1053/j.gastro.2022.01.044 8. Yao J, Jiang X, You JHS. Proactive therapeutic drug monitoring of adalimumab for pediatric Crohn's disease patients: a cost-effectiveness analysis. J Gastroenterol Hepatol. 2021;36(9):2397-2407. doi:10.1111/jgh.15373 9. Kato M, Sugimoto K, Ikeya K, et al. Therapeutic monitoring of adalimumab at non-trough levels in patients with inflammatory bowel disease. PLoS One. 2021;16(7):e0254548 10. Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. Gastroenterology. 2017;153(3):835-857.e6. doi: 10.1053/j.gastro.2017.07.031 11. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology. 2017;153(3):827-834. doi:10.1053/j.gastro.2017.07.032 12. Sejournet L, Kerever S, Mathis T,

Kodjikian L, Jamilloux Y, Seve P. Therapeutic drug monitoring guides the management of patients with chronic non-infectious uveitis treated with adalimumab: a retrospective study. Br J Ophthalmol. 2022;106(10):1380-1386. doi:10.1136/bjophthalmol-2021-319072 13. Gomez-Arango C, Gorostiza I, Ucar E, et al. Cost-effectiveness of therapeutic drug monitoring-guided adalimumab therapy in rheumatic diseases: A Prospective, Pragmatic Trial. Rheumatol Ther. 2021;8(3):1323-1339. doi:10.1007/s40744-021-00345-5 14. Abdalla T, Mansour M, Bouazzi D, Lowes MA, Jemec GBE, Alavi A. Therapeutic drug monitoring in patients with suboptimal response to adalimumab for hidradenitis suppurativa: A retrospective case series. Am J Clin Dermatol. 2021;22(2):275-283. doi:10.1007/s40257-020-00575-3

ADALP
620309

Adalimumab Quantitative with Antibody, Serum

Clinical Information: Adalimumab, sold under the brand names Amjevita and Humira, is a US Food and Drug Administration-approved medication used to treat rheumatoid arthritis, psoriatic arthritis, Crohn disease, ulcerative colitis, and chronic psoriasis, among others. It is usually self-administered as a subcutaneous injection every other week at a fixed dose of 40 mg in adults, although dosing can vary. Adalimumab is a tumor necrosis factor (TNF)-inhibiting, antiinflammatory, biologic medication. TNF-alpha normally binds to TNF-alpha receptors, leading to the inflammatory response of autoimmune diseases. By binding to TNF-alpha, adalimumab can reduce the inflammatory response. Because TNF-alpha is also part of the immune system that protects the body from infection, treatment with adalimumab may increase the risk of infections. Treatment with adalimumab is effective in reducing disease activity, offers significant benefits in quality of life, and may have the potential to slow or halt the progression of the disease when given early. However, over 30% of patients fail to respond to anti-TNF-alpha therapy, and approximately 60% of patients who responded initially lose the response over time and require either drug dose-escalation or a switch to an alternative therapy in order to maintain response.(1) Reasons for primary loss of response may include disease processes mediated by proinflammatory molecules other than TNF. Secondary loss of response, on the other hand, is associated with low serum albumin, high body-mass index, the degree of systemic inflammation and development of an immune response to therapy, or immunogenicity.(2,3) Antidrug antibody formation may increase drug clearance in treated patients or neutralize the drug effect, thereby potentially contributing to the loss of response. Antidrug antibodies could also cause adverse events such as serum sickness and hypersensitivity reactions.(4) Currently, adalimumab quantitation is commonly performed in conjunction with immunogenicity assessment for antibodies to adalimumab (ATA). Most often, this testing is ordered in patients on therapy who are experiencing partial or complete loss of response but can also be performed at any stage during therapy, whether patients are responding well to the therapy or not. There is positive correlation between the concentration of serum biologic drug concentration and favorable therapeutic outcome; whereas low or undetectable drug concentrations are associated with immunogenicity and treatment failure. Thus, therapeutic drug monitoring of TNF inhibitors and antidrug antibody is a useful tool for optimizing the use of these medications and maximize their effectiveness.(5) In addition, TNF inhibitor therapies are expensive and adverse events include greater risk for infections, such as reactivation of latent tuberculosis or hepatitis B; infusion or injection site reactions; cutaneous reactions; and reports of hepatoxicity, demyelinating disease, and higher incidence of mortality and hospitalization in patients with heart failure have been documented. This assay has been verified to measure the reference product adalimumab (Humira, AbbVie) and the biosimilar adalimumab-atto (Amjevita, Amgen) with no analytical differences in the quantitation of the medications. Humira and Amjevita have the same primary amino acid sequence. Therefore, adalimumab will be used to refer to both the reference product and the biosimilar product interchangeably. This test cannot distinguish between Humira and the adalimumab biosimilar product.

Useful For: Therapeutic drug monitoring of adalimumab concentration and antibody levels

Interpretation:

Reference Values:
ADALIMUMAB QUANTITATIVE:
Limit of quantitation is 0.8 mcg/mL. Optimal therapeutic ranges are disease specific.

ADALIMUMAB ANTIBODY:
<14.0 AU/mL

Clinical References: 1. Willrich MAV, Murray DL, Snyder MR. Tumor necrosis factor inhibitors: Clinical utility in autoimmune diseases. Transl Res. 2015;165(2):270-282 2. Ordas I, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther. 2012;91(4):635-646 3. Ordas I, Feagan BG, Sandborn WJ. Therapeutic drug monitoring of tumor necrosis factor antagonists in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2012;10(10):1079-1087; quiz e85-86 4. Restellini S, Chao CY, Lakatos PL, et al. Therapeutic drug monitoring guides the management of Crohn's patients with secondary loss of response to adalimumab. Inflamm Bowel Dis. 2018;24(7):1531-1538 5. Cheifetz AS, Abreu MT, Afif W, et al. A comprehensive literature review and expert consensus statement on therapeutic drug monitoring of biologics in inflammatory bowel disease. Am J Gastroenterol. 2021;116(10):2014-2025. doi:10.14309/ajg.0000000000001396 6. American Gastroenterological Association: Therapeutic drug monitoring in inflammatory bowel disease: Clinical decision support tool. Gastroenterology. 2017;153(3):858-859. doi:10.1053/j.gastro.2017.07.039 7. D'Haens GR, Sandborn WJ, Loftus EV Jr, et al. Higher vs standard adalimumab induction dosing regimens and two maintenance strategies: Randomized SERENE CD trial results. Gastroenterology. 2022;162(7):1876-1890. doi:10.1053/j.gastro.2022.01.044 8. Yao J, Jiang X, You JHS. Proactive therapeutic drug monitoring of adalimumab for pediatric Crohn's disease patients: a cost-effectiveness analysis. J Gastroenterol Hepatol. 2021;36(9):2397-2407. doi:10.1111/jgh.15373 9. Kato M, Sugimoto K, Ikeya K, et al. Therapeutic monitoring of adalimumab at non-trough levels in patients with inflammatory bowel disease. PLoS One. 2021;16(7):e0254548 10. Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. Gastroenterology. 2017;153(3):835-857.e6. doi:10.1053/j.gastro.2017.07.031 11. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology. 2017;153(3):827-834. doi:10.1053/j.gastro.2017.07.032 12. Sejournet L, Kerever S, Mathis T, Kodjikian L, Jamilloux Y, Seve P. Therapeutic drug monitoring guides the management of patients with chronic non-infectious uveitis treated with adalimumab: a retrospective study. Br J Ophthalmol. 2022;106(10):1380-1386. doi:10.1136/bjophthalmol-2021-319072 13. Gomez-Arango C, Gorostiza I, Ucar E, et al. Cost-effectiveness of therapeutic drug monitoring-guided adalimumab therapy in rheumatic diseases: A Prospective, Pragmatic Trial. Rheumatol Ther. 2021;8(3):1323-1339. doi:10.1007/s40744-021-00345-5 14. Abdalla T, Mansour M, Bouazzi D, Lowes MA, Jemec GBE, Alavi A. Therapeutic drug monitoring in patients with suboptimal response to adalimumab for hidradenitis suppurativa: A retrospective case series. Am J Clin Dermatol. 2021;22(2):275-283. doi:10.1007/s40257-020-00575-3

ADALX
64863

Adalimumab Quantitative with Reflex to Antibody, Serum

Clinical Information: Adalimumab, sold under the brand names Amjevita and Humira, is a US Food and Drug Administration-approved medication used to treat rheumatoid arthritis, psoriatic arthritis, Crohn disease, ulcerative colitis, and chronic psoriasis, among others. It is usually self-administered as a subcutaneous injection every other week at a fixed dose of 40 mg in adults, although dosing can vary. Adalimumab is a tumor necrosis factor (TNF)-inhibiting, antiinflammatory, biologic medication. TNF-alpha normally binds to TNF-alpha receptors, leading to the inflammatory response of autoimmune diseases. By binding to TNF-alpha, adalimumab can reduce the inflammatory response. Because TNF-alpha is also part of the immune system that protects the body from infection, treatment

with adalimumab may increase the risk of infections. Treatment with adalimumab is effective in reducing disease activity, offers significant benefits in quality of life, and may have the potential to slow or halt the progression of the disease when given early. However, over 30% of patients fail to respond to anti-TNF-alpha therapy, and approximately 60% of patients who responded initially lose the response over time and require either drug dose-escalation or a switch to an alternative therapy in order to maintain response.(1) Reasons for primary loss of response may include disease processes mediated by proinflammatory molecules other than TNF. Secondary loss of response, on the other hand, is associated with low serum albumin, high body-mass index, the degree of systemic inflammation and development of an immune response to therapy, or immunogenicity.(2,3) Antidrug antibody formation may increase drug clearance in treated patients or neutralize the drug effect, thereby potentially contributing to the loss of response. Antidrug antibodies could also cause adverse events such as serum sickness and hypersensitivity reactions.(4) Currently, adalimumab quantitation is commonly performed in conjunction with immunogenicity assessment for antibodies to adalimumab (ATAs). Most often, this testing is ordered for patients on therapy who are experiencing partial or complete loss of response but can also be performed at any stage during therapy, whether patients are responding well to the therapy or not. There is positive correlation between the concentration of serum biologic drug concentration and favorable therapeutic outcome; whereas low or undetectable drug concentrations are associated with immunogenicity and treatment failure. Thus, therapeutic drug monitoring of TNF inhibitors and antidrug antibody is a useful tool for optimizing the use of these medications and maximize their effectiveness.(5) In addition, TNF inhibitor therapies are expensive and adverse events include greater risk for infections, such as reactivation of latent tuberculosis or hepatitis B; infusion or injection site reactions; cutaneous reactions; and reports of hepatoxicity, demyelinating disease, and higher incidence of mortality and hospitalization in patients with heart failure have been documented. This assay has been verified to measure the reference product adalimumab (Humira, AbbVie) and the biosimilar adalimumab-atto (Amjevita, Amgen) with no analytical differences in the quantitation of the medications. Humira and Amjevita have the same primary amino acid sequence. Therefore, adalimumab will be used to refer to both the reference product and the biosimilar product interchangeably. This test cannot distinguish between Humira and the adalimumab biosimilar product.

Useful For: Therapeutic drug monitoring of adalimumab concentration and antibody levels, if appropriate

Interpretation: Adalimumab quantitation is generally performed in conjunction with immunogenicity assessment for antibodies to adalimumab (ATAs). Most often, this testing is ordered for patients with inflammatory bowel disease (IBD) who are on adalimumab therapy and who are experiencing loss of response (reactive monitoring)(6), but the testing may be ordered for anyone on adalimumab-even when treatment is going well (proactive monitoring).(7-9) Results from adalimumab and ATAs testing play an important role in patient management. In the setting of loss of response to adalimumab therapy for adults with active IBD, a clinical decision tool from the American Gastroenterology Association(6,10,11) suggests the following scenarios for a blood draw that occurred at trough, ie, immediately before the next injected dose: -For patients who have undetectable or low concentrations of adalimumab (<8 mcg/mL) but no detectable ATAs, the patient care team may choose to increase the dose of adalimumab in an attempt to increase the amount of the drug in circulation. -If the patient has subtherapeutic adalimumab concentrations (<8 mcg/mL) in the presence of an ATA, the patient care team may switch the patient to another tumor necrosis factor inhibitor. -For patients with increased trough concentrations of adalimumab (therapeutic or greater), whether an ATA is present or not, it may be necessary to switch the patient to a therapy with a different mechanism of action such as the anti-alpha4-beta-7-integrin antibody vedolizumab or the IL12/IL23 antibody ustekinumab. -Low trough concentrations may be correlated with loss of response to adalimumab. Adalimumab concentration results above 35 mcg/mL are suggestive of a blood draw at a timepoint in treatment other than trough. Test interpretation relies on clinical presentation and may differ from the statements above, which were designed for adults with IBD experiencing loss of response. For individuals on adalimumab therapy for other conditions such as rheumatoid arthritis, or pediatric patient populations or proactive monitoring, drug concentration therapeutic targets and patient management decision may be individualized.

Reference Values:
ADALIMUMAB QUANTITATIVE:
Limit of quantitation is 0.8 mcg/mL. Optimal therapeutic ranges are disease specific.

ADALIMUMAB ANTIBODY:
<14.0 AU/mL

Clinical References: 1. Willrich MAV, Murray DL, Snyder MR. Tumor necrosis factor inhibitors: clinical utility in autoimmune diseases. Transl Res. 2015;165(2):270-282 2. Ordas I, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther. 2012;91(4):635-646 3. Ordas I, Feagan BG, Sandborn WJ. Therapeutic drug monitoring of tumor necrosis factor antagonists in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2012;10(10):1079-1087 e86 4. Restellini S, Chao CY, Lakatos PL, et al. Therapeutic drug monitoring guides the management of Crohn's patients with secondary loss of response to adalimumab. Inflamm Bowel Dis. 2018;24(7):1531-1538 5. Cheifetz AS, Abreu MT, Afif W, et al. A comprehensive literature review and expert consensus statement on therapeutic drug monitoring of biologics in inflammatory bowel disease. Am J Gastroenterol. 2021;116(10):2014-2025. doi:10.14309/ajg.0000000000001396 6. American Gastroenterological Association: Therapeutic drug monitoring in inflammatory bowel disease: Clinical decision support tool. Gastroenterology. 2017;153(3):858-859. doi:10.1053/j.gastro.2017.07.039 7. D'Haens GR, Sandborn WJ, Loftus EV Jr, et al. Higher vs standard adalimumab induction dosing regimens and two maintenance strategies: Randomized SERENE CD trial results. Gastroenterology. 2022;162(7):1876-1890. doi:10.1053/j.gastro.2022.01.044 8. Yao J, Jiang X, You JHS. Proactive therapeutic drug monitoring of adalimumab for pediatric Crohn's disease patients: a cost-effectiveness analysis. J Gastroenterol Hepatol. 2021;36(9):2397-2407. doi:10.1111/jgh.15373 9. Kato M, Sugimoto K, Ikeya K, et al. Therapeutic monitoring of adalimumab at non-trough levels in patients with inflammatory bowel disease. PLoS One. 2021;16(7):e0254548 10. Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. Gastroenterology. 2017;153(3):835-857.e6. doi:10.1053/j.gastro.2017.07.031 11. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology. 2017;153(3):827-834. doi:10.1053/j.gastro.2017.07.032 12. Sejournet L, Kerever S, Mathis T, Kodjikian L, Jamilloux Y, Seve P. Therapeutic drug monitoring guides the management of patients with chronic non-infectious uveitis treated with adalimumab: a retrospective study. Br J Ophthalmol. 2022;106(10):1380-1386. doi:10.1136/bjophthalmol-2021-319072 13. Gomez-Arango C, Gorostiza I, Ucar E, et al. Cost-effectiveness of therapeutic drug monitoring-guided adalimumab therapy in rheumatic diseases: A Prospective, Pragmatic Trial. Rheumatol Ther. 2021;8(3):1323-1339. doi:10.1007/s40744-021-00345-5 14. Abdalla T, Mansour M, Bouazzi D, Lowes MA, Jemec GBE, Alavi A. Therapeutic drug monitoring in patients with suboptimal response to adalimumab for hidradenitis suppurativa: A retrospective case series. Am J Clin Dermatol. 2021;22(2):275-283. doi:10.1007/s40257-020-00575-3

QNADL
620310

Adalimumab Quantitative, Serum

Clinical Information:

Useful For: Therapeutic drug monitoring of adalimumab concentration

Interpretation:

Reference Values:
Only orderable as part of profile. For more information see ADALP / Adalimumab Quantitative with

Antibody, Serum.

ADALIMUMAB QUANTITATIVE:
Limit of quantitation is 0.8 mcg/mL. Optimal therapeutic ranges are disease specific.

Clinical References: 1. Willrich MAV, Murray DL, Snyder MR. Tumor necrosis factor inhibitors: clinical utility in autoimmune diseases. Transl Res. 2015;165(2):270-282 2. Ordas I, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther. 2012;91(4):635-646 3. Ordas I, Feagan BG, Sandborn WJ. Therapeutic drug monitoring of tumor necrosis factor antagonists in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2012;10(10):1079-1087 e86 4. Restellini S, Chao CY, Lakatos PL, et al. Therapeutic drug monitoring guides the management of Crohn's patients with secondary loss of response to adalimumab. Inflamm Bowel Dis. 2018;24(7):1531-1538 5. American Gastroenterological Association. Therapeutic drug monitoring in inflammatory bowel disease: Clinical decision support tool. Gastroenterology. 2017;153(3):858-859. doi:10.1053/j.gastro.2017.07.039 6. D'Haens GR, Sandborn WJ, Loftus EV Jr, et al. Higher vs standard adalimumab induction dosing regimens and two maintenance strategies: Randomized SERENE CD trial results. Gastroenterology. 2022;162(7):1876-1890. doi:10.1053/j.gastro.2022.01.044 7. Yao J, Jiang X, You JHS. Proactive therapeutic drug monitoring of adalimumab for pediatric Crohn's disease patients: a cost-effectiveness analysis. J Gastroenterol Hepatol. 2021;36(9):2397-2407. doi:10.1111/jgh.15373 8. Kato M, Sugimoto K, Ikeya K, et al. Therapeutic monitoring of adalimumab at non-trough levels in patients with inflammatory bowel disease. PLoS One. 2021;16(7):e0254548 9. Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. Gastroenterology. 2017;153(3):835-857.e6. doi:10.1053/j.gastro.2017.07.031 10. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology. 2017;153(3):827-834. doi:10.1053/j.gastro.2017.07.032 11. Sejournet L, Kerever S, Mathis T, Kodjikian L, Jamilloux Y, Seve P. Therapeutic drug monitoring guides the management of patients with chronic non-infectious uveitis treated with adalimumab: a retrospective study. Br J Ophthalmol. 2022;106(10):1380-1386. doi:10.1136/bjophthalmol-2021-319072 12. Gomez-Arango C, Gorostiza I, Ucar E, et al. Cost-effectiveness of therapeutic drug monitoring-guided adalimumab therapy in rheumatic diseases: A Prospective, Pragmatic Trial. Rheumatol Ther. 2021;8(3):1323-1339. doi:10.1007/s40744-021-00345-5 13. Abdalla T, Mansour M, Bouazzi D, Lowes MA, Jemec GBE, Alavi A. Therapeutic drug monitoring in patients with suboptimal response to adalimumab for hidradenitis suppurativa: A retrospective case series. Am J Clin Dermatol. 2021;22(2):275-283. doi:10.1007/s40257-020-00575-3

ADAMS
620816

ADAMTS13 Activity Assay, Plasma

Clinical Information: Thrombotic thrombocytopenic purpura (TTP), a rare (estimated incidence of 3.7 cases per million) and potentially fatal thrombotic microangiopathy syndrome, is characterized by a pentad of symptoms: thrombocytopenia, microangiopathic hemolytic anemia (intravascular hemolysis and presence of peripheral blood schistocytes), neurological symptoms, fever, and kidney dysfunction. A large majority of patients initially present with thrombocytopenia and peripheral blood evidence of microangiopathy and, in the absence of any other potential explanation for such findings, satisfy criteria for early initiation of plasma exchange, which is critical for patient survival. TTP may rarely be congenital (Upshaw-Shulman syndrome) but, far more commonly, is acquired. Acquired TTP may be considered primary or idiopathic (the most frequent type) or associated with distinctive clinical conditions (secondary TTP) such as medications, hematopoietic stem cell or solid organ transplantation, sepsis, and malignancy. The isolation and characterization of an IgG autoantibody frequently found in patients with idiopathic TTP clarified the basis of this entity and led to the isolation and characterization of a metalloprotease called ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13 repeats), which is the target for the IgG autoantibody, leading to a functional deficiency of

ADAMTS-13. ADAMTS-13 cleaves the ultra-high-molecular-weight multimers of von Willebrand factor (VWF) at the peptide bond Tyr1605-Met1606 to disrupt VWF-induced platelet aggregation. The IgG antibody prevents this cleavage and leads to TTP. Although the diagnosis of TTP may be confirmed with ADAMTS-13 activity and inhibition studies, the decision to initiate plasma exchange should not be delayed pending results of this assay. ADAMTS13 activity results can have an impact on overall survival, ultimate clinical outcome, responsiveness to plasma exchange, and relapse are still controversial in recent literature. Therefore, clinical correlation is essential.

Useful For: Assisting with the diagnosis and monitoring of congenital, immune, or acquired thrombotic thrombocytopenic purpura

Interpretation: Less than 10% ADAMTS-13 activity is highly indicative of thrombotic thrombocytopenic purpura (TTP) in an appropriate clinical setting.

Reference Values:

> or =70%

Although not verified, the pediatric (<1 years old) reference range could be similar to or lower than that of adults.

Clinical References: 1. Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood. 2008;112(1):11-18. doi.org/10.1182/blood-2008-02-078170 2. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. Blood. 2010;116(20):4060-4069. doi:10.1182/blood-2010-07-271445 3. Upshaw JD: Congenital deficiency of a factor in normal plasma that reverses microangiopathic hemolysis and thrombocytopenia. N Engl J Med. 1978;298(24):1350-1352. doi:10.1056/NEJM197806152982407 4. Chiasakul T, Cuker A. Clinical and laboratory diagnosis of TTP: an integrated approach. Hematology Am Soc Hematol Educ Program. 2018;2018(1):530-538. doi:10.1182/asheducation-2018.1.530 5. Mackie I, Mancini I, Muia J, et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of ADAMTS13. Int J Lab Hematol. 2020;42(6):685-696. doi:10.1111/ijlh.13295

ADAMP
620815

ADAMTS13 Activity with Reflex Inhibitor Profile, Plasma

Clinical Information: Thrombotic thrombocytopenic purpura (TTP), a rare (estimated incidence of 3.7 cases per million) and potentially fatal thrombotic microangiopathy syndrome, is characterized by a pentad of symptoms: thrombocytopenia, microangiopathic hemolytic anemia (intravascular hemolysis and presence of peripheral blood schistocytes), neurological symptoms, fever, and kidney dysfunction. A large majority of patients initially present with thrombocytopenia and peripheral blood evidence of microangiopathy and, in the absence of any other potential explanation for such findings, satisfy criteria for early initiation of plasma exchange, which is critical for patient survival. TTP may rarely be congenital (Upshaw-Shulman syndrome) but, far more commonly, is acquired. Acquired TTP may be considered primary or idiopathic (the most frequent type) or associated with distinctive clinical conditions (secondary TTP) such as medications, hematopoietic stem cell or solid organ transplantation, sepsis, and malignancy. The isolation and characterization of an IgG autoantibody frequently found in patients with idiopathic TTP clarified the basis of this entity and led to the isolation and characterization of a metalloprotease called ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13 repeats), which is the target for the IgG autoantibody, leading to a functional deficiency of ADAMTS13. ADAMTS13 cleaves the ultra-high-molecular-weight multimers of von Willebrand factor (VWF) at the peptide bond Tyr1605-Met1606 to disrupt VWF-induced platelet aggregation. The IgG antibody prevents this cleavage and leads to TTP. Although the diagnosis of TTP may be confirmed with ADAMTS13 activity and inhibition studies, the decision to initiate plasma exchange should not be delayed pending results of this assay. ADAMTS13 and inhibitor Bethesda titer results can have an impact on overall survival, ultimate clinical outcome, responsiveness to plasma exchange, and relapse

are still controversial in recent literature. Therefore, clinical correlation is essential.

Useful For: Assisting with the diagnosis of immune or acquired thrombotic thrombocytopenic purpura

Interpretation: Less than 10% ADAMTS13 activity is highly indicative of thrombotic thrombocytopenic purpura (TTP) in an appropriate clinical setting. The presence of ADAMTS13 measurable Bethesda titer is most consistent with an acquired (autoimmune) TTP.

Reference Values:
ADAMTS13 Activity Assay
> or =70%
Although not verified, the pediatric (<1 years old) reference range could be similar to or lower than that of adults.

ADAMTS13 Inhibitor Titer
<0.5 BU

Clinical References: 1. Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood. 2008;112(1):11-18. doi:10.1182/blood-2008-02-078170 2. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. Blood. 2010;116(20):4060-4069. doi:10.1182/blood-2010-07-271445 3. Upshaw JD Jr. Congenital deficiency of a factor in normal plasma that reverses microangiopathic hemolysis and thrombocytopenia. N Engl J Med. 1978;298(24):1350-1352. doi:10.1056/NEJM197806152982407 4. Chiasakul T, Cuker A. Clinical and laboratory diagnosis of TTP: an integrated approach. Hematology Am Soc Hematol Educ Program. 2018;2018(1):530-538. doi:10.1182/asheducation-2018.1.530 5. Mackie I, Mancini I, Muia J, et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of ADAMTS13. Int J Lab Hematol. 2020;42(6):685-696. doi.10.1111/ijlh.13295

ADMB
620817

ADAMTS13 Inhibitor Bethesda Titer, Plasma

Clinical Information: Thrombotic thrombocytopenic purpura (TTP), a rare (estimated incidence of 3.7 cases per million) and potentially fatal thrombotic microangiopathy (TMA) syndrome, is characterized by a pentad of symptoms: thrombocytopenia, microangiopathic hemolytic anemia (intravascular hemolysis and presence of peripheral blood schistocytes), neurological symptoms, fever, and kidney dysfunction. A large majority of patients initially present with thrombocytopenia and peripheral blood evidence of microangiopathy, and in the absence of any other potential explanation for such findings, satisfy criteria for early initiation of plasma exchange, which is critical for patient survival. TTP may rarely be congenital (Upshaw-Shulman syndrome) but, far more commonly, is acquired. Acquired TTP may be considered primary or idiopathic (the most frequent type) or associated with distinctive clinical conditions (secondary TTP) such as medications, hematopoietic stem cell or solid organ transplantation, sepsis, and malignancy. The isolation and characterization of an IgG autoantibody frequently found in patients with idiopathic TTP, clarified the basis of this entity and led to the isolation and characterization of a metalloprotease called ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13 repeats), which is the target for the IgG autoantibody, leading to a functional deficiency of ADAMTS13. ADAMTS13 cleaves the ultra-high-molecular-weight multimers of von Willebrand factor (VWF) at the peptide bond Tyr1605-Met1606 to disrupt VWF-induced platelet aggregation. The IgG antibody prevents this cleavage and leads to TTP. Although the diagnosis of TTP may be confirmed with ADAMTS13 activity and inhibition studies, the decision to initiate plasma exchange should not be delayed pending results of this assay. ADAMTS13 and inhibitor Bethesda titer results can have an impact on overall survival, ultimate clinical outcome, responsiveness to plasma exchange, and relapse are still controversial in recent literature. Therefore, clinical correlation is essential.

Useful For: Assisting with the diagnosis of congenital, immune or acquired thrombotic thrombocytopenic purpura as a part of a profile

Interpretation: Assisting with the diagnosis of congenital, immune or acquired thrombotic thrombocytopenic purpura as a part of a profile

Reference Values:
Only orderable as a reflex. For more information see ADAMP / ADAMTS13 Activity with Reflex Inhibitor Profile, Plasma.

<0.5 BU

Clinical References: 1. Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood. 2008;112(1):11-18. doi:10.1182/blood-2008-02-078170 2. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. Blood. 2010;116(20):4060-4069. doi:10.1182/blood-2010-07-271445 3. Upshaw JD. Congenital deficiency of a factor in normal plasma that reverses microangiopathic hemolysis and thrombocytopenia. N Engl J Med. 1978;298(24):1350-1352. doi:10.1056/NEJM197806152982407 4. Chiasakul T, Cuker A. Clinical and laboratory diagnosis of TTP: an integrated approach. Hematology Am Soc Hematol Educ Program. 2018;2018(1):530-538. doi:10.1182/asheducation-2018.1.530 5. Mackie I, Mancini I, Muia J, et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of ADAMTS13. Int J Lab Hematol. 2020;42(6):685-696. doi:10.1111/ijlh.13295

ADMI
621149

ADAMTS13 Interpretation

Clinical Information: Thrombotic thrombocytopenic purpura (TTP), a rare (estimated incidence of 3.7 cases per million) and potentially fatal thrombotic microangiopathy syndrome, is characterized by a pentad of symptoms: thrombocytopenia, microangiopathic hemolytic anemia (intravascular hemolysis and presence of peripheral blood schistocytes), neurological symptoms, fever, and kidney dysfunction. A large majority of patients initially present with thrombocytopenia and peripheral blood evidence of microangiopathy and, in the absence of any other potential explanation for such findings, satisfy criteria for early initiation of plasma exchange, which is critical for patient survival. TTP may rarely be congenital (Upshaw-Shulman syndrome) but, far more commonly, is acquired. Acquired TTP may be considered primary or idiopathic (the most frequent type) or associated with distinctive clinical conditions (secondary TTP) such as medications, hematopoietic stem cell or solid organ transplantation, sepsis, and malignancy. The isolation and characterization of an IgG autoantibody frequently found in patients with idiopathic TTP clarified the basis of this entity and led to the isolation and characterization of a metalloprotease called ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13 repeats), which is the target for the IgG autoantibody, leading to a functional deficiency of ADAMTS13. ADAMTS13 cleaves the ultra-high-molecular-weight multimers of von Willebrand factor (VWF) at the peptide bond Tyr1605-Met1606 to disrupt VWF-induced platelet aggregation. The IgG antibody prevents this cleavage and leads to TTP. Although the diagnosis of TTP may be confirmed with ADAMTS13 activity and inhibition studies, the decision to initiate plasma exchange should not be delayed pending results of this assay. ADAMTS13 activity results can have an impact on overall survival, ultimate clinical outcome, responsiveness to plasma exchange, and relapse are still controversial in recent literature. Therefore, clinical correlation is essential.

Useful For: Technical interpretation of testing performed to assist in the diagnosis of congenital, immune, or acquired thrombotic thrombocytopenic purpura

Interpretation: Interpretive comments are provided. Less than 10% ADAMTS13 activity is highly indicative of thrombotic thrombocytopenic purpura (TTP) in an appropriate clinical setting.

Reference Values:
Only orderable as part of profile. For more information see ADAMP / ADAMTS13 Activity with Reflex Inhibitor Profile, Plasma.

ADAMTS13 ACTIVITY ASSAY
> or =70%
ADMTS13 INHIBITOR TITER
<0.5 BU

Clinical References: 1. Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood. 2008;112(1):11-18. doi.org/10.1182/blood-2008-02-078170 2. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. Blood. 2010;116(20):4060-4069. doi:10.1182/blood-2010-07-271445 3. Upshaw JD: Congenital deficiency of a factor in normal plasma that reverses microangiopathic hemolysis and thrombocytopenia. N Engl J Med. 1978;298(24):1350-1352. doi:10.1056/NEJM197806152982407 4. Chiasakul T, Cuker A. Clinical and laboratory diagnosis of TTP: an integrated approach. Hematology Am Soc Hematol Educ Program. 2018;2018(1):530-538. doi:10.1182/asheducation-2018.1.530 5. Mackie I, Mancini I, Muia J, et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of ADAMTS13. Int J Lab Hematol. 2020;42(6):685-696. doi:10.1111/ijlh.13295

AADAM
620818

ADAMTS13 Profile Interpretation

Clinical Information: Thrombotic thrombocytopenic purpura (TTP), a rare (estimated incidence of 3.7 cases per million) and potentially fatal thrombotic microangiopathy (TMA) syndrome, is characterized by a pentad of symptoms: thrombocytopenia, microangiopathic hemolytic anemia (intravascular hemolysis and presence of peripheral blood schistocytes), neurological symptoms, fever, and kidney dysfunction. A large majority of patients initially present with thrombocytopenia and peripheral blood evidence of microangiopathy, and in the absence of any other potential explanation for such findings, satisfy criteria for early initiation of plasma exchange, which is critical for patient survival. TTP may rarely be congenital (Upshaw-Shulman syndrome) but, far more commonly, is acquired. Acquired TTP may be considered primary or idiopathic (the most frequent type) or associated with distinctive clinical conditions (secondary TTP) such as medications, hematopoietic stem cell or solid organ transplantation, sepsis, and malignancy. The isolation and characterization of an IgG autoantibody frequently found in patients with idiopathic TTP, clarified the basis of this entity and led to the isolation and characterization of a metalloprotease called ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13 repeats), which is the target for the IgG autoantibody, leading to a functional deficiency of ADAMTS13. ADAMTS13 cleaves the ultra-high-molecular-weight multimers of von Willebrand factor (VWF) at the peptide bond Tyr1605-Met1606 to disrupt VWF-induced platelet aggregation. The IgG antibody prevents this cleavage and leads to TTP. Although the diagnosis of TTP may be confirmed with ADAMTS13 activity and inhibition studies, the decision to initiate plasma exchange should not be delayed pending results of this assay. ADAMTS13 and inhibitor Bethesda titer results can have an impact on overall survival, ultimate clinical outcome, responsiveness to plasma exchange, and relapse are still controversial in recent literature. Therefore, clinical correlation is essential.

Useful For: Technical interpretation of a profile to assist with the diagnosis of congenital, immune, or acquired thrombotic thrombocytopenic purpura including inhibitor studies

Interpretation: Interpretive comments are provided. Less than 10% ADAMTS13 activity is highly indicative of thrombotic thrombocytopenic purpura (TTP) in an appropriate clinical setting. The presence of ADAMTS-13 measurable Bethesda titer is most consistent with an acquired (autoimmune) TTP.

Reference Values:

Only orderable as a reflex. For more information see ADAMP / ADAMTS13 Activity with Reflex Inhibitor Profile, Plasma

ADAMTS13 ACTIVITY ASSAY
> or =70%
ADMTS13 Inhibitor Titer
<0.5 BU

Clinical References: 1. Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood. 2008;112(1):11-18. doi:10.1182/blood-2008-02-078170 2. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. Blood. 2010;116(20):4060-4069. doi:10.1182/blood-2010-07-271445 3. Upshaw JD. Congenital deficiency of a factor in normal plasma that reverses microangiopathic hemolysis and thrombocytopenia. N Engl J Med. 1978;298(24):1350-1352. doi:10.1056/NEJM197806152982407 4. Chiasakul T, Cuker A. Clinical and laboratory diagnosis of TTP: an integrated approach. Hematology Am Soc Hematol Educ Program. 2018;2018(1):530-538. doi:10.1182/asheducation-2018.1.530 5. Mackie I, Mancini I, Muia J, et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of ADAMTS13. Int J Lab Hematol. 2020;42(6):685-696. doi:10.1111/ijlh.13295

APBCS 615861 Adaptor Protein 3 Beta2 (AP3B2) Antibody, Cell-Binding Assay, Serum

Clinical Information: AP3B2 (adaptor protein 3 beta2)-IgG is a marker of an autoimmune disorder unified by gait instability as the predominant neurologic presentation. Patients present with either cerebellar, dorsal column, or sensory neuronal dysfunction. Clinical improvement following treatment has been reported. AP3B2 autoimmunity appears rare, is accompanied by ataxia (sensory or cerebellar), and is potentially treatable.

Useful For: The differential diagnosis of patients presenting with mixed cerebellar and sensory ataxia and myeloneuropathy Evaluating AP3B2 (adaptor protein 3 beta2)-IgG by cell-binding assay using serum specimens

Interpretation: A positive result supports a diagnosis of neurological autoimmunity. Neurological phenotypes encountered include cerebellar ataxia, spinocerebellar ataxia, myelopathy, sensory neuronopathy and autonomic neuropathy. Neurological stabilization or improvement may occur with immune therapy.

Reference Values:
Only orderable as a reflex. For more information see:
-AIAES / Axonal Neuropathy, Autoimmune/Paraneoplastic Evaluation, Serum
-DYS2 / Dysautonomia, Autoimmune/Paraneoplastic Evaluation, Serum
-GID2 / Gastrointestinal Dysmotility, Autoimmune/Paraneoplastic Evaluation, Serum
-MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum

Negative

Clinical References: Honorat JA, Lopez-Chiriboga AS, Kryzer, TJ, et al: Autoimmune gait disturbance accompanying adaptor protein-3B2-IgG. Neurology. 2019 Sep 3;93(10):e954-e963.

APBCC
615860

Adaptor Protein 3 Beta2 (AP3B2) Antibody, Cell-Binding Assay, Spinal Fluid

Clinical Information: AP3B2 (adaptor protein 3 beta2)-IgG is a marker of an autoimmune disorder unified by gait instability as the predominant neurologic presentation. Patients present with either cerebellar, dorsal column, or sensory neuronal dysfunction. Clinical improvement following treatment has been reported. AP3B2 autoimmunity appears rare, is accompanied by ataxia (sensory or cerebellar), and is potentially treatable.

Useful For: The differential diagnosis of patients presenting with mixed cerebellar and sensory ataxia and myeloneuropathy Evaluating AP3B2 (adaptor protein 3 beta2)-IgG by cell-binding assay using spinal fluid specimens

Interpretation: A positive result supports a diagnosis of neurological autoimmunity. Neurological phenotypes encountered include cerebellar ataxia, spinocerebellar ataxia, myelopathy, sensory neuronopathy and autonomic neuropathy. Neurological stabilization or improvement may occur with immune therapy.

Reference Values:
Only orderable as a part of a profile. For more information see MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

Negative

Clinical References: Honorat JA, Lopez-Chiriboga AS, Kryzer, TJ, et al: Autoimmune gait disturbance accompanying adaptor protein-3B2-IgG. Neurology. 2019 Sep 3;93(10):e954-e963

APBTS
616109

Adaptor Protein 3 Beta2 (AP3B2) Antibody, Tissue Immunofluorescence Titer, Serum

Clinical Information: AP3B2 (adaptor protein 3 beta2)-IgG is a marker of an autoimmune disorder unified by gait instability as the predominant neurologic presentation. Patients present with either cerebellar, dorsal column, or sensory neuronal dysfunction. Clinical improvement following treatment has been reported. AP3B2 autoimmunity appears rare, is accompanied by ataxia (sensory or cerebellar), and is potentially treatable.

Useful For: The differential diagnosis of patients presenting with mixed cerebellar and sensory ataxia and myeloneuropathy Reporting an end titer result from serum specimens

Interpretation: A positive result supports a diagnosis of neurological autoimmunity. Neurological phenotypes encountered include cerebellar ataxia, spinocerebellar ataxia, myelopathy, sensory neuronopathy and autonomic neuropathy. Neurological stabilization or improvement may occur with immune therapy.

Reference Values:
Only orderable as a reflex. For more information see:
-AIAES / Axonal Neuropathy, Autoimmune/Paraneoplastic Evaluation, Serum
-DYS2 / Dysautonomia, Autoimmune/Paraneoplastic Evaluation, Serum
-GID2 / Gastrointestinal Dysmotility, Autoimmune/Paraneoplastic Evaluation, Serum
-MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum

<1:240

Clinical References: Honorat JA, Lopez-Chiriboga AS, Kryzer, TJ, et al: Autoimmune gait disturbance accompanying adaptor protein-3B2-IgG. Neurology. 2019 Sep 3;93(10):e954-e963

APBTC 616110 Adaptor Protein 3 Beta2 (AP3B2) Antibody, Tissue Immunofluorescence Titer, Spinal Fluid

Clinical Information: AP3B2 (adaptor protein 3 beta2)-IgG is a marker of an autoimmune disorder unified by gait instability as the predominant neurologic presentation. Patients present with either cerebellar, dorsal column, or sensory neuronal dysfunction. Clinical improvement following treatment has been reported. AP3B2 autoimmunity appears rare, is accompanied by ataxia (sensory or cerebellar), and is potentially treatable.

Useful For: The differential diagnosis of patients presenting with mixed cerebellar and sensory ataxia and myeloneuropathy Reporting an end titer result from spinal fluid specimens

Interpretation: A positive result supports a diagnosis of neurological autoimmunity. Neurological phenotypes encountered include cerebellar ataxia, spinocerebellar ataxia, myelopathy, sensory neuronopathy and autonomic neuropathy. Neurological stabilization or improvement may occur with immune therapy.

Reference Values:
Only orderable as part of a profile. For more information see:
-MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

<1:2

Clinical References: Honorat JA, Lopez-Chiriboga AS, Kryzer, TJ, et al: Autoimmune gait disturbance accompanying adaptor protein-3B2-IgG. Neurology. 2019 Sep 3;93(10):e954-e963

ADMPU 615908 Addiction Medicine Profile with Reflex, 22 Drug Classes, High Resolution Mass Spectrometry and Immunoassay Screen, Random, Urine

Clinical Information: This test uses screening techniques that involve immunoassay testing and high-resolution accurate mass spectrometry screening for drugs by class. All positive immunoassay screening results are confirmed by gas chromatography mass spectrometry (GC-MS) or liquid chromatography tandem mass spectrometry (LC-MS/MS), and quantitated, before a positive result is reported. The following drugs/drug classes are tested by immunoassay and confirmed by GC-MS: -Barbiturates -Cocaine The following drugs/drug classes are tested by immunoassay and confirmed by LC-MS/MS: -Carboxy-tetrahydrocannabinol -Ethyl glucuronide The targeted opioid, benzodiazepine, and stimulant screen portions are performed using LC-MS/MS high-resolution accurate mass and are completed for all opioids, benzodiazepines, and stimulants. Opioids are a large class of medications commonly used to relieve acute and chronic pain or help manage opioid abuse and dependence. Medications that fall into this class include buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, and others. Opioids work by binding to the opioid receptors that are found in the brain, spinal cord, gastrointestinal

tract, and other organs. Common side effects for opioids include drowsiness, confusion, nausea, constipation, and, in severe cases, respiratory depression. These are dose dependant and vary with tolerance. These medications can also produce physical and psychological dependence and have a high risk for abuse and diversion, which is one of the main reasons many professional practice guidelines recommend compliance testing in patients prescribed these medications. Opioids are readily absorbed from the gastrointestinal tract, nasal mucosa, lungs, and after subcutaneous or intermuscular injection. Opioids are primarily excreted from the kidney in both free and conjugated forms. This assay does not hydrolyze the urine sample and looks for both parent drugs and metabolites (including glucuronide forms). The detection window for most opioids in urine is approximately 1 to 3 days with longer detection times for some compounds (ie, methadone). Benzodiazepines represent a large family of medications used to treat a wide range of disorders from anxiety to seizures and are also used in pain management. With a high risk for abuse and diversion, professional practice guidelines recommend compliance monitoring for these medications using urine drug tests. However, traditional benzodiazepine immunoassays suffer from a lack of cross-reactivity with all the benzodiazepines, so many compliant patients taking either clonazepam (Klonopin) or lorazepam (Ativan) may screen negative by immunoassay but are positive when confirmatory testing is done. The new targeted benzodiazepine screening test provides a more sensitive and specific test to check for compliance to all the commonly prescribed benzodiazepines and looks for both parent drugs and metabolites in the urine. Stimulants are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Amphetamine and methamphetamine are also prescription drugs used in the treatment of narcolepsy and attention-deficit disorder/attention-deficit hyperactivity disorder (ADHD). Methylphenidate is another stimulant used to treat ADHD. Phentermine is indicated for the management of obesity. All other amphetamines (eg, methylenedioxymethamphetamine: MDMA) are Drug Enforcement Administration-scheduled Class I compounds. Due to their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis. Ethyl glucuronide is a direct metabolite of ethanol that is formed by enzymatic conjugation of ethanol with glucuronic acid. Alcohol in urine is normally detected for only a few hours, whereas ethyl glucuronide can be detected in the urine for 1 to 3 days. This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (eg, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate to the antibody's ability to cross-react with different drugs in the class for which it is being screened. Tobacco use is the leading cause of death in the United States. Nicotine, coadministered in tobacco products such as cigarettes, pipe, cigar, or chew is an addicting substance that causes individuals to continue use of tobacco despite concerted efforts to quit. Nicotine stimulates dopamine release and increases dopamine concentration in the nucleus accumbens, a mechanism that is thought to be the basis for addiction for drugs of abuse. Nicotine is rapidly metabolized in the liver to cotinine, exhibiting an elimination half-life of 2 hours. Cotinine exhibits an apparent elimination half-life of approximately 15 to 19 hours. Patients using tobacco products excrete nicotine in urine in the concentration range of 1000 to 5000 ng/mL. Cotinine accumulates in urine in proportion to dose and hepatic metabolism, which is genetically determined; most tobacco users excrete cotinine in the range of 1000 to 8000 ng/mL. Urine concentrations of nicotine and metabolites in these ranges indicate the subject is using tobacco or is receiving high-dose nicotine patch therapy. In addition to nicotine and metabolites, tobacco products also contain other alkaloids that can serve as unique markers of tobacco use. Two such markers are anabasine and nornicotine. Anabasine is present in tobacco products but not nicotine replacement therapies. Nornicotine is present as an alkaloid in tobacco products and as a metabolite of nicotine. The presence of anabasine greater than 10 ng/mL or nornicotine greater than 30 ng/mL in urine indicates current tobacco use irrespective of whether the subject is on nicotine replacement therapy. The presence of nornicotine without anabasine is consistent with use of nicotine replacement products. Heavy tobacco users who abstain from tobacco for 2 weeks exhibit urine nicotine values below 30 ng/mL, cotinine values below 50 ng/mL, anabasine levels below 2 ng/mL, and nornicotine levels below 2 ng/mL. Passive exposure to tobacco smoke can cause accumulation of nicotine metabolites in nontobacco users. Urine cotinine has

been observed to accumulate up to 20 ng/mL from passive exposure. Neither anabasine nor nornicotine accumulates from passive exposure. Tobacco users engaged in programs to abstain from tobacco require support in the form of counseling, pharmacotherapy, and continuous encouragement. Occasionally, counselors may elect to monitor abstinence by biochemical measurement of nicotine and metabolites in a random urine specimen to verify abstinence. If results of biologic testing indicate the patient is actively using a tobacco product during therapy, additional counseling or intervention may be appropriate. Quantification of urine nicotine and metabolites while a patient is actively using a tobacco product is useful to define the concentrations that a patient achieves through self-administration of tobacco. Nicotine replacement dose can then be tailored to achieve the same concentrations early in treatment to assure adequate nicotine replacement so the patient may avoid the strong craving they may experience early in the withdrawal phase. This can be confirmed by measurement of urine nicotine and metabolite concentrations at steady state (2-3 days after replacement therapy is started). Once the patient is stabilized on the dose necessary to achieve complete replacement and responding well to therapy, the replacement dose can be slowly tapered to achieve complete withdrawal. This test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

Useful For: Detecting drug use involving stimulants, barbiturate, benzodiazepines, cocaine, opioids, tetrahydrocannabinol, alcohol, and nicotine This test is not intended for use in employment-related testing.

Interpretation: A positive result derived by this testing indicates that the patient has used one of the drugs detected by these techniques in the recent past. For information about drug testing, including estimated detection times and Result Interpretations, see Addiction rehabilitation monitoring on MayoClinicLabs.com.

Reference Values:

ADULTERANT SURVEY:
Cutoff concentrations
Oxidants: 200 mg/L
Nitrites: 500 mg/L

DRUG IMMUNOASSAY PANEL:
Negative
Screening cutoff concentrations:
Barbiturates: 200 ng/mL
Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

TARGETED OPIOID SCREEN:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Codeine: 25 ng/mL
Codeine-6-beta-glucuronide: 100 ng/mL
Morphine: 25 ng/mL
Morphine-6-beta-glucuronide: 100 ng/mL
6-monoacetylmorphine: 25 ng/mL
Hydrocodone: 25 ng/mL
Norhydrocodone: 25 ng/mL
Dihydrocodeine: 25 ng/mL
Hydromorphone: 25 ng/mL

Hydromorphone-3-beta-glucuronide: 100 ng/mL
Oxycodone: 25 ng/mL
Noroxycodone: 25 ng/mL
Oxymorphone: 25 ng/mL
Oxymorphone-3-beta-glucuronide: 100 ng/mL
Noroxymorphone: 25 ng/mL
Fentanyl: 2 ng/mL
Norfentanyl: 2 ng/mL
Meperidine: 25 ng/mL
Normeperidine: 25 ng/mL
Naloxone: 25 ng/mL
Naloxone-3-beta-glucuronide: 100 ng/mL
Methadone: 25 ng/mL
2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP): 25 ng/mL
Propoxyphene: 25 ng/mL
Norpropoxyphene: 25 ng/mL
Tramadol: 25 ng/mL
O-desmethyltramadol: 25 ng/mL
Tapentadol: 25 ng/mL
N-desmethyltapentadol: 50 ng/mL
Tapentadol-beta-glucuronide: 100 ng/mL
Buprenorphine: 5 ng/mL
Norbuprenorphine: 5 ng/mL
Norbuprenorphine glucuronide: 20 ng/mL

TARGETED BENZODIAZEPINE SCREEN:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Alprazolam: 10 ng/mL
Alpha-hydroxyalprazolam: 10 ng/mL
Alpha-hydroxyalprazolam glucuronide: 50 ng/mL
Chlordiazepoxide: 10 ng/mL
Clobazam: 10 ng/mL
N-desmethylclobazam: 200 ng/mL
Clonazepam: 10 ng/mL
7-Aminoclonazepam: 10 ng/mL
Diazepam: 10 ng/mL
Nordiazepam: 10 ng/mL
Flunitrazepam: 10 ng/mL
7-Aminoflunitrazepam: 10 ng/mL
Flurazepam: 10 ng/mL
2-Hydroxy ethyl flurazepam: 10 ng/mL
Lorazepam: 10 ng/mL
Lorazepam glucuronide: 50 ng/mL
Midazolam: 10 ng/mL
Alpha-hydroxymidazolam: 10 ng/mL
Oxazepam: 10 ng/mL
Oxazepam glucuronide: 50 ng/mL
Prazepam: 10 ng/mL
Temazepam: 10 ng/mL
Temazepam glucuronide: 50 ng/mL
Triazolam: 10 ng/mL
Alpha-hydroxytriazolam: 10 ng/mL

Zolpidem: 10 ng/mL
Zolpidem phenyl-4-carboxylic acid: 10 ng/mL

TARGETED STIMULANT SCREEN:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Methamphetamine: 100 ng/mL
Amphetamine: 100 ng/mL
3,4-Methylenedioxymethamphetamine (MDMA): 100 ng/mL
3,4-Methylenedioxy-N-ethylamphetamine (MDEA): 100 ng/mL
3,4-Methylenedioxyamphetamine (MDA): 100 ng/mL
Ephedrine: 100 ng/mL
Pseudoephedrine: 100 ng/mL
Phentermine: 100 ng/mL
Phencyclidine (PCP): 20 ng/mL
Methylphenidate: 20 ng/mL
Ritalinic acid: 100 ng/mL

ETHYL GLUCURONIDE SCREEN:
Negative

Screening cutoff concentration:
Ethyl glucuronide: 500 ng/mL

NICOTINE AND METABOLITES:
Non-tobacco user with no passive exposure:
Nicotine: <5.0 ng/mL
Cotinine: <5.0 ng/mL
Anabasine: <2.0 ng/mL
Nornicotine: <2.0 ng/mL

Clinical References: 1. Physicians' Desk Reference; 60th ed. Medical Economics Company, 2006 2. Bruntman LL, ed. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Book Company; 2006 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 4. Gutstein HB, Akil H. Opioid analgesics. In. Brunton LL, Lazo JS, Parker KL, eds: Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Companies; 2006 5. Rovine T, Ferrero CL, American Pain Society: Chronic Pain in America: Roadblocks to Relief. Roper Starch Worldwide, Inc; 1999. Updated 2001. Accessed December 13, 2024. Available at http://accurateclinic.com/wp-content/uploads/2016/04/Chronic-Pain-In-America-Roadblocks-To-Relief-1999.pdf 6. Magnani B, Kwong T. Urine drug testing for pain management. Clin Lab Med. 2012;32(32):379-390 7. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline-using clinical laboratory tests to monitor drug therapy in pain management patients. J Appl Lab Med. 2018;2(4):489-526 8. McMillin GA, Marin SJ, Johnson-Davis KL, Lawlor BG, Strathmann FG. A hybrid approach to urine drug testing using high-resolution mass spectrometry and select immunoassays. Am J Clin Pathol. 2015;143(2):234-240 9. Cone EJ, Caplan YH, Black DL, Robert T, Moser F. Urine drug testing of chronic pain patients: licit and illicit drug patterns. J Anal Toxicol. 2008;32(8):530-543 10. American Society of Addiction Medicine Consensus Statement. Appropriate Use of Drug Testing in Clinical Addiction Medicine. American Society of Addiction Medicine; 2017. Accessed December 13, 2024. Available at www.asam.org/docs/default-source/quality-science/the-asam-appropriate-use-of-drug-testing-in-clinical-addiction-medicine-full-document.pdf

ADSTM
62206

Additional Flow Stimulant (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

AGSTM
62208

Additional Flow Stimulant, LPAGF (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MGSTM
62207

Additional Flow Stimulant, LPMGF (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

VID2
45455

Additional Testing Virus Ident (Bill Only)

Reference Values:
This test is for Billing Purposes Only.
This is not an orderable test.

FADCF
75666

Adenosine Deaminase in CSF

Reference Values:
0-9 U/L

FADFL
75665

Adenosine Deaminase in Peritoneal Fluid

Reference Values:
0 - 30 U/L

FADDP
75667

Adenosine Deaminase, Pericardial Fluid

Reference Values:
0-40 U/L

FADPF
75664

Adenosine Deaminase, Pleural Fluid

Reference Values:
0 - 30 U/L

FADBC
75553

Adenosine Deaminase, RBC

Interpretation: Adenosine Deaminase (ADA) deficiency is an autosomal recessive disorder of purine metabolism primarily affecting lymphocyte development, viability, and function. Affected individuals have less than 1 percent of normal ADA catalytic activity in red cell hemolysates. ADA deficiency is the cause of 20-30 percent of SCID cases. If the patient has been recently transfused, ADA deficiency may be masked; interpret results with caution. Heterozygotes cannot be identified by this test.

Reference Values:
400 - 900 mU/g Hb

ADVQU
622150

Adenovirus DNA Detection and Quantification, Plasma

Clinical Information: Human adenoviruses (ADV) are ubiquitous, nonenveloped, double-stranded DNA viruses capable of infecting humans. ADV are classified into 7 species (A through G), and over 100 types based on serological and genetic analysis.(1) While infections can be asymptomatic, a variety of clinical presentations can occur following infection, in part due to differences in cell tropism across ADV types.(2) The most common clinical presentations include respiratory, gastrointestinal, and ocular infections. Adenovirus infections are commonly acquired in early childhood, but infections and outbreaks have been reported in adult populations as well.(3) In immunocompetent individuals, infections are typically self-limiting and do not require medical intervention. However, there is a higher risk of more severe infection, including disseminated disease, in immunocompromised patients such as solid organ and hematopoietic stem cell transplant recipients. In individuals at risk for severe disease, the most common diagnostic method is detection of the ADV DNA with various molecular assays, which have been developed to detect and quantify various ADV species and types associated with human disease.(2) Additionally, plasma specimens are used for diagnostic screening in high-risk transplant patients as a marker of dissemination. However, presence of ADV in non-blood specimens is not a definitive marker of disease, as it can be shed in urine, saliva, tears, or stool of asymptomatic patients.(3,4) Therefore, serial quantitative measurement of ADV viral load in plasma of high-risk patients is recommended to guide clinical management strategies, but there is no consensus on a definitive ADV viral load thresholds to guide therapeutic intervention.(3,4) Currently, the primary use of quantitative plasma ADV DNA assays is to monitor the trend of viral load over time as a surrogate for disease progression.

Useful For: Aiding in the diagnosis of disseminated adenovirus infections in at-risk individuals
Measuring adenoviral load in plasma to monitor disease progression and antiviral response in individuals with disseminated infection

Interpretation: The quantification range of this assay is 30 to 10,000,000 IU/mL (1.48 log to 7.00 log IU/mL), with a limit of detection (at 95% detection rate) at 30 IU/mL. An "Undetected" result indicates that ADV DNA is not detected in the plasma specimen (see Cautions). In at-risk individuals, follow-up serial weekly testing is recommended. A result of "<30 IU/mL" indicates that the ADV DNA level present in the plasma specimen is below 30 IU/mL (1.48 log IU/mL), and the assay cannot accurately quantify the ADV DNA present below this level. A quantitative value (reported in IU/mL and log IU/mL) indicates the ADV DNA level (ie, viral load) present in the plasma specimen. A result of ">10,000,000 IU/mL" indicates that the ADV DNA level present in the plasma specimen is above 10,000,000 IU/mL (7.00 log IU/mL), and this assay cannot accurately quantify the ADV DNA present above this level. An "Inconclusive" result indicates that the presence or absence of ADV DNA in the plasma specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to polymerase chain reaction inhibition or presence of interfering substance. Submission of a new specimen for testing is recommended if clinically indicated.

Reference Values:
Undetected

Clinical References: 1. Lion T. Adenovirus infections in immunocompetent and immunocompromised patients. Clin Microbiol Rev. 2014;27(3):441-462. doi:10.1128/cmr.00116-13 2. Hiwarkar P, Kosulin K, Cesaro S, et al. Management of adenovirus infection in patients after haematopoietic stem cell transplantation: state-of-the-art and real-life current approach. Rev Med Virol. 2018;28(3):e1980. doi:10.1002/rmv.1980 3. Florescu DF, Schaenman JM. AST Infectious Diseases Community of Practice. Adenovirus in solid organ transplant recipients: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13527. doi:10.1111/ctr.13527 4. Shirley JD, Yao JD. Laboratory diagnosis of adenoviral infections in transplant recipients. Clin Microbiol News. 2023;45(22):189-199. doi:10.1016/j.clinmicnews.2024.01.003

ADV
70352

Adenovirus Immunostain, Technical Component Only

Clinical Information: Adenoviruses are 65 to 80 nm, nonenveloped, regular icosahedron pathogens containing double-stranded DNA. Adenovirus infection is often associated with respiratory (HAdV-B and C) and gastrointestinal illness (HAdV-F serotypes 40 and 41) as well as conjunctivitis (HAdV-B and D). Over 51 types of immunologically distinct adenovirus serotypes have been categorized.

Useful For: Identification of adenovirus infection

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Wu E, Nemerow GR. Virus yoga: the role of flexibility in virus host cell recognition. Trends Microbiol 2004;124(4):162-169 2. Ohori NP, Michaels MG, Jaffe R, et al. Adenovirus pneumonia in lung transplant recipients. Hum Pathol 1995;26(10):1073-1079 3. Koneru B, Jaffe R, Esquivel CO, et al. Adenoviral infections in pediatric liver transplant recipients. JAMA 1987;258(4):489-492 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

LADV
89074

Adenovirus, Molecular Detection, PCR, Varies

Clinical Information: Human adenoviruses cause a variety of diseases, including pneumonia, cystitis, conjunctivitis, diarrhea, hepatitis, myocarditis, and encephalitis. In humans, adenoviruses have been recovered from almost every organ system. Infections can occur at any time of the year and in all age groups. Currently, there are over 50 adenovirus serotypes that have been grouped into 6 separate subgenera. Although adenovirus can be recovered in cell culture, it can take up to 3 weeks for the virus to be identified by culture methods (Mayo Clinic's shell vial culture provides more rapid results, reported at 2 and 5 days). Serological tests have faster turnaround times but can be less sensitive compared to culture. Polymerase chain reaction assays offer a rapid, specific, and sensitive means of diagnosis by detecting adenovirus DNA.

Useful For: Aiding in the diagnosis of adenovirus infections

Interpretation: A positive result indicates the presence of adenovirus DNA in the clinical specimen. A negative result does not rule out the presence of adenovirus because viral DNA may be present at levels below the detection limits of this assay.

Reference Values:
Negative

Clinical References: 1. Florescu DF, Schaenman JM. Adenovirus in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13527 2. Buckwalter SP, Teo R, Espy MJ, Sloan LM, Smith TF, Pritt BS. Real-time qualitative PCR for 57 human adenovirus types from multiple specimen sources. J Clin Microbiol. 2012;50(3):766-771. doi:10.1128/jcm.05629-11 3. Ebner K, Pinsker W, Lion T. Comparative sequence analysis of the hexon gene in the entire spectrum of human adenovirus serotypes: phylogenetic, taxonomic, and clinical implications. J Virol. 2005;79(20):12635-12642 4. Ebner K, Suda M, Watzinger F, Lion T. Molecular detection and quantitative analysis of the entire spectrum of human adenoviruses by a two-reaction real-time PCR assay. J Clin Microbiol. 2005;43(7):3049-3053 5. Jothikumar N, Cromeans TL, Hill VR, Lu X, Sobsey MD, Erdman DD. Quantitative real-time PCR assays for the detection of human adenoviruses and identification of serotypes 40 and 41. Appl Environ Microbiol. 2005;71(6):3131-3136 6. Robinson C, Echavarria M: Adenovirus. In: Murray PR, Baron EJ, Jorgensen JH, eds. Manual of Clinical Microbiology. ASM Press; 2007:1589-1600 7. Kaneko H, Maruko I, Iida T, et al. The possibility of human adenovirus detection from the conjunctiva in asymptomatic cases during a nosocomial infection. Cornea. 2008;27(5):527-530

AKC
608421

Adenylate Kinase Enzyme Activity, Blood

Clinical Information: Adenylate kinase (AK) is a monomeric enzyme that catalyzes the nucleotide phosphoryl interconversion of adenosine triphosphate (ATP) and adenosine monophosphate (AMP) to 2 molecules of adenosine diphosphate (ADP). The level of enzyme activity in neonates is normally mildly to moderately lower than in adults. AK deficiency (OMIM 612631) is a rare cause of autosomal recessive nonspherocytic hemolytic anemia. Although rare, AK deficient-associated anemia has been described in multiple families of varied ethnic origin. Those individuals with heterozygous genetic alterations are predominantly asymptomatic and show a normal phenotype. Those individuals with homozygous or compound heterozygous genetic alterations display congenital chronic nonspherocytic hemolytic anemia (hemoglobin [Hb] levels of 8-9 g/dL) with hyperbilirubinemia and gallstones. Patients typically present at birth or in early childhood. Some patients have psychomotor impairment, although the pathogenesis is not well understood. Concurrent glucose 6-phosphate dehydrogenase (G6PD) deficiency exacerbates the anemia (Hb 6 g/dL). AK activity levels range from 0% to 44%, although most show less than 30% activity. Carriers have normal to only mildly decreased enzyme activity (1). Patients may respond well to splenectomy.

Useful For: Assessment of adenylate kinase activity as part of the evaluation of chronic nonspherocytic hemolytic anemia

Interpretation: In adenylate kinase deficiency, values are expected to be less than 30% of normal mean, although this value should be interpreted in the context of age of the patient and other enzyme values.

Reference Values:
Only available as part of a profile. For more information see:
-HAEV1 / Hemolytic Anemia Evaluation, Blood
-EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation, Blood

> or =12 months: 195-276 U/g Hb
Reference values have not been established for patients who are younger than 12 months of age.

Clinical References: 1. Niizuma H, Kanno H, Sato A, Ogura H, Imaizumi M: Splenectomy resolves hemolytic anemia caused by adenylate kinase deficiency. Pediatr Int. 2017;59(2):228-230 2. Rapley S, Harris H. Red cell adenylate kinase activity in AK1 and AK 2-1 phenotypes. Annals of Human Genetics. 1970;33:361-364. doi:10.1111/j.1469-1809 3. Mohrenweiser HW. Frequency of enzyme deficiency variants in erythrocytes of newborn infants. Proc Natl Acad Sci U S A. 1981;78(8):5046-5050 4. Corrons JL, Garcia E, Tusell JJ, Varughese KI, West C, Beutler E. Red cell adenylate kinase deficiency: molecular study of 3 new mutations (118G>A, 190G>A, and GAC deletion) associated with hereditary nonspherocytic hemolytic anemia. Blood. 2003;102(1):353-356 5. Toren A., Brok-Simoni F, Ben-Bassat I, et al. Congenital haemolytic anaemia associated with adenylate kinase deficiency. Brit. J. Haemat. 1994;87:376-380 6. Bianchi P, Zappa M, Bredi E, et al. A case of complete adenylate kinase deficiency due to a nonsense mutation in AK-1 gene (arg107-to-stop, CGA-to-TGA) associated with chronic haemolytic anaemia. Brit. J. Haemat. 1999;105(1):75-79 7. Lachant NA, Zerez CR, Barredo J, et al. Hereditary erythrocyte adenylate kinase deficiency: A defect of multiple phosphotransferases? Blood. 1991;77(12):2774-2784 8. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia-pathophysiology, clinical aspects and laboratory diagnosis. Int J Lab Hematol. 2014;36:388-397

AK1
607455

Adenylate Kinase Enzyme Activity, Blood

Clinical Information: Adenylate kinase (AK) is a monomeric enzyme that catalyzes the nucleotide phosphoryl interconversion of adenosine triphosphate and adenosine monophosphate to 2 molecules of adenosine diphosphate. The level of enzyme activity in neonates is normally mildly to moderately lower than in adults. AK deficiency (OMIM 612631) is a rare cause of autosomal recessive nonspherocytic hemolytic anemia. Although rare, AK deficient-associated anemia has been described in multiple families of varied ethnic origin. Those individuals with heterozygous genetic alterations are predominantly asymptomatic and show a normal phenotype. Those individuals with homozygous or compound heterozygous genetic alterations display congenital chronic nonspherocytic hemolytic anemia (hemoglobin [Hb] levels of 8-9 g/dL) with hyperbilirubinemia and gallstones. Patients typically present at birth or in early childhood. Some patients have psychomotor impairment, although the pathogenesis is not well understood. Concurrent glucose 6-phosphate dehydrogenase (G6PD) deficiency exacerbates the anemia (Hb 6 g/dL). AK activity levels range from 0% to 44%, although most show less than 30% activity. Carriers have normal to only mildly decreased enzyme activity.(1) Patients may respond well to splenectomy.

Useful For: Evaluation of chronic nonspherocytic hemolytic anemia

Interpretation: In adenylate kinase deficiency, values are expected to be less than 30% of normal mean, although this value should be interpreted in the context of age of the patient and other enzyme values.

Reference Values:
> or =12 months: 195-276 U/g Hb
Reference values have not been established for patients younger than 12 months.

Clinical References: 1. Niizuma H, Kanno H, Sato A, Ogura H, Imaizumi M. Splenectomy resolves hemolytic anemia caused by adenylate kinase deficiency. Pediatr Int. 2017;59(2):228-230 2. Rapley S, Harris H. Red cell adenylate kinase activity in AK1 and AK 2-1 phenotypes. Annals of Human Genetics. 1970;33:361-364. doi:10.1111/j.1469-1809 3. Mohrenweiser HW. Frequency of enzyme deficiency

variants in erythrocytes of newborn infants. Proc Natl Acad Sci U S A. 1981;78(8):5046-5050 4. Corrons JL, Garcia E, Tusell JJ, Varughese KI, West C, Beutler E. Red cell adenylate kinase deficiency: molecular study of 3 new mutations (118G>A, 190G>A, and GAC deletion) associated with hereditary nonspherocytic hemolytic anemia. Blood. 2003;102(1):353-356 5. Toren A., Brok-Simoni F, Ben-Bassat I, et al. Congenital haemolytic anaemia associated with adenylate kinase deficiency. Brit J Haemat. 1994;87(2):376-380 6. Bianchi P, Zappa M, Bredi E, et al. A case of complete adenylate kinase deficiency due to a nonsense mutation in AK-1 gene (arg107-to-stop, CGA-to-TGA) associated with chronic haemolytic anaemia. Brit J Haemat. 1999;105(1):75-79 7. Lachant NA, Zerez CR, Barredo J, et al. Hereditary erythrocyte adenylate kinase deficiency: A defect of multiple phosphotransferases? Blood. 1991;77(12):2774-2784 8. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia-pathophysiology, clinical aspects and laboratory diagnosis. Int J Lab Hematol. 2014;36(3):388-397

ACC
604986

Adrenal Mass Panel, 24 Hour, Urine

Clinical Information: Approximately 80 million computerized tomography (CT) scans are performed in the United States every year. Adrenal tumors are found incidentally in about 5% of patients undergoing abdominal CT. Most of these tumors will be benign, but a small fraction are adrenal cortical carcinomas (ACC), a cancer with high mortality and frequent recurrence. Even for localized disease, the 5-year survival rates do not exceed 65%, while distant spread is associated with a greater than 90% mortality rate. Early diagnosis of a malignant adrenal mass is therefore imperative to assure timely and appropriate therapy. Unfortunately, CT imaging alone is very limited in its ability to distinguish benign from malignant adrenal tumors since only very small and hypodense lesions can be easily dismissed as benign. The sizeable group of patients with larger or denser tumors ends up with an arduous workup that frequently includes additional imaging studies, hormonal testing, and biopsy. However, even the latter has both a high diagnostic false-positive and false-negative rate, and ultimately the tumor is often resected, sometimes unnecessarily. On the other hand, the delays due to the diagnostic work might compromise optimal care for those tumors that prove malignant. In addition, patients who are believed to probably not have adrenal cancer after their workup, and those who opt out of surgery, often still require long-term follow up with regular re-imaging and repeated hormone testing, with resultant radiation exposure and high healthcare costs. This adrenal mass panel is a noninvasive and more accurate test to diagnose malignant adrenal tumors, via urinary steroid profiling. It differentiates ACC, a rare and lethal tumor, from benign adrenocortical adenomas (ACA), including those that overproduce corticosteroids, or mineral steroids, or sex steroids, or those that are hormonally inactive. The test utilizes both clinical and laboratory data. The clinical parameters are age at diagnosis and sex of the patient, the size of the tumor by CT scanning and its CT density in Hounsfield units, whether it was detected incidentally or not, and whether there is evidence of hormone overproduction. All of this data are readily available for almost all patients with an adrenal mass and are used by an algorithm to calculate the pretest probability of having ACC. The steroid profile testing is then performed, and the results are added into the risk calculation algorithm to generate an integrated probability. The final result will provide the referring physicians a highly accurate probability for ACC and will thereby facilitate the optimal choice of further investigation, if any, based on an informed discussion between doctor and patient. In addition, it allows, albeit with lesser accuracy, the detection of malignant adrenal tumors that are not ACCs. Finally, standalone steroid profiles can be performed for the purpose of offering the diagnosis of complex assessment of steroidal disorders, disease monitoring of patients with ACC, and for novel investigations, such as biopharma studies. Understanding the Adrenal Glands: The human body has 2 adrenal glands, one above each kidney. Adrenal glands influence many processes and functions of the body, mainly through production of 3 types of steroid hormones: -Mineralocorticoids (eg, aldosterone, which helps control blood pressure) -Glucocorticoids (eg, cortisol, which is important for metabolism, immune response, and stress) -Sex steroids (eg, DHEAS, a precursor of testosterone and estradiol) These steroids are all synthesized from cholesterol via enzymes in the adrenal glands. In benign ACA, near-normal levels of precursor and bioactive steroids are produced. By contrast, ACC frequently shows abnormal patterns of steroid production. By

measuring 25 different steroid metabolites, even subtle abnormalities can be detected. This is the basis for the assessment capability of profiling 25 steroids. In addition, catecholamines-the "flight or fight hormones"-are also synthesized in a different portion of the adrenal glands. This portion is not examined in the ACC panel. Epidemiology of Adrenal Tumors: Adrenal masses are found in 1% to 5% of the adult population. The prevalence increases with age, to around 10% in 70-year-old patients. Although the majority of these tumors are benign, around 30% of adrenal tumors (>4cm) are malignant (half are represented by ACC), and the survival rate for these patients is very poor unless detected early.

Useful For: Aiding in assessing malignancy in adrenal masses May aid in improving diagnostic and prognostic prediction and dissect disease mechanisms for the following applications: -Diagnostic assessment and follow up of adrenal cortical carcinoma -Differential diagnostic assessment of adrenal tumors -Additional assessment related to Cushing syndrome, mild autonomous cortisol secretion, primary aldosteronism, inborn errors of steroidogenesis, polycystic ovary syndrome This test is not useful for establishing eligibility for a specific treatment as results must be interpreted in conjunction with the clinical status of the patient.

Interpretation: Test provides clinical risk values based on clinical data alone as well as integrated risk values based on clinical data in combination with biochemical steroid data. Reported risk values correspond to the probability of a malignant adrenal cortical carcinoma or other malignancy (eg, sarcoma, lymphoma) as well as the probability of a benign mass (eg, adenoma, myelolipoma, cyst). Test results provide the referring physician with probabilities for a variety of outcomes, thereby aiding the interpretation of clinical status and optimal paths for further investigation, if any, based on an informed discussion between provider and patient. Test results should always be interpreted in conjunction with all other clinical findings as they cannot be interpreted as absolute evidence for the presence or absence of malignant disease. For more information see Adrenal Mass Panel Clinical Data Definition of Malignancy Predictors.

Reference Values:

Note: Due to the wide range of urine steroid metabolite concentrations seen in healthy individuals and their skewed distribution, the reference values are based on the back calculated +/- 3SD of log transformed data.

Males 18-49 years:
Androsterone: 182-29,212 mcg/24 h
Etiocholanolone: 133-23,272 mcg/24 h
Dehydroepiandrosterone: <5-81,554 mcg/24 h
16a-OH-Dehydroepiandrosterone: 13-29,945 mcg/24 h
5-Pregnenetriol: 23-7,328 mcg/24 h
5-Pregnenediol: 13-2,823 mcg/24 h
Tetrahydro-11-Corticosterone: 8-1,961 mcg/24 h
Tetrahydro-11-Deoxycorticosterone: <5-316 mcg/24 h
Pregnanediol: 12-3,812 mcg/24 h
17a-OH-Pregnanolone: 15-2,466 mcg/24 h
Pregnanetriol: 66-9,409 mcg/24 h
Pregnanetriolone: <5-550 mcg/24 h
Tetrahydrodeoxycortisol: 7-1520 mcg/24 h
Cortisol: <5-903 mcg/24 h
6B-OH-Cortisol: 13-2,303 mcg/24 h
Tetrahydrocortisol: 152-22,723 mcg/24 h
5a-Tetrahydrocortisol: 157-24,059 mcg/24 h
B-Cortol: 30-5,115 mcg/24 h
11B-OH-Androsterone: 108-11,987 mcg/24 h
11B-OH-Etiocholanolone: 22-8,312 mcg/24 h
Cortisone: 12-842 mcg/24 h

Tetrahydrocortisone: 271-44,355 mcg/24 h
a-Cortolone: 140-14,885 mcg/24 h
B-Cortolone: 72-9,740 mcg/24 h
11-Oxoetiocholanolone: 70-8,446 mcg/24 h

Males > or =50 years:
Androsterone: 118-25,389 mcg/24 h
Etiocholanolone: 127-15,640 mcg/24 h
Dehydroepiandrosterone: 7-4,260 mcg/24 h
16a-OH-Dehydroepiandrosterone: 11-6,183 mcg/24 h
5-Pregnenetriol: 24-2,162 mcg/24 h
5-Pregnenediol: 17-1,296 mcg/24 h
Tetrahydro-11-Corticosterone: 16-1,674 mcg/24 h
Tetrahydro-11-Deoxycorticosterone: <5-297 mcg/24 h
Pregnanediol: 23-1,846 mcg/24 h
17a-OH-Pregnanolone: 18-1,747 mcg/24 h
Pregnanetriol: 115-5,432 mcg/24 h
Pregnanetriolone: 5-221 mcg/24 h
Tetrahydrodeoxycortisol: 12-1,277 mcg/24 h
Cortisol: 12-597 mcg/24 h
6B-OH-Cortisol: 22-2,406 mcg/24 h
Tetrahydrocortisol: 331-19,009 mcg/24 h
5a-Tetrahydrocortisol: 155-35,266 mcg/24 h
B-Cortol: 56-3,541 mcg/24 h
11B-OH-Androsterone: 142-13,135 mcg/24 h
11B-OH-Etiocholanolone: 69-6,805 mcg/24 h
Cortisone: 24-732 mcg/24 h
Tetrahydrocortisone: 454-34,576 mcg/24 h
a-Cortolone: 211-17,591 mcg/24 h
B-Cortolone: 114-8,434 mcg/24 h
11-Oxoetiocholanolone: 155-7,174 mcg/24 h

Females 18-49 years:
Androsterone: 90-29,625 mcg/24 h
Etiocholanolone: 127-24,568 mcg/24 h
Dehydroepiandrosterone: <5-12,317 mcg/24 h
16a-OH-Dehydroepiandrosterone: 5-31,248 mcg/24 h
5-Pregnenetriol: 17-4,166 mcg/24 h
5-Pregnenediol: 6-2,900 mcg/24 h
Tetrahydro-11-Corticosterone: 13-1,548 mcg/24 h
Tetrahydro-11-Deoxycorticosterone: <5-833 mcg/24 h
Pregnanediol: 8-44,760 mcg/24 h
17a-OH-Pregnanolone: 7-3,208 mcg/24 h
Pregnanetriol: 50-9,768 mcg/24 h
Pregnanetriolone: <5-139 mcg/24 h
Tetrahydrodeoxycortisol: 7-1,047 mcg/24 h
Cortisol: 11-642 mcg/24 h
6B-OH-Cortisol: 22-2,061 mcg/24 h
Tetrahydrocortisol: 185-16,515 mcg/24 h
5a-Tetrahydrocortisol: 45-22,591 mcg/24 h
B-Cortol: 28-4260 mcg/24 h
11B-OH-Androsterone: 59-12,462 mcg/24 h
11B-OH-Etiocholanolone: 32-6,354 mcg/24 h
Cortisone: 19-749 mcg/24 h

Tetrahydrocortisone: 262-32,461 mcg/24 h
a-Cortolone: 207-13,931 mcg/24 h
B-Cortolone: 63-7,489 mcg/24 h
11-Oxoetiocholanolone: 63-7,449 mcg/24 h

Females > or =50 years:
Androsterone: 32-10,134 mcg/24 h
Etiocholanolone: 52-10,946 mcg/24 h
Dehydroepiandrosterone: <5-10,046 mcg/24 h
16a-OH-Dehydroepiandrosterone: <5-9,982 mcg/24 h
5-Pregnenetriol: 10-1,901 mcg/24 h
5-Pregnenediol: <5-2,732 mcg/24 h
Tetrahydro-11-Corticosterone: 14-1,229 mcg/24 h
Tetrahydro-11-Deoxycorticosterone: <5-123 mcg/24 h
Pregnanediol: 8-2,138 mcg/24 h
17a-OH-Pregnanolone: <5-571 mcg/24 h
Pregnanetriol: 26-3,444 mcg/24 h
Pregnanetriolone: <5-348 mcg/24 h
Tetrahydrodeoxycortisol: 8-801 mcg/24 h
Cortisol: 9-336 mcg/24 h
6B-OH-Cortisol: 25-1,365 mcg/24 h
Tetrahydrocortisol: 237-14,050 mcg/24 h
5a-Tetrahydrocortisol: 92-12,604 mcg/24 h
B-Cortol: 29-3289 mcg/24 h
11B-OH-Androsterone: 86-9,280 mcg/24 h
11B-OH-Etiocholanolone: 40-7,002 mcg/24 h
Cortisone: 15-555 mcg/24 h
Tetrahydrocortisone: 359-24,320 mcg/24 h
a-Cortolone: 125-17,472 mcg/24 h
B-Cortolone: 82-5,784 mcg/24 h
11-Oxoetiocholanolone: 78-6,571 mcg/24 h

Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Arlt W, Biehl M, Taylor AE, et al. Urine steroid metabolomics as a biomarker tool for detecting malignancy in adrenal tumors. J Clin Endocrinol Metab. 2011;96(12):3775-3784. doi:10.1210/jc.2011-1565 2. Hines JM, Bancos I, Bancos C, et al. High-resolution, accurate-mass (HRAM) mass spectrometry urine steroid profiling in the diagnosis of adrenal disorders. Clin Chem. 2017;63(12):1824-1835. doi:10.1373/clinchem.2017.271106 3. Bancos I, Arlt W. Diagnosis of a malignant adrenal mass: the role of urinary steroid metabolite profiling. Curr Opin Endocrinol Diabetes Obes. 2017;24(3):200-207. doi:10.1097/MED.0000000000000333 4. Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;175(2):G1-G34. doi:10.1530/EJE-16-0467

ACTHI
70351

Adrenocorticotropic Hormone (ACTH) Immunostain, Technical Component Only

Clinical Information: Adrenocorticotropic hormone (ACTH) is a hormone produced and secreted by corticotrophs in the adenohypophysis (anterior lobe) of the pituitary gland. Normal pituitary exhibits positive staining in a large population of cells (approximately 15% to 20%). Immunohistochemical detection of ACTH may be useful in the classification of pituitary adenomas.

Useful For: Aiding in the classification of pituitary adenomas and neoplasms with ectopic hormone production

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Hamid Z, Mrak RE, Ijaz MT, Faas FH. Sensitivity and specificity of immunohistochemistry in pituitary adenomas. The Endocrinologist. 2009;19(1):38-43 2. Osamura RY, Kajiva H, Takei M, et al: Pathology of the human pituitary adenomas. Histochem Cell Biol. 2008;130(3):495-507 3. Scheithauer BW, Jaap AJ, Horvath E, et al, Clinically silent corticotroph tumors of the pituitary gland. Neurosurgery. 2000;47(3):723-730 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

ACTH
8411

Adrenocorticotropic Hormone, Plasma

Clinical Information: Corticotropin (previously adrenocorticotropic hormone: ACTH) is synthesized by the pituitary in response to corticotropin-releasing hormone (CRH), which is released by the hypothalamus. ACTH stimulates adrenal cortisol production. Plasma ACTH and cortisol levels exhibit peaks (6-8 a.m.) and nadir (11 p.m.). Disorders of cortisol production that might affect circulating ACTH concentrations include: Hypercortisolism -Cushing syndrome: - Cushing disease (pituitary ACTH-producing tumor) - Ectopic ACTH-producing tumor - Ectopic CRH - Adrenal cortisol-producing tumor - Adrenal hyperplasia (non-ACTH dependent, autonomous cortisol-producing adrenal nodules) Hypocortisolism -Addison disease-primary adrenal insufficiency -Secondary adrenal insufficiency -Pituitary insufficiency -Hypothalamic insufficiency -Congenital adrenal hyperplasia-defects in enzymes involved in cortisol synthesis

Useful For: Determining the cause of hypercortisolism and hypocortisolism

Interpretation: In a patient with hypocortisolism, an elevated corticotropin (previously adrenocorticotropic hormone: ACTH) indicates primary adrenal insufficiency, whereas a value that is not elevated is consistent with secondary adrenal insufficiency from a pituitary or hypothalamic cause. In a patient with hypercortisolism (Cushing syndrome), a suppressed value is consistent with a cortisol-producing adrenal adenoma or carcinoma, primary adrenal micronodular hyperplasia, or exogenous corticosteroid use. Normal or elevated ACTH in a patient with Cushing syndrome puts the patient in the ACTH-dependent Cushing syndrome category. This is due to either an ACTH-producing pituitary adenoma or ectopic production of ACTH (bronchial carcinoid, small cell lung cancer, others). Further diagnostic studies such as dexamethasone suppression testing, corticotropin-releasing hormone stimulation testing, petrosal sinus sampling, and imaging studies are usually necessary to define the ACTH source. ACTH concentrations vary considerably depending on physiological conditions. Therefore, ACTH results should always be evaluated with simultaneously measured cortisol concentrations.

Reference Values:
7.2-63 pg/mL (a.m. draws)
Reference ranges are based on samples drawn between 7 a.m.-10 a.m.
No established reference values for p.m. draws
Pediatric reference values are the same as adults, as confirmed by peer reviewed literature.

Petersen KE. ACTH in normal children and children with pituitary and adrenal diseases. I. Measurement in plasma by radioimmunoassay-basal values. Acta Paediatr Scand. 1981;70(3):341-345

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364-389. 2. Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2008;93(5):1526-1540.

ADLTX
62710

Adulterants Survey, Chain of Custody, Random, Urine

Clinical Information: Specimen adulteration is the manipulation of a sample that may cause false-negative test results for the presence of drugs of abuse. Common adulterants that may affect testing are water, soap, bleach, vinegar, oxidants, and salt. The adulteration testing includes assessment of creatinine concentration, pH, urine specific gravity, presence or absence of an oxidant, and presence or absence of nitrite. Chain of custody is a record of the disposition of a specimen to document the individuals who collected the specimen, handled it, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Assess the possible adulteration of a urine specimen submitted for drug of abuse testing Providing the urine creatinine concentration for normalization purposes Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: For information see Adulterant Survey Algorithm.

Reference Values:
Cutoff concentrations
Oxidants: 200 mg/L
Nitrites: 500 mg/L

Clinical References: 1. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration (SAMHSA). Mandatory Guidelines for Federal Workplace Drug Testing Programs. Federal Register. 2017 January 23;82(13):FR 7920. Accessed July 15, 2024. Available at www.samhsa.gov/sites/default/files/workplace/frn_vol_82_7920_.pdf 2. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration (SAMHSA). Drug-Free Workplace Programs: Employer Resources. Updated October 11, 2023. Accessed July 15, 2024. Available at www.samhsa.gov/workplace/resources 3. US Department of Health and Human Services (HHS), Substance Abuse and Mental Health Services Administration (SAMHSA). Mandatory Guidelines for Federal Workplace Drug Testing Programs. Updated October 12, 2023. Accessed July 15, 2024. Available at www.federalregister.gov/documents/2023/10/12/2023-21734/mandatory-guidelines-for-federal-workplace-drug-testing-programs

ADULT
29345

Adulterants Survey, Random, Urine

Clinical Information: Specimen adulteration is the manipulation of a sample that may cause false-negative test results for the presence of drugs of abuse. Common adulterants that may affect testing are water, soap, bleach, vinegar, oxidants, and salt. The adulteration testing includes assessment of creatinine concentration, pH, urine specific gravity, presence or absence of an oxidant, and presence or absence of nitrite.

Useful For: Assessment of possible adulteration of a urine specimen submitted for drug of abuse testing Providing the creatinine concentration for normalization purposes

Interpretation: For information see Adulterant Survey Algorithm.

Reference Values:
Cutoff concentrations
Oxidants: 200 mg/L
Nitrites: 500 mg/L

Clinical References: 1. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration (SAMHSA). Mandatory Guidelines for Federal Workplace Drug Testing Programs. Federal Register. January 23, 2017;82(13):FR 7920. Accessed December 13, 2024. Available at www.samhsa.gov/sites/default/files/workplace/frn_vol_82_7920_.pdf 2. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration (SAMHSA). Drug-Free Workplace Programs: Employer Resources. Updated July 23, 2024. Accessed December 13, 2024. Available at www.samhsa.gov/workplace/resources 3. US Department of Health and Human Services (HHS), Substance Abuse and Mental Health Services Administration (SAMHSA). Mandatory Guidelines for Federal Workplace Drug Testing Programs. Updated October 12, 2023. Accessed December 13, 2024. Available at www.federalregister.gov/documents/2023/10/12/2023-21734/mandatory-guidelines-for-federal-workplace-drug-testing-programs

ISAE 45246 Aerobe Identification by Sequencing (Bill Only)

Reference Values:
This test is for billing purposes only. This is not an orderable test.

AERMC 604916 Aeromonas Culture, Feces

Clinical Information:

Useful For: Determining whether Aeromonas species may be the cause of diarrhea This test is generally not useful for patients hospitalized more than 3 days because the yield from specimens from these patients is very low, as is the likelihood of identifying a pathogen that has not been detected previously.

Interpretation: The growth of Aeromonas species identifies a potential cause of diarrhea.

Reference Values:
No growth of pathogen

Clinical References: 1. Pillai DR. Fecal culture for aerobic pathogens of gastroenteritis. In: Clinical Microbiology Procedures Handbook, 4th ed. ASM Press; 2016, Section 3.8.1 2. Pillai DR. Fecal culture for Campylobacter and related organisms. In: Clinical Microbiology Procedures

Handbook, 4th ed. ASM Press; 2016, Section 3.8.2 3. DuPont HL. Persistent diarrhea: A clinical review. JAMA. 2016;315(24):2712-2723 doi:10.1001/jama.2016.7833

ALAGP
618030

Alagille Syndrome Gene Panel, Varies

Clinical Information: Alagille syndrome (ALGS) is a multisystemic genetic condition with a wide spectrum of clinical variability. Characteristic features of ALGS include bile duct paucity, cholestasis, congenital heart defects, butterfly vertebrae, eye findings, and facial features including a broad forehead, deeply set eyes, and a small, pointed chin.(1) Approximately 40% of individuals also have kidney disease. The kidney features may include structural abnormalities (eg, small hyperechoic kidney, kidney cysts, or ureteropelvic obstruction) as well as kidney dysfunction, such as renal tubular acidosis. Disease-causing variants in the JAG1 gene account for approximately 94% to 97% of ALGS, while disease-causing NOTCH2 gene variants account for approximately 1% to 3% of cases.(1,2) A small percentage of individuals with a clinical diagnosis of ALGS do not have an identified disease-causing variant in either JAG1 or NOTCH2. The severity of ALGS is highly variable among individuals, ranging from mild and subclinical, to severe heart or liver disease requiring transplantation. ALGS is inherited in an autosomal dominant manner. Approximately 30% to 50% of individuals inherit ALGS from an affected parent, while about 50% to 70% of cases are de novo. Parental somatic mosaicism and germline mosaicism have been reported.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of Alagille syndrome Establishing a diagnosis of Alagille syndrome

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Spinner NB, Gilbert MA, Loomes KM, Krantz ID: Alagille syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated December 12, 2019. Accessed June 7, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1273/ 2. Turnpenny P, Ellard S: Alagille syndrome: pathogenesis, diagnosis and management. Eur J Hum Genet. 2012 Mar;20(3):251-257 3. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

ALT
8362

Alanine Aminotransferase (ALT) (GPT), Serum

Clinical Information: Alanine aminotransferase (ALT) is present primarily in liver cells. In viral hepatitis and other forms of liver disease associated with hepatic necrosis, serum ALT is elevated even before the clinical signs and symptoms of the disease appear. Although serum levels of both aspartate aminotransferase (AST) and ALT become elevated whenever disease processes affect liver cell integrity, ALT is a more liver-specific enzyme. Serum elevations of ALT are rarely observed in conditions other than parenchymal liver disease. Moreover, the elevation of ALT activity persists longer than does AST activity.

Useful For: Diagnosis and monitoring of liver disease associated with hepatic necrosis

Interpretation: Elevated alanine aminotransferase (ALT) values are seen in parenchymal liver diseases characterized by a destruction of hepatocytes. Values are typically at least 10 times above the normal range. Levels may reach values as high as 100 times the upper reference limit, although 20- to 50-fold elevations are most frequently encountered. In infectious hepatitis and other inflammatory conditions affecting the liver, ALT is characteristically as high as or higher than aspartate aminotransferase (AST), and the ALT:AST ratio, which normally and in other condition is less than 1, becomes greater than unity. ALT levels are usually elevated before clinical signs and symptoms of disease appear.

Reference Values:

Males

> or =1 year: 7-55 U/L

Reference values have not been established for patients who are <12 months of age.

Females

> or =1 year: 7-45 U/L

Reference values have not been established for patients who are <12 months of age.

Clinical References: Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. Philadelphia, WB Saunders Company, 1994

ALB24
606718

Albumin, 24 Hour, Urine

Clinical Information: Albumin excretion increases in patients with diabetes who are destined to develop diabetic nephropathy. More importantly, at this phase of increased albumin excretion before overt proteinuria develops, therapeutic maneuvers can be expected to significantly delay, or possibly prevent, development of nephropathy. These maneuvers include aggressive blood pressure maintenance (particularly with angiotensin-converting enzyme inhibitors), aggressive blood sugar control, and possibly decreased protein intake. Thus, there is a need for addressing small amounts of urinary albumin excretion (in the range of 30-300 mg/day, ie, microalbuminuria). The National Kidney Foundation convened an expert panel to recommend guidelines for the management of patients with diabetes and microalbuminuria. These guidelines recommend that all type 1 diabetic patients older than 12 years and all type 2 diabetic patients younger than 70 years should have their urine tested for microalbuminuria yearly when they are under stable glucose control.(1) The preferred specimen is a 24-hour collection, but a 10-hour overnight collection (9 p.m.-7 a.m.) or a random collection are acceptable. Recent studies have shown that correcting albumin for creatinine excretion rates has similar discriminatory value with respect to diabetic renal involvement, and it is now suggested that an albumin/creatinine ratio from a random urine specimen is a valid screening tool.(2) Several studies have addressed the question of whether this needs to be a fasting urine, an exercised urine, or an overnight urine specimen. From these studies, it is clear that the first-morning urine specimen is less sensitive, but more specific. A positive result should be confirmed by a first-morning random or 24-hour timed urine specimen. Studies have also shown that microalbuminuria is a marker of generalized vascular disease and is associated with stroke and heart disease.

Useful For: Evaluating diabetic patients to assess the potential for early onset of nephropathy

Interpretation: An albumin excretion rate of more than 30 mg/24 hours is considered to be microalbuminuric. By definition, the upper end of microalbuminuria is thought to be 300 mg/24 hours. Although this level has not been rigorously defined, it is felt that at this level it is more difficult to change the course of diabetic nephropathy. Laboratory normal values agree with the 30 mg/24 hour level. A normal excretion rate of 20 mcg/minute has also been established in the literature and is

consistent with the laboratory data. Thus, microalbuminuria has been defined at 30 to 300 mg/24 hours. The literature has defined the albumin/creatinine ratio (mg/g) below 17 as normal for males and below 25 for females(2) and is consistent with the laboratory's normal data. A ratio of albumin to creatinine of 300 or more indicates overt albuminuria. Thus, microalbuminuria has been defined as an albumin/creatinine ratio of 17 to 299 for males and 25 to 299 for females. Due to biologic variability, any patient who has an albumin/creatinine ratio or urinary albumin excretion rate in the positive microalbuminuria range should have this confirmed with a second specimen. If there is discrepancy, a third specimen is recommended. If 2 of 3 results are in the positive microalbuminuria range, this is evidence for incipient nephropathy and warrants increased efforts at glucose control, aggressive blood pressure control, and institution of therapy with an angiotensin-converting enzyme inhibitor (if the patient can tolerate it).

Reference Values:

24-Hour excretion: <30 mg/24 hours
Excretion rate: <20 mcg/min

Clinical References: 1. Bennett PH, Haffner S, Kasiske BL, et al: Screening and management of microalbuminuria in patients with diabetes mellitus: recommendations to the Scientific Advisory Board of the National Kidney Foundation from an ad hoc committee of the Council on Diabetes Mellitus of the National Kidney Foundation. Am J Kidney Dis. 1995;25:107-112 2. Zelmanovitz T, Gross JL, Oliveira JR, et al: The receiver operating characteristics curve in the evaluation of a random urine specimen as a screening test for diabetic nephropathy. Diabetes Care. 1997;20:516-519 3. Krolewski AS, Laffel LM, Krolewski M, et al: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. N Engl J Med. 1995;332:1251-1255 4.Miller GW, Bruns DE, Hortin GL, et al: Current Issues in Measurement and Reporting of Urinary Albumin Excretion. Clin Chem. 2009;55(1):24-38 5. Lamb EJ, Jones GRD: Kidney functions tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:480-488 6. Sacks DB: Diabetes mellitus. In: Rifai N, Horvath AR, Wittwer CT, eds.Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. In: Elsevier; 2018:1197-1199

ALBFL
60622

Albumin, Body Fluid

Clinical Information: Peritoneal fluid: Ascites is the pathologic accumulation of excess fluid in the peritoneal cavity caused by changes in vascular permeability, hydrostatic pressure, and oncotic pressure. The most common causes of ascites in individuals are cirrhosis (80%), malignancy (10%), cardiac failure (5%), and infection. Total protein results of 3.0 g/dL or greater, historically used to classify ascites fluid as transudate or exudate, has a reported accuracy of only 55% in identifying exudates and has been largely replaced with measurement of the serum-ascites albumin gradient (SAAG), calculated as serum albumin concentration minus ascites albumin concentration. SAAG has been shown to correlate directly with portal pressure and SAAG results of 1.1 g/dL or greater are 97% accurate at identifying portal hypertension. Conditions associated with high SAAG include cirrhosis, acute liver failure, fatty liver disease, alcoholic hepatitis, portal vein thrombosis, hepatic malignancy, and veno-occlusive disease. Cardiac ascitic fluid caused by congestive heart failure has both a high SAAG result (> or =1.1 g/dL) and total protein concentration greater than 2.5 g/dL. Conditions associated with low SAAG measurement (<1.1 g/dL) include peritoneal malignancy, tuberculosis, pancreatitis, connective tissue disease, and nephrotic syndrome. Pleural fluid: Pleural fluid is normally present within the pleural cavity surrounding the lungs, serving as a lubricant between the lungs and inner chest wall. Pleural effusion develops when the pleural cavity experiences an overproduction of fluid due to increased capillary hydrostatic and osmotic pressure that exceeds the ability of the lymphatic or venous system to return the fluid to circulation. Laboratory-based criteria are often used to classify pleural effusions as either exudative or transudative. Exudative effusions form due to infection or inflammation of the capillary membranes allowing excess fluid into the pleural cavity. Patients with these conditions benefit from further investigation and treatment of the local cause of inflammation. Transudative effusions form due to systemic conditions such as volume overload, end-stage renal disease, and heart failure that can lead to

excess fluid accumulation in the pleural cavity. Patients with transudative effusions benefit from treatment of the underlying condition.(1) Dr. Richard Light derived criteria in the 1970s for patients with pleural effusions that are still used today.(2) Dr. Light's criteria were designed to be sensitive for detecting exudates at the expense of specificity.(3) Heart failure and recent diuretic use contribute to most misclassifications by Dr. Light's criteria (transudates falsely categorized as exudates). Serum-to-fluid protein or albumin gradient (serum protein or albumin minus fluid protein or albumin) may be calculated in these cases and when more than 3.1 g/dL (protein) or 1.2 g/dL (albumin) suggests the patient has a transudative effusion.

Useful For: Aiding in identifying the cause of ascites Aiding in differentiating exudative and transudative pleural effusions

Interpretation: Peritoneal fluid albumin is used to calculate the serum-ascites albumin gradient. Values of 1.1 g/dL or higher suggest portal hypertension. Pleural fluid albumin may be used to calculate a serum-effusion albumin gradient. Values above 1.2 g/dL are most consistent with a transudative process. For all other fluids, the albumin concentration and gradient have only been evaluated in peritoneal and pleural fluids. All other fluid albumin concentrations should be interpreted in conjunction with serum albumin concentration and other clinical findings.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving MA, McHutchison JG. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. Ann Intern Med. 1992;117(3):215-220. doi:10.7326/0003-4819-117-3-215 2. Clinical and Laboratory Standards Institute: Analysis of Body Fluids in Clinical Chemistry; Approved Guideline. CLSI document C49-A (ISBN 1-56238-638-7). Clinical and Laboratory Standards Institute, 2007 3. Block DR, Algeciras-Schimnich A. Body fluid analysis: Clinical utility and applicability of published studies to guide interpretation of today's laboratory testing in serous fluids. Crit Rev Clin Lab Sci. 2013; 50(4-5):107-124 4. Heffner JE, Brown LK, Barbieri CA. Diagnostic value of tests that discriminate between exudative and transudative pleural effusions. Chest. 1997;111(4):970-980 5. Du L, Wei N, Maiwall R, Song Y. Differential diagnosis of ascites: etiologies, ascitic fluid analysis, diagnostic algorithm. ClinChem Lab Med.. 2023;62(7):1266-1276. Published 2023 Dec 20. doi:10.1515/cclm-2023-1112

RALB
603287

Albumin, Random, Urine

Clinical Information: Diabetic nephropathy is a complication of diabetes and is characterized by proteinuria (normal urinary albumin excretion is <30 mg/day; overt proteinuria is >300 mg/day). Before overt proteinuria develops, albumin excretion increases in those diabetic patients who are destined to develop diabetic nephropathy. Therapeutic maneuvers (eg, aggressive blood pressure maintenance, particularly with angiotensin-converting enzyme inhibitors; aggressive blood sugar control; and possibly decreased protein intake) can significantly delay, or possibly prevent, development of nephropathy. Thus, there is a need to identify small, but abnormal, increases in the excretion of urinary albumin (in the range of 30-300 mg/day, ie, microalbuminuria). The National Kidney Foundation guidelines for the management of patients with diabetes and microalbuminuria recommend that all type 1 diabetic patients older than 12 years and all type 2 diabetic patients younger than 70 years have their urine tested for microalbuminuria yearly when they are under stable glucose control.(1) The preferred specimen is a 24-hour collection, but a random collection is acceptable. Studies have shown that correcting albumin for creatinine excretion rates has similar discriminatory value with respect to diabetic renal involvement. The albumin:creatinine ratio from a random urine specimen is also considered a valid screening tool.(2) Several studies have addressed whether the specimen needs to be a

fasting urine, an exercised urine, or an overnight urine specimen. These studies have shown that the first-morning urine specimen is less sensitive, but more specific. Studies also have shown that microalbuminuria is a marker of generalized vascular disease and is associated with stroke and heart disease.

Useful For: Assessing the potential for early onset of nephropathy in diabetic patients using random urine specimens

Interpretation: In random urine specimens, normal urinary albumin excretion is below 17 mg/g creatinine for males and below 25 mg/g creatinine for females.(3) Microalbuminuria is defined as an albumin:creatinine ratio of 17 to 299 for males and 25 to 299 for females. A ratio of albumin:creatinine of 300 or higher is indicative of overt proteinuria. Due to biologic variability, positive results should be confirmed by a second, first-morning random or 24-hour timed urine specimen. If there is discrepancy, a third specimen is recommended. When 2 out of 3 results are in the microalbuminuria range, this is evidence for incipient nephropathy and warrants increased efforts at glucose control, blood pressure control, and institution of therapy with an angiotensin-converting-enzyme (ACE) inhibitor (if the patient can tolerate it).

Reference Values:
Males: <17 mg/g creatinine
Females: <25 mg/g creatinine

Clinical References: 1. Bennett PH, Haffner S, Kasiske BL, et al: Screening and management of microalbuminuria in patients with diabetes mellitus: recommendations to the Scientific Advisory Board of the National Kidney Foundation from an ad hoc committee of the Council on Diabetes Mellitus of the National Kidney Foundation. Am J Kidney Dis. 1995 Jan;25:107-112. doi: 10.1016/0272-6386(95)90636-3 2. Krolewski AS, Laffel LM, Krolewski M, Quinn M, Warram JH: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. N Engl J Med. 1995 May 11;332:1251-1255. doi: 10.1056/NEJM199505113321902 3. Zelmanovitz T, Gross JL, Oliveira JR, Paggi A, Tatsch M, Azevedo MJ: The receiver operating characteristics curve in the evaluation of a random urine specimen as a screening test for diabetic nephropathy. Diabetes Care. 1997 April;20:516-519. doi: 10.2337/diacare.20.4.516 4. Miller GW, Bruns DE, Hortin GL, et al: Current Issues in Measurement and Reporting of Urinary Albumin Excretion. Clinical Chemistry. 2009 Jan;55:1(24-38). doi: 10.1373/clinchem.2008.106567 5. Lamb EJ, Jones GRD: Kidney functions tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:480-488 6. Sacks DB: Diabetes mellitus. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. In: Elsevier; 2018:1197-1199

ALBR
609731

Albumin, Random, Urine

Clinical Information: Diabetic nephropathy is a complication of diabetes and is characterized by proteinuria (normal urinary albumin excretion is <30 mg/day; overt proteinuria is >300 mg/day). Before overt proteinuria develops, albumin excretion increases in those diabetic patients who are destined to develop diabetic nephropathy. Therapeutic maneuvers (eg, aggressive blood pressure maintenance, particularly with angiotensin-converting enzyme inhibitors; aggressive blood sugar control; and possibly decreased protein intake) can significantly delay, or possibly prevent, development of nephropathy. Thus, there is a need to identify small, but abnormal, increases in the excretion of urinary albumin (in the range of 30-300 mg/day, ie, microalbuminuria). The National Kidney Foundation guidelines for the management of patients with diabetes and microalbuminuria recommend that all type 1 diabetic patients older than 12 years and all type 2 diabetic patients younger than 70 years have their urine tested for microalbuminuria yearly when they are under stable glucose control.(1) The preferred specimen is a

24-hour collection, but a random collection is acceptable. Studies have shown that correcting albumin for creatinine excretion rates has similar discriminatory value with respect to diabetic renal involvement. The albumin:creatinine ratio from a random urine specimen is also considered a valid screening tool.(2) Several studies have addressed whether the specimen needs to be a fasting urine, an exercised urine, or an overnight urine specimen. These studies have shown that the first-morning urine specimen is less sensitive, but more specific. Studies also have shown that microalbuminuria is a marker of generalized vascular disease and is associated with stroke and heart disease.

Useful For: Assessing the potential for early onset of nephropathy in diabetic patients using random urine specimens

Interpretation: In random urine specimens, normal urinary albumin excretion is below 17 mg/g creatinine for males and below 25 mg/g creatinine for females.(3) Microalbuminuria is defined as an albumin:creatinine ratio of 17 to 299 for males and 25 to 299 for females. A ratio of albumin:creatinine of 300 or higher is indicative of overt proteinuria. Due to biologic variability, positive results should be confirmed by a second, first-morning random or 24-hour timed urine specimen. If there is discrepancy, a third specimen is recommended. When 2 out of 3 results are in the microalbuminuria range, this is evidence for incipient nephropathy and warrants increased efforts at glucose control, blood pressure control, and institution of therapy with an angiotensin-converting-enzyme (ACE) inhibitor (if the patient can tolerate it).

Reference Values:
Males: <17 mg/g creatinine
Females: <25 mg/g creatinine

Clinical References: 1. Bennett PH, Haffner S, Kasiske BL, et al: Screening and management of microalbuminuria in patients with diabetes mellitus: recommendations to the Scientific Advisory Board of the National Kidney Foundation from an ad hoc committee of the Council on Diabetes Mellitus of the National Kidney Foundation. Am J Kidney Dis. 1995 Jan;25:107-112. doi: 10.1016/0272-6386(95)90636-3 2. Krolewski AS, Laffel LM, Krolewski M, Quinn M, Warram JH: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. N Engl J Med. 1995 May 11;332:1251-1255. doi: 10.1056/NEJM199505113321902 3. Zelmanovitz T, Gross JL, Oliveira JR, Paggi A, Tatsch M, Azevedo MJ: The receiver operating characteristics curve in the evaluation of a random urine specimen as a screening test for diabetic nephropathy. Diabetes Care. 1997 April;20:516-519. doi: 10.2337/diacare.20.4.516 4. Miller GW, Bruns DE, Hortin GL, et al: Current issues in measurement and reporting of urinary albumin excretion. Clin Chem. 2009 Jan;55(1):24-38. doi: 10.1373/clinchem.2008.106567 5. Lamb EJ, Jones GRD: Kidney functions tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:480-488 6. Sacks DB: Diabetes mellitus. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. In: Elsevier; 2018:1197-1199

RALB1
606730

Albumin, Random, Urine

Clinical Information: Diabetic nephropathy is a complication of diabetes and is characterized by proteinuria (normal urinary albumin excretion is <30 mg/day; overt proteinuria is >300 mg/day). Before overt proteinuria develops, albumin excretion increases in those diabetic patients who are destined to develop diabetic nephropathy. Therapeutic maneuvers (eg, aggressive blood pressure maintenance, particularly with angiotensin-converting enzyme inhibitors; aggressive blood sugar control; and possibly decreased protein intake) can significantly delay, or possibly prevent, development of nephropathy. Thus, there is a need to identify small, but abnormal, increases in the excretion of urinary albumin (in the range of 30-300 mg/day, ie, microalbuminuria). The National Kidney Foundation

guidelines for the management of patients with diabetes and microalbuminuria recommend that all type 1 diabetic patients older than 12 years and all type 2 diabetic patients younger than 70 years have their urine tested for microalbuminuria yearly when they are under stable glucose control.(1) The preferred specimen is a 24-hour collection, but a random collection is acceptable. Studies have shown that correcting albumin for creatinine excretion rates has similar discriminatory value with respect to diabetic renal involvement. The albumin:creatinine ratio from a random urine specimen is also considered a valid screening tool.(2) Several studies have addressed whether the specimen needs to be a fasting urine, an exercised urine, or an overnight urine specimen. These studies have shown that the first-morning urine specimen is less sensitive, but more specific. Studies also have shown that microalbuminuria is a marker of generalized vascular disease and is associated with stroke and heart disease.

Useful For: Assessing the potential for early onset of nephropathy in diabetic patients using random urine specimens

Interpretation: In random urine specimens, normal urinary albumin excretion is below 17 mg/g creatinine for males and below 25 mg/g creatinine for females.(3) Microalbuminuria is defined as an albumin:creatinine ratio of 17 to 299 for males and 25 to 299 for females. A ratio of albumin:creatinine of 300 or higher is indicative of overt proteinuria. Due to biologic variability, positive results should be confirmed by a second, first-morning random or 24-hour timed urine specimen. If there is discrepancy, a third specimen is recommended. When 2 out of 3 results are in the microalbuminuria range, this is evidence for incipient nephropathy and warrants increased efforts at glucose control, blood pressure control, and institution of therapy with an angiotensin-converting-enzyme (ACE) inhibitor (if the patient can tolerate it).

Reference Values:
Only orderable as part of a profile. For more information see:
-ALBR / Albumin, Random, Urine
-RALB / Albumin, Random, Urine.

Males: <17 mg/g creatinine
Females: <25 mg/g creatinine

Clinical References: 1. Bennett PH, Haffner S, Kasiske BL, et al: Screening and management of microalbuminuria in patients with diabetes mellitus: recommendations to the Scientific Advisory Board of the National Kidney Foundation from an ad hoc committee of the Council on Diabetes Mellitus of the National Kidney Foundation. Am J Kidney Dis. 1995 Jan;25:107-112. doi: 10.1016/0272-6386(95)90636-3 2. Krolewski AS, Laffel LM, Krolewski M, Quinn M, Warram JH: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. N Engl J Med. 1995 May 11;332:1251-1255. doi: 10.1056/NEJM199505113321902 3. Zelmanovitz T, Gross JL, Oliveira JR, Paggi A, Tatsch M, Azevedo MJ: The receiver operating characteristics curve in the evaluation of a random urine specimen as a screening test for diabetic nephropathy. Diabetes Care. 1997 April;20:516-519. doi: 10.2337/diacare.20.4.516 4. Miller GW, Bruns DE, Hortin GL, et al: Current issues in measurement and reporting of urinary albumin excretion. Clin Chem 2009 Jan;55(1):24-38. doi: 10.1373/clinchem.2008.106567 5. Lamb EJ, Jones GRD: Kidney functions tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:480-488 6. Sacks DB: Diabetes mellitus. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. In: Elsevier; 2018:1197-1199

ALB
8436

Albumin, Serum

Clinical Information: Albumin is a carbohydrate-free protein, which constitutes 55% to 65% of total

plasma protein. It maintains oncotic plasma pressure, is involved in the transport and storage of a wide variety of ligands, and is a source of endogenous amino acids. Albumin binds and solubilizes various compounds, including bilirubin, calcium, long-chain fatty acids, toxic heavy metal ions, and numerous pharmaceuticals. Hypoalbuminemia is caused by several factors: impaired synthesis due either to liver disease (primary) or due to diminished protein intake (secondary), increased catabolism as a result of tissue damage and inflammation, malabsorption of amino acids, and increased renal excretion (eg, nephrotic syndrome).

Useful For: Assessing nutritional status

Interpretation: Hyperalbuminemia is of little diagnostic significance except in the case of dehydration. When plasma or serum albumin values fall below 2.0 g/dL, edema is usually present.

Reference Values:
> or =12 months: 3.5-5.0 g/dL

Reference values have not been established for patients who are <12 months of age.

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

ALBS1
610525

Albumin, Serum

Clinical Information: Albumin is a carbohydrate-free protein, which constitutes 55% to 65% of total plasma protein. It maintains oncotic plasma pressure, is involved in the transport and storage of a wide variety of ligands, and is a source of endogenous amino acids. Albumin binds and solubilizes various compounds, including bilirubin, calcium, long-chain fatty acids, toxic heavy metal ions, and numerous pharmaceuticals. Hypoalbuminemia is caused by several factors: impaired synthesis due either to liver disease (primary) or due to diminished protein intake (secondary), increased catabolism as a result of tissue damage and inflammation, malabsorption of amino acids, and increased renal excretion (eg, nephrotic syndrome). Measurement of albumin in serum is helpful when paired with albumin measured in cerebrospinal fluid (CSF) along with total IgG in serum and CSF as an aid in evaluating multiple sclerosis and other conditions where the integrity of the blood brain barrier is reviewed. The combination of these four analytes is referred to as CSF IgG index.

Useful For: Assessing nutritional status Aiding in the diagnosis of multiple sclerosis when used in conjunction with serum IgG, and cerebrospinal fluid IgG and albumin concentrations

Interpretation: Hyperalbuminemia is of little diagnostic significance except in the case of dehydration. When plasma or serum albumin values fall below 2.0 g/dL, edema is usually present.

Reference Values:
Only orderable as part of profile. For more information see: SFIG / Cerebrospinal Fluid (CSF) IgG Index Profile, Serum and Spinal Fluid.

> or =12 months: 3500-5000 mg/dL
Reference values have not been established for patients who are <12 months of age.

Clinical References: 1. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018 2. Peters T, Jr: Serum albumin. In: Putnam F, ed. The plasma proteins. Vol 1. 2nd ed. Academic Press; 1975

ALBSF
68001

Albumin, Spinal Fluid

Clinical Information: Elevated albumin concentration in spinal fluid may serve as an indicator of the permeability status of the blood-brain barrier. Comparison to a serum albumin concentration is recommended.

Useful For: Assessment of blood-brain barrier permeability

Interpretation: Elevated albumin concentrations may be observed in patients with a compromised blood-brain barrier.

Reference Values:
0.0-27.0 mg/dL

Clinical References: 1. Schliep G, Felgenhauer K. Serum-CSF protein gradients, the blood-GSF barrier and the local immune response. J Neurol. 1978;218(2):77-96 2. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

A_CR
606732

Albumin/Creatinine Ratio

Clinical Information: Diabetic nephropathy is a complication of diabetes and is characterized by proteinuria (normal urinary albumin excretion is <30 mg/day; overt proteinuria is >300 mg/day). Before overt proteinuria develops, albumin excretion increases in those diabetic patients who are destined to develop diabetic nephropathy. Therapeutic maneuvers (eg, aggressive blood pressure maintenance, particularly with angiotensin-converting enzyme inhibitors; aggressive blood sugar control; and possibly decreased protein intake) can significantly delay, or possibly prevent, development of nephropathy. Thus, there is a need to identify small, but abnormal, increases in the excretion of urinary albumin (in the range of 30-300 mg/day, ie, microalbuminuria). The National Kidney Foundation guidelines for the management of patients with diabetes and microalbuminuria recommend that all type 1 diabetic patients older than 12 years and all type 2 diabetic patients younger than 70 years have their urine tested for microalbuminuria yearly when they are under stable glucose control.(1) The preferred specimen is a 24-hour collection, but a random collection is acceptable. Studies have shown that correcting albumin for creatinine excretion rates has similar discriminatory value with respect to diabetic renal involvement. The albumin:creatinine ratio from a random urine specimen is also considered a valid screening tool.(2) Several studies have addressed whether the specimen needs to be a fasting urine, an exercised urine, or an overnight urine specimen. These studies have shown that the first-morning urine specimen is less sensitive, but more specific. Studies also have shown that microalbuminuria is a marker of generalized vascular disease and is associated with stroke and heart disease.

Useful For: Calculating the albumin concentration per creatinine Assessing the potential for early onset of nephropathy in diabetic patients using random urine specimens

Interpretation: In random urine specimens, normal urinary albumin excretion is below 17 mg/g creatinine for males and below 25 mg/g creatinine for females.(3) Microalbuminuria is defined as an albumin:creatinine ratio of 17 to 299 for males and 25 to 299 for females. A ratio of albumin:creatinine of 300 or higher is indicative of overt proteinuria. Due to biologic variability, positive results should be confirmed by a second, first-morning random or 24-hour timed urine specimen. If there is discrepancy, a third specimen is recommended. When 2 out of 3 results are in the microalbuminuria range, this is evidence for incipient nephropathy and warrants increased efforts at glucose control, blood pressure control, and institution of therapy with an angiotensin-converting-enzyme (ACE) inhibitor (if the patient can tolerate it).

Reference Values:
Only orderable as part of a profile. For more information see:
ALBR / Albumin, Random, Urine
RALB / Albumin, Random, Urine.

Males: <17 mg/g creatinine
Females: <25 mg/g creatinine

Clinical References: 1. Bennett PH, Haffner S, Kasiske BL, et al: Screening and management of microalbuminuria in patients with diabetes mellitus: recommendations to the Scientific Advisory Board of the National Kidney Foundation from an ad hoc committee of the Council on Diabetes Mellitus of the National Kidney Foundation. Am J Kidney Dis. 1995 Jan;25:107-112. doi: 10.1016/0272-6386(95)90636-3 2. Krolewski AS, Laffel LM, Krolewski M, Quinn M, Warram JH: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. N Engl J Med. 1995 May 11;332:1251-1255. doi: 10.1056/NEJM199505113321902 3. Zelmanovitz T, Gross JL, Oliveira JR, Paggi A, Tatsch M, Azevedo MJ: The receiver operating characteristics curve in the evaluation of a random urine specimen as a screening test for diabetic nephropathy. Diabetes Care. 1997 April;20:516-519. doi: 10.2337/diacare.20.4.516 4. Miller GW, Bruns DE, Hortin GL, et al: Current issues in measurement and reporting of urinary albumin excretion. Clin Chem. 2009 Jan;55:1(24-38). doi: 10.1373/clinchem.2008.106567 Lamb EJ, Jones GRD: Kidney functions tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:480-488 6. Sacks DB: Diabetes mellitus. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. In: Elsevier; 2018:1197-1199

FALBU
90309

Albuterol, Serum/Plasma

Reference Values:
Reporting limit determined each analysis

None Detected ng/mL

Peak plasma levels following a 180 mcg dose via an inhaler: 1.5 ng/mL at 13 minutes post dose

Peak plasma levels following inhalation of a cumulative dose of 1 mg and 4 mg: approximately 5 and 20 ng/mL, respectively, 5 minutes post dose

Peak plasma levels following a single 8 mg oral-sustained release tablet: 13 ng/mL at 5.0 hours post dose

Average steady-state peak and trough plasma levels following a 4 mg (normal release tablet) every 6 hours for 5 days: 15 and 9.9 ng/mL, respectively.

Serum/plasma concentrations may vary significantly depending on dose, formulation, route of administration, device, lung function, and user mechanics.

ALS
606872

Aldolase, Serum

Clinical Information: Aldolase is necessary for glycolysis in muscle as a rapid response pathway for production of adenosine triphosphate independent of tissue oxygen. Aldolase catalyzes the conversion of fructose 1,6-diphosphate into dihydroxyacetone phosphate and glyceraldehyde

3-phosphate, an important reaction in the glycolytic breakdown of glucose to lactate in muscle. Aldolase is a tetramer whose primary structure depends upon the tissue from which it was synthesized (highest expression in liver, muscle, brain). Elevated values are found in muscle diseases, such as Duchenne muscular dystrophy, dermatomyositis, polymyositis, and limb-girdle muscular dystrophy. While elevated creatinine kinase (CK) levels are more sensitive and specific for muscle disease, occasionally elevated aldolase is observed in some patients with myositis that have normal CK values.

Useful For: Detection of muscle disease

Interpretation: Measuring serum muscle enzymes is common in the evaluation of patients with muscle weakness or muscle myalgia. When elevated, serum muscle enzymes can help differentiate muscle disease derived muscle weakness from a neurogenic cause. The highest levels of aldolase are found in progressive (Duchenne) muscular dystrophy. Lesser elevations are found in dermatomyositis, polymyositis, and limb-girdle muscular dystrophy. In dystrophic conditions causing hyperaldolasemia, the increase in aldolase becomes less dramatic as muscle mass decreases.

Reference Values:
<18 years: <14.5 U/L
> or =18 years: <7.7 U/L

Clinical References: 1. Bohlmeyer TJ, Wu AH, Perryman MB. Evaluation of laboratory tests as a guide to diagnosis and therapy of myositis. Rheum Dis Clin of North Am. 1994;20(4):845-856 2. Bohan A, Peter JB, Bowman RL, Pearson CM. Computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. Medicine (Baltimore). 1977;56(4):255-286. doi:10.1097/00005792-197707000-00001 3. Thompson RA, Vignos PJ Jr. Serum aldolase in muscle disease. AMA Arch Intern Med. 1959;103(4):551-564. doi:10.1001/archinte.1959.00270040037004 4. Ganguly A. Management of muscular dystrophy during osteoarthritis disorder: A topical phytotherapeutic treatment protocol. Caspian J Intern Med. 2019;10(2):183-196. doi:10.22088/cjim.10.2.183

ALDNA
15150

Aldosterone with Sodium, 24 Hour, Urine

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone can stimulate aldosterone secretion. Urinary aldosterone levels are inversely correlated with urinary sodium excretion. Normal individuals will show a suppression of urinary aldosterone with adequate sodium repletion. Primary hyperaldosteronism, which may be caused by aldosterone-secreting adrenal adenoma/carcinomas or adrenal cortical hyperplasia, is characterized by hypertension accompanied by increased aldosterone levels, hypernatremia, and hypokalemia. Secondary hyperaldosteronism (eg, in response to renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome) is characterized by increased aldosterone levels and increased plasma rennin activity.

Useful For: Investigating primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (eg, renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome) in conjunction with urine sodium levels

Interpretation: Under normal circumstances, if the 24-hour urinary sodium excretion is greater than 200 mmol, the urinary aldosterone excretion should be less than 10 mcg/24 hours. Urinary aldosterone

excretion greater than 12 mcg/24 hours as part of an aldosterone suppression test is consistent with hyperaldosteronism. Twenty-four-hour urinary sodium excretion should exceed 200 mmol to document adequate sodium repletion. For more information see Renin-Aldosterone Studies Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology; call 800-533-1710.

Reference Values:

ALDOSTERONE
0-30 days: 0.7-11.0 mcg/24 h*
1-11 months: 0.7-22.0 mcg/24 h*
> or =1 year: 2.0-20.0 mcg/24 h

*Loeuille GA, Racadot A, Vasseur P, Vandewalle B. Blood and urinary aldosterone levels in normal neonates, infants and children. Pediatrie 1981;36(5):335-344

SODIUM
41-227 mmol/24 h
If the 24-hour urinary sodium excretion is greater than 200 mmol, the urinary aldosterone excretion should be less than10 mcg.

Clinical References: 1. Young WF Jr. Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev. 1999;7(4):207-214 2. Young WF Jr. Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am. 1997;26(4):801-827 3. Fredline VF, Taylor PJ, Dodds HM, Johnson AG. A reference method for the analysis of aldosterone in blood by high-performance liquid chromatography-atmospheric pressure chemical ionization-tandem mass spectrometry. Anal Biochem. 1997;252(2):308-313 4. Carey RM, Padia SH. Primary mineralocorticoid excess disorders and hypertension. In: Jameson JL, De Groot LJ, de Kretser DM, Giudice LC, et al: eds. Endocrinology: Adult and Pediatric. 7th ed. WB Saunders; 2016:1871-1891

ALDU
8556

Aldosterone, 24 Hour, Urine

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone can stimulate aldosterone secretion. Urinary aldosterone levels are inversely correlated with urinary sodium excretion. Normal individuals will show a suppression of urinary aldosterone with adequate sodium repletion. Primary hyperaldosteronism, which may be caused by aldosterone-secreting adrenal adenoma/carcinomas or adrenal cortical hyperplasia, is characterized by hypertension accompanied by increased aldosterone levels, hypernatremia, and hypokalemia. Secondary hyperaldosteronism (eg, in response to renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter's syndrome) is characterized by increased aldosterone levels and increased plasma rennin activity.

Useful For: Investigating primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome) using 24-hour urine collections

Interpretation: Urinary aldosterone excretion greater than 12 mcg/24 hours as part of an aldosterone suppression test is consistent with hyperaldosteronism. For more information see Renin-Aldosterone

Studies.

Reference Values:
0-30 days: 0.7-11.0 mcg/24 h*
31 days-11 months: 0.7-22.0 mcg/24 h*
> or =1 year: 2.0-20.0 mcg/24 h

*Loeuille GA, Racadot A, Vasseur P, Vandewalle B. Blood and urinary aldosterone levels in normal neonates, infants and children. Pediatrie. 1981;36(5):335-344

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Young WF Jr. Primary aldosteronism: a common and curable form of hypertension. Cardiol Rev. 1999;7(4):207-214 2. Young WF Jr. Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am. 1997;26(4):801-827 3. Fredline VF, Taylor PJ, Dodds HM, Johnson AG. A reference method for the analysis of aldosterone in blood by high-performance liquid chromatography-atmospheric pressure chemical ionization-tandem mass spectrometry. Analytical Biochem. 1997;252(2):308-313 4. Carey RM, Padia SH. Primary mineralocorticoid excess disorders and hypertension. In: Jameson JL, De Groot LJ, de Kretser DM, Giudice LC, et al, eds. Endocrinology: Adult and Pediatric. 7th ed. WB Saunders; 2016:1871-1891

APIVC
65425

Aldosterone, Inferior Vena Cava, Plasma

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. For more information see Steroid Pathways.

Useful For: Investigation using inferior vena cava plasma specimen for: -Primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) -Secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

Interpretation: A high ratio of plasma aldosterone (PA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour is a positive screening test result, a finding that warrants further testing. A PA:PRA ratio of 20 or greater is only interpretable with a PA of 15 ng/dL or greater and indicates probable primary aldosteronism. Kidney disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) above1.5. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology; call 800-533-1710.

Reference Values:
No established reference values.

Clinical References: 1. Young WF Jr. Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev. 1999;7(4):207-214 2. Young WF Jr. Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am. 1997;26(4):801-827 3. Hurwitz S, Cohen RJ, Williams GH. Diurnal variation of aldosterone and plasma renin activity: timing relation to

melatonin and cortisol and consistency after prolonged bed rest. J Appl Physiol. 2004;96:1406-1414 4. Inoue K, Goldwater D, Allison M, Seeman T, Kestenbaum BR, Watson KE. Serum aldosterone concentration, blood pressure, and coronary artery calcium: The Multi-Ethnic Study of Atherosclerosis. [published correction appears in Hypertension. 2021 Mar 3;77(3):e34].Hypertension. 2020;76(1):113-120. doi:10.1161/HYPERTENSIONAHA.120.15006

AIVC
6503

Aldosterone, Inferior Vena Cava, Serum

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. For more information see Steroid Pathways.

Useful For: Investigation using inferior vena cava specimen for: -Primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) -Secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

Interpretation: A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour is a positive screening test result, a finding that warrants further testing. An SA:PRA ratio 20 or higher is only interpretable with an SA of 15 ng/dL or higher and indicates probable primary aldosteronism. Kidney disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) greater than 1.5. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology and may be obtained by calling 800-533-1710.

Reference Values:
No established reference values.

Clinical References: 1. Young WF Jr: Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev. 1999 Jul-Aug;7(4):207-214 2. Young WF Jr: Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am. 1997 Dec;26(4):801-827 3. Hurwitz S, Cohen RJ, Williams GH: Diurnal variation of aldosterone and plasma renin activity: timing relation to melatonin and cortisol and consistency after prolonged bed rest. J Appl Physiol. 2004 Apr;96(4):1406-1414 4. Inoue K, Goldwater D, Allison M, Seeman T, Kestenbaum BR, Watson KE: Serum aldosterone concentration, blood pressure, and coronary artery calcium: The Multi-Ethnic Study of Atherosclerosis. Hypertension. 2020 Jul;76(1):113-120. doi: 10.1161/HYPERTENSIONAHA.120.15006. Erratum in: Hypertension. 2021 Mar 3;77(3):e34

APLAV
65427

Aldosterone, Left Adrenal Vein, Plasma

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone

secretion. For more information see Steroid Pathways.

Useful For: Investigation using left adrenal vein plasma specimen for: -Primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) -Secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

Interpretation: A high ratio of plasma aldosterone (PA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour is a positive screening test result, a finding that warrants further testing. A PA:PRA ratio of 20 or greater is only interpretable with a PA of 15 ng/dL or greater and indicates probable primary aldosteronism. Kidney disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) above 1.5. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology; call 800-533-1710.

Reference Values:
No established reference values.

Clinical References: 1. Young WF Jr. Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev. 1999;7(4):207-214 2. Young WF Jr. Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am. 1997;26(4):801-827 3. Hurwitz S, Cohen RJ, Williams GH. Diurnal variation of aldosterone and plasma renin activity: timing relation to melatonin and cortisol and consistency after prolonged bed rest. J Appl Physiol. 2004;96:1406-1414 4. Inoue K, Goldwater D, Allison M, Seeman T, Kestenbaum BR, Watson KE. Serum aldosterone concentration, blood pressure, and coronary artery calcium: The Multi-Ethnic Study of Atherosclerosis. [published correction appears in Hypertension. 2021 Mar 3;77(3):e34]. Hypertension. 2020;76(1):113-120. doi:10.1161/HYPERTENSIONAHA.120.15006

ALAV
6349

Aldosterone, Left Adrenal Vein, Serum

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. For more information see Steroid Pathways.

Useful For: Investigation using left adrenal vein specimen for: -Primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) -Secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

Interpretation: A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour is a positive screening test result, a finding that warrants further testing. An SA:PRA ratio of 20 or higher is only interpretable with an SA of 15 ng/dL or higher and indicates probable primary aldosteronism. Kidney disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) above 1.5. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology and may be obtained by calling 800-533-1710.

Reference Values:
No established reference values.

Clinical References: 1. Young WF Jr: Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev. 1999 Jul-Aug;7(4):207-214 2. Young WF Jr: Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am. 1997 Dec;26(4):801-827 3. Hurwitz S, Cohen RJ, Williams GH: Diurnal variation of aldosterone and plasma renin activity: timing relation to melatonin and cortisol and consistency after prolonged bed rest. J Appl Physiol. 2004 Apr;96(4):1406-1414 4. Inoue K, Goldwater D, Allison M, Seeman T, Kestenbaum BR, Watson KE: Serum aldosterone concentration, blood pressure, and coronary artery calcium: The Multi-Ethnic Study of Atherosclerosis. Hypertension. 2020 Jul;76(1):113-120. doi: 10.1161/HYPERTENSIONAHA.120.15006. Erratum in: Hypertension. 2021 Mar 3;77(3):e34

PALD
65424

Aldosterone, Plasma

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. For more information see Steroid Pathways.

Useful For: Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome) using plasma specimens

Interpretation: A high ratio of plasma aldosterone (PA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour, is a positive screening test result, a finding that warrants further testing. An PA/PRA ratio greater than or equal to 20 is only interpretable with an PA greater than or equal to 15 ng/dL and indicates probable primary aldosteronism. Kidney disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) greater than 1.5. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology and may be obtained by calling 800-533-1710.

Reference Values:
0-30 days: 17-154 ng/dL*
31 days-11 months: 6.5-86 ng/dL*
1-10 years:
< or =40 ng/dL (supine)*
< or =124 ng/dL (upright)*
> or =11 years: < or =21 ng/dL (a.m. peripheral vein specimen)

*Loeuille GA, Racadot A, Vasseur P, Vandewalle B. Blood and urinary aldosterone levels in normal neonates, infants and children. Pediatrie. 1981;36(5):335-344

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Young WF Jr. Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev. 1999;7(4):207-214 2. Young WF Jr. Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am. 1997;26(4):801-827 3. Hurwitz S, Cohen RJ, Williams GH. Diurnal variation of aldosterone and plasma renin activity: timing

relation to melatonin and cortisol and consistency after prolonged bed rest. J Appl Physiol. 2004;96(4):1406-1414 4. Inoue K, Goldwater D, Allison M, Seeman T, Kestenbaum BR, Watson KE. Serum aldosterone concentration, blood pressure, and coronary artery calcium: The Multi-Ethnic Study of Atherosclerosis. [published correction appears in Hypertension. 2021 Mar 3;77(3):e34]. Hypertension. 2020;76(1):113-120. doi:10.1161/HYPERTENSIONAHA.120.15006

APRAV 65426 Aldosterone, Right Adrenal Vein, Plasma

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. For more information see Steroid Pathways.

Useful For: Investigation using right adrenal vein plasma specimen for: -Primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) -Secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

Interpretation: A high ratio of plasma aldosterone (PA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour is a positive screening test result, a finding that warrants further testing. A PA:PRA ratio of 20 or greater is only interpretable with a PA of 15 ng/dL or greater and indicates probable primary aldosteronism. Kidney disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) above 1.5. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology; call 800-533-1710.

Reference Values:
No established reference values.

Clinical References: 1. Young WF Jr. Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev. 1999;7(4):207-214 2. Young WF Jr. Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am. 1997;26(4):801-827 3. Hurwitz S, Cohen RJ, Williams GH. Diurnal variation of aldosterone and plasma renin activity: timing relation to melatonin and cortisol and consistency after prolonged bed rest. J Appl Physiol. 2004;96:1406-1414 4. Inoue K, Goldwater D, Allison M, Seeman T, Kestenbaum BR, Watson KE. Serum aldosterone concentration, blood pressure, and coronary artery calcium: The Multi-Ethnic Study of Atherosclerosis. [published correction appears in Hypertension. 2021 Mar 3;77(3):e34]. Hypertension. 2020;76(1):113-120. doi:10.1161/HYPERTENSIONAHA.120.15006

ARAV 6348 Aldosterone, Right Adrenal Vein, Serum

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. For more

information see Steroid Pathways.

Useful For: Investigation using right adrenal vein specimen for: -Primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) -Secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

Interpretation: A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour is a positive screening test result, a finding that warrants further testing. An SA:PRA ratio of 20 or higher is only interpretable with an SA of 15 ng/dL or higher and indicates probable primary aldosteronism. Kidney disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected:normal) above 1.5. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology and may be obtained by calling 800-533-1710.

Reference Values:
No established reference values.

Clinical References: 1. Young WF Jr: Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev. 1999 Jul-Aug;7(4):207-214 2. Young WF Jr: Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am. 1997 Dec;26(4):801-827 3. Hurwitz S, Cohen RJ, Williams GH: Diurnal variation of aldosterone and plasma renin activity: timing relation to melatonin and cortisol and consistency after prolonged bed rest. J Appl Physiol. 2004 Apr;96(4):1406-1414 4. Inoue K, Goldwater D, Allison M, Seeman T, Kestenbaum BR, Watson KE: Serum aldosterone concentration, blood pressure, and coronary artery calcium: The Multi-Ethnic Study of Atherosclerosis. Hypertension. 2020 Jul;76(1):113-120. doi: 10.1161/HYPERTENSIONAHA.120.15006. Erratum in: Hypertension. 2021 Mar 3;77(3):e34

ALDS
8557

Aldosterone, Serum

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. For more information see Steroid Pathways

Useful For: Investigating primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

Interpretation: A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour, is a positive screening test result, a finding that warrants further testing. An SA/PRA ratio greater than or equal to 20 is only interpretable with an SA greater than or equal to 15 ng/dL and indicates probable primary aldosteronism. Kidney disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) greater than 1.5. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology; call 800-533-1710.

Reference Values:
0-30 days: 17-154 ng/dL*

31 days-11 months: 6.5-86 ng/dL*
1-10 years:
< or =40 ng/dL (supine)*
< or =124 ng/dL (upright)*
> or =11 years: < or =21 ng/dL (a.m. peripheral vein specimen)

*Loeuille GA, Racadot A, Vasseur P, Vandewalle B: Blood and urinary aldosterone levels in normal neonates, infants and children. Pediatrie 1981 Jul-Aug;36(5):335-344

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Young WF Jr: Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev. 1999 Jul-Aug;7(4):207-214 2. Young WF Jr: Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am. 1997 Dec;26(4):801-827 3. Hurwitz S, Cohen RJ, Williams GH: Diurnal variation of aldosterone and plasma renin activity: timing relation to melatonin and cortisol and consistency after prolonged bed rest. J Appl Physiol. 2004;96:1406-1414 4. Inoue K, Goldwater D, Allison M, Seeman T, Kestenbaum BR, Watson KE: Serum aldosterone concentration, blood pressure, and coronary artery calcium: The Multi-Ethnic Study of Atherosclerosis. Hypertension. 2020;76(1):113-120. doi: 10.1161/HYPERTENSIONAHA.120.15006

FALPE
57945

Alfalfa (Medicago sativa) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 5 6 17.50-49.99 50.0-99.99 >99.99 Very High Positive Very High Positive Very High Positive

Reference Values:
<0.35 kU/L

ALKT
619694

ALK Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information:

Useful For: Identifying mutations within the ALK gene that predict resistance to ALK-inhibitors

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. doi:10.1038/s41598-018-25462-0 3. Ou SI, Zhu VW, Nagasaka M: Catalog of 5' Fusion Partners in ALK-positive NSCLC Circa 2020. JTO Clin Res Rep. 2020 Feb 19;1(1):100015 4. Cooper AJ, Sequist LV, Lin JJ: Third-generation EGFR and ALK inhibitors: mechanisms of resistance and management. Nat Rev Clin Oncol. 2022 Aug;19(8):499-514 5. Schneider JL, Lin JJ, Shaw AT: ALK-positive lung cancer: a moving target. Nat Cancer. 2023

Mar;4(3):330-343 6. Trigg RM, Turner SD: ALK in Neuroblastoma: Biological and Therapeutic Implications. Cancers (Basel). 2018 Apr 10;10(4):113 7. Brady SW, Liu Y, Ma X, et al: Pan-neuroblastoma analysis reveals age- and signature-associated driver alterations. Nat Commun. 2020 Oct 14;11(1):5183

ALPI
622349

Alkaline Phosphatase Isoenzymes, Serum

Clinical Information: Alkaline phosphatase (ALP) is present in a number of tissues including liver, bone, intestine, and placenta. The activity of ALP found in serum is a composite of isoenzymes from those sites. Serum ALP is of interest in the diagnosis of hepatobiliary disease and bone disease associated with increased osteoblastic activity. A rise in liver ALP activity occurs with all forms of cholestasis, particularly with obstructive jaundice. Bone ALP is elevated in disorders of the skeletal system that involve osteoblast hyperactivity and bone remodeling, such as Paget disease, rickets, osteomalacia, fractures, and malignant tumors. Moderate elevation ALP may be seen in other disorders such as Hodgkin disease, congestive heart failure, ulcerative colitis, regional enteritis, and intra-abdominal bacterial infections.

Useful For: Aid in the diagnosis and treatment of liver, bone, intestinal, and parathyroid diseases Determining the tissue source of increased alkaline phosphatase (ALP) activity in serum Differentiating between liver and bone sources of elevated ALP

Interpretation: Liver alkaline phosphatase (ALP) isoenzyme is most frequently elevated when total ALP is elevated. Increased liver ALP is associated with a wide group of conditions including acute hepatitis, cirrhosis, fatty liver, drug induced liver disease, obstruction of biliary flow, bile duct stricture, primary biliary cirrhosis and metastatic carcinoma of the liver. Bone ALP is elevated due to increased osteoblastic activity. Abnormally elevated bone ALP may be indicative of bone tumors, Paget disease or renal rickets. Intestinal ALP is detectable in approximately 20% of samples tested. Intestinal ALP is most frequently noted postprandially in patients with blood group O or B. Transient hyperphosphatasemia is a temporary condition in children under 5 years, in which serum ALP activity is elevated 3-20 times the upper reference range with no clinical indications for the elevation. Transient hyperphosphatasemia of infancy and early childhood is characterized by a marked elevation of serum alkaline phosphatase in the absence of detectable liver or bone disease, with a return to normal levels within weeks or months.

Reference Values:
Only orderable as part of a profile. For more information see ALKP / Alkaline Phosphatase, Total and Isoenzymes, Serum.

Ages:
< or =17 years: Reference values have not been established for patients younger than 18 years.
> or =18 years:
Liver %: 30.2-74.7
Liver U/L: 15.8-71.9
Bone %: 23.8-68.3
Bone U/L: 12.0-56.7
Intestine %: <=22.5
Intestine U/L: <=12.6

Clinical References: 1. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 6th ed. Elsevier; 2018 2. Lowe D, Sanvictores T, John S. Alkaline phosphatase. In: StatPearls [Internet]. StatPearls Publishing; 2021. Updated October 29, 2023. Accessed April 22, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK459201 3. Teitelbaum JE,

Laskowski A, Barrows FP. Benign transient hyperphosphatasemia in infants and children: a prospective cohort. J Pediatr Endocrinol Metab. 2011;24(5-6):351-353 4. Jassam NJ, Horner J, Marzo-Ortega H, Sinclair M, Barth JH. Transient rise in alkaline phosphatase activity in adults. BMJ Case Rep. 2009;2009:bcr09.2009.2250 5. Verma J, Gorard DA. Persistently elevated alkaline phosphatase. BMJ Case Rep. 2012;2012:bcr2012006768 6. Sharma U, Pal D, Prasad R. Alkaline phosphatase: an overview. Indian J Clin Biochem. 2014;29(3):269-278

ALP
8340

Alkaline Phosphatase, Serum

Clinical Information: Alkaline phosphatase in serum consists of 4 structural genotypes: liver-bone-kidney, intestinal, and placental types, and the variant from the germ cells. It is found in osteoblasts, hepatocytes, leukocytes, the kidneys, spleen, placenta, prostate, and the small intestine. The liver-bone-kidney type is particularly important. A rise in the alkaline phosphatase occurs with all forms of cholestasis, particularly with obstructive jaundice. It is also elevated in diseases of the skeletal system, such as Paget disease, hyperparathyroidism, rickets, and osteomalacia, as well as with fractures and malignant tumors. A considerable rise in the alkaline phosphatase activity is sometimes seen in children and teenagers. It is caused by increased osteoblast activity following accelerated bone growth.

Useful For: Diagnosing and monitoring treatment of liver, bone, intestinal, and parathyroid diseases

Interpretation: Increases in serum alkaline phosphatase (ALP) activity commonly originate from either one or both of 2 sources: liver and bone. Consequently, serum ALP measurements are of particular interest in the investigation of 2 groups of conditions: hepatobiliary disease and bone disease associated with increased osteoblastic activity. Serum ALP was the first enzyme to be used for the investigation of hepatic disease. The response of the liver to any form of biliary tree obstruction induces the synthesis of ALP by hepatocytes. The newly formed coenzyme is released from the cell membrane by the action of bile salts and enters the circulation to increase the enzyme activity in serum. Increase tends to be more notable (greater than 4-fold the upper reference value [URV]) in extrahepatic obstruction (eg, by stone, by cancer of the head of the pancreas) than in intrahepatic obstruction and is greater the more complete the obstruction. Serum enzyme activities may reach 10 to 12 times the URV and usually return to baseline on surgical removal of the obstruction. A similar increase is seen in patients with advanced primary liver cancer or widespread secondary hepatic metastases. ALP increase (greater than 2-fold the URV) can predict transplant-free survival rates of patients with primary biliary cirrhosis. Liver diseases that principally affect parenchymal cells, such as infectious hepatitis, typically show only moderately (less than 3-fold) increased or even normal serum ALP activities. Increases may also be seen as a consequence of a reaction to drug therapy, and ALT/ALP-based criteria to discriminate the type of liver injury in drug-induced hepatic toxicity have been recommended. Intestinal ALP isoenzyme, an asialoglycoprotein normally cleared by the hepatic asialoglycoprotein receptors, is often increased in patients with liver cirrhosis.

Reference Values:

Males
0-14 days: 83-248 U/L
15 days-<1 year: 122-469 U/L
1-<10 years: 142-335 U/L
10-<13 years: 129-417 U/L
13-<15 years: 116-468 U/L
15-<17 years: 82-331 U/L
17-<19 years: 55-149 U/L
> or =19 years: 40-129 U/L

Females

0-14 days: 83-248 U/L
15 days-<1 year: 122-469 U/L
1-<10 years: 142-335 U/L
10-<13 years: 129-417 U/L
13-<15 years: 57-254 U/L
15-<17 years: 50-117 U/L
> or =17 years: 35-104 U/L

Clinical References: 1. Panteghini M, Bais R: Serum enzymes. In: Rifai N, Horvath AR, Wittwer C, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. Elsevier; 2018:404-434 2. Abicht K, El-Samalouti V, Junge W, et al: Multicenter evaluation of new GGT and AlP reagents with new reference standardization and determination of 37 degrees C reference intervals. Clin Chem Lab Med. 2001;39(Special Suppl):S346 3. Estey MP, Cohen AH, Colantonio DA, et al: CLSI-based transference of the CALIPER database of pediatric reference intervals from Abbott to Beckman, Ortho, Roche and Siemens Clinical Chemistry Assays: Direct validation using reference samples from the CALIPER cohort. Clin Biochem. 2013;46:1197-1219 4. Lammers WJ, van Buuren HR, Hirschfield GM, et al: Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: An international follow-up study. Gastroenterology. 2014; 147: pp. 1338-1349

ALKP
622157

Alkaline Phosphatase, Total and Isoenzymes, Serum

Clinical Information: Serum alkaline phosphatase (ALP) is used in the diagnosis of hepatobiliary disease and bone disease associated with increased osteoblastic activity. ALP is present in a number of tissues including liver, bone, intestine, and placenta. The activity of ALP found in serum is a composite of isoenzymes from those sites. A rise in liver ALP activity occurs with all forms of cholestasis, particularly with obstructive jaundice. Bone ALP is elevated in disorders of the skeletal system that involve osteoblast hyperactivity and bone remodeling, such as Paget disease, rickets, osteomalacia, fractures, and malignant tumors. Moderate elevation of ALP may be seen in other disorders such as Hodgkin disease, congestive heart failure, ulcerative colitis, regional enteritis, and intra-abdominal bacterial infections.

Useful For: Aid in the diagnosis and treatment of liver, bone, intestinal, and parathyroid diseases Determining the tissue source of increased alkaline phosphatase (ALP) activity in serum Differentiating between liver and bone sources of elevated ALP

Interpretation: Liver alkaline phosphatase (ALP) isoenzyme is most frequently elevated when total ALP is elevated. Increased liver ALP is associated with a wide group of conditions including acute hepatitis, cirrhosis, fatty liver, drug induced liver disease, obstruction of biliary flow, bile duct stricture, primary biliary cirrhosis, and metastatic carcinoma of the liver. Bone ALP is elevated due to increased osteoblastic activity. Abnormally elevated bone ALP may be indicative of bone tumors, Paget's disease, or renal rickets. Intestinal ALP is detectable in approximately 20% of samples tested. Intestinal ALP is most frequently noted postprandially in patients with blood group O or B. Transient hyperphosphatasemia is a temporary condition in children under 5 years, in which serum ALP activity is elevated 3-20 times the upper reference range with no clinical indications for the elevation. Transient hyperphosphatasemia of infancy and early childhood is characterized by a marked elevation of serum alkaline phosphatase in the absence of detectable liver or bone disease, with a return to normal levels within weeks or months.

Reference Values:
ALKALINE PHOSPHATASE
Males

0-14 days: 83-248 U/L
15 days-<1 year: 122-469 U/L
1-<10 years: 142-335 U/L
10-<13 years: 129-417 U/L
13-<15 years: 116-468 U/L
15-<17 years: 82-331 U/L
17-<19 years: 55-149 U/L
> or =19 years: 40-129 U/L
Females
0-14 days: 83-248 U/L
15 days-<1 year: 122-469 U/L
1-<10 years: 142-335 U/L
10-<13 years: 129-417 U/L
13-<15 years: 57-254 U/L
15-<17 years: 50-117 U/L
> or =17 years: 35-104 U/L

ALKALINE PHOSPHATASE ISOENZYMES
Ages:
< or =17 years: Reference values have not been established for patients younger than 18 years.
> or =18 years:
Liver %: 30.2-74.7
Liver U/L: 15.8-71.9
Bone %: 23.8-68.3
Bone U/L: 12.0-56.7
Intestine %: < or =22.5
Intestine U/L: < or =12.6

Clinical References: 1. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 6th ed. Elsevier; 2018 2. Lowe D, Sanvictores T, John S. Alkaline phosphatase. In: StatPearls [Internet]. StatPearls Publishing; 2021. Updated October 29, 2023. Accessed April 22, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK459201 3. Teitelbaum JE, Laskowski A, Barrows FP. Benign transient hyperphosphatasemia in infants and children: a prospective cohort. J Pediatr Endocrinol Metab. 2011;24(5-6):351-353 4. Jassam NJ, Horner J, Marzo-Ortega H, Sinclair M, Barth JH. Transient rise in alkaline phosphatase activity in adults. BMJ Case Rep. 2009;2009:bcr09.2009.2250 5. Verma J, Gorard DA. Persistently elevated alkaline phosphatase. BMJ Case Rep. 2012;2012:bcr2012006768 6. Sharma U, Pal D, Prasad R. Alkaline phosphatase: an overview. Indian J Clin Biochem. 2014;29(3):269-278

FABP2
57698

Allergic Bronchopulmonary Aspergillosis Panel II

Clinical Information: Aspergillus fumigatus IgG Antibody levels greater than the reference range indicate that the patient has been immunologically sensitized to the antigen. The significance of eleveated IgG depends on the nature of the antigen and the patient's clinical history. Aspergillus fumigatus Mix Gel Diffusion The gel diffusion method was used to test this patient's serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and immunological sensitization. The clinical significance varies, depending on the history and symptoms. This test was developed and its performance characteristics determined by Viracor Eurofins. It has not been cleared or approved by the FDA

Interpretation: Aspergillus fumigatus IgE Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 17.50-49.99 Very

High Positive	5	50.00-99.99	Very High Positive	6	>99.99	Very High Positive

Reference Values:

Total IgE

Age Related	Reference Range
1-11 months	0-12
1 year	0-15
2 year	1-29
3 year	4-35
4 year	2-33
5 year	8-56
6 year	3-95
7 year	2-88
8 year	5-71
9 year	3-88
10 year	7-110
11-14 year	7-111
15-19 year	6-96
20-30 year	4-59
31-50 year	5-79
51-80 year	3-48

Aspergillus fumigatus IgE
Reference Range: <0.35 kU/L
Aspergillus fumigatus IgG
Reference Range: <46 mcg/mL
Aspergillus fumigatus Mix Gel Diffusion
Reference Range: Negative

ALLOI
88888

Allo-isoleucine, Blood Spot

Clinical Information: Maple syrup urine disease (MSUD) is an inborn error of metabolism caused by the deficiency of the branched-chain-ketoacid dehydrogenase (BCKDH) complex. The BCKDH complex is involved in the metabolism of the branched-chain amino acids (BCAA) isoleucine (Ile), leucine (Leu), and valine (Val). Classic MSUD presents in the neonate with feeding intolerance, failure to thrive, vomiting, lethargy, and maple syrup odor to urine and cerumen. If untreated, it progresses to irreversible intellectual disability, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. Maple syrup urine disease is a panethnic condition but is most prevalent in the Old Order Mennonite community in Lancaster, Pennsylvania with an incidence there of 1 in 760 live births. The incidence of MSUD is approximately 1 in 185,000 live births in the general population. Newborn screening includes the measurement of BCAA (Leu, Ile, and Val), which are elevated in MSUD. However, unaffected infants receiving total parenteral nutrition frequently have increased levels of BCAA, a situation that often triggers unnecessary follow-up investigations. Abnormal concentrations of allo-isoleucine (Allo-Ile) are pathognomonic for MSUD. The determination of Allo-Ile (second-tier testing) in the same newborn screening specimens that reveal elevated BCAA allows for positive identification of patients with MSUD and differentiation from BCAA elevations due to dietary artifacts, reducing the occurrence of false-positive newborn screening results. Treatment of MSUD aims to normalize the concentration of BCAA by dietary restriction of these amino acids. BCAA are essential amino acids, which require frequent adjustment of the dietary treatment. Dietary monitoring is accomplished by regular determination of BCAA and Allo-Ile concentrations.

Useful For: Evaluation of newborn screening specimens that test positive for branched-chain amino acids elevations Follow-up of patients with maple syrup urine disease

Interpretation: Allo-isoleucine is nearly undetectable in individuals not affected by maple syrup urine disease (MSUD). Accordingly, its presence is diagnostic for MSUD, and its absence is sufficient to rule-out MSUD.

Reference Values:
Allo-isoleucine: <4 nmol/mL
Leucine: 52-269 nmol/mL
Isoleucine: 22-167 nmol/mL
Valine: 84-414 nmol/mL

An interpretive report will also be provided.

Clinical References: 1. Chace DH, Kalas TA, Naylor EW. Use of tandem mass spectrometry for multianalyte screening of dried blood specimens from newborns. Clin Chem. 2003;49(11):1797-1817. doi:10.1373/clinchem.2003.022178 2. Simon E, Fingerhut R, Baumkotter J, Konstantopoulou V, Ratschmann R, Wendel U. Maple syrup urine disease: Favorable effect of early diagnosis by newborn screening on the neonatal course of the disease. J Inherit Metab Dis. 2006;29(4):532-537. doi:10.1007/s10545-006-0315-y 3. Strauss KA, Puffenberger EG, Carson VJ. Maple syrup urine disease. In: Adam MP, Ardinger HH, Pagon RA, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated April 23, 2020. Accessed December 19, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1319/ 4. Frazier DM, Allgeier C, Homer C, et al. Nutrition management guideline for maple syrup urine disease: An evidence- and consensus-based approach. Mol Genet Metab. 2014:112(3)210-217. doi:10.1016/j.ymgme.2014.05.006 5. Blackburn PR, Gass JM, Vairo FPE, et al. Maple syrup urine disease: mechanisms and management. Appl Clin Genet. 2017;10:57-66. doi:10.2147/TACG.S125962

FALFG
57519

Almond Food IgG

Clinical Information: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

ALM
82882

Almond, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by

respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to almonds Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ALPS
82449

Alpha Beta Double-Negative T Cells for Autoimmune Lymphoproliferative Syndrome, Blood

Clinical Information: Autoimmune lymphoproliferative syndrome (ALPS) (also known as Canale-Smith syndrome) is a complex clinical disorder of dysregulated lymphocyte homeostasis that is characterized by lymphoproliferative disease, autoimmune cytopenias, splenomegaly, and lymphadenopathy with an increased susceptibility to malignancy.(1) Typically, ALPS is diagnosed by childhood or young adulthood. Genetic defects in the apoptosis (programmed cell death) pathway have been determined for most cases of ALPS. Apoptosis plays a role in normal immune homeostasis by limiting lymphocyte accumulation and autoimmune reactivity. The interaction of the surface receptor CD95 (FAS) and its ligand (CD95L; FASL) triggers the apoptotic pathway in lymphocytes. Germline variants in CD95 (FAS) are the most common cause (60-75%) of ALPS(2), followed by somatic mutations in CD95 (FAS). Variants in CD95L (FASL), CASP10, and others are rare causes. Currently

up to 20% of patients do not have an identifiable genetic variant (ALPS-U). Patients with ALPS have an increase in a normally rare population of T cells (typically <1%) that are alpha beta T-cell receptor (TCR)-positive, as well as negative for both CD4 and CD8 coreceptors (double-negative T cells: DNT).(1) The alpha beta TCR+DNT cells from ALPS patients may also express an unusual B-cell-specific CD45R isoform, called B220.(3,4) Several other diseases can present with an ALPS-like phenotype, including other inborn errors of immunity, like CTLA4 and LRBA deficiency, and gain-of function variants in STAT3 and CARD11 genes(2,5), as well as independent conditions like Evans syndrome (a combination of autoimmune hemolytic anemia and autoimmune thrombocytopenic purpura), Rosai-Dorfman disease (massive painless cervical lymphadenopathy that may be accompanied by leukocytosis, elevated erythrocyte sedimentation rate, and hypergammaglobulinemia), and nodular lymphocyte-predominant Hodgkin disease, among others.(1,2,5) B220 expression on double negative T cells has also been described in large granular lymphocyte leukemias.(4)

Useful For: Diagnosing autoimmune lymphoproliferative syndrome, primarily in patients younger than 45 years

Interpretation: The presence of increased circulating T cells (CD3+) that are negative for CD4 and CD8 (double-negative T cells: DNT) and positive for the alpha/beta T-cell receptor (TCR) is required for the diagnosis of autoimmune lymphoproliferative syndrome (ALPS). The laboratory finding of increased alpha beta TCR+DNT cells is consistent with ALPS only with the appropriate clinical picture (nonmalignant lymphadenopathy, splenomegaly, and autoimmune cytopenias). Conversely, there are other immunological disorders, including common variable immunodeficiency (CVID), which have subsets for patients with this clinical picture, but no increase in alpha beta TCR+DNT cells. If the percent of the absolute count of either the alpha beta TCR+DNT cells or alpha beta TCR+DNT B220+ cells is abnormal, additional testing is indicated. All abnormal alpha beta TCR+DNT cell results should be confirmed (for ALPS) with additional testing for defective in vitro lymphocyte apoptosis followed by confirmatory genetic testing (ALPSG / Autoimmune Lymphoproliferative Syndrome [ALPS] Gene Panel, Varies).

Reference Values:

Alpha beta TCR+DNT cells
2-18 years: <2% CD3 T cells
19-70+ years: <3% CD3 T cells
Reference values have not been established for patients that are younger than 24 months of age.

Alpha beta TCR+DNT cells
2-18 years: <35 cells/mcL
19-70+ years: <35 cells/mcL
Reference values have not been established for patients that are younger than 24 months of age.

Alpha beta TCR+DNT B220+ cells
2-18 years: <0.4% CD3 T cells
19-70+ years: <0.3% CD3 T cells
Reference values have not been established for patients that are younger than 24 months of age.

Alpha beta TCR+DNT B220+ cells
2-18 years: <7 cells/mcL
19-70+ years: <6 cells/mcL
Reference values have not been established for patients that are younger than 24 months of age.

TCR = T-cell receptor
DNT = Double negative T cell

Clinical References: 1. Oliveira JB, Bleesing JJ, Dianzani U, et al. Revised diagnostic criteria and

classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH International Workshop. Blood. 2010;116(14):e35-40 2. Consonni F, Gambineri E, Favre C. ALPS, FAS, and beyond: from inborn errors of immunity to acquired immunodeficiencies. Ann Hematol. 2022;101(3):469-484. doi:10.1007/s00277-022-04761-7 3. Bleesing JJ, Brown MR, Dale JK, et al. TCR alpha beta+ CD4-CD8-T-cells in humans with the autoimmune lymphoproliferative syndrome express a novel CD45 isoform that is analogous to urine B220 and represents a marker of altered O-glycan biosynthesis. Clin Immunol. 2001;100(3):314-324 4. Bleesing JJ, Janik JE, Fleisher TA. Common expression of an unusual CD45 isoform on T-cells from patients with large granular lymphocyte leukemia and autoimmune lymphoproliferative syndrome. Br J Haematol. 2003;120(1):93-96 5. Lopez-Nevado M, Gonzalez-Granado LI, Ruiz-Garcia R, et al. Primary immune regulatory disorders with an autoimmune lymphoproliferative syndrome-like phenotype: Immunologic evaluation, early diagnosis and management. Front Immunol. 2021;12:671755. doi:10.3389/fimmu.2021.671755

ALDEF
607710

Alpha Defensin, Lateral Flow Assay, Synovial Fluid

Clinical Information: Diagnosis of prosthetic joint infections (PJI) may be challenging in certain clinical scenarios. Multiple societies have defined criteria for establishing the presence of a PJI, including results from laboratory tests, clinical findings, and tissue histopathology. The challenge, however, is that results of these tests are frequently not available at the time of or after surgery. As an alternative, determining the cell count and differential on synovial fluid are frequently used biomarkers for PJI, however there is a lack of consensus on the optimal thresholds to use for a PJI diagnosis. Additionally, cell count and differential results require clinician interpretation as laboratories do not report abnormal levels correlating with PJI. Alpha defensins are antimicrobial peptides released by activated neutrophils in response to infection and served as part of the host-defense innate immune system with broad antimicrobial activity against gram-positive and gram-negative bacteria, mycobacteria, fungi, and viruses. The presence of alpha defensins in synovial fluid may therefore be used by clinicians as a marker of PJI.

Useful For: Detection of alpha defensins 1-3, human host response proteins, in synovial fluid of adults with a total joint replacement who are being evaluated for revision surgery This test is not intended to be used to determine timing for reimplantation in 2-stage procedures.

Interpretation: Negative: No alpha defensin detected in synovial fluid, suggesting absence of prosthetic joint infection. Positive: Alpha defensin in synovial fluid detected suggesting presence of prosthetic joint infection. Additional microbiologic studies (eg, culture, molecular detection) are recommended.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: Bonanzinga T, Ferrari MC, Tanzi G, Vandenbulcke F, Zahar A, Marcacci M. The role of alpha defensin in prosthetic joint infection (PJI) diagnosis: a literature review. EFORT Open Rev. 2019;4(1):10-13

AFSH
71768

Alpha Follicle Stimulating Hormone Immunostain, Technical Component Only

Clinical Information: Follicle stimulating hormone (FSH) alpha subunit is a component common to all glycoprotein hormones produced by the anterior pituitary (luteinizing hormone, thyroid-

stimulating hormone, and FSH). Glycoprotein hormone-producing cells (approximately 30% of the total cell population) in normal pituitary stain in a cytoplasmic pattern. Immunohistochemical detection of alpha-FSH may be useful in the classification of pituitary adenomas.

Useful For: May aid in the classification of pituitary adenomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Hamid Z, Mrak RE, Ijaz MT, Faas FH. Sensitivity and specificity of immunohistochemistry in pituitary adenomas. The Endocrinologist. 2009;19(1):38-43 2. Osamura RY, Kajiya H, Takei M, et al. Pathology of the human pituitary adenomas. Histochem Cell Biol. 2008;130(3):495-507 3. Osamura RY, Watanabe K. Immunohistochemical studies of human FSH producing pituitary adenomas. Virchows Arch A Pathol Anat Histopathol. 1988;413(1):61-68 4. Pawlikowski M, Pisarek H, Kubiak R, Jaranowska M, Stepien H. Immunohistochemical detection of FSH receptors in pituitary adenomas and adrenal tumors. Folia Histochem Cytobiol. 2012;50(3):325-330 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. Doi:10.1007/978-1-4939-8935-5_25

WAGDR
621361

Alpha Globin Cluster Locus Deletion/Duplication, Blood

Clinical Information: Thalassemias are a group of inherited conditions characterized by decreased synthesis of one or more of the globin chains, resulting in an imbalance in the relative amounts of the alpha and beta chains. The excess normal chains precipitate in the cell, damaging the membrane and leading to premature red blood cell destruction. Additionally, the defect in hemoglobin synthesis produces a hypochromic, microcytic anemia. The frequency of thalassemia is due to the protective advantage against malaria that it gives carriers. Consequently, thalassemias are prevalent in populations from equatorial regions in the world where malaria is endemic. Alpha-thalassemia is caused by decreased synthesis of alpha-globin chains. Four alpha-globin genes are normally present (2 on each chromosome 16). One, 2, 3, or 4 alpha-globin genes may be deleted or, less commonly, contain variants. Deletions account for approximately 90% of disease-causing alleles in alpha thalassemia. Phenotypically, these deletions result in 4 categories of disease expression: -Deletion of 1 alpha-chain: Silent carrier state, with a normal phenotype -Deletion of 2 alpha-chains: Alpha-thalassemia trait (alpha-1 thalassemia), with mild hematologic changes but no major clinical difficulties -Deletion of 3 alpha-chains: Hemoglobin H disease, which is extremely variable but usually includes anemia due to hemolysis, jaundice, and hepatosplenomegaly -Deletion of all 4 alpha-chains: Hemoglobin Barts hydrops fetalis, and almost invariably in utero fetal demise or early after birth, if left untreated. Samples with protein effects of intrauterine transfusion are increasingly common. Less frequently, alpha-thalassemia results from single point alterations, such as hemoglobin Constant Spring (HBA2: c.427T >C). Alpha-thalassemia occurs in all ancestral groups but is especially common in individuals of Southeast Asian and African ancestry. It is also frequent in individuals of Mediterranean ancestry. The carrier frequency is estimated to be 1 in 20 for Southeast Asians, 1 in 30 for Africans, and 1 in 30 to 1 in 50 for individuals of Mediterranean ancestry. Both deletional and nondeletional (caused by sequence alterations) forms of alpha-thalassemia are found in individuals with Mediterranean ancestry. Those of Arab ancestry can carry a fairly common sequence alteration, called alpha T-Saudi. Deletions in cis (two deletions on the same chromosome) are rare in African or Mediterranean populations but are prevalent in Asian populations. Couples in which both partners carry deletions in cis are at risk of having a child with hemoglobin H disease or hemoglobin Bart

hydrops fetalis syndrome.

Useful For: Diagnosis of alpha-thalassemia Carrier screening for individuals from high-risk populations for alpha-thalassemia This test is not useful for diagnosis or confirmation of beta-thalassemia or hemoglobinopathies.

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Harteveld CL, Voskamp A, Phylipsen M, et al. Nine unknown rearrangements in 16p13.3 and 11p15.4 causing alpha- and beta-thalassaemia characterized by high resolution multiplex ligation-dependent probe amplification. J Med Genet. 2005;42(12):922-931. doi:10.1136/jmg.2005.033597 2. Harteveld CL, Higgs DR. Alpha-thalassemia. Orphanet J Rare Dis. 2010;5:13. doi:10.1186/1750-1172-5-13 3. Bunn HF, Forget BG. Hemoglobin: Molecular, Genetic and Clinical Aspects. 2nd ed. WB Saunders Company; 1986 4. Weatherall DJ, Higgs DR, Clegg JB, Hill AS, Nicholls R. Heterogeneity and origins of the alpha-thalassemias. Birth Defects Origi Artic Ser. 1987;23(5A):3-14 5. Musallam KM, Cappellini DM, Coates TD, et al. ?lpha-thalassemia: A practical overview. Blood Rev. 2024;64:101165. doi.10.1016/j.blre.2023.101165

AGDD
620985

Alpha Globin Cluster Locus Deletion/Duplication, Varies

Clinical Information: Thalassemias are a group of inherited conditions characterized by decreased synthesis of one or more of the globin chains, resulting in an imbalance in the relative amounts of the alpha and beta chains. The excess normal chains precipitate in the cell, damaging the membrane and leading to premature red blood cell destruction. Additionally, the defect in hemoglobin synthesis produces a hypochromic, microcytic anemia. The frequency of thalassemia is due to the protective advantage against malaria that it gives carriers. Consequently, thalassemias are prevalent in populations from equatorial regions in the world where malaria is endemic. Alpha-thalassemia is caused by decreased synthesis of alpha-globin chains. Four alpha-globin genes are normally present (2 on each chromosome 16). One, 2, 3, or 4 alpha-globin genes may be deleted or, less commonly, contain variants. Deletions account for approximately 90% of disease-causing alleles in alpha thalassemia. Phenotypically, these deletions result in 4 categories of disease expression: -Deletion of 1 alpha-chain: Silent carrier state, with a normal phenotype -Deletion of 2 alpha-chains: Alpha-thalassemia trait (alpha-1 thalassemia), with mild hematologic changes but no major clinical difficulties -Deletion of 3 alpha-chains: Hemoglobin H disease, which is extremely variable but usually includes anemia due to hemolysis, jaundice, and hepatosplenomegaly -Deletion of all 4 alpha-chains: Hemoglobin Barts hydrops fetalis and, almost invariably, in utero fetal demise or early after birth if left untreated. Samples with protein effects of intrauterine transfusion are increasingly common. Less frequently, alpha-thalassemia results from single point alterations, such as hemoglobin Constant Spring (HBA2: c.427T >C). Alpha-thalassemia occurs in all ancestral groups but is especially common in individuals of Southeast Asian and African ancestry. It is also frequent in individuals of Mediterranean ancestry. The carrier frequency is estimated to be 1 in 20 for Southeast Asians, 1 in 30 for African, and 1 in 30 to 1 in 50 for individuals of Mediterranean ancestry. Both deletional and nondeletional (caused by sequence alterations) forms of alpha-thalassemia are found in individuals with Mediterranean ancestry. Those of Arab ancestry can carry a fairly common sequence alteration, called alpha-T-Saudi. Deletions in cis (two deletions on the same chromosome) are rare in African or Mediterranean populations but are prevalent in Asian populations. Couples in which both partners carry deletions in cis are at risk of having a child with hemoglobin H disease or hemoglobin Bart hydrops fetalis syndrome.

Useful For: Diagnosis of alpha-thalassemia Carrier screening for individuals from high-risk populations for alpha-thalassemia This test is not useful for diagnosis or confirmation of beta-thalassemia or hemoglobinopathies.

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Harteveld CL, Voskamp A, Phylipsen M, et al. Nine unknown rearrangements in 16p13.3 and 11p15.4 causing alpha- and beta-thalassaemia characterized by high resolution multiplex ligation-dependent probe amplification. J Med Genet. 2005;42(12):922-931. doi:10.1136/jmg.2005.033597 2. Harteveld CL, Higgs DR. Alpha-thalassemia. Orphanet J Rare Dis. 2010;5:13. doi:10.1186/1750-1172-5-13 3. Bunn HF, Forget BG. Hemoglobin: Molecular, Genetic and Clinical Aspects. 2nd ed. WB Saunders Company; 1986 4. Weatherall DJ, Higgs DR, Clegg JB, Hill AS, Nicholls R. Heterogeneity and origins of the alpha-thalassemias. Birth Defects Origi Artic Ser. 1987;23(5A):3-14 5. Musallam KM, Cappellini DM, Coates TD, et al. Alpha-thalassemia: A practical overview. Blood Rev. 2024;64:101165. doi:10.1016/j.blre.2023.101165

WASEQ 61362 Alpha Globin Gene Sequencing, Varies

Clinical Information: Alpha-globin gene sequencing detects alpha-globin variants and nondeletional alpha-thalassemia variants. Alpha thalassemia is the most common monogenic condition in the world. It is estimated that up to 5% of the world's population carries at least one alpha-thalassemia variant and, in the United States, approximately 30% of African Americans are thought to carry an alpha-thalassemia variant. Alpha-thalassemia variations are most common in individuals of Southeastern Asian, African, Mediterranean, Indian, and Middle Eastern descent, but they can be found in persons from any ethnic group. Four alpha-globin genes are normally present, 2 copies on each chromosome 16. Alpha-thalassemia variants result in decreased alpha-globin chain production. In general, alpha thalassemia is characterized by hypochromic, microcytic anemia and varies clinically from asymptomatic (alpha-thalassemia silent carrier and alpha-thalassemia trait) to lethal hemolytic anemia (hemoglobin [Hb] Barts hydrops fetalis). Large deletions of the alpha-globin genes account for approximately 90% of alpha-thalassemia alterations, and these variations will not be detected by alpha-globin gene sequencing. Other variants, such as point alterations or small deletions within the alpha-globin genes, account for most of the remaining 10% of alpha-thalassemia variations. These nondeletional subtypes can be detected by alpha-globin gene sequencing. The most common nondeletional alpha-thalassemia variant is Hb Constant Spring. The majority of alpha-globin chain variants are clinically and hematologically benign however, some cause erythrocytosis and chronic hemolytic anemia. Hemoglobin electrophoresis may not be able to confirm their identity. In these instances, alpha-globin gene sequencing can be useful.

Useful For: Diagnosing nondeletional alpha thalassemia Testing for nondeletional alpha thalassemia in a symptomatic individual Follow-up testing to an abnormal hemoglobin electrophoresis that identified an alpha-globin chain variant

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Harteveld CL, Higgs DR: Alpha-thalassemia. Orphanet J Rare Dis. 2010;5:13 2. Hoyer JD, Hoffman DR: The Thalassemia and hemoglobinopathy syndromes. In:

McClatchey, KD, ed. Clinical Laboratory Medicine. 2nd ed. Lippincott Williams and Wilkins. 2002;866-895 3. Farashi S, Harteveld CL: Molecular basis of a-thalassemia. Blood Cells Mol Dis. 2018 May;70:43-53. doi: 10.1016/j.bcmd.2017.09.004 4. Henderson SJ, Timbs AT, McCarthy J, et al: Ten years of routine a- and B-globin gene sequencing in UK hemoglobinopathy referrals reveals 60 novel mutations. Hemoglobin. 2016;40(2):75-84. doi: 10.3109/03630269.2015.1113990

FALG
57663

Alpha Lactalbumin IgG

Clinical Information: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

FA1GP
57736

Alpha-1-Acid Glycoprotein

Reference Values:
Adults: 39 – 115 mg/dL

A1AFS
604982

Alpha-1-Antitrypsin Clearance, Feces and Serum

Clinical Information: Alpha-1-antitrypsin (AAT) is a 54-kDa glycoprotein that is resistant to degradation by digestive enzymes and is, therefore, used as an endogenous marker for the presence of blood proteins in the intestinal tract. AAT clearance is reliable for measuring protein loss distal to the pylorus. A serum sample is required to interpret results as a serum deficiency of AAT would make the AAT fecal excretion lower and could invalidate the test utility. Gastrointestinal protein enteropathy has been associated with regional enteritis, sprue, Whipple intestinal lipodystrophy, gastric carcinoma, allergic gastroenteropathy, intestinal lymphangiectasia, constrictive pericarditis, congenital hypogammaglobulinemia, and iron deficiency anemia associated with intolerance to cow's milk. Increased fecal excretion of AAT can be found in small and large intestine disease and is applicable to adult and children.

Useful For: Diagnosing protein-losing enteropathies

Interpretation: Elevated alpha-1-antitrypsin (AAT) clearance suggests excessive gastrointestinal protein loss. The positive predictive value of the test has been found to be 97.7% and the negative predictive value is 75%. Patients with protein-losing enteropathies generally have AAT clearance values greater than 50 mL/24 hours and AAT fecal concentrations above 100 mg/dL. Borderline elevations above the normal range are equivocal for protein-losing enteropathies.

Reference Values:
CLEARANCE:
< or =27 mL/24 h

FECAL ALPHA-1-ANTRYPSIN CONCENTRATION:
< or =54 mg/dL

SERUM ALPHA-1-ANTRYPSIN CONCENTRATION:
100-190 mg/dL

Clinical References: 1. Florent C, L'Hirondel C, Desmazures C, Aymes C, Bernier JJ. Intestinal clearance of alpha 1-antitrypsin. A sensitive method for the detection of protein losing enteropathy. Gastroenterology. 1981;81(4):777-780 2. Crossley JR, Elliott RB. Simple method for diagnosing protein-losing enteropathies. Br Med J. 1977;1(6058):428-429 3. Perrault J, Markowitz H. Protein-losing gastroenteropathy and the intestinal clearance of serum alpha-1-antitrypsin. Mayo Clin Proc. 1984;59(4):278-279 4. Schmidt PN, Blirup-Jensen S, Svendsen PJ, Wandall JH. Characterization and quantification of plasma proteins excreted in faeces from healthy humans. Scand J Clin Lab Invest. 1995;55(1):35-45 5. Davidson NO: Intestinal lipid absorption. In: Yamada T, Alpers DH, Kaplowitz N, eds. Textbook of Gastroenterology. JB Lippincott; 2003:413 6. Rybolt AH, Bennett RG, Laughon BE, Thomas DR, Greenough WB 3rd, Bartlett JG: Protein-losing enteropathy associated with Clostridium difficile infection. Lancet. 1989;1(8651):1353-1355 7. Molina JF, Brown RF, Gedalia A, Espinoza LR. Protein losing enteropathy as the initial manifestation of childhood systemic lupus erythematosus. J Rheumatol. 1996;23(7):1269-1271 8. Umar SB, DiBaise JK. Protein-losing enteropathy: case illustrations and clinical review. Am J Gastroenterol. 2010;105(1):43-49 9. Levitt DG, Levitt MD. Protein losing enteropathy: comprehensive review of the mechanistic association with clinical and subclinical disease states. Clin Exp Gastroenterol. 2017;10:147-168 10. Murray FR, Morell B, Biedermann L, Schreiner P. Protein-losing enteropathy as precursor of inflammatory bowel disease: A review of the literature. BMJ Case Rep. 2021;14(1):e238802

AATRP
70350

Alpha-1-Antitrypsin Immunostain, Technical Component Only

Clinical Information: Alpha-1-antitrypsin (AAT) is a plasma protein synthesized in the liver and present in serum and tissue fluids where it acts as an inhibitor of proteases, especially elastase. AAT deficiency is associated with development of emphysema and liver disease. In liver disease, abnormal accumulation of AAT is seen as cytoplasmic globules in hepatocytes.

Useful For: Identification of abnormal accumulation of alpha-1-antitrypsin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Callea F, Fevery J, Massi G, Lievens C, de Groote J, Desmet VJ. Alpha-1-antitrypsin (AAT) and its stimulation in the liver of PiMZ phenotype individuals. A "recruitment-secretory block" ("R-SB") phenomenon. Liver. 1984:4(5):325-337 2. Lam M, Torbenson M, Yeh MM, Vivekanandan P, Ferrell L. HFE mutations in alpha-1-antitrypsin deficiency: an examination of cirrhotic explants. Mod Pathol. 2010;23:637-643 3. Theaker JM, Fleming KA. Alpha-1-antitrypsin and the liver: a routine immunohistological screen. J Clin Pathol. 1986;39(1):58-62 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

A1APP
26953

Alpha-1-Antitrypsin Phenotype, Serum

Clinical Information: Alpha-1-antitrypsin (A1A) is the most abundant serum protease inhibitor and inhibits trypsin and elastin, as well as several other proteases. The release of proteolytic enzymes from plasma onto organ surfaces and into tissue spaces results in tissue damage unless inhibitors are present. Congenital deficiency of A1A is associated with the development of emphysema at an unusually early age and with an increased incidence of neonatal hepatitis, usually progressing to cirrhosis. The gene for A1A appears to be coded at a single locus whose alleles are inherited in a co-dominant manner. Most normal individuals have the M phenotype (M, M1, or M2). Over 99% of M phenotypes are genetically homozygous M (MM). In the absence of family studies, the phenotype (M) and quantitative level can be used to infer the genotype MM. The most common alleles associated with a quantitative deficiency are Z and S. For more information see Alpha-1-Antitrypsin-A Comprehensive Testing Algorithm.

Useful For: Identification of homozygous and heterozygous phenotypes of the alpha-1-antitrypsin deficiency

Interpretation: There are greater than 40 alpha-1-antitrypsin (A1A) phenotypes (most of these are associated with normal quantitative levels of protein). The most common normal phenotype is M (M, M1, or M2), and greater than 90% of individuals of European descent are genetically homozygous M (MM). Alpha-1-antitrypsin deficiency is usually associated with the Z phenotype (homozygous ZZ), but SS and SZ are also associated with decreased A1A levels.

Reference Values:
ALPHA-1-ANTITRYPSIN
100-190 mg/dL

ALPHA-1-ANTITRYPSIN PHENOTYPE
The interpretive report will identify the alleles present. For rare alleles, the report will indicate whether they have been associated with reduced quantitative levels of alpha-1-antitrypsin.

Clinical References: 1. Morse JO. Alpha-1-antitrypsin deficiency. N Engl J Med. 1978;299:1045-1048;1099(20) 1099-1105 2. Donato LJ, Jenkins SM, Smith C, et al. Reference and interpretive ranges for alpha(1)-antitrypsin quantitation by phenotype in adult and pediatric populations. Am J Clin Pathol.2012;138(3):398-405 3. Stoller JK, Lacbawan FL, Aboussouan SF: Alpha-1 antitrypsin deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews.[Internet]. University of Washington, Seattle; 2006. Updated June 1, 2023. Accessed May 21, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1519/ 4. Rosenberg W, Badrick T, Tanwar S: Liver disease. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1348-1397

A1ALC
61767

Alpha-1-Antitrypsin Proteotype S/Z, LC-MS/MS, Serum

Clinical Information: Alpha-1-antitrypsin (A1A) is a protein that inhibits the enzyme neutrophil elastase. It is predominantly synthesized in the liver and secreted into the bloodstream. The inhibition function is especially important in the lungs because it protects against excess tissue degradation. Tissue degradation due to A1A deficiency is associated with an increased risk for early onset panlobular emphysema, which initially affects the lung bases (as opposed to smoking-related emphysema, which presents with upper-lung field emphysema). Patients may become symptomatic in their 30s and 40s. The most frequent symptoms reported in a National Institute of Health study of 1129 patients with severe deficiency (mean age 46 years) included cough (42%), wheezing (65%), and dyspnea with exertion (84%). Many patients were misdiagnosed as having asthma. It is estimated that approximately one-sixth of all lung transplants are for A1A deficiency. Liver disease can also occur, particularly in children; it occurs much less commonly than emphysema in adults. Alpha-1-antitrypsin deficiency is a

relatively common disorder in those of Northern European ancestry. The diagnosis of A1A deficiency is initially made by quantitation of protein levels in serum followed by determination of specific allelic variants by isoelectric focusing (IEF). While there are many different alleles in this gene, only 3 are common. The 3 major alleles include: M (full functioning, normal allele), S (associated with reduced levels of protein), and Z (disease-causing variant associated with liver disease and premature emphysema). The S and Z alleles account for the majority of the abnormal alleles detected in affected patients. As a codominant disorder, both alleles are expressed. An individual of SZ or S-null genotype may have a small increased risk for emphysema (but not liver disease) due to slightly reduced protein levels. On the other hand, an individual with the ZZ genotype is at greater risk for early onset liver disease and premature emphysema. Smoking appears to hasten development of emphysema by 10 to 15 years. These individuals should be monitored closely for lung and liver function. Historically, IEF has been the primary method for characterizing variants, although in some cases, the interpretation is difficult and prone to error. Serum quantitation is helpful in establishing a diagnosis but can be influenced by other factors. A proteomic method using trypsin-digested sera can detect the mutated peptides of the S and Z alleles but can miss disease alleles other than the S and Z alleles. This test combines all of these methods to provide a comprehensive result.

Useful For: Identification of homozygous and heterozygous S and Z proteotypes of alpha-1-antitrypsin deficiency

Interpretation: For each of the possible alpha-1-antitrypsin (A1A) genotypes there is an expected range for the total serum level of A1A. However, a number of factors can influence either the A1A serum level or the A1A proteotype results, including acute illness (A1A is an acute-phase reactant), protein replacement therapy, the presence of other rare variants, or the presence of rare DNA alterations (ie, polymorphisms). When the serum level differs from what is expected for that proteotype (ie, discordant), additional studies are performed to ensure the most appropriate interpretation of test results. Additional follow-up may include A1A phenotyping by isoelectric focusing, obtaining additional clinical information, and DNA sequencing. See Alpha-1-Antitrypsin Testing Result Table.

Reference Values:
ALPHA-1-ANTITRYPSIN:
100-190 mg/dL

ALPHA-1-ANTITRYPSIN PROTEOTYPE:
Negative for S and Z phenotype (Non S Non Z)

Clinical References: 1. Murray JD, Willrich MA, Krowka MJ, et al. Liquid chromatography-tandem mass spectrometry based alpha1-antitypsin (AAT) testing. Am J Clin Clin Pathol. 2021;155(4):547-552 2. Chen Y, Snyder MR, Zhu Y, et al. Simultaneous phenotyping and quantification of alpha-1-antitrypsin by liquid chromatography-tandem mass spectrometry. Clin Chem. 2011;57(8):1161-1168

A1AF
182

Alpha-1-Antitrypsin, Random, Feces

Clinical Information: Alpha-1-antitrypsin (AAT) is a 54-kDa glycoprotein that is resistant to degradation by digestive enzymes and is, therefore, used as an endogenous marker for the presence of blood proteins in the intestinal tract. AAT clearance is reliable for measuring protein loss distal to the pylorus. A serum sample is required to interpret results as a serum deficiency of AAT would make the AAT fecal excretion lower and could invalidate the test utility. Gastrointestinal protein enteropathy has been associated with regional enteritis, sprue, Whipple intestinal lipodystrophy, gastric carcinoma, allergic gastroenteropathy, intestinal lymphangiectasia, constrictive pericarditis, congenital hypogammaglobulinemia, and iron deficiency anemia associated with intolerance to cow's milk. Increased fecal excretion of AAT can be found in small and large intestine disease and is applicable to adults and

children.

Useful For: Diagnosing protein-losing enteropathies, especially when used in conjunction with serum alpha-1-antitrypsin (AAT) levels as a part of AAT clearance studies

Interpretation: Patients with protein-losing enteropathies generally have alpha-1-antitrypsin fecal concentrations over 100 mg/dL. Borderline elevations above the normal range are equivocal for protein-losing enteropathies.

Reference Values:
< or =54 mg/dL

Clinical References: 1. Florent C, L'Hirondel C, Desmazures C, Aymes C, Bernier JJ. Intestinal clearance of alpha 1-antitrypsin. A sensitive method for the detection of protein losing enteropathy. Gastroenterology. 1981;81(4):777-780 2. Crossley JR, Elliott RB. Simple method for diagnosing protein-losing enteropathies. Br Med J. 1977;1(6058):428-429 3. Perrault J, Markowitz H. Protein-losing gastroenteropathy and the intestinal clearance of serum alpha-1-antitrypsin. Mayo Clin Proc. 1984;59(4):278-279 4. Levitt DG, Levitt MD: Protein losing enteropathy: comprehensive review of the mechanistic association with clinical and subclinical disease states. Clin Exp Gastroenterol. 2017;10:147-168 5. Murray FR, Morell B, Biedermann L, Schreiner P. Protein-losing enteropathy as precursor of inflammatory bowel disease: A review of the literature. BMJ Case Rep. 2021;14(1):e238802

AAT
8161

Alpha-1-Antitrypsin, Serum

Clinical Information: Alpha-1-antitrypsin (A1A) is the most abundant serum protease inhibitor, and it inhibits trypsin and elastin as well as several other proteases. The release of proteolytic enzymes from plasma onto organ surfaces and into tissue spaces results in tissue damage unless inhibitors are present. Congenital deficiency of A1A is associated with the development of emphysema at an unusually early age and with an increased incidence of neonatal hepatitis, usually progressing to cirrhosis. For more information see Alpha-1-Antitrypsin-A Comprehensive Testing Algorithm.

Useful For: Workup of individuals with suspected disorders such as familial chronic obstructive lung disease Diagnosing alpha-1-antitrypsin deficiency

Interpretation: Patients with serum levels less than 70 mg/dL may have a homozygous deficiency and are at risk for early lung disease. Alpha-1-antitrypsin proteotype testing should be done to confirm the presence of homozygous deficiency alleles. If clinically indicated, patients with serum levels less than 125 mg/dL should have proteotype testing in order to identify heterozygous individuals. Heterozygotes do not appear to be at increased risk for early emphysema.

Reference Values:
100-190 mg/dL

Clinical References: 1. Tejwani V, Stoller JK. The spectrum of clinical sequelae associated with alpha-1 antitrypsin deficiency. Ther Adv Chronic Dis. 2021;12_ suppl:2040622321995691. doi:10.1177/2040622321995691 2. Patel D, McAllister SL, Teckman JH. Alpha-1 antitrypsin deficiency liver disease. Transl Gastroenterol Hepatol. 2021;6:23. doi:10.21037/tgh.2020.02.23 3. Donato LJ, Snyder MR, Greene DN. Measuring and interpreting serum AAT concentration. Methods Mol Biol. 2017;1639:21-32. doi:10.1007/978-1-4939-7163-3_3

A124
610363

Alpha-1-Microglobulin, 24 Hour, Urine

Clinical Information: Alpha-1-microglobulin is a low-molecular-weight protein of 26 kDa and a member of the lipocalin protein superfamily.(1) It is synthesized in the liver, freely filtered by glomeruli, and reabsorbed by renal proximal tubules cells where it is catabolized.(1) Due to extensive tubular reabsorption, under normal conditions very little filtered alpha-1-microglobulin appears in the final excreted urine. Therefore, an increase in the urinary concentration of alpha-1-microglobulin indicates proximal tubule injury and/or impaired proximal tubular function. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated excretion. Elevated alpha-1-microglobulin in patients with urinary tract infections may indicate renal involvement (pyelonephritis). Measurement of urinary excretion of retinol-binding protein, another low-molecular-weight protein, is an alternative to the measurement of alpha-1-microglobulin. To date, there are no convincing studies to indicate that one test has better clinical utility than the other. Urinary excretion of alpha-1-microglobulin can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of alpha-1-microglobulin is divided by the urinary creatinine concentration. This corrected value adjusts alpha-1-microglobulin for variabilities in urine concentration.

Useful For: Assessment of renal tubular injury or dysfunction using 24-hour urine collections Screening for tubular abnormalities Detecting chronic asymptomatic renal tubular dysfunction(2)

Interpretation: Alpha-1-microglobulin above the reference values may be indicative of a proximal tubular dysfunction.

Reference Values:

Alpha-1-Microglobulin/Creatinine Ratio
Not applicable

Alpha-1-Microglobulin Concentration
> or =18 years: <23 mg/24 hours

Reference values have not been established for patients who are less than 18 years of age.

Creatinine
Normal values mg per 24 hours:
Males: 930-2955 mg/24 hours
Females: 603-1783 mg/24 hours

Reference values have not been established for patients who are less than 18 years of age.

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Akerstrom B, Logdberg L, Berggard T, Osmark P, Lindqvist A. Alpha(1)-microglobulin: a yellow-brown lipocalin. Biochim Biophys Acta. 2000;1482(1-2):172-184 2. Yu H, Yanagisawa Y, Forbes M, Cooper EH, Crockson RA, MacLennan RC. Alpha-1-microglobulin: an indicator protein for renal tubular function. J Clin Pathol. 1983;36(3):253-259 3. Hjorth L, Helin I, Grubb A. Age-related reference limits for urine levels of albumin, orosomucoid, immunoglobulin G, and protein HC in children. Scand J Clin Lab Invest. 2000;60(1):65-73 4. Pagana K, Pagana T, Papana T, eds. Mosby's Diagnostic and Laboratory Test Reference. Mosby; 2020:632

RA1U
610364

Alpha-1-Microglobulin, Random, Urine

Clinical Information: Alpha-1-microglobulin is a low-molecular-weight protein of 26 kDa and a member of the lipocalin protein superfamily.(1) It is synthesized in the liver, freely filtered by glomeruli, and reabsorbed by renal proximal tubules cells where it is catabolized.(1) Due to extensive tubular reabsorption, under normal conditions very little filtered alpha-1-microglobulin appears in the final excreted urine. Therefore, an increase in the urinary concentration of alpha-1-microglobulin indicates proximal tubule injury and/or impaired proximal tubular function. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated urinary alpha-1-microglobulin excretion. Elevated alpha-1-microglobulin in patients with urinary tract infections may indicate renal involvement (pyelonephritis). Measurement of urinary excretion of retinol-binding protein, another low-molecular-weight protein, is an alternative to the measurement of alpha-1-microglobulin. To date, there are no convincing studies to indicate that one test has better clinical utility than the other. Urinary excretion of alpha-1-microglobulin can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of alpha-1-microglobulin is divided by the urinary creatinine concentration. This corrected value adjusts alpha-1-microglobulin for variabilities in urine concentration.

Useful For: Assessment of renal tubular injury or dysfunction using random urine specimens Screening for tubular abnormalities Detecting chronic asymptomatic renal tubular dysfunction (2)

Interpretation: Alpha-1-microglobulin above the reference values may indicate a proximal tubular dysfunction. As suggested in the literature, 7 mg/g creatinine is an upper reference limit for pediatric patients aged 1 month to 15 years.(3)

Reference Values:
ALPHA 1- MICROGLOBULIN/CREATININE RATIO:
> or =18 years: <35 mg/g creatinine
Reference values have not been established for patients younger than 18 years of age.

CREATININE:
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients younger than 18 years of age.

Clinical References: 1. Akerstrom B, Logdberg L, Berggard T, Osmark P, Lindqvist A. Alpha(1)-microglobulin: a yellow-brown lipocalin. Biochim Biophys Acta. 2000;1482(1-2):172-184 2. Yu H, Yanagisawa Y, Forbes M, Cooper EH, Crockson RA, MacLennan RC. Alpha-1-microglobulin: an indicator protein for renal tubular function. J Clin Pathol. 1983r;36(3):253-259 3. Hjorth L, Helin I, Grubb A. Age-related reference limits for urine levels of albumin, orosomucoid, immunoglobulin G, and protein HC in children. Scand J Clin Lab Invest. 2000;60(1):65-73 4. Pagana K, Pagana T, Papana T, eds: Mosby's Diagnostic and Laboratory Test Reference. Mosby; 2020:632

A2PI
602169

Alpha-2 Plasmin Inhibitor, Plasma

Clinical Information: Alpha-2 plasmin inhibitor (antiplasmin) is synthesized in the liver with a biological half-life of approximately 3 days. It inactivates plasmin, the primary fibrinolytic enzyme responsible for remodeling the fibrin thrombus, and binds fibrin together with factor XIIIa making the clot more difficult to lyse. Absence of alpha-2 plasmin inhibitor results in uncontrolled plasmin-mediated breakdown of the fibrin clot and is associated with increased risk of bleeding.

Useful For: Diagnosing congenital alpha-2 plasmin inhibitor deficiencies (rare) Providing a complete assessment of disseminated intravascular coagulation, intravascular coagulation and fibrinolysis, or hyperfibrinolysis (primary fibrinolysis), when measured in conjunction with fibrinogen, fibrin D-dimer, fibrin degradation products, soluble fibrin monomer complex, and plasminogen Evaluating liver disease Evaluating the effects of fibrinolytic or antifibrinolytic therapy

Interpretation: Patients with congenital homozygous deficiency (with levels of <10%) are clinically affected (bleeding). Heterozygous individuals having levels of 30% to 60% of mean normal activity are usually asymptomatic. Lower than normal levels may be suggestive of consumption due to activation of plasminogen and its inhibition by alpha-2 plasmin inhibitor. The clinical significance of high levels of alpha-2 plasmin inhibitor is unknown.

Reference Values:
Adults: 80-140%
Normal, full-term, and premature infants may have mildly decreased levels (> or =50%) that reach adult levels within 90 days postnatal.*
*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing.

Clinical References: 1. Lijnen HR, Collen D. Congenital and acquired deficiencies of components of the fibrinolytic system and their relation to bleeding or thrombosis. Blood Coagul Fibrinolysis. 1989;3(2):67-77. doi:10.1016/0268-9499(89)90034-9 2. Francis RB Jr. Clinical disorders of fibrinolysis: A critical review. Blut. 1989;59(1):1-14 3. Aoki N. Hemostasis associated with abnormalities of fibrinolysis. Blood Rev. 1989;3(1):11-17 4. Singh S, Saleem S, Reed GL. Alpha2-antiplasmin: The devil you don't know in cerebrovascular and cardiovascular disease. Front Cardiovasc Med. 2020;7:608899

A2M
9270

Alpha-2-Macroglobulin, Serum

Clinical Information: Alpha-2-macroglobulin is a protease inhibitor and is one of the largest plasma proteins. It transports hormones and enzymes, exhibits effector and inhibitor functions in the development of the lymphatic system, and inhibits components of the complement and hemostasis systems. Increased levels of alpha-2-macroglobulin are found in nephrotic syndrome when lower molecular weight proteins are lost but alpha-2-macroglobulin is retained because of its large size. In patients with liver cirrhosis and diabetes, the levels are found to be elevated. Patients with acute pancreatitis exhibit low serum concentrations, which correlate with the severity of the disease. In hyperfibrinolytic states, after major surgery, in septicemia, and severe hepatic insufficiency, the measured levels of alpha-2-macroglobulin are often low. Acute myocardial infarction patients with low alpha-2-macroglobulin have been reported to have a significantly better prognosis with regard to the greater than a year survival time.

Useful For: Evaluating patients with nephrotic syndrome and pancreatitis

Interpretation: Values are elevated in the nephrotic syndrome in proportion to the severity of protein loss (lower molecular weight). Values are low in proteolytic diseases such as pancreatitis.

Reference Values:
< or =18 years: 178-495 mg/dL
>18 years: 100-280 mg/dL

Clinical References: 1. McMahon MJ, Bowen M, Mayer AD, Cooper EH. Relation of alpha-2-macroglobulin and other antiproteases to the clinical features of acute pancreatitis. Am J Surg. 1984;147(1):164-170. doi:10.1016/0002-9610(84)90052-7 2. Haines AP, Howarth D, North WR, et al. Haemostatic variables and the outcome of myocardial infarction. Thromb Haemost. 1983;50(4):800-803

3. Hofmann W, Schmidt D, Guder WG, Edel HH. Differentiation of hematuria by quantitative determination of urinary marker proteins. Klin Wochenschr. 1991;69(2):68-75. doi:10.1007/BF01666819 4. Solerte SB, Adamo S, Viola C, et al. Acute-phase protein reactants pattern and alpha 2 macroglobulin in diabetes mellitus. Pathophysiological aspects in diabetic microangiopathy. RIC Clin Lab. 1984;14(3):575-579. doi:10.1007/BF02904891 5. Silverman LM, Christenson RH, Grant GH. Basic chemistry of amino acids and proteins. In: Tietz, NW ed. Clinical Guide to Laboratory Tests. 2nd ed. WB Saunders Comp; 1990:380-381 6. Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

AAMY
82866

Alpha-Amylase, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to Alpha-Amylase Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ALFP
70353

Alpha-Fetoprotein (AFP) Immunostain, Technical Component Only

Clinical Information: Alpha-fetoprotein (AFP) is an oncofetal antigen normally expressed in fetal liver, but not present in normal adult tissues. AFP can be expressed in yolk sac tumors and in hepatocellular carcinomas.

Useful For: Aiding in the identification of yolk sac tumors and hepatocellular carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Melms JC, Thummalapalli R, Shaw K, et al. Alpha-fetoprotein (AFP) as tumor marker in a patient with urothelial cancer with exceptional response to anti-PD-1 therapy and an escape lesion mimic. J Immunother Cancer. 2018;6(1):89. doi:10.1186/s40425-018-0394-y 2. Suzuki A, Koide N, Kitazawa M, et al. Gastric composite tumor of alpha fetoprotein-producing carcinoma/hepatoid adenocarcinoma and endocrine carcinoma with reference to cellular phenotypes. Patholog Res Int. 2012;2012:1-8 3. Tsung SH. The characteristics of immunoreactivity of alpha-fetoprotein producing gastric cancer. Cancer and Clinical Oncology. 2013;2(1):73-79 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

L3AFP
88878

Alpha-Fetoprotein (AFP) L3% and Total, Hepatocellular Carcinoma Tumor Marker, Serum

Clinical Information: Worldwide, hepatocellular carcinoma is the third leading cause of death from cancer.(1) While hepatocellular carcinoma can be treated effectively in its early stages, most patients are not diagnosed until they are symptomatic and at higher grades and stages, which are less responsive to therapies. Alpha-fetoprotein (AFP) is the standard serum tumor marker utilized in the evaluation of suspected hepatocellular carcinoma. However, increased serum concentrations of AFP may be found in chronic hepatitis and liver cirrhosis as well as in other tumor types (eg, germ cell tumors),(2) decreasing the specificity of AFP testing for hepatocellular carcinoma. Furthermore, AFP is not expressed at high levels in all hepatocellular carcinoma patients, resulting in decreased sensitivity, especially in potentially curable small tumors. AFP is differentially glycosylated in several hepatic diseases. For example, uridine diphosphate-alpha-(1->6)-fucosyltransferase is differentially expressed in hepatocytes following malignant transformation.(3) This enzyme incorporates fucose residues on the carbohydrate chains of AFP. Different glycosylated forms of AFP can be recognized following electrophoresis by reaction with different carbohydrate-binding plant lectins. The fucosylated form of serum AFP, which is most closely associated with hepatocellular carcinoma, is recognized by a lectin from the common lentil (Lens culinaris). This is designated as AFP-L3 (third electrophoretic form of lentil lectin-reactive AFP). AFP-L3 is most useful in the differential diagnosis of individuals with total serum AFP of 200 ng/mL or below, which may result from a variety of benign pathologies, such as chronic liver diseases. AFP-L3 should be utilized as an adjunct to high-resolution ultrasound for surveillance of individuals at significant risk for

developing hepatic lesions.

Useful For: Distinguishing between hepatocellular carcinoma and chronic liver disease Monitoring individuals with hepatic cirrhosis from any etiology for progression to hepatocellular carcinoma Surveillance for development of hepatocellular carcinoma in individuals with a positive family history of hepatic cancer Surveillance for development of hepatocellular carcinoma in individuals within specific ethnic and sex groups who do not have hepatic cirrhosis but have a confirmed diagnosis of chronic infection by hepatitis B acquired early in life, including: -African men above the age of 20 -Asian men above the age of 40 -Asian women above the age of 50

Interpretation: Alpha-fetoprotein (AFP)-L3 results of 10% or above are associated with a 7-fold increased risk of developing hepatocellular carcinoma. Patients with AFP-L3 at this level should be monitored more intensely for evidence of hepatocellular carcinoma according to current practice guidelines. A total serum AFP above 200 ng/mL is highly suggestive of a diagnosis of hepatocellular carcinoma. In patients with liver disease, a total serum AFP at this level is near 100% predictive of hepatocellular carcinoma. With lower total AFP levels, there is an increased likelihood that chronic liver disease, rather than hepatocellular carcinoma, is responsible for the AFP elevation. AFP concentrations over 100,000 ng/mL have been reported in normal newborns, and the values rapidly decline in the first 6 years of life.

Reference Values:
TOTAL ALPHA-FETOPROTEIN (AFP):
<4.7 ng/mL

AFP %L3:
<10%

Clinical References: 1. Kawai K, Kojima T, Miyanaga N, et al. Lectin-reactive alpha-fetoprotein as a marker for testicular tumor activity. Int J Urol. 2005;12(3):284-289 2. Noda K, Miyoshi E, Kitada T, et al. The enzymatic basis for the conversion of nonfucosylated to fucosylated alpha-fetoprotein by acyclic retinoid treatment in human hepatoma cells: Activation of alpha 1-6 fucosyltransferase. Tumor Biol. 2002;23(4):202-211 3. Leerapun A, Suravarapu S, Bida JP, et al. The utility of serum AFP-L3 in the diagnosis of hepatocellular carcinoma: Evaluation in a U.S. referral population. Clin Gastroenterol Hepatol. 2007;5(3):394-402 4. Chaiteerakij R, Addissie BD, Roberts LR. Update on biomarkers of hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2015;13(2):237-245. doi: 10.1016/j.cgh.2013.10.038 5. Johnson P, Pirrie S, Cox T, et al: The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev. 2014;23(1):144-153. doi: 10.1158/1055-9965.EPI-13-0870 6. Yang JD, Addissie BD, Mara KC, et al. GALAD Score for Hepatocellular Carcinoma Detection in Comparison with Liver Ultrasound and Proposal of GALADUS Score. Cancer Epidemiol Biomarkers Prev. 2019;28(3):531-538. doi: 10.1158/1055-9965.EPI-18-0281 7. Zhou JM, Wang T, Zhang KH. AFP-L3 for the diagnosis of early hepatocellular carcinoma: A meta-analysis. Medicine (Baltimore). 2021;100(43):e27673. doi: 10.1097/MD.0000000000027673

AFP
8162

Alpha-Fetoprotein (AFP) Tumor Marker, Serum

Clinical Information: Alpha-fetoprotein (AFP) is a glycoprotein that is produced in early fetal life by the liver and by a variety of tumors including hepatocellular carcinoma, hepatoblastoma, and nonseminomatous germ cell tumors of the ovary and testis (eg, yolk sac and embryonal carcinoma). Most studies report elevated AFP concentrations in approximately 70% of patients with hepatocellular carcinoma. Elevated AFP concentrations are found in 50% to 70% of patients with nonseminomatous testicular tumors.(1) AFP is elevated during pregnancy. Persistence of AFP in the mother following

birth is a rare hereditary condition.(2) Neonates have markedly elevated AFP levels (>100,000 ng/mL) that rapidly fall to below 100 ng/mL by 150 days and gradually return to normal over their first year.(2) Concentrations of AFP above the reference range also have been found in the serum of patients with benign liver disease (eg, viral hepatitis, cirrhosis), gastrointestinal tract tumors, and along with carcinoembryonic antigen, in ataxia telangiectasia. The biological half-life of AFP is approximately 5 days.

Useful For: Follow-up management of patients undergoing cancer therapy, especially for testicular and ovarian tumors and for hepatocellular carcinoma Often used in conjunction with human chorionic gonadotropin.(2) This test is not recommended as a screening procedure for cancer detection in the general population. This test is not intended for the detection of neural tube defects. This test is not useful for patients with pure seminoma or dysgerminoma.

Interpretation: Alpha-fetoprotein (AFP) levels may be elevated in association with a variety of malignancies or benign diseases. Failure of the AFP value to return to normal by approximately one month after surgery suggests the presence of residual tumor. Elevation of AFP after remission suggests tumor recurrence; however, tumors originally producing AFP may recur without an increase in AFP.

Reference Values:
<8.4 ng/mL
Reference values are for nonpregnant subjects only; fetal production of alpha-fetoprotein elevates values in pregnant women.

Range for newborns is not available, but concentrations over 100,000 ng/mL have been reported in normal newborns, and the values rapidly decline in the first 6 months of life.(See literature reference: Ped Res 1981;15:50-52) For further interpretive information, see Alpha-Fetoprotein (AFP)

Serum markers are not specific for malignancy, and values may vary by method.

Clinical References: 1. Sturgeon CM, Duffy MJ, Stenman UH, et al: National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. Clin Chem. 2008 Dec; 54(12):e11-79 2. Blohm ME, Vesterling-Horner D, Calaminus G, et al: Alpha-1-fetoprotein (AFP) reference values in infants up to 2 years of age. Pediatr Hematol Onco. 1998 Mar-April;15(2):135-142 3. Milose JC, Filson CP, Weizer AZ, et al: Role of biochemical markers in testicular cancer: diagnosis, staging, and surveillance. Open Access J Urol. 2011 Dec 30;4:1-8 4. Schefer H, Mattmann S, Joss RA: Hereditary persistence of alpha-fetoprotein. Case report and review of the literature. Ann Oncol. 1998 June;9(6):667-672

AFPPT
61534

Alpha-Fetoprotein (AFP), Peritoneal Fluid

Clinical Information: Malignancy accounts for approximately 7% of cases of ascites formation. Malignant disease can cause ascites by various mechanisms including peritoneal carcinomatosis (53%), massive liver metastasis causing portal hypertension (13%), peritoneal carcinomatosis plus massive liver metastasis (13%), hepatocellular carcinoma plus cirrhosis (7%), and chylous ascites due to lymphoma (7%). The evaluation and diagnosis of malignancy-related ascites is based on the patient clinical history, ascites fluid analysis, and imaging tests. The overall sensitivity of cytology for the detection of malignancy-related ascites ranges from 58% to 75%. Cytology examination is most successful in patients with ascites related to peritoneal carcinomatosis as viable malignant cells are exfoliated into the ascitic fluid. However, only approximately 53% of patients with malignancy-related ascites have peritoneal carcinomatosis. Patients with other causes of malignancy-related ascites almost always have a negative cytology. Alpha-fetoprotein (AFP) measurement in serum is used in the management of patients with hepatocellular carcinoma (HCC). Measurement of AFP in ascites fluid might be useful when used in

conjunction with cytology in patients with a history of HCC in whom a cause of peritoneal fluid accumulation is uncertain.

Useful For: An adjunct to cytology to differentiate between malignancy-related ascites and benign causes of ascites formation

Interpretation: A peritoneal fluid alpha-fetoprotein (AFP) concentration greater than 6.0 ng/mL is suspicious but not diagnostic of ascites related to hepatocellular carcinoma (HCC). This clinical decision limit cutoff yielded a sensitivity of 58%, specificity of 96% in a study of 137 patients presenting with ascites. AFP concentrations were significantly higher in ascites caused by HCC. Ascites caused by malignancies other than HCC routinely had AFP concentrations less than 6.0 ng/mL. Therefore, negative results should be interpreted with caution.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Sari R, Yildirim B, Sevinc A, Bahceci F, Hilmioglu F. The importance of serum and ascites fluid alpha-fetoprotein, carcinoembryonic antigen, CA 19-9, and CA 15-3 levels in differential diagnosis of ascites etiology. Hepatogastroenterology. 2001;48(42):1616-1621 2. Owen WE, Hunsaker JJH, Genzen JR. Alpha-fetoprotein in pericardial, peritoneal, and pleural fluids: A body fluid matrix evaluation. Clin Biochem. 2018;56:109-112. doi:10.1016/j.clinbiochem.2018.04.019 3. Block DR, Algeciras-Schimnich A. Body fluid analysis: clinical utility and applicability of published studies to guide interpretation of today's laboratory testing in serous fluids. Crit Rev Clin Lab Sci. 2013;50(4-5):107-124. doi:10.3109/10408363.2013.844679

MAFP1 113382 Alpha-Fetoprotein (AFP), Single Marker Screen, Maternal, Serum

Clinical Information: Alpha-fetoprotein (AFP) is a fetal protein that is initially produced in the fetal yolk sac and liver. A small amount is produced by the gastrointestinal tract. By the end of the first trimester, nearly all AFP is produced by the fetal liver. The concentration of AFP peaks in fetal serum between 10 to 13 weeks. Fetal AFP diffuses across the placental barrier into the maternal circulation. A small amount also is transported from the amniotic cavity. The AFP concentration in maternal serum rises throughout pregnancy, from the nonpregnancy level of 0.2 ng/mL to about 250 ng/mL at 32 weeks gestation. If the fetus has an open neural tube defect (NTD), AFP is thought to leak directly into the amniotic fluid causing unexpectedly high concentrations of AFP. Subsequently, the AFP reaches the maternal circulation, producing elevated serum levels. Other fetal abnormalities such as omphalocele, gastroschisis, congenital kidney disease, esophageal atresia, and other fetal distress situations (eg, threatened abortion and fetal demise) also may result in maternal serum AFP elevations. Increased maternal serum AFP concentrations also may be seen in multiple pregnancies and in unaffected singleton pregnancies in which the gestational age has been underestimated. Lower maternal serum AFP concentrations have been associated with an increased risk for genetic conditions such as trisomy 21 (Down syndrome) and trisomy 18 (Edwards syndrome). Risks for these syndrome disorders are only provided with the use of multiple marker screening (QUAD1 / Quad Screen [Second Trimester] Maternal, Serum). Measurement of maternal serum AFP values is a standard tool used in obstetrical care to identify pregnancies that may have an increased risk for NTD. The screen is performed by measuring AFP in maternal serum and comparing this value to the median AFP value in an unaffected population to obtain a multiple of the median (MoM). The laboratory has established a MoM cutoff of 2.5, which classifies each screen as either screen-positive or screen-negative. A screen-positive result indicates that the value obtained exceeds the established cutoff. A positive screen does not provide a diagnosis but indicates that further evaluation should be considered.

Useful For: Prenatal screening for open neural tube defect

Interpretation: A screen-negative result indicates that the calculated alpha-fetoprotein (AFP) multiple of the median (MoM) falls below the established cutoff of 2.50 MoM. A negative screen does not guarantee the absence of neural tube defects (NTD). A screen-positive result indicates that the calculated AFP MoM is 2.50 or greater and may indicate an increased risk for open NTD. The actual risk depends on the level of AFP and the individual's pretest risk of having a child with NTD based on family history, geographical location, maternal conditions such as diabetes and epilepsy, and use of folate prior to conception. A screen-positive result does not infer a definitive diagnosis of a NTD but indicates that further evaluation should be considered. Approximately 80% of pregnancies affected with an open NTD have elevated AFP MoM values greater than 2.50. Follow up: Upon receiving maternal serum screening results, all information used in the risk calculation should be reviewed for accuracy (ie, weight, diabetic status, gestational dating). If any information is incorrect the laboratory should be contacted for a recalculation of the estimated risks. Screen-negative results typically do not warrant further evaluation. Ultrasound is recommended to confirm dates for NTD screen-positive results. If ultrasound yields new dates that differ by at least 7 days, a recalculation should be considered. If dates are confirmed, high-resolution ultrasound and amniocentesis (including amniotic fluid AFP and acetylcholinesterase measurements for NTD) are typically offered.

Reference Values:
An alpha-fetoprotein (AFP) multiple of the median (MoM) <2.5 is reported as screen negative.
AFP MoM > or =2.5 (singleton and twin pregnancies) are reported as screen positive.

An interpretive report will be provided.

Clinical References: 1. Christensen RL, Rea MR, Kessler G, Crane JP, Valdes R Jr. Implementation of a screening program for diagnosing open neural tube defects: selection, evaluation, and utilization of alpha-fetoprotein methodology. Clin Chem. 1986;32(10):1812-1817 2. American College of Obstetricians and Gynecologists: Practice Bulletin No. 163: Screening for Fetal Aneuploidy. Obstet Gynecol. 2016;127(5):e123-137 3. Zhang J, Lambert-Messerlian G, Palomaki GE, Canick JA. Impact of smoking on maternal serum markers and prenatal screening in the first and second trimesters. Prenat Diagn. 2011;31(6):583-588 4. Yarbrough ML, Stout M, Gronowski AM. Pregnancy and its disorders. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1655-1696

AFPSF
8876

Alpha-Fetoprotein (AFP), Spinal Fluid

Clinical Information:

Useful For: An adjunct in the diagnosis of central nervous system (CNS) germinomas and meningeal carcinomatosis Evaluating the presence of germ-cell tumors in the CNS, in conjunction with cerebrospinal fluid (CSF) beta-human chorionic gonadotropin measurement A supplement to CSF cytologic analysis

Interpretation: Alpha-fetoprotein (AFP) concentrations that exceed the upper end of normal are consistent with the presence of central nervous system (CNS) germinoma. The presence of germinomas in the CNS, CNS involvement in metastatic cancer, and meningeal carcinomatosis may result in increased cerebrospinal fluid AFP concentrations in approximately 20% of germinomas.

Reference Values:
<1.5 ng/mL
Values for alpha-fetoprotein in cerebrospinal fluid have not been formally established for newborns and infants. The available literature indicates that by 2 months of age, levels comparable to adults should be

reached.(Ann Clin Biochem 2005;42:24-29)

Clinical References: 1. Jubran RF, Finlay J: Central nervous system germ cell tumors: controversies in diagnosis and treatment. Oncology. 2005 May;19(6):705-711 2. Seregni E, Massimino M, Nerini Molteni S, et al: Serum and cerebrospinal fluid human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) in intracranial germ cell tumors. Int J Biol Markers. 2002 Apr-Jun;17(2):112-118 3. Hu M, Guan H, Lau CC,et al: An update on the clinical diagnostic value of beta-hCG and alpha FP for intracranial germ cell tumors. Eur J Med Res. 2016 Mar 12;21:10. doi: 10.1186/s40001-016-0204-2 4. Shi Q, Tian C, Pu C, Yu S, Huang X: CSF and serum AFP in patients without gestational or neoplastic AFP-secretion. Scand J Clin Lab Invest. 2012 Dec;72(8):619-22. doi: 10.3109/00365513.2012.725865 5. Coakley J, Kellie SJ: Interpretation of alpha-fetoprotein concentrations in cerebrospinal fluid of infants. Ann Clin Biochem. 2005 Jan;42:24-29 6. Shajani-Yi Z, Martin IW, Brunelle AA, Cervinski MA: Method validation of human chorionic gonadotropin and alpha-fetoprotein in cerebrospinal fluid: Aiding the diagnosis of intracranial germ cell tumors. J Appl Lab Med. 2017 Jul 1;2(1):65-75. doi: 10.1373/jalm.2016.022822

AFPA
9950

Alpha-Fetoprotein, Amniotic Fluid

Clinical Information: Alpha-fetoprotein (AFP) is a single polypeptide chain glycoprotein with a molecular weight of approximately 70,000 Da. Synthesis of AFP occurs primarily in the liver and yolk sac of the fetus. It is secreted in fetal serum, reaching a peak at approximately 13 weeks gestation, after which it rapidly declines until about 22 weeks gestation and then gradually declines until term. Transfer of AFP into maternal circulation is accomplished primarily through diffusion across the placenta. Maternal serum AFP levels rise from the normal non-pregnancy level of 0.20 ng/mL to about 250 ng/mL at 32 weeks gestation. If the fetus has an open neural tube defect, AFP is thought to leak directly into the amniotic fluid, causing unexpectedly high concentrations of AFP. Other fetal abnormalities such as omphalocele, gastroschisis, congenital kidney disease, and esophageal atresia; and other fetal distress situations such as threatened abortion, prematurity, and fetal demise, may also show AFP elevations. Decreased amniotic fluid AFP values may be seen when gestational age has been overestimated.

Useful For: Screening for open neural tube defects or other fetal abnormalities Follow-up testing for patients with elevated serum alpha-fetoprotein results or in conjunction with cytogenetic testing

Interpretation: A screening alpha-fetoprotein (AFP) cutoff level of 2.0 multiples of median (MoM), followed by acetylcholinesterase (AChE) confirmatory testing on positive results, is capable of detecting 96% of open spina bifida cases with a false-positive rate of only 0.06% in non-blood-stained specimens. Acetylcholinesterase analysis is an essential confirmatory test for all amniotic fluid specimens with positive AFP results. Normal amniotic fluid does not contain AChE, unless contributed by the fetus as a result of open communication between fetal central nervous system (eg, open neural tube defects) or, to a lesser degree, fetal circulation. All amniotic fluid specimens testing positive for AFP will have the AChE test performed. False-positive AChE may occur from a bloody tap, which may cause both elevated AFP and AChE levels.

Reference Values:
< 2.0 multiples of median (MoM)

Clinical References: 1. Clinical Laboratory Standards Institute (CLSI): Maternal Serum Screening: Approved Standard. 2nd ed. I/LA25-A2 CLSI; 2011 2. Cuckle H. Prenatal screening using maternal markers. J Clin Med. 2014;3(2):504-520. doi:10.3390/jcm3020504 3. Bernard JP, Cuckle HS, Bernard MA, Brochet C, Salomon LJ, Ville Y. Combined screening for open spina bifida at 11-13 weeks using fetal biparietal diameter and maternal serum markers. Am J Obstet Gynecol.

FUCW
8814

Alpha-Fucosidase, Leukocytes

Clinical Information: Fucosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent alpha-L-fucosidase enzyme activity. This enzyme is involved in degrading asparagine-linked, fucose-containing complex molecules (oligosaccharides and glycoasparagines) present in cells. Reduced or absent activity of this enzyme results in the abnormal accumulation of these molecules in the tissues and body fluids. Severe and mild subgroups of fucosidosis, designated types I and II, have been described, although recent data suggests individual patients may represent a continuum within a wide spectrum of severity. The more severe type is characterized by infantile onset, rapid psychomotor regression, and severe neurologic deterioration. Additionally, dysostosis multiplex and elevated sweat sodium chloride are frequent findings. Death typically occurs within the first decade of life. Those with the milder phenotype express comparatively mild psychomotor and neurologic regression, radiologic signs of dysostosis multiplex, and skin lesions (angiokeratoma corporis diffusum). Normal sweat salinity, the presence of the skin lesions, and survival into adulthood most readily distinguish milder from more severe phenotypes. Fucosidosis is an autosomal recessive condition resulting from two biallelic disease-causing variants in the FUCA1 gene. Although the disorder is panethnic, the majority of reported patients with fucosidosis have been from Italy and the southwestern United States. To date, about 100 cases have been reported worldwide. An initial diagnostic workup includes a urine screening assay for several oligosaccharidosis (OLIGU / Oligosaccharide Screen, Random, Urine). If the screening assay is suggestive of fucosidosis, enzyme analysis of alpha-L-fucosidase can confirm the diagnosis.

Useful For: Detection of fucosidosis This test is not useful for establishing carrier status for fucosidosis.

Interpretation: Values below 0.3 nmol/mg protein are consistent with a diagnosis of fucosidosis.

AGABS
89407

Alpha-Galactosidase, Blood Spot

Clinical Information: Fabry disease is an X-linked lysosomal storage disorder resulting from deficient activity of the enzyme alpha-galactosidase A (alpha-Gal A) and the subsequent deposition of glycosylsphingolipids in tissues throughout the body, in particular, the kidney, heart, and brain. Variants within the GLA gene cause Fabry disease with severity and symptom onset dependent on the amount of residual enzyme activity. The classic form of Fabry disease occurs in male patients who have less than 1% alpha-Gal A activity. Symptoms usually appear in childhood or adolescence and can include acroparesthesias (burning pain in the extremities), gastrointestinal issues, multiple angiokeratomas, reduced or absent sweating, corneal opacity, and proteinuria. In addition, progressive renal involvement leading to kidney failure (formerly end-stage renal disease) typically occurs in adulthood, followed by cardiovascular and cerebrovascular disease. The estimated incidence varies from 1 in 3000 infants detected via newborn screening to 1 in 10,000 male patients diagnosed after onset of symptoms. Measurement of alpha-Gal A in blood spots, leukocytes (AGAW / Alpha-Galactosidase, Leukocytes), or serum (AGAS / Alpha-Galactosidase, Serum) can reliably diagnose classic or variant Fabry disease in males. Male patients with residual alpha-Gal A activity greater than 1% may present with 1 of 3 variant forms of Fabry disease with onset of symptoms later in life: a kidney variant associated with kidney failure but without the pain or skin lesions; a cardiac variant typically presenting in the sixth to eighth decade with left ventricular hypertrophy, cardiomyopathy and arrhythmia, and proteinuria, but without kidney failure; and a cerebrovascular variant presenting as stroke or transient ischemic attack. The variant forms of Fabry disease may be underdiagnosed. Molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) allows for confirmation of a diagnosis of classic of variant Fabry disease in affected male patients with reduced alpha-Gal A activity. Female patients who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals will have normal levels. Therefore, molecular genetic analysis of the GLA gene

(FABRZ / Fabry Disease, Full Gene Analysis, Varies) is recommended as the most appropriate diagnostic test to detect asymptomatic or symptomatic female carriers. The biomarkers globotriaosylsphingosine (LGB3S / Globotriaosylsphingosine, Serum) and ceramide trihexosides (CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine) may be elevated in patients with Fabry disease and can also be used in follow up of absent or reduced alpha-Gal A activity in both male and female patients. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy has led to significant clinical improvement in affected individuals. In addition, some (adult) patients may be candidates for an oral chaperone therapy. For this reason, early diagnosis and treatment are desirable, and in a few US states early detection of Fabry disease through newborn screening has been implemented. Molecular genetic testing is the recommended diagnostic test for female patients

Useful For: Diagnosis of Fabry disease in male patients using blood spot specimens Verifying abnormal serum alpha-galactosidase results in male patients with a clinical presentation suggestive of Fabry disease Follow-up to an abnormal newborn screen for Fabry disease This test is not useful for patients undergoing a workup for a meat or meat-derived product allergy.

Interpretation: In male patients, results less than 1.2 nmol/mL/hour in properly submitted specimens are consistent with Fabry disease. Normal results (> or =1.2 nmol/mL/hour) are not consistent with Fabry disease. In female patients, normal results (> or =2.8 nmol/mL/hour) in properly submitted specimens are typically not consistent with carrier status for Fabry disease; however, enzyme analysis, in general, is not sufficiently sensitive to detect all carriers. Because a carrier range has not been established in females, molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) should be considered when alpha-galactosidase A activity is less than 2.9 nmol/mL/hour, or if clinically indicated. Pseudodeficiency results in low measured alpha-galactosidase A activity but is not consistent with Fabry disease; FABRZ / Fabry Disease, Full Gene Analysis, Varies should be performed to resolve the clinical question. For more information see Fabry Disease Diagnostic Testing Algorithm.

Reference Values:
Males: > or =1.2 nmol/mL/hour
Females: > or =2.8 nmol/mL/hour
An interpretive report will be provided.

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Accessed October 30, 2023. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Desnick RJ, Ioannou YA, Eng CM. Alpha-galactosidase A deficiency: Fabry disease. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed November 7, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225546984 3. Matern D, Gavrilov D, Oglesbee D, Raymond K, Rinaldo P, Tortorelli S. Newborn screening for lysosomal storage disorders. Semin Perinatol. 2015;39(3):206-216 4. Mehta A, Hughes DA: Fabry Disease. In: Pagon RA, Adam MP, Ardinger HH, et al: eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated March 9, 2023. Accessed November 7, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1292/ 5. Laney DA, Bennett RL, Clarke V, et al. Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2013;22(5):555-564

AGAW
606261

Alpha-Galactosidase, Leukocytes

Clinical Information: Fabry disease is an X-linked lysosomal storage disorder resulting from deficient activity of the enzyme alpha-galactosidase A (alpha-Gal A) and the subsequent deposition of

glycosylsphingolipids in tissues throughout the body, in particular in the kidney, heart, and brain. Variants within the GLA gene cause Fabry disease and more than 630 genetic alterations have been identified. Severity and onset of symptoms are dependent on the amount of residual enzyme activity. The classic form of Fabry disease occurs in male patients who have less than 1% alpha-Gal A activity. Symptoms usually appear in childhood or adolescence and can include acroparesthesias (burning pain in the extremities), gastrointestinal issues, multiple angiokeratomas, reduced or absent sweating, corneal opacity, and proteinuria. In addition, progressive kidney involvement leading to end-stage kidney disease (ESRD) typically occurs in adulthood, followed by cardiovascular and cerebrovascular disease. The estimated incidence varies from 1 in 3000 infants detected via newborn screening to 1 in 10,000 male patients diagnosed after onset of symptoms. Male patients with residual alpha-Gal A activity greater than 1% may present with 1 of 3 variant forms of Fabry disease with onset of symptoms later in life: a kidney variant associated with ESRD but without the pain or skin lesions; a cardiac variant typically presenting in the 6th to 8th decade with left ventricular hypertrophy, cardiomyopathy and arrhythmia, and proteinuria, but without ESRD; and a cerebrovascular variant presenting as stroke or transient ischemic attack. The variant forms of Fabry disease may be underdiagnosed. Female patients who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals will have normal levels. Therefore, molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) is recommended to detect carriers. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy has led to significant clinical improvement in affected individuals. In addition, some adult patients may be candidates for an oral chaperone therapy. For this reason, early diagnosis and treatment are desirable and, in a few US states, early detection of Fabry disease through newborn screening has been implemented. Absent or reduced alpha-Gal A in blood spots (AGABS / Alpha-Galactosidase, Blood Spot), leukocytes (this test), or serum (AGAS / Alpha-Galactosidase, Serum) can indicate a diagnosis of classic or variant Fabry disease. The biomarkers globotriaosylsphingosine (LGBWB / Globotriaosylsphingosine, Blood) and ceramide trihexosides (CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine) may be elevated in patients with Fabry disease and may aid in the diagnostic evaluation of female patients. Molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) allows for detection of the disease-causing variant in both male and female patients.

Useful For: Diagnosis of Fabry disease in male patients Verifying abnormal serum alpha-galactosidase results in male patients with a clinical presentation suggestive of Fabry disease This test is not useful for patients undergoing a work-up for a meat or meat-derived product allergy.

Interpretation: Values below the reference range are consistent with a diagnosis Fabry Disease. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro, confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

> or =10.32 nmol/hour/mg protein

An interpretative report will be provided.

Note: Results from this assay do not reflect carrier status because of individual variation of alpha-galactosidase enzyme levels.

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Accessed October 30, 2023. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Desnick RJ, Ioannou YA, Eng CM: Alpha-galactosidase A deficiency: Fabry disease. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of

Inherited Disease. McGraw-Hill; 2019. Accessed March 3, 2022. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225546984 3. De Schoenmakere G, Poppe B, Wuyts B, et al: Two-tier approach for the detection of alpha-galactosidase A deficiency in kidney transplant recipients. Nephrol Dial Transplant. 2008 Dec;23(12):4044-4048. doi: 10.1093/ndt/gfn370 4. Mehta A, Hughes DA: Fabry disease. In: Adam MP, Ardinger HH, Pagon RA, et al: eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated January 27, 2022. Accessed March 3, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1292/ 5. Laney DA, Bennett RL, Clarke V, et al: Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2013 Oct;22(5):555-564. doi: 10.1007/s10897-013-9613-3 6. Laney DA, Peck DS, Atherton AM, et al: Fabry disease in infancy and early childhood: a systematic literature review. Genet Med. 2015 May;17(5):323-330. doi: 10.1038/gim.2014.120

AGAS
8784

Alpha-Galactosidase, Serum

Clinical Information: Fabry disease is an X-linked lysosomal storage disorder resulting from deficient activity of the enzyme alpha-galactosidase A (alpha-Gal A) and the subsequent deposition of glycosphingolipids in tissues throughout the body; in particular, in the kidney, heart, and brain. Variants within the GLA gene cause Fabry disease and more than 630 variants have been identified. Severity and onset of symptoms are dependent on the amount of residual enzyme activity. The classic form of Fabry disease occurs in male patients who have less than 1% alpha-Gal A activity. Symptoms usually appear in childhood or adolescence and can include acroparesthesias (burning pain in the extremities), gastrointestinal issues, multiple angiokeratomas, reduced or absent sweating, corneal opacity, and proteinuria. In addition, progressive renal involvement leading to kidney failure, also called end-stage renal (kidney) disease (ESRD), typically occurs in adulthood, followed by cardiovascular and cerebrovascular disease. The estimated incidence varies from 1 in 3000 infants detected via newborn screening to 1 in 10,000 males diagnosed after onset of symptoms. Male patients with residual alpha-Gal A activity greater than 1% may present with 1 of 3 variant forms of Fabry disease with onset of symptoms later in life: a renal variant associated with ESRD but without the pain or skin lesions; a cardiac variant typically presenting in the sixth to eighth decade with left ventricular hypertrophy, cardiomyopathy and arrhythmia, and proteinuria, but without ESRD; and a cerebrovascular variant presenting as stroke or transient ischemic attack. The variant forms of Fabry disease may be underdiagnosed. Female patients who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals have normal levels of alpha-Gal A. Therefore, molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) is recommended to detect carriers. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy has led to significant clinical improvement in affected individuals. In addition, some (adult) patients may be candidates for oral chaperone therapy. For this reason, early diagnosis and treatment are desirable, and in a few US states, early detection of Fabry disease through newborn screening has been implemented. Absent or reduced alpha-Gal A in blood spots (AGABS / Alpha-Galactosidase, Blood Spot), leukocytes (AGAW / Alpha-Galactosidase, Leukocytes), or serum (AGAS / Alpha-Galactosidase, Serum) can indicate a diagnosis of classic or variant Fabry disease. Molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) allows for detection of the disease-causing variant in both male and female patients. The biomarkers globotriaosylsphingosine (LGB3S / Globotriosylsphingosine, Serum) and ceremide trihexosides (CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine) are typically elevated in symptomatic patients with Fabry disease and may aid in the diagnostic evaluation of female patients and individuals with a variant of uncertain significance in GLA. See Fabry Disease Testing Algorithm and Fabry Disease: Newborn Screen-Positive Follow-up

Useful For: Diagnosis of Fabry disease in male patients Preferred screening test (serum) for Fabry disease This test is not useful for patients undergoing a work up for a meat or meat-derived product allergy.

Interpretation: Deficiency (<0.016 U/L) of alpha-galactosidase in properly submitted specimens is diagnostic for Fabry disease in male patients. If concerned about specimen integrity, recheck using leukocyte testing (AGAW / Alpha-Galactosidase, Leukocytes).

Reference Values:
0.074-0.457 U/L

Note: Results from this assay are not useful for female carrier determination. Carriers usually have levels in the normal range.

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Accessed October 30, 2023. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Desnick RJ, Ioannou YA, Eng CM: Alpha-galactosidase A deficiency: Fabry disease. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed October 30, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225546984 3. Mehta A, Hughes DA. Fabry Disease. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. GeneReviews. Seattle (WA): University of Washington, Seattle; August 5, 2002 4. Laney DA, Bennett RL, Clarke V, et al. Fabry disease practice guidelines: Recommendations of the National Society of Genetic Counselors. J Genet Couns. 2013;22(5):555-564. doi: 10.1007/s10897-013-9613-3 5. Laney DA, Peck DS, Atherton AM, et al. Fabry disease in infancy and early childhood: a systematic literature review. Genet Med. 2015;17(5)323-330. doi: 10.1038/gim.2014.120 6. Ferreira S, Auray-Blais C, Boutin M, et al. Variations in the GLA gene correlate with globotriaosylceramide and globotriaosylsphingosine analog levels in urine and plasma. Clin Chim Acta. 2015;447:96-104. doi: 10.1016/j.cca.2015.06.003 7. Nowak A, Beuschlein F, Sivasubramaniam V, Kasper D, Warnock DG. Lyso-Gb3 associates with adverse long-term outcome in patients with Fabry disease. J Med Genet. 2022;59(3):287-293. doi: 10.1136/jmedgenet-2020-107338

WASQR 47958 Alpha-Globin Gene Sequencing, Blood

Clinical Information: Alpha-globin gene sequencing detects alpha-globin variants and nondeletional alpha-thalassemia variants. Alpha thalassemia is the most common monogenic condition in the world. It is estimated that up to 5% of the world's population carries at least one alpha-thalassemia variant, and in the United States, approximately 30% of African Americans are thought to carry an alpha-thalassemia variant. Alpha-thalassemia variants are most common in individuals of Southeastern Asian, African, Mediterranean, Indian, and Middle Eastern descent, but they can be found in persons from any ethnic group. Four alpha-globin genes are normally present, 2 copies on each chromosome 16. Alpha-thalassemia variants result in decreased alpha-globin chain production. In general, alpha thalassemia is characterized by hypochromic, microcytic anemia and varies clinically from asymptomatic (alpha-thalassemia silent carrier and alpha-thalassemia trait) to lethal hemolytic anemia (hemoglobin [Hb] Barts hydrops fetalis). Large deletions of the alpha-globin genes account for approximately 90% of alpha-thalassemia alterations, and these will not be detected by alpha-globin gene sequencing. Other alterations, such as point alterations or small deletions within the alpha-globin genes, account for most of the remaining 10% of alpha-thalassemia variants. These nondeletional subtypes can be detected by alpha-globin gene sequencing. The most common nondeletional alpha-thalassemia variant is Hb Constant Spring. The majority of alpha-globin chain variants are clinically and hematologically benign; however, some cause erythrocytosis and chronic hemolytic anemia. Hemoglobin electrophoresis may not be able to confirm their identity. In these instances, alpha-globin gene sequencing can be useful.

Useful For: Testing for nondeletional alpha thalassemia in a symptomatic individual Follow-up testing to an abnormal hemoglobin electrophoresis that identified an alpha-globin chain variant Evaluating for

nondeletional alpha thalassemias in an algorithmic process for: -HAEV1 / Hemolytic Anemia Evaluation, Blood -HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood -MEV1 / Methemoglobinemia Evaluation, Blood -REVE2 / Erythrocytosis Evaluation, Blood -THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum

Interpretation: A summary interpretation will be provided as a part of the HAEV1 / Hemolytic Anemia Evaluation, Blood; HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood; MEV1 / Methemoglobinemia Evaluation, Blood; REVE2 / Erythrocytosis Evaluation, Blood; THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum.

Reference Values:
Only orderable as a reflex. For more information see:
-HAEV1 / Hemolytic Anemia Evaluation, Blood
-HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood
-MEV1 / Methemoglobinemia Evaluation, Blood
-REVE2 / Erythrocytosis Evaluation, Blood
-THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum

An interpretive report will be provided.

Clinical References: 1. Harteveld CL, Higgs DR: Alpha-thalassemia. Orphanet J Rare Dis. 2010 May 28;5:13 2. Hoyer JD, Hoffman DR: The Thalassemia and hemoglobinopathy syndromes. In: McClatchey KD, ed. Clinical Laboratory Medicine. 2nd ed. Lippincott Williams and Wilkins; 2002:866-895 3. Farashi S, Harteveld CL: Molecular basis of a-thalassemia. Blood Cells Mol Dis. 2018 May;70:43-53. doi: 10.1016/j.bcmd.2017.09.004 4. Henderson SJ, Timbs AT, McCarthy J, ed al: Ten years of routine a- and B-globin gene sequencing in UK hemoglobinopathy referrals reveals 60 novel mutations. Hemoglobin. 2016;40(2):75-84. doi: 10.3109/03630269.2015.1113990

IDUAW
606276

Alpha-L-Iduronidase, Leukocytes

Clinical Information: The mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate, also known as glycosaminoglycans (GAG) or mucopolysaccharides. Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs. There are 11 known disorders that involve the accumulation of GAG. MPS disorders involve multiple organ systems and are characterized by coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature, and skeletal abnormalities. Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by reduced or absent activity of the enzyme alpha-L-iduronidase due to variants in the IDUA gene. Deficiency of alpha-L-iduronidase can result in a wide range of phenotypes categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because these syndromes cannot be distinguished biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, intellectual disabilities or learning difficulties, and cardiac valvular disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Individuals with MPS I typically demonstrate elevated levels of the GAG dermatan sulfate and heparan sulfate (see MPSSC / Mucopolysaccharides Screen, Random, Urine; MPSWB / Mucopolysaccharides, Blood). Reduced or absent activity of alpha L-iduronidase can confirm a diagnosis of MPS I; however, enzymatic testing is not reliable for carrier detection. Molecular sequence analysis of the IDUA gene

allows for detection of a disease-causing variant in affected individuals and subsequent carrier detection in relatives (see MPS1Z / Hurler Syndrome, Full Gene Analysis, Varies). To date, a clear genotype-phenotype correlation has not been established.

Useful For: Diagnosis of mucopolysaccharidosis I, Hurler, Scheie, and Hurler-Scheie syndromes in leukocytes This test is not useful for determining carrier status.

Interpretation: Results below 2.06 nmol/hour/mg protein in properly submitted specimens are consistent with alpha-L-iduronidase deficiency (mucopolysaccharidosis I). Further differentiation between Hurler, Scheie, and Hurler-Scheie syndromes is dependent upon the clinical findings. Normal results (> or =2.06 nmol/hour/mg protein) are not consistent with alpha-L-iduronidase deficiency.

Reference Values:
> or =2.06 nmol/hour/mg protein
An interpretive report will be provided.

Clinical References: 1. Newborn Screening ACT Sheet [alpha-L-iduronidase deficiency with or without glycosaminoglycan (GAG) accumulation] Mucopolysaccharidosis Type I (MPS I). American College of Medical Genetics and Genomics; 2023. Updated November 2023. Accessed June 10, 2024. Available at www.acmg.net/PDFLibrary/MPSI-ACT-Sheet.pdf 2. Clark LA, Atherton AM, Burton BK, et al: Mucopolysaccharidosis type I newborn screening: Best practices for diagnosis and management. J Pediatr. 2017 Mar;182:363-370 3. Martins AM, Dualibi AP, Norato D, et al: Guidelines for the management of mucopolysaccharidosis type I. J Pediatr. 2009 Oct:155(4 Suppl):S32-S46 4. Enns GM, Steiner RD, Cowan TM: Lysosomal disorders: mucopolysaccharidoses. In: Sarafoglou K, Hoffmann GF, Roth KS, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. McGraw-Hill, Medical Publishing Division; 2009:721-730 5. Clarke LA: Mucopolysaccharidosis type I. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated February 25, 2021. Accessed March 23, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1162/ 6. Elliott S, Buroker N, Cournoyer JJ, et al: Pilot study of newborn screening for six lysosomal storage diseases using tandem mass spectrometry. Mol Genet Metab. 2016 Aug;118(4):304-309

ALFA
82897

Alpha-Lactalbumin, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to alpha-lactalbumin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MANN
62511

Alpha-Mannosidase, Leukocytes

Clinical Information: Alpha-mannosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent acid alpha-mannosidase enzyme activity. This enzyme is involved in glycoprotein catabolism, with absent or reduced activity resulting in the accumulation of undigested mannose-containing complex oligosaccharides in the lysosomes, disrupting the normal functioning of cells. Clinical features and severity of symptoms are widely variable within alpha-mannosidosis but, in general, the disorder is characterized by skeletal abnormalities, immune deficiency, hearing impairment, and intellectual disability. Three clinical subtypes of the disorder have been described and vary with respect to age of onset and clinical presentation. Type 1 is generally classified by a mild presentation and slow progression with onset after 10 years of age and absence of skeletal abnormalities. Type 2 is generally a more moderate form with slow progression and onset prior to 10 years of age with skeletal abnormalities and myopathy. Type 3 is the most severe form with onset in early infancy, skeletal abnormalities such as dysostosis multiplex, and severe central nervous system involvement. Although treatment is mostly supportive and aimed at preventing complications, hematopoietic stem cell transplant has been reported to be a feasible therapeutic option. The incidence of alpha-mannosidosis is estimated at 1 in 500,000 live births. An initial diagnostic workup may include a screening assay for several oligosaccharides in urine, OLIGU / Oligosaccharide Screen, Random, Urine. If the urine oligosaccharide screening assay is suggestive of alpha-mannosidosis, enzyme analysis of acid alpha-mannosidase can confirm the diagnosis. Molecular analysis of the MAN2B1 gene allows for detection of a disease-causing variant in affected individuals and subsequent carrier detection in relatives (see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing; specify MAN2B1 gene list ID: IEMCP-MUMNLV).

Useful For: Diagnosis of alpha-mannosidosis This test is not useful for establishing carrier status for

alpha-mannosidosis.

Interpretation: Values below 0.54 nmol/min/mg protein are consistent with a diagnosis of alpha-mannosidosis.

Reference Values:
> or =0.54 nmol/min/mg protein

Clinical References: 1. Malm D, Nilssen O. Alpha-mannosidosis. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle. 2001. Updated July 18, 2019. Accessed June 10, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1396/ 2. Thomas GH. Disorders of glycoprotein degradation: alpha-mannosidosis, beta-mannosidosis, fucosidosis, and sialidosis. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed June 10, 2025. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225545029 3. Mynarek M, Tolar J, Albert MH, et al. Allogeneic hematopoietic SCT for alpha-mannosidosis: an analysis of 17 patients. Bone Marrow Transplant. 2012;47(3):352-359. doi:10.1038/bmt.2011.99 4. Guffon N, Tylki-Szymanska AT, Borgwardt L, et al. Recognition of alpha-mannosidosis in paediatric and adult patients: Presentation of a diagnostic algorithm from an international working group. Mol Genet Metab. 2019;126(4):470.474. doi:10.1016/j.ymgme.2019.01.024

APGH
9003

Alpha-Subunit Pituitary Tumor Marker, Serum

Clinical Information: The 3 human pituitary glycoprotein hormones: luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyrotropin, and the placenta-derived chorionic gonadotropin, are closely related tropic hormones. They signal through G-protein-coupled receptors, regulating the hormonal activity of their respective endocrine target tissues. Each is composed of an alpha- and a beta-subunit, coupled by strong noncovalent bonds. The alpha-subunits of all 4 hormones are essentially identical (92 amino acids; molecular weight [MW] of the "naked" protein:10,205 Da), being transcribed from the same gene and showing only variability in glycosylation (MW of the glycosylated proteins: 13,000-18,000 Da). The alpha-subunits are essential for receptor transactivation. By contrast, all the different beta-subunits are transcribed from separate genes, show less homology, and convey the receptor specificity of the dimeric hormones. Under physiological conditions, alpha- and beta-chain synthesis and secretions are tightly coupled, and only small amounts of monomeric subunits are secreted. However, under certain conditions, coordinated production of intact glycoprotein hormones may be disturbed and disproportionate quantities of free alpha-subunits are secreted. In particular, some pituitary adenomas may overproduce alpha subunits. Although most commonly associated with gonadotroph- or thyrotroph-derived tumors, alpha-subunit secretion has also been observed in corticotroph, lactotroph, and somatotroph pituitary adenomas. Overall, depending on cell type and tumor size, 5% to 30% of pituitary adenomas will produce sufficient free alpha-subunits to result in elevated serum levels, which usually fall with successful treatment. Stimulation testing with hypothalamic releasing factors (eg, gonadotropin-releasing hormone [GnRH] or thyrotropin-releasing hormone [TRH]) may result in further elevations disproportionate to those seen in individuals without tumors. Measurement of free alpha-subunit after GnRH-stimulation testing can also be useful in the differential diagnosis of constitutional delay of puberty (CDP) versus hypogonadotrophic hypogonadism (HH). CDP is a benign, often familial, condition in which puberty onset is significantly delayed, but eventually occurs and then proceeds normally. By contrast, HH represents a disease state characterized by lack of gonadotropin production. Its causes are varied, including hypothalamic and pituitary inflammatory or neoplastic disorders, a range of specific genetic abnormalities, as well as unknown causes. In children, HH results in complete failure to enter puberty without medical intervention. In children with CDP, in normal pubertal children, in normal adults and, to a lesser degree, in normal prepubertal children, GnRH administration results in increased serum LH, FSH, and alpha-subunit levels. This response is greatly attenuated in patients with HH, particularly

regarding the post-GnRH rise in alpha-subunit concentrations.

Useful For: Adjunct in the diagnosis of pituitary tumors As part of the follow-up of treated pituitary tumor patients Differential diagnosis of thyrotropin-secreting pituitary tumor versus thyroid hormone resistance Differential diagnosis of constitutional delay of puberty versus hypogonadotrophic hypogonadism

Interpretation: In the case of pituitary adenomas that do not produce significant amounts of intact tropic hormones, diagnostic differentiation between sellar- and suprasellar tumors of non-pituitary origin (eg, meningiomas or craniopharyngiomas) can be difficult. In addition, if such nonsecreting adenomas are very small, they can be difficult to distinguish from physiological pituitary enlargements. In a proportion of these cases, free alpha-subunit may be elevated, aiding in diagnosis. Overall, 5% to 30% of pituitary adenomas produce measurable elevation in serum free alpha-subunit concentrations. There is also evidence that an exuberant free alpha-subunit response to thyrotropin-releasing hormone (TRH) administration may occur in some pituitary adenoma patients that do not have elevated baseline free alpha-subunit levels. A more than 2-fold increase in free alpha-subunit serum concentrations at 30 to 60 minutes following intravenous administration of 500 mcg of TRH is generally considered abnormal, but some investigators consider any increase of serum free alpha-subunit that exceeds the reference range as abnormal. TRH testing is not performed in the laboratory but in specialized clinical testing units under the supervision of a physician. In pituitary tumors patients with pre-treatment elevations of serum free alpha-subunit, successful treatment is associated with a reduction of serum free alpha-subunit levels. Failure to lower levels into the normal reference range may indicate incomplete cure, and secondary rises in serum free alpha-subunit levels can indicate tumor recurrence. Small thyrotropin (TSH)-secreting pituitary tumors are difficult to distinguish from thyroid hormone resistance. Both types of patients may appear clinically euthyroid or mildly hyperthyroid and may have mild-to-modest elevations in peripheral thyroid hormone levels along with inappropriately (for the thyroid hormone level) detectable TSH, or mildly-to-modestly elevated TSH. Elevated serum free alpha-subunit levels in such patients suggest a TSH secreting tumor, but mutation screening of the thyroid hormone receptor gene may be necessary for a definitive diagnosis. Constitutional delay of puberty (CDP) is a benign, often familial condition in which puberty onset is significantly delayed but eventually occurs and then proceeds normally. By contrast, hypogonadotrophic hypogonadism (HH) represents a disease state characterized by lack of gonadotropin production. Its causes are varied, ranging from idiopathic over specific genetic abnormalities to hypothalamic and pituitary inflammatory or neoplastic disorders. In children, it results in complete failure to enter puberty without medical intervention. CDP and HH can be extremely difficult to distinguish from each other. Intravenous administration of 100 mcg gonadotropin releasing hormone (GnRH) results in much more substantial rise in free alpha-subunit levels in CDP patients, compared with HH patients. A greater than 6-fold rise at 30- or 60-minutes post-injection is seen in more than 75% of patients with CDP, while a less than 2-fold rise appears diagnostic of HH. Increments between 2- and 6-fold are nondiagnostic. GnRH testing is not performed in the laboratory but in specialized clinical testing units under the supervision of a physician.

Reference Values:

PEDIATRIC
< or =5 days: < or =50 ng/mL
6 days-12 weeks: < or =10 ng/mL
3 months-17 years: < or =1.2 ng/mL
Tanner II-IV*: < or =1.2 ng/mL

ADULTS
Males: < or =0.5 ng/mL
Premenopausal females: < or =1.2 ng/mL
Postmenopausal females: < or =1.8 ng/mL

Pediatric and adult reference values based on Mayo studies.

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

Clinical References: 1. Preissner CM, Klee GG, Scheithauer BW, Abboud CF. Free alpha subunit of the pituitary glycoprotein hormones. Measurement in serum and tissue of patients with pituitary tumors. Am J Clin Pathol. 1990;94(4):417-421 2. Samejima N, Yamada S, Takada K, et al. Serum alpha-subunit levels in patients with pituitary adenomas. Clin Endocrinol. 2001:54(4):479-484 3. Mainieri AS, Elnecave RH. Usefulness of the free alpha-subunit to diagnose hypogonadotropic hypogonadism. Clin Endocrinol. 2003;59(3):307-313 4. Socin HV, Chanson P, Delemer B, et al. The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. Eur J Endocrinol. 2003;148(4):433-442 5. Solarski M, Rotondo F, Syro LV, Cusimano MD, Kovacs K. Alpha subunit in clinically non-functioning pituitary adenomas: An immunohistochemical study. Pathol Res Pract. 2017;213(9):1130-1133

ASYN
70635

Alpha-Synuclein Immunostain, Technical Component Only

Clinical Information: Alpha-synuclein is a member of a family of cytoplasmic proteins found predominantly in the presynaptic nerve terminal of the brain. Synucleins are thought to be involved in neuronal plasticity, synaptic function, and neurodegenerative disease. Alpha-synuclein is abundant in Lewy bodies in sporadic Parkinson disease and dementia with Lewy bodies. It is a major component of amyloid plaques in Alzheimer disease.

Useful For: Identification of alpha-synuclein in neurogenerative disorders

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Jellinger KA. Formation and development of Lewy pathology: a critical update. J Neurol. 2009;256 Suppl 3:270-279 2. Kotzbauer PT, Trojanowsk JQ, Lee VM. Lewy body pathology in Alzheimer's disease. J Mol Neurosci. 2001;17(2):225-232 3. Spillantini MG, Goedert M. The alpha-synucleinopathies: Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Y Acad Sci. 2000;920:16-27 4. Baba M, Nakajo S, Tu PH, et al. Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. Am J Pathol. 1998;152(4):879-884 5. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology. 1996;47(5):1113-1124 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

ASYNC
622855

Alpha-Synuclein Protein Aggregates, Spinal Fluid

Clinical Information: Synucleinopathies are a family of neurodegenerative disorders diagnosed pathologically based on the presence of inclusions composed of aggregates of misfolded alpha-synuclein protein in the brain. Synucleinopathies are divided into two major subgroups: Lewy body disease (LBD)

and multiple system atrophy (MSA). LBD is characterized by deposits of aggregated alpha-synuclein that develop in neurons (Lewy bodies or Lewy neurites); LBDs include Parkinson disease, dementia with Lewy bodies, and Parkinson disease dementia. MSA is characterized by deposits of aggregated alpha-synuclein that develop in oligodendrocytes (called glial cytoplasmic inclusions). Synuclein pathology is often also present as a co-pathology in other neurodegenerative disorders, including Alzheimer disease and mixed dementias. Therefore, the presence or absence of synuclein pathology is an important factor influencing diagnosis and disease course across a spectrum of motor and cognitive neurodegenerative disorders. Historically, synucleinopathies have been diagnosed during life based on clinical symptoms, sometimes augmented by dopamine transporter single-photon emission computed tomography imaging, with definitive diagnosis only possible through identification of synuclein aggregates in the brain at autopsy. The alpha-synuclein seed amplification assay (SAA) detects aggregates of alpha-synuclein in cerebrospinal fluid (CSF). Studies have shown that detection of alpha-synuclein aggregates in CSF during life by SAA correlates with high sensitivity and specificity to the presence of synuclein pathology identified in the brain at autopsy.

Useful For: Detection of pathogenic alpha-synuclein (alpha-synuclein aggregates) in adult patients being assessed for clinically uncertain cognitive decline or clinically uncertain parkinsonian syndromes

Interpretation: Detection of alpha-synuclein aggregates in cerebrospinal fluid is consistent with the presence of a synucleinopathy (eg, Parkinson disease, dementia with Lewy bodies, Alzheimer disease with Lewy body pathology, and multiple system atrophy).

Reference Values:
An interpretive report will be provided

Clinical References: 1. Rizzo G, Copetti M, Arcuti S, Martino D, Fontana A, Logroscino G. Accuracy of clinical diagnosis of Parkinson disease: A systematic review and meta-analysis. Neurology. 2016;86(6):566-576. doi:10.1212/WNL.0000000000002350 2. Rizzo G, Arcuti S, Copetti M, et al. Accuracy of clinical diagnosis of dementia with Lewy bodies: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2018;89(4):358-366. doi:10.1136/jnnp-2017-316844 3. Wenning GK, Stankovic I, Vignatelli L, et al. The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy. Mov Disord. 2022;37(6):1131-1148. doi:10.1002/mds.29005

ABCRS
70636

Alpha/Beta Crystallin IHC, Technical Component Only

Clinical Information: Alpha-beta crystallin is a lens protein and a member of the superfamily of small heat shock proteins. It is expressed in a variety of tissues, such as skeletal muscle, cardiac muscle, smooth muscle, renal tubular epithelium, Schwann cells, glial cells, thyroid epithelium, colonic epithelium, and stratified squamous epithelium. It is also found in ubiquitinated intermediate filament inclusion bodies, such as Lewy bodies (neurofilaments), Rosenthal fibers (glial filaments), and Mallory bodies (cytokeratins) present in certain disease states.

Useful For: Characterization of neuroectodermal tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Romi F, Helgeland G, Gilhus NE. Heat-shock proteins in clinical neurology. Eur Neurol. 2011;66(2):65-69 2. Fort PE, Lampi KJ. New focus on alpha-crystallins in

retinal neurodegenerative diseases. Exp Eye Res. 2011;92(2):98-103 3. Pinder SE, Balsitis M, Ellis IO, et al. The expression of alpha B-crystallin in epithelial tumours: a useful tumour marker? J Pathol. 1994;174(3):209-215 4. Leach IH, Tsang ML, Church RJ, Lowe J. Alpha-B crystallin in the normal human myocardium and cardiac conducting system. J Pathol. 1994;173(3):255-260 5. Lowe J, McDermott H, Pike I, et al. Alpha B crystallin expression in non-lenticular tissues and selective presence in ubiquitinated inclusion bodies in human disease. J Pathol. 1992;166(1):61-68 6. Iwaki T, Wisniewski T, Iwaki A, et al. Accumulation of alpha B-crystallin in central nervous system glia and neurons in pathologic conditions. Am J Pathol. 1992;140(2):345-356 7. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

ALPRT
70593

Alport (Collagen IV Alpha 5 and Alpha 2) Immunofluorescent Stain, Renal Biopsy

Clinical Information: Alport syndrome is a hereditary disease of basement membrane collagen type IV. Variants in collagen IV alpha genes cause characteristic abnormal immunofluorescence staining patterns within the glomerular basement membrane. Alport syndrome is characterized by hematuria, proteinuria, progressive kidney failure, and high-tone sensorineural hearing loss.

Useful For: Assisting in the diagnosis of hereditary nephritis (Alport syndrome)

Interpretation: This test (when not accompanied by a pathology consultation request) will be reported as one of the following: 1) Normal pattern 2) Consistent with X-linked hereditary nephritis 3) Consistent with autosomal hereditary nephritis If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test and send the corresponding renal pathology light microscopy and immunofluorescence (IF) slides (or IF images on a CD), electron microscopy images (prints or CD), and the pathology report.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Kagawa M, Kishiro Y, Naito I, et al. Epitope-defined monoclonal antibodies against type-IV collagen for diagnosis of Alport's syndrome. Nephrol Dial Transplant. 1997;12(6):1238-1241 2. Hashimura Y, Nozu K, Kaito H, et al. Milder clinical aspects of X-linked Alport syndrome in men positive for the collagen IV alpha 5 chain. Kidney Int. 2014;85(5):1208-1213 3. Kamiyoshi N, Nozu K, Fu XJ, et al. Genetic, clinical, and pathologic backgrounds of patients with autosomal dominant Alport syndrome. Clin J Am Soc Nephrol. 2016;11(8):1441-1449 4. Said SM, Fidler ME, Valeri AM, et al. Negative staining for COL4A5 correlates with worse prognosis and more severe ultrastructural alterations in males with Alport syndrome. Kidney Int Rep. 2016;2(1):44-52

ALPGP
618044

Alport Syndrome Gene Panel, Varies

Clinical Information: Alport syndrome (AS) is a genetic disorder characterized by kidney disease, sensorineural hearing loss, and ocular findings. The disease spectrum, severity, and progression are variable; in many cases, kidney disease progresses to kidney failure.(1) The genes associated with AS form the collagen IV alpha 345 network of basement membranes and have 3 different modes of inheritance. Disease-causing variants in the COL4A5 gene cause X-linked AS (XLAS) and account for approximately two thirds of disease.(1) In hemizygous male patients, XLAS tends to be more severe, while heterozygous female patients typically have a milder presentation (usually only hematuria).(2) Autosomal recessive AS (ARAS) accounts for approximately 15% of cases and is caused by biallelic

disease-causing variants in COL4A3 or COL4A4.(3) Some carriers of ARAS may develop thin basement membrane nephropathy. Digenic inheritance with disease-causing variants in both COL4A3 and COL4A4 has also been reported.(4) Autosomal dominant AS, caused by heterozygous disease-causing variants in COL4A3 or COL4A4, accounts for approximately 20% of cases and tends to exhibit slower disease progression (1,5) Large deletions that span the adjacent 5' ends of COL4A5 and COL4A6 are associated with a contiguous gene syndrome characterized by AS and diffuse leiomyomatosis in the esophagus, however, disease-causing COL4A6 variants do not appear to be associated with isolated Alport syndrome.(6)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of Alport syndrome Establishing a diagnosis of Alport syndrome

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Kashtan CE: Alport syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews [Internet]. University of Washington, Seattle; 2001. Updated February 21, 2019. Accessed June 6, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1207/ 2. Jais JP, Knebelmann B, Giatras I, et al: X-linked Alport syndrome: natural history and genotype-phenotype correlations in girls and women belonging to 195 families: a European Community Alport Syndrome Concerted Action study. J Am Soc Nephrol. 2003 Oct;14(10):2603-2610 3. Gubler MC, Knebelmann B, Beziau A, et al: Autosomal recessive Alport syndrome: immunohistochemical study of type IV collagen chain distribution. Kidney Int. 1995 Apr;47(4):1142-1147 4. Mencarelli MA, Heidet L, Storey H, et al: Evidence of digenic inheritance in Alport syndrome. J Med Genet. 2015 Mar;52(3):163-174 5. van der Loop FT, Heidet L, Timmer ED, et al: Autosomal dominant Alport syndrome caused by a COL4A3 splice site mutation. Kidney Int. 2000 Nov;58(5):1870-1875 6. Nozu K, Minamikawa S, Yamada S, et al: Characterization of contiguous gene deletions in COL4A6 and COL4A5 in Alport syndrome-diffuse leiomyomatosis. J Hum Genet. 2017 Jul;62(7):733-735 7. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

FALPX
75156

Alprazolam (Xanax)

Reference Values:
5 – 25 ng/mL

Reporting Limit: 2.0 ng/mL

ALTN
82910

Alternaria tenuis, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend

upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Alternaria tenuis Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

AH50
88676

Alternative Complement Pathway, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1. The classical pathway 2. The alternative (or properdin) pathway 3. The lectin (or mannose-binding lectin, MBL) pathway The total complement (CH50) assay (COM / Complement, Total, Serum) assesses the classical complement pathway including early components that activate the pathway in response to immune complexes (C1q, C2 and C4), as well as the terminal complement components (C3, C5, C6, C7, C8, C9) involved in the formation of the membrane attack complex (MAC). The CH50 assay will be abnormal if there are specific hereditary or acquired C1-C9 complement component deficiencies or if there is consumption of complement due to immune (or

autoimmune) complexes. This assay is a screening test for complement abnormalities in the alternative pathway. The alternative complement (AH50) pathway shares C3 and C5-C9 components but has unique early complement components designated factors D, B, and properdin, as well as control proteins factor H and factor I. This pathway can be activated by spontaneous hydrolysis of C3 or by microbial polysaccharides and does not require immune complex formation. Patients with disseminated infections with pyogenic bacteria in the presence of a normal CH50 may have a decreased AH50 due to hereditary or acquired deficiencies of the alternative pathway. Patients with deficiencies in the alternative pathway factors (D, B, properdin, H, and I) or late complement components (C3, C5-C9) are highly susceptible to recurrent Neisserial meningitis. The use of the CH50 and AH50 assays allow identification of the specific pathway abnormality. Functional testing for complement pathways activity is indicated in the study of complement components deficiency, where testing serves as a first-tier screening, or in the study of complement dysregulation. Complement dysregulation is a general grouping of complement conditions where there is loss of control of the complement cascade with over-activation. In several cases, the complement system will attack the host and the over-activation of the complement cascade may cause disease. Over-activation of the alternative pathway usually presents with renal function impairment, in rare conditions such as atypical hemolytic uremic syndrome and C3 glomerulopathies (dense deposit disease and C3 glomerulonephritis). The use of complement inhibitor therapies such as eculizumab and ravulizumab will result in the blocking of C5. C5 is necessary for the AH50 test to progress until the formation of the MAC. Hence, in the presence of eculizumab or ravulizumab, AH50 results will be decreased or undetectable.

Useful For: Investigation of suspected alternative pathway complement deficiency, atypical hemolytic uremic syndrome, C3 glomerulonephritis, and dense-deposit disease

Interpretation: Absent complement alternative pathway (AH50) in the presence of a normal total hemolytic complement (CH50) suggests an alternative pathway component deficiency. Normal AH50 with absent CH50 suggests an early (C1, C2, C4) classic pathway deficiency. Absent AH50 and CH50 suggests a late (C3, C5, C6, C7, C8, C9) component deficiency or complement consumption. Absent AH50 and CH50 in the presence of a normal C3 and C4 suggests a late (C5, C6, C7, C8, C9) component deficiency. Normal CH50 and AH50 in the presence of recurrent infection and continued suspicion of complement deficiency, suggest testing for lectin pathway function.

Reference Values:
> or =46% normal

Clinical References: 1. Frank MM. Medical intelligence current concepts: complement in the pathophysiology of human disease. N Engl J Med. 1987;316(24):1525-1530. doi:10.1056/NEJM198706113162407 2. Thurman JM, Holers VM. Brief reviews: the central role of the alternative complement pathway in human disease. J Immunol. 2006;176(3):1305-1310. doi:10.4049/jimmunol.176.3.1305 3. Frank MM. Complement deficiencies. Pediatr Clin North Am. 2000;47(6):1339-1354. doi:10.1016/s0031-3955(05)70274-1 4. Go RS, Winters JL, Leung N, et al. Thrombotic microangiopathy care pathway: A consensus statement for the Mayo Clinic Complement Alternative Pathway-Thrombotic Microangiopathy (CAP-TMA) Disease-Oriented Group. Mayo Clin Proc. 2016;91(9):1189-1211. doi:10.1016/j.mayocp.2016.05.015 5. Willrich MAV, Andreguetto BD, Sridharan M, et al. The impact of eculizumab on routine complement assays. J Immunol Methods. 2018;460:63-71. doi:10.1016/j.jim.2018.06.010

ALU
8828

Aluminum, 24 Hour, Urine

Clinical Information: Under normal physiologic conditions, the usual daily dietary intake of aluminum (5-10 mg) is eliminated completely. Excretion is accomplished by avid filtration of aluminum from the blood by the glomeruli of the kidney. Patients in kidney failure lose the ability to clear

aluminum and are candidates for aluminum toxicity. Many factors increase the incidence of aluminum toxicity in patients with kidney failure: -Aluminum-laden dialysis water can expose dialysis patients to aluminum. -Aluminum-laden albumin can expose patients to an aluminum burden they cannot eliminate. -The dialysis process is not highly effective at eliminating aluminum. -Aluminum-based phosphate binder gels are administered orally to minimize phosphate accumulation; a small fraction of this aluminum may be absorbed and accumulated. If it is not removed by kidney filtration, aluminum accumulates in the blood where it binds to proteins such as albumin and is rapidly distributed through the body. Aluminum overload leads to accumulation of aluminum at two sites: brain and bone. Brain deposition has been implicated as a cause of dialysis dementia. In bone, aluminum replaces calcium at the mineralization front, disrupting normal osteoid formation. Urine aluminum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Monitoring aluminum exposure Preferred matrix for assessment of exposure in patients with normal kidney function since rapidly filtered by kidneys Monitoring metallic prosthetic implant wear This test is not an acceptable substitute for serum aluminum measurements and is not recommended for routine aluminum screening.

Interpretation: Daily excretion greater than 10 mcg/24 hours indicates exposure to excessive amounts of aluminum. In kidney failure, the ability of the kidney to excrete aluminum decreases, while the exposure to aluminum increases (aluminum-laden dialysis water, aluminum-laden albumin, and aluminum-laden phosphate binders). Patients receiving chelation therapy with desferrioxamine (for iron- or aluminum-overload states) also excrete considerably more aluminum in their urine than normal. Prosthesis wear is known to result in increased circulating concentration of metal ions.(1) Modest increase (10-20 mcg/24 hours) in urine aluminum concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations above 50 mcg/ 24 hours in a patient with an aluminum-based implant and not undergoing dialysis, suggests significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

Reference Values:
0-17 years: Not established
> or =18 years: <13 mcg/24 hours

Clinical References: 1. Liu TK, Liu SH, Chang CH, Yang RS: Concentration of metal elements in the blood and urine in the patients with cementless total knee arthroplasty. Tohoku J Exp Med. 1998;185:253-262 2. O'Shea S, Johnson DW: Review article: Addressing risk factors in chronic kidney disease mineral and bone disorder: Can we influence patient-level outcomes? Nephrology. 2009;14:416-427 3. Meyer-Baron M, Schuper M, Knapp G, van Thriel C: Occupational aluminum exposure: Evidence in support of its neurobehavioral impact. NeuroToxicology. 2007;28:1068-1078 4. Strathmann FG, Blum LM: Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:455.e55 5. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. Toxicological Profile for Aluminum. HHS; 2006. Accessed August 29, 2023. Available at www.atsdr.cdc.gov/toxprofiles/tp22.pdf 6. Willhite CC, Karyakina NA, Yokel RA, et al: Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide, and its soluble salts. Crit Rev Toxicol. 2014;44 Suppl 4(Suppl 4):1-80. doi:10.3109/10408444.2014.934439

AL 8373 Aluminum, Serum

Clinical Information: Under normal physiologic conditions, the usual daily dietary intake of aluminum (5-10 mg) is eliminated completely. Excretion is accomplished by avid filtration of aluminum from the blood by the glomeruli of the kidney. Patients in kidney failure lose the ability to clear aluminum and are candidates for aluminum toxicity. Many factors increase the incidence of aluminum toxicity in patients with kidney failure: -Aluminum-laden dialysis water can expose dialysis patients to aluminum. -Aluminum-laden albumin can expose patients to an aluminum burden they cannot eliminate. -The dialysis process is not highly effective at eliminating aluminum. -Aluminum-based phosphate binder gels are administered orally to minimize phosphate accumulation; a small fraction of this aluminum may be absorbed and accumulated. If it is not removed by kidney filtration, aluminum accumulates in the blood where it binds to proteins such as albumin and is rapidly distributed through the body. Aluminum overload leads to accumulation of aluminum at two sites: brain and bone. Brain deposition has been implicated as a cause of dialysis dementia. In bone, aluminum replaces calcium at the mineralization front, disrupting normal osteoid formation. Deposition of aluminum in bone also interrupts normal calcium exchange. The calcium in bone becomes unavailable for resorption back into blood under the physiologic control of parathyroid hormone (PTH) and results in secondary hyperparathyroidism. While PTH is typically quite elevated in kidney failure, two different processes may occur: 1) High-turnover bone disease associated with high PTH (>150 pg/mL) and relatively low aluminum (<20 ng/mL) 2) Low-turnover bone disease with lower PTH (<50 pg/mL) and high aluminum (>60 ng/mL). Low-turnover bone disease indicates aluminum intoxication. Serum aluminum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside, typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Preferred monitoring for aluminum toxicity in patients undergoing dialysis Preferred test for routine aluminum screening Monitoring metallic prosthetic implant wear

Interpretation: Patients in kidney failure not receiving dialysis therapy invariably have serum aluminum levels above the 60 ng/mL range. McCarthy(1) and Hernandez(2) describe a biochemical profile that is characteristic of aluminum overload disease in dialysis patients: -Patients in kidney failure with no signs or symptoms of osteomalacia or encephalopathy usually had serum aluminum below 20 ng/mL and parathyroid hormone (PTH) concentrations above 150 pg/mL, which is typical of secondary hyperparathyroidism. -Patients with signs and symptoms of osteomalacia or encephalopathy had serum aluminum above 60 ng/mL and PTH concentrations below 50 pg/mL (PTH above the reference range, but low for secondary hyperparathyroidism). -Patients who had serum aluminum above 60 ng/mL but below 100 ng/mL were identified as candidates for later onset of aluminum-overload disease and required aggressive efforts to reduce their daily aluminum exposure. This was done by switching them from aluminum-containing phosphate binders to calcium-containing phosphate binders, by ensuring that their dialysis water had less than 10 ng/mL of aluminum, and ensuring the albumin used during postdialysis therapy was aluminum free. Prosthesis wear is known to result in increased circulating concentration of metal ions.(3) Modest increase (6-10 ng/mL) in serum aluminum concentration is likely to be associated with a prosthetic device in good condition. Serum concentrations above 10 ng/mL in a patient with an aluminum-based implant not undergoing dialysis suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

Reference Values:
<7 ng/mL
<60 ng/mL (dialysis patients)

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. McCarthy JT, Milliner DS, Kurtz SB, Johnson WJ, Moyer TP. Interpretation of serum aluminum values in dialysis patients. Am J Clin Pathol. 1986;86(5):629-636 2. Hernandez JD, Wesseling K, Salusky IB. Role of parathyroid hormone and therapy with active vitamin D sterols in renal osteodystrophy. Semin Dial. 2005;18(4):290-295 3. Liu TK, Liu SH, Chang CH, Yang RS. Concentration of metal elements in the blood and urine in the patients with cementless total knee arthroplasty. Tohoku J Exp Med. 1998;185(4):253-262 4. Schwarz C, Sulzbacher R, Oberbauer R. Diagnosis of renal osteodystrophy. Eur J Clin Invest. 2006;36 Suppl 2:13-22 5. Sharma AK, Toussaint ND, Pickering J, Beeston T, Smith ER, Holt SG. Assessing the utility of testing aluminum levels in dialysis patients. Hemodial Int. 2015;19(2):256-262 doi:10.1111/hdi.12231 6. Riihimaki V, Aitio A. Occupational exposure to aluminum and its biomonitoring in perspective. Crit Rev Toxicol. 2012;42(10):827-853 doi:10.3109/10408444.2012.725027 7. Strathmann FG, Blum LM: Toxic elements In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:455e55 8. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. Toxicological Profile for Aluminum. HHS; 2006. Accessed August 29, 2023. Available at www.atsdr.cdc.gov/toxprofiles/tp22.pdf 9. Willhite CC, Karyakina NA, Yokel RA, et al. Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide, and its soluble salts. Crit Rev Toxicol. 2014;44 Suppl 4(Suppl 4):1-80. doi:10.3109/10408444.2014.934439

ALUCR
610838

Aluminum/Creatinine Ratio, Random, Urine

Clinical Information: Under normal physiologic conditions, the usual daily dietary intake of aluminum (5-10 mg) is eliminated completely. Excretion is accomplished by avid filtration of aluminum from the blood by the glomeruli of the kidney. Patients in kidney failure lose the ability to clear aluminum and are candidates for aluminum toxicity. Many factors increase the incidence of aluminum toxicity in patients with kidney failure: -Aluminum-laden dialysis water can expose dialysis patients to aluminum. -Aluminum-laden albumin can expose patients to an aluminum burden they cannot eliminate. -The dialysis process is not highly effective at eliminating aluminum. -Aluminum-based phosphate binder gels are administered orally to minimize phosphate accumulation; a small fraction of this aluminum may be absorbed and accumulated. If it is not removed by kidney filtration, aluminum accumulates in the blood where it binds to proteins such as albumin and is rapidly distributed through the body. Aluminum overload leads to accumulation of aluminum at two sites: brain and bone. Brain deposition has been implicated as a cause of dialysis dementia. In bone, aluminum replaces calcium at the mineralization front, disrupting normal osteoid formation. Urine aluminum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Monitoring aluminum exposure when a 24-hour urine cannot be collected Monitoring metallic prosthetic implant wear when a 24-hour urine cannot be collected This test is not an acceptable substitute for serum aluminum measurements and is not recommended for routine aluminum screening.

Interpretation: Daily excretion more than 10 mcg/24 hours indicates exposure to aluminum. Prosthesis wear is known to result in increased circulating concentration of metal ions.(1) Modest increase (10-20 mcg/24 hours) in urine aluminum concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations more than 50 mcg/24 hours in a patient with an aluminum-based implant, not undergoing dialysis, suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. In kidney failure, the ability of the kidney to excrete aluminum decreases, while the exposure to aluminum increases (aluminum-laden dialysis water, aluminum-laden albumin, and aluminum-laden phosphate binders). Patients receiving chelation therapy with desferrioxamine (for iron- or aluminum-overload states) also excrete considerably more aluminum in their urine than normal.

Reference Values:
ALUMINUM:
0-17 years: Not established
> or =18 years: <14 mcg/g creatinine

CREATININE:
16-326 mg/dL
Reference values have not been established for patients younger than 18 years of age.

Clinical References: 1. Liu TK, Liu SH, Chang CH, Yang RS. Concentration of metal elements in the blood and urine in the patients with cementless total knee arthroplasty. Tohoku J Exp Med. 1998;185(4):253-262 2. O'Shea S, Johnson DW. Review article: Addressing risk factors in chronic kidney disease mineral and bone disorder: Can we influence patient-level outcomes? Nephrology. 2009;14(4):416-427 3. Meyer-Baron M, Schuper M, Knapp G, van Thriel C. Occupational aluminum exposure: Evidence in support of its neurobehavioral impact. NeuroToxicology. 2007;28(6):1068-1078 4. Strathmann FG, Blum LM: Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:455.e55 5. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. Toxicological Profile for Aluminum. HHS; 2006. Accessed August 29, 2023. Available at www.atsdr.cdc.gov/toxprofiles/tp22.pdf 6. Willhite CC, Karyakina NA, Yokel RA, et al. Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide, and its soluble salts. Crit Rev Toxicol. 2014;44 Suppl 4(Suppl 4):1-80. doi:10.3109/10408444.2014.934439

ALCU
610839

Aluminum/Creatinine Ratio, Urine

Clinical Information: Under normal physiologic conditions, the usual daily dietary intake of aluminum (5-10 mg) is eliminated completely. Excretion is accomplished by avid filtration of aluminum from the blood by the glomeruli of the kidney. Patients in kidney failure lose the ability to clear aluminum and are candidates for aluminum toxicity. Many factors increase the incidence of aluminum toxicity in patients with kidney failure: -Aluminum-laden dialysis water can expose dialysis patients to aluminum. -Aluminum-laden albumin can expose patients to an aluminum burden they cannot eliminate. -The dialysis process is not highly effective at eliminating aluminum. -Aluminum-based phosphate binder gels are administered orally to minimize phosphate accumulation; a small fraction of this aluminum may be absorbed and accumulated. If it is not removed by kidney filtration, aluminum accumulates in the blood where it binds to proteins such as albumin and is rapidly distributed through the body. Aluminum overload leads to accumulation of aluminum at two sites: brain and bone. Brain deposition has been implicated as a cause of dialysis dementia. In bone, aluminum replaces calcium at the mineralization front, disrupting normal osteoid formation. Urine aluminum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Measurement of aluminum concentration as a part of assessing for aluminum exposure

Interpretation: Daily excretion more than 10 mcg/24 hours indicates exposure to aluminum. Prosthesis wear is known to result in increased circulating concentration of metal ions.(1) Modest increase (10-20 mcg/24 hours) in urine aluminum concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations more than 50 mcg/24 hours in a patient with an aluminum-based implant, not undergoing dialysis, suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not

independently predict prosthesis wear or failure. In kidney failure, the ability of the kidney to excrete aluminum decreases, while the exposure to aluminum increases (aluminum-laden dialysis water, aluminum-laden albumin, and aluminum-laden phosphate binders). Patients receiving chelation therapy with desferrioxamine (for iron- or aluminum-overload states) also excrete considerably more aluminum in their urine than normal.

Reference Values:
Only orderable as part of a profile. For more information see ALUCR / Aluminum/Creatinine Ratio, Random, Urine.

Not applicable

Clinical References: 1. Liu TK, Liu SH, Chang CH, Yang RS. Concentration of metal elements in the blood and urine in the patients with cementless total knee arthroplasty. Tohoku J Exp Med. 1998;185(4):253-262 2. O'Shea S, Johnson DW. Review article: Addressing risk factors in chronic kidney disease mineral and bone disorder: Can we influence patient-level outcomes? Nephrology. 2009;14(4):416-427 3. Meyer-Baron M, Schuper M, Knapp G, van Thriel C. Occupational aluminum exposure: Evidence in support of its neurobehavioral impact. NeuroToxicology. 2007;28(6):1068-1078 4. Strathmann FG, Blum LM: Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:455.e55 5. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. Toxicological Profile for Aluminum. HHS; 2006. Accessed August 29, 2023. Available at www.atsdr.cdc.gov/toxprofiles/tp22.pdf 6. Willhite CC, Karyakina NA, Yokel RA, et al. Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide, and its soluble salts. Crit Rev Toxicol. 2014;44 Suppl 4(Suppl 4):1-80. doi:10.3109/10408444.2014.934439

FOXOF
35281

Alveolar Rhabdomyosarcoma (ARMS), 13q14 (FOXO1 or FKHR) Rearrangement, FISH, Tissue

Clinical Information: Rhabdomyosarcomas are a heterogeneous group of malignant tumors showing skeletal muscle differentiation. They can be divided into 3 subtypes: alveolar, embryonal, and pleomorphic. The rarer alveolar rhabdomyosarcomas (ARMS) are seen in older children, are more likely to occur in limbs, and are associated with higher stage disease and an unfavorable prognosis. Most cases of ARMS are associated with the rearrangement of the FOXO1 gene on chromosome 13. Detection of a FOX01 rearrangement by FISH may help to support a histologic diagnosis of ARMS.

Useful For: Supporting the diagnosis of alveolar rhabdomyosarcomas when used in conjunction with an anatomic pathology consultation

Interpretation: FOXO1 will be clinically interpreted as positive or negative. A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the FOXO1 probe set. A positive result is consistent with rearrangement of the FOXO1 gene and likely reflects FOXO1 fusion with a partner gene. The significance of this finding is dependent on the clinical and pathologic features. A positive result is consistent with rearrangement of the FOXO1 gene, likely reflects FOXO1 fusion with a partner gene, and is consistent with a subset of alveolar rhabdomyosarcomas (ARMS). The significance of this finding is dependent on the clinical and pathologic features. A negative result suggests a FOXO1 gene rearrangement is not present but does not exclude the diagnosis of ARMS.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Galili N, Davis RJ, Fredericks WJ, et al: Fusion of a fork head domain gene to PAX3 in the solid tumor alveolar rhabdomyosarcoma. Nat Genet. 1993;5(3):230-235 2. Nishio J, Althof PA, Bailey JM, et al. Use of a novel FISH assay on paraffin-embedded tissues as an adjunct to diagnosis of alveolar rhabdomyosarcoma. Lab Invest. 2006;86(6):547-556 3. Barr FG. Gene fusions involving PAX and FOX family members in alveolar rhabdomyosarcoma. Oncogene. 2001;20(40):5736-5746 4. WHO Classification of Tumours Editorial Board. Soft tissue and bone tumours. 5th ed. IARC; 2020. WHO Classification of Tumours Series. Vol. 3, 203-208

TFE3F
35319

Alveolar Soft Part Sarcoma (ASPS)/Renal Cell Carcinoma (RCC), Xp11.23 (TFE3), FISH, Tissue

Clinical Information: Alveolar soft-part sarcoma (ASPS) is a rare malignant tumor typically occurring in patients in their 20s to 30s within the muscle and deep tissues of the extremities. ASPS is slow growing and refractory to chemotherapy with a propensity to metastasize. Prolonged survival is possible even with metastasis, although the long-term disease-related mortality rate is high. ASPS is characterized by a translocation that results in fusion of TFE3 on chromosome Xp11.2 with ASPSCR1 (also called ASPL or RCC17) on chromosome 17q25.3. Both balanced and unbalanced forms (loss of the derivative X chromosome) of the translocation have been observed. Another tumor, a rare subset of papillary renal cell carcinoma (RCC) with a distinctive pathologic morphology, has rearrangements of TFE3 with ASPSCR1 or other fusion partner genes. This tumor predominantly affects children and young adults, presents at an advanced stage but with an indolent clinical course, and is a distinct entity in the World Health Organization classification. Typically a balanced form of the translocation is present in the RCC variant. An assay to detect rearrangement of TFE3 is useful to resolve diagnostic uncertainty in these tumor types, as immunohistochemistry for TFE3 is not reliable.

Useful For: An aid in the diagnosis of alveolar soft-part sarcoma or renal cell carcinoma variant when used in conjunction with an anatomic pathology consultation

Interpretation: A neoplastic clone is detected when the percent of nuclei with the abnormality exceeds the established normal cutoff for the TFE3 probe set. A positive result of TFE3 rearrangement is consistent with a diagnosis of alveolar soft-part sarcoma (ASPS) or renal cell carcinoma (RCC) variant. A negative result suggests that TFE3 is not rearranged, but does not exclude the diagnosis of ASPS or RCC variant.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Zhong M, De Angelo P, Osborne L, et al: Dual-color break-apart FISH assay on paraffin-embedded tissues as an adjunct to diagnosis of Xp11 translocation renal cell carcinoma and alveolar soft part sarcoma. Am J Surg Pathol 2010;34(6):757-766 2. Ladanyi M, Lui MY, Antonescu CR, et al: The der(17)t(X;17)(p11;q25) of human alveolar soft part sarcoma fuses the TFE3 transcription factor gene to ASPL, a novel gene at 17q25. Oncogene 2001;20:48-57 3. Ross H, Argani P: Xp11 translocation renal cell carcinoma. Pathology 2010;42(4):369-373

ADEVL
607273

Alzheimer Disease Evaluation, Spinal Fluid

Clinical Information: Two neuropathologic features observed in the brain of patients with Alzheimer disease (AD) dementia are the presence of plaques composed of beta-amyloid (Abeta) peptides and intracellular neurofibrillary tangles containing hyperphosphorylated Tau (tubulin-associated unit) proteins. These 2 groups of molecules are the most established biomarkers of the

disease used in clinical and research practice. Positron emission tomography (PET) imaging using US Food and Drug Administration approved amyloid radiotracer (amyloid-PET) to visualize the presence of amyloid lesions in the cerebral cortex is available in some specialized centers. Measuring Abeta42 peptides and certain phosphorylated Tau (such as p-Tau181) proteins in cerebrospinal fluid (CSF) may be used as a means to assess the presence of amyloid pathology. In particular, the use of the p-Tau181/Abeta42 ratio has been shown to be an excellent surrogate marker of amyloid plaque burden, caused by increased deposition of beta-amyloid 1-42 in the brain. The use of these biomarkers has been included in the new consensus research diagnostic criteria for AD, mild cognitive impairment (MCI), and preclinical AD proposed by the National Institute on Aging and Alzheimer's Association Research Framework. The CSF assays included in this evaluation are beta-amyloid (1-42; Abeta42), total Tau (t-Tau), and phosphorylated Tau (p-Tau181). Abeta42 is approximately 4-kDa protein of 42 amino acids that is formed following proteolytic cleavage of a transmembrane protein known as amyloid precursor protein. Due to its hydrophobic nature, Abeta42 has the propensity to form aggregates and oligomers. Oligomers form fibrils that accumulate into amyloid plaques. These pathological changes in Abeta42 are reflected by the decrease in the CSF concentrations of Abeta42 and/or by the increase in the brain uptake of specific tracers during beta-amyloid PET. Tau is present as six isoforms in human brain tissue. These isoforms are generated by alternative splicing of the pre-messenger RNA. The t-Tau assay measures all these isoforms. The most common post-translational modification of Tau proteins is phosphorylation. During neurodegeneration, abnormal phosphorylation leads to the formation of intracellular neurofibrillary tangles composed of the Tau protein that has undergone hyperphosphorylation and developed aggregates of hyperphosphorylated Tau proteins called p-Tau. The p-Tau assay detects phosphorylated Tau at threonine 181 (p-Tau181). Pathological changes associated with AD are reflected by an increase in the CSF concentrations of t-Tau and p-Tau. Increases in CSF t-Tau reflect the intensity of the neuronal and axonal damage and degeneration and are associated with a faster progression from MCI to AD. Increases in CSF p-Tau concentrations are also associated with a faster progression from MCI to AD with more rapid cognitive decline in AD patients and in mild AD dementia cases. The Alzheimer's Association has developed appropriate use criteria to guide safe and optimal use of CSF testing for AD pathology detection in the diagnostic process. The use of CSF biomarker testing may be indicated for the following patient groups: 1. Patients with subjective cognitive decline who are considered at increased risk for AD 2. Patients with MCI that is persistent, progressing, and unexplained 3. Patients with symptoms that suggest possible AD 4. MCI or dementia with an onset at an early age (younger than 65 years) 5. Patients meeting core clinical criteria for probable AD with typical age of onset 6. Patients whose dominant symptom is a change in behavior (eg, Capgras syndrome, paranoid delusions, unexplained delirium, combative symptoms, and depression) and where AD diagnosis is being considered.

Useful For: Assessment of adults with cognitive impairment being evaluated for Alzheimer disease and other causes of cognitive impairment These assays should not be used to predict the development of dementia or other neurologic conditions or to monitor response to therapies.

Interpretation: A beta-amyloid (1-42; Abeta42) result greater than 834 pg/mL is consistent with a negative amyloid positron emission tomography (PET) scan. A negative amyloid PET scan indicates the presence of no or sparse neuritic plaques and is inconsistent with a neuropathological diagnosis of Alzheimer disease (AD). An Abeta42 result greater than 834 pg/mL is associated with a reduced likelihood that a patient's cognitive impairment is due to AD. Total Tau (t-Tau) and phosphorylated Tau (p-Tau181) cerebrospinal fluid (CSF) concentrations increase approximately 2 to 3-times as much in patients with mild-moderate AD as compared to age-matched controls. A t-Tau and/or p-Tau181 concentration of less than or equal to 238 pg/mL and less than or equal to 21.6 pg/mL, respectively, reduces the likelihood that a patient's cognitive impairment is due to AD. The use of p-Tau181/Abeta42 ratio provides better concordance with amyloid PET scan when compared to Abeta42, p-Tau181, and t-Tau individually. The p-Tau/Abeta42 ratio provides better concordance with amyloid PET imaging when compared to Abeta42, phospho-Tau and total-Tau individually. A cut-off of 0.028 provides optimal balance between negative percent agreement (NPA) and positive percent agreement (PPA) when compared to amyloid PET results. A p-Tau/Abeta42 ratio of 0.028 or less has a 92% NPA with normal

amyloid PET. A ratio above 0.028 has a 92% PPA with abnormal amyloid PET. High CSF t-Tau protein concentrations are found in other neurodegenerative diseases such as prion disease or Creutzfeldt-Jakob disease (CJD). In this situation, an elevated t-Tau concentration and an increased t-Tau to p-Tau ratio has a very high specificity for differential diagnoses of CJD. Abnormal (+)/normal (-) Individual comments for AD reporting values Abeta42 (-) phospho Tau (-) total Tau (-) Normal concentrations of Abeta42, phospho-Tau, and total-Tau concentrations are present in CSF. These results are not consistent with the presence of pathological changes associated with Alzheimer disease. Abeta42 (+) phospho-Tau (-) total-Tau (-) Abnormal Abeta42 concentrations are present in CSF. Phospho-Tau and total-Tau concentrations are normal. These results may be consistent with Alzheimer-related pathologic change. Abeta42 (+) phospho-Tau (+) total-Tau (-) Abnormal Abeta42 and phospho-Tau concentrations are present in CSF. The total-Tau concentration is normal. These results are consistent with the presence of Alzheimer disease. Abeta42 (+) phospho Tau (+) total Tau (+) Abnormal Abeta42, phospho-Tau and total-Tau concentrations are present in CSF. These results are consistent with the presence of Alzheimer disease. Abeta42 (+) phospho Tau (-) total Tau (+) Abnormal Abeta42, and total-Tau concentrations are present in CSF. The phospho-Tau concentration is normal. These results may be consistent with Alzheimer-related pathologic change. Abeta42 (-) phospho-Tau (+) total-Tau (-) Abnormal phospho-Tau concentrations are present in CSF. Abeta42 and total-Tau concentrations are normal. These results are not consistent with the presence of pathological changes associated with Alzheimer disease. Abeta42 (-) phospho tau (-) total-Tau (+) Abnormal total-Tau concentrations are present in CSF. The Abeta42 and phospho-Tau concentrations are normal. These results are not consistent with the presence of pathological changes associated with Alzheimer disease. Abeta42 (-) phospho-Tau (+) total-Tau (+) Abnormal phospho-Tau and total-Tau concentrations are present in CSF. The Abeta42 concentration is normal. These results are not consistent with the presence of pathological changes associated with Alzheimer disease. This table and interpretations are based on the National Institute on Aging and Alzheimer's Association research framework diagnostic recommendations.

Reference Values:
Beta-amyloid (1-42) (Abeta42): >834 pg/mL

Total-Tau: < or =238 pg/mL

Phosphorylated-Tau 181: < or =21.6 pg/mL

p-Tau/Abeta42: < or =0.028

Clinical References: 1. Peyro Saint Paul L, Debruyne D, Bernard D, Mock DM, Defer GL. Pharmacokinetics and pharmacodynamics of MD1003 (high-dose biotin) in the treatment of progressive multiple sclerosis. Expert Opin Drug Metab Toxicol. 2016;12(3):327-344 2. Grimsey P, Frey N, Bendig G, et al. Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. J Pharmacokinet Pharmacodyn. 2017;2(4):247-256. doi:10.4155/ipk-2017-0013 3. van Harten AC, Wiste HJ, Weigand SD, et al. Detection of Alzheimer's disease amyloid beta 1-42, p-tau, and t-tau assays. Alzheimers Dement. 2022;18(4):635-644. doi:10.1002/alz.12406 4. Campbell MR, Ashrafzadeh-Kian S, Petersen RC, et al. P-tau/AB42 and AB42/40 ratios in CSF are equally predictive of amyloid PET status. Alzheimers Dement (Amst). 2021;13(1):e12190. doi:10.1002/dad2.12190 5. Blennow K, Stomrud E, Zetterberg H, et al. Second-generation Elecsys cerebrospinal fluid immunoassays aid diagnosis of early Alzheimer's disease. Clin Chem Lab Med. 2022;61(2):234-244. doi:10.1515/cclm-2022-0516 6. Leuzy A, Mattsson-Carlgren N, Cullen NC, et al. Robustness of CSF AB42/40 and AB42/P-tau181 measured using fully automated immunoassays to detect AD-related outcomes. Alzheimers Dement. 2023;19(7):2994-3004. doi:10.1002/alz.12897 7. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535-562 8. Lifke V, Kollmorgen G, Manuilova E, et al. Elecsys Total-Tau and Phospho-Tau (181P) CSF assays: Analytical performance of the novel, fully automated immunoassays for quantification of tau proteins in human cerebrospinal fluid. Clin Biochem. 2019;72:30-38 9. Hansson O, Seibyl J, Stomrud E et al. CSF

biomarkers of Alzheimer's disease concord with amyloid-beta PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimers Dement. 2018;14(11):1470-1481 10. Shaw LM, Arias J, Blennow K, et al. Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease. Alzheimers Dement. 2018;14(11):1505-1521 11. Hansson O, Batrla R, Brix B, et al. The Alzheimer's Association international guidelines for handling of cerebrospinal fluid for routine clinical measurements of amyloid beta and tau. Alzheimers Dement. 2021;17(9):1575-1582. doi:10.1002/alz.12316

FAMAN
91132

Amantadine (Symmetrel)

Reference Values:
Units: ng/mL

Therapeutic range has not been established.

Expected steady state amantadine concentrations in patients receiving recommended daily dosages: 200-1000 ng/mL
Toxicity reported at greater than 2000 ng/mL

PAMIK
37032

Amikacin, Peak, Serum

Clinical Information: Amikacin is an aminoglycoside used to treat severe blood infections by susceptible strains of gram-negative bacteria. Aminoglycosides induce bacterial death by irreversibly binding bacterial ribosomes to inhibit protein synthesis. Amikacin is minimally absorbed from the gastrointestinal tract, and thus can been used orally to reduce intestinal flora. Peak serum concentrations are seen 30 minutes after intravenous infusion, or 60 minutes after intramuscular administration. Serum half-lives in patients with normal renal function are generally 2 to 3 hours. Excretion of aminoglycosides is principally renal, and all aminoglycosides may accumulate in the kidney at 50 to 100 times the serum concentration. Toxicity can present as dizziness, vertigo, or, if severe, ataxia and a Meniere disease-like syndrome. Auditory toxicity may be manifested by simple tinnitus or any degree of hearing loss, which may be temporary or permanent, and can extend to total irreversible deafness. Nephrotoxicity is most frequently manifested by transient proteinuria or azotemia, which may occasionally be severe. Aminoglycosides also are associated with variable degrees of neuromuscular blockade leading to apnea.

Useful For: Monitoring adequacy of serum concentration during amikacin therapy

Interpretation: For conventional (nonpulse) dosing protocols, clinical effects may not be achieved if the peak serum concentration is <20.0 mcg/mL. Toxicity may occur if the peak serum concentration is maintained >35.0 mcg/mL for a prolonged period of time.

Reference Values:
Peak: 20.0-35.0 mcg/mL Toxic peak: >40.0 mcg/mL

Clinical References: 1. Wilson JW, Estes LL: Mayo Clinic Antimicrobial Therapy Quick Guide, 2008 2. Hammett-Stabler CA, Johns T: Laboratory guidelines for monitoring of antimicrobial drugs. national academy of clinical biochemistry. Clin Chem 1998 May;44(5):1129-1140 3. Gonzalez LS III, Spencer JP: Aminoglcosides: a practical review. Am Fam Physician 1998 Nov 15;58(8):1811-1820

RAMIK
37033

Amikacin, Random, Serum

Clinical Information: Amikacin is an aminoglycoside used to treat severe blood infections by susceptible strains of gram-negative bacteria. Aminoglycosides induce bacterial death by irreversibly binding bacterial ribosomes to inhibit protein synthesis. Amikacin is minimally absorbed from the gastrointestinal tract, and thus can been used orally to reduce intestinal flora. Peak serum concentrations are seen 30 minutes after intravenous infusion, or 60 minutes after intramuscular administration. Serum half-lives in patients with normal renal function are generally 2 to 3 hours. Excretion of aminoglycosides is principally renal, and all aminoglycosides may accumulate in the kidney at 50 to 100 times the serum concentration. Toxicity can present as dizziness, vertigo, or, if severe, ataxia and a Meniere disease-like syndrome. Auditory toxicity may be manifested by simple tinnitus or any degree of hearing loss, which may be temporary or permanent, and can extend to total irreversible deafness. Nephrotoxicity is most frequently manifested by transient proteinuria or azotemia, which may occasionally be severe. Aminoglycosides also are associated with variable degrees of neuromuscular blockade leading to apnea.

Useful For: Monitoring adequacy of blood concentration during amikacin therapy

Interpretation: For conventional (nonpulse) dosing protocols, clinical effects may not be achieved if the peak serum concentration is <20.0 mcg/mL. Toxicity may occur if, for prolonged periods of time, peak serum concentrations are maintained >35.0 mcg/mL, or trough concentrations are maintained at >10.0 mcg/mL.

Reference Values:
Peak: 20.0-35.0 mcg/mL
Toxic peak: >40.0 mcg/mL
Trough: <8.0 mcg/mL
Toxic trough:>10.0 mcg/mL

Clinical References: 1. Wilson JW, Estes LL: Mayo Clinic Antimicrobial Therapy Quick Guide, 2008 2. Hammett-Stabler CA, Johns T: Laboratory Guidelines for Monitoring of Antimicrobial Drugs. National Academy of Clinical Biochemistry. Clin Chem. 1998 May;44(5):1129-1140 3. Gonzalez LS III, Spencer JP: Aminoglcosides: a practical review. Am Fam Physician 1998 Nov 15;58(8):1811-1820

TAMIK
37031

Amikacin, Trough, Serum

Clinical Information: Amikacin is an aminoglycoside used to treat severe blood infections by susceptible strains of gram-negative bacteria. Aminoglycosides induce bacterial death by irreversibly binding bacterial ribosomes to inhibit protein synthesis. Amikacin is minimally absorbed from the gastrointestinal tract, and thus can been used orally to reduce intestinal flora. Peak serum concentrations are seen 30 minutes after intravenous infusion, or 60 minutes after intramuscular administration. Serum half-lives in patients with normal renal function are 2 to 3 hours. Excretion of aminoglycosides is principally renal, and all aminoglycosides may accumulate in the kidney at 50 to 100 times the serum concentration. Toxicity can present as dizziness, vertigo, or, if severe, ataxia and a Meniere disease-like syndrome. Auditory toxicity may be manifested by simple tinnitus or any degree of hearing loss, which may be temporary or permanent, and can extend to total irreversible deafness. Nephrotoxicity is most frequently manifested by transient proteinuria or azotemia, which may occasionally be severe. Aminoglycosides also are associated with variable degrees of neuromuscular blockade leading to apnea.

AAMSD
60200

Amino Acids, Maple Syrup Urine Disease Panel, Plasma

Clinical Information: Maple syrup urine disease (MSUD) is an inborn error of metabolism caused by the deficiency of the branched-chain alpha-keto acid dehydrogenase (BCKDH) complex. The

BCKDH complex is involved in the metabolism of the branched-chain amino acids (BCAA): isoleucine, leucine, and valine. MSUD can be divided into 5 phenotypes: classic, intermediate, intermittent, thiamine-responsive, and dihydrolipoyl dehydrogenase (E3)-deficient, depending on the clinical presentation and response to thiamin administration. Classic MSUD, the most common and most severe form, presents in the neonate with feeding intolerance, failure to thrive, vomiting, lethargy, and maple syrup odor to urine and cerumen. If untreated, it progresses to irreversible intellectual disabilities, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. Age of onset for individuals with variant forms of MSUD is variable and some have initial symptoms as early as 2 years of age. Symptoms include poor growth and feeding, irritability, and developmental delays. These patients can also experience severe metabolic intoxication and encephalopathy during periods of sufficient catabolic stress. MSUD is a panethnic condition but is particularly prevalent in the Old Order Mennonite community in Lancaster, Pennsylvania with an incidence of 1:760 live births. The incidence of MSUD is approximately 1:185,000 live births in the general population. Treatment of MSUD aims to normalize the concentration of BCAA by dietary restriction of these amino acids. Because BCAA are essential amino acids, the dietary treatment requires frequent adjustment, which is accomplished by regular determination of BCAA and allo-isoleucine concentrations. Orthotopic liver transplantation has been used with success and is an effective therapy for MSUD.

Useful For: Follow-up of patients with maple syrup urine disease Monitoring of dietary compliance for patients with maple syrup urine disease

Interpretation: The quantitative results of isoleucine, leucine, valine, and allo-isoleucine with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical interpretation.

Reference Values:

Isoleucine
<24 months: 23-149 nmol/mL
2-17 years: 26-150 nmol/mL
> or =18 years: 29-153 nmol/mL

Leucine
<24 months: 59-213 nmol/mL
2-17 years: 51-216 nmol/mL
> or =18 years: 79-217 nmol/mL

Valine
<24 months: 94-382 nmol/mL
2-17 years: 111-367 nmol/mL
> or =18 years: 134-357 nmol/mL

Allo-isoleucine
<5 nmol/mL

Clinical References: 1. Chuang DT, Shih VE, Max Wynn RR. Maple syrup urine disease (Branched-chain ketoaciduria). In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed October 24, 2024. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225084607 2. Strauss KA, Puffenberger EG, Morton DH: Maple syrup urine disease. In: MP Adam, Feldman J, Mirzaa GM, et al, eds. GeneReviews[Internet]. University of Washington, Seattle; 2006. Updated April 23, 2020. Accessed October 24, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1319 3. Diaz VM, Camarena C, de la Vega A, et al. Liver transplantation for classical maple syrup urine disease: Long-term follow-up. J Pediatr Gastroenterol Nutr. 2014;59(5):636-639. doi:10.1097/MPG.0000000000000469 4. Blackburn PR, Gass JM, Vairo FPE, et al. Maple syrup urine disease: mechanisms and management. Appl Clin Genet.

2017;10:57-66. doi:10.2147/TACG.S125962

AAQP
9265

Amino Acids, Quantitative, Plasma

Clinical Information: Amino acids are the basic structural units that comprise proteins and are found throughout the body. Many inborn errors of amino acid metabolism, such as phenylketonuria and tyrosinemia, have been identified. Amino acid disorders can manifest at any age, but most become evident in infancy or early childhood. These disorders result in the accumulation or the deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the specific amino acid disorder. The clinical presentation is dependent upon the specific amino acid disorder. In general, affected patients may experience failure to thrive, neurologic symptoms, digestive problems, dermatologic findings, and physical and cognitive delays. If not diagnosed and treated promptly, amino acid disorders can result in intellectual disabilities and, possibly, death. Treatment for amino acid disorders includes very specific dietary modifications. Nonessential amino acids are synthesized by the body, while essential amino acids are not and must be obtained through an individual's diet. Therapeutic diets are coordinated and closely monitored by a dietician or physician. They are structured to provide the necessary balance of amino acids with particular attention to essential amino acids and those that are abnormal in a particular disorder. Patients must pay close attention to the protein content in their diet and generally need to supplement with medical formulas and foods. Dietary compliance is monitored by periodic analysis of plasma amino acids. In addition, plasma amino acid analysis may have clinical importance in the evaluation of several acquired conditions, including endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, kidney failure, and burns.

Useful For: Evaluating patients with possible inborn errors of metabolism using plasma specimens May aid in evaluation of endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, kidney failure, and burns Monitoring of patients treated for various inborn errors of metabolism or other causes of amino acid imbalances

Interpretation: When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

Amino acids	Age groups
	2-17 years
Taurine (Tau)	31-354
Asparagine (Asn)	18-94
Serine (Ser)	59-224
Hydroxyproline (Hyp)	
Glycine (Gly)	80-500
Glutamine (Gln)	356-857
Aspartic Acid (Asp)	

Ethanolamine (EtN)	
Histidine (His)	46-147
Threonine (Thr)	49-358
Citrulline (Cit)	8-42
Sarcosine (Sar)	
b-Alanine (bAla)	
Alanine (Ala)	139-474
Glutamic Acid (Glu)	28-376
1-Methylhistidine (1MHis)	
3-Methylhistidine (3MHis)	
Argininosuccinic Acid (Asa)	
Homocitruline (Hcit)	
Arginine (Arg)	28-164
a-Aminoadipic Acid (Aad)	
g-Amino-n-butyric Acid (GABA)	
b-Aminoisobutyric Acid (bAib)	
a-Amino-n-butyric Acid (Abu)	
Hydroxylysine (Hyl)	
Proline (Pro)	102-342
Ornithine (Orn)	32-171
Cystathionine (Cth)	
Cystine (Cys)	6-131
Lysine (Lys)	83-304
Methionine (Met)	12-57
Valine (Val)	94-382
Tyrosine (Tyr)	27-188
Isoleucine (IIe)	23-149
Leucine (Leu)	59-213
Phenylalanine (Phe)	36-105
Tryptophan (Trp)	12-103
Alloisoleucine (Allolle)	

Clinical References: 1. Part 8. Amino Acids. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill, 2019. Accessed October 24, 2024 Available at https://ommbid.mhmedical.com/book.aspx?bookID=2709#225069340 2. Pasquali M, Longo N. Amino acids. In: Blau N, Dionisi Vici C, Ferreira CR, Vianey-Saban C, van Karnebeek CDM, eds. Physician's Guide to the Diagnosis, Treatment and Follow-up of Inherited Metabolic Diseases. 2nd ed. Springer-Verlag; 2022:41-50

AAPD
60475

Amino Acids, Quantitative, Random, Urine

Clinical Information: Amino acids are the basic structural units that comprise proteins and are found throughout the body. Many inborn errors of amino acid metabolism that affect amino acid transport or metabolism have been identified, such as phenylketonuria and tyrosinemia. Amino acid disorders can manifest at any age, but most become evident in infancy or early childhood. These disorders result in the accumulation or the deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the specific amino acid disorder. The clinical presentation is dependent upon the specific amino acid disorder. In general, affected patients may experience failure to thrive, neurologic symptoms, digestive problems, dermatologic findings, and physical and cognitive delays. If not diagnosed and treated promptly, amino acid disorders can result in intellectual disabilities and, possibly, death. In addition, amino acid analysis may have clinical importance in the evaluation of several acquired conditions including endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, kidney failure, and burns. General elevations in urine amino acid levels, called aminoaciduria, can be seen in disorders with amino acid transport defects, such as lysinuric protein intolerance and Hartnup disease, as well as in conditions with renal tubular dysfunction including Lowe syndrome and Dent disease.

Useful For: Evaluating patients with possible inborn errors of metabolism using random urine specimens May aid in evaluation of endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, kidney failure, and burns

Interpretation: When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

Amino Acid	Age groups
< 2 months	2-35 months
Taurine	Tau
Asparagine	Asn
Serine	Ser
Hydroxyproline	Hyp
Glycine	Gly

Glutamine	Gln
Aspartic Acid	Asp
Ethanolamine	EtN
Histidine	His
Threonine	Thr
Citrulline	Cit
Sarcosine	Sar
Beta-Alanine	bAla
Alanine	Ala
Glutamic Acid	Glu
1-Methylhistidine	1MHis
3-Methylhistidine	3MHis
Argininosuccinic Acid	Asa
Homocitrulline	Hcit
Arginine	Arg
Alpha-aminoadipic Acid	Aad
Gamma Amino-n-butyric Acid	GABA
Beta-aminoisobutyric Acid	bAib
Alpha-amino-n-butyric Acid	Abu
Hydroxylysine	Hyl
Proline	Pro
Ornithine	Orn
Cystathionine	Cth
Cystine	Cys
Lysine	Lys
Methionine	Met
Valine	Val
Tyrosine	Tyr
Isoleucine	Ile
Leucine	Leu
Phenylalanine	Phe
Tryptophan	Trp
Allo-isoleucine	AlloIle

Clinical References: 1. Part 8: Amino Acids. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill, 2019. Accessed October 24, 2024. Available at https://ommbid.mhmedical.com/book.aspx?bookID=2709#225069340 2. Pasquali M, Longo N. Amino acids. In: Blau N, Dionisi Vici C, Ferreira CR, Vianey-Saban C, van Karnebeek CDM, eds. Physician's Guide to the Diagnosis, Treatment and Follow-up of Inherited Metabolic Diseases. 2nd ed. Springer-Verlag; 2022:41-50

AACSF
81934

Amino Acids, Quantitative, Spinal Fluid

Clinical Information: Amino acids are the basic structural units that comprise proteins and are found throughout the body. Many inborn errors of amino acid metabolism that affect amino acid transport and metabolism have been identified. Amino acid disorders can manifest at any age, but most become evident in infancy or early childhood. These disorders result in the accumulation or deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the specific amino acid disorder. The clinical presentation is dependent upon the specific amino acid disorder. In general, affected patients may experience failure to thrive, neurologic symptoms, digestive problems, dermatologic findings, and physical and cognitive delays. If not diagnosed and treated promptly, amino acid disorders can result in intellectual disabilities and, possibly, death. Cerebrospinal fluid (CSF) specimens are highly informative for a subset of these conditions, such as nonketotic hyperglycinemia and serine biosynthesis defects. CSF specimens are most informative when a plasma specimen is collected at the same time, and the ratio of the amino acid concentrations in CSF to those in plasma is calculated.

Useful For: Evaluating patients with possible inborn errors of amino acid metabolism, particularly nonketotic hyperglycinemia (glycine encephalopathy) and serine biosynthesis defects, especially when used in conjunction with concomitantly collected plasma specimens

Interpretation: When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is provided. This interpretation includes an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies, and the telephone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

Amino Acid	Age groups
< or =31 days	32 days-23 months
Taurine (Tau)	8-28
Asparagine (Asn)	7-25
Serine (Ser)	43-127
Hydroxyproline (Hyp)	
Glycine (Gly)	
Glutamine (Gln)	447-1547
Aspartic Acid (Asp)	
Ethanolamine (EtN)	11-152

Histidine (His)	19-63
Threonine (Thr)	35-212
Citrulline (Cit)	
Sarcosine (Sar)	
Beta-alanine (bAla)	
Alanine (Ala)	20-92
Glutamic Acid (Glu)	
1-Methylhistidine (1MHis)	
3-Methylhistidine (3MHis)	
Argininosuccinic Acid (Asa)	
Homocitrulline (Hcit)	
Arginine (Arg)	7-37
Alpha-aminoadipic Acid (Aad)	
Gamma-amino-n-butyric Acid (GABA)	
Beta-aminoisobutyric Acid (bAib)	
Alpha-amino-n-butyric Acid (Abu)	
Hydroxylysine (Hyl)	
Proline (Pro)	
Ornithine (Orn)	
Cystathionine (Cth)	
Cystine (Cys)	
Lysine (Lys)	16-67
Methionine (Met)	
Valine (Val)	16-83
Tyrosine (Tyr)	
Isoleucine (Ile)	2-30
Leucine (Leu)	14-72
Phenylalanine (Phe)	9-49
Tryptophan (Trp)	
Allo-isoleucine (AlloIle)	

Clinical References: 1. Rinaldo P, Hahn S, Matern D. Inborn errors of amino acid, organic acid, and fatty acid

metabolism. In: Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnosis. 4th ed. WB Saunders Company; 2005:2207-2247 2. Van Hove JLK, Coughlin C II, Swanson M, et al. Nonketotic hyperglycinemia. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated May 23, 2019. Accessed October 24, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1357/ 3. El-Hattab AW. Serine biosynthesis and transport defects. Mol Genet Metab. 2016;118(3):153-159. doi:10.1016/j.ymgme.2016.04.010 4. Pasquali M, Longo N. Amino acids. In: Blau N, Dionisi Vici C, Ferreira CR, Vianey-Saban C, van Karnebeek CDM, eds. Physician's Guide to the Diagnosis, Treatment and Follow-up of Inherited Metabolic Diseases. 2nd ed. Springer-Verlag; 2022:41-50

AAUCD
60202

Amino Acids, Urea Cycle Disorders Panel, Plasma

Clinical Information: Urea cycle disorders (UCD) are a group of inherited disorders of nitrogen detoxification that result when any of the enzymes in the urea cycle (carbamoylphosphate synthetase I [CPS I], ornithine transcarbamylase [OTC], argininosuccinic acid synthetase, argininosuccinic acid lyase, arginase, or the cofactor producer, N-acetyl glutamate synthetase [NAGS]), have deficient or reduced activity. The role of the urea cycle is to metabolize and clear waste nitrogen, and defects in any of the steps of the pathway can result in an accumulation of ammonia, which can be toxic to the nervous system. The urea cycle is also responsible for endogenous production of the amino acids citrulline, ornithine, and arginine. Infants with a complete urea cycle enzyme deficiency typically appear normal at birth but, as ammonia levels rise, present during the neonatal period with lethargy, seizures, hyper- or hypoventilation, and, ultimately, coma or death. Individuals with partial enzyme deficiency may present later in life, typically following an acute illness or other stressors. Symptoms may be less severe and may present with episodes of psychosis, lethargy, cyclical vomiting, and behavioral abnormalities. Patients with impaired ornithine metabolism due to ornithine aminotransferase deficiency may present with childhood-onset myopia progressing to vision loss in the 4th to 6th decades of life. Patients may or may not have accompanying hyperammonemia but display marked elevations in plasma ornithine. All UCD are inherited autosomal recessively, with the exception of OTC deficiency, which is X-linked. UCD may be suspected in cases with elevated ammonia, normal anion gap, and a normal glucose. Plasma amino acids can be used to aid in the diagnosis of UCD and may aid in monitoring treatment effectiveness. Measurement of urinary orotic acid, enzyme activity (CPS I, OTC, or NAGS), and molecular genetic testing can help to distinguish the conditions and allows for diagnostic confirmation. Acute treatment for UCD consists of dialysis and administration of nitrogen scavenger drugs to reduce ammonia concentration. Chronic management typically involves restriction of dietary protein with essential amino acid supplementation. More recently, orthotopic liver transplantation has been used with success in treating some patients.

Useful For: Follow-up of patients with urea cycle disorders

Interpretation: The quantitative results of glutamine, ornithine, citrulline, arginine, and argininosuccinic acid with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical interpretation.

Reference Values:

Glutamine
<24 months: 356-857 nmol/mL
2-17 years: 353-790 nmol/mL
> or =18 years: 447-774 nmol/mL

Ornithine
<24 months: 32-171 nmol/mL

2-17 years: 32-148 nmol/mL
> or =18 years: 39-154 nmol/mL

Citrulline
<24 months: 8-42 nmol/mL
2-17 years: 12-44 nmol/mL
> or =18 years: 18-57 nmol/mL

Arginine
<24 months: 28-164 nmol/mL
2-17 years: 28-156 nmol/mL
> or =18 years: 45-144 nmol/mL

Argininosuccinic Acid
<5 nmol/mL

Reference value applies to all ages.

Clinical References: 1. Brusilow SW, Horwich AL. Urea cycle enzymes. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed April 22, 2024. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225084071 2. Haberle J, Burlina A, Chakrapani A, et al. Suggested guidelines for diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis. 2019;42(6):1192-1230. doi:10.1002/jimd.12100 3. Valle D, Simell O. The Hyperornithinemias. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed April 22, 2024. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225083672 4. Ah Mew N, McCarter R, Izem R, et al. Comparing Treatment Options for Urea Cycle Disorders. Washington (DC): Patient-Centered Outcomes Research Institute (PCORI); December 2020

AACYL
621427

Aminoacylase-1 Deficiency, Urine

Clinical Information: Aminoacylase-1 deficiency (ACY1D) is a very rare autosomal recessive metabolic disorder caused by disease-causing variants in the ACY1 gene and characterized by increased urinary excretion of N-acetylated amino acids, including the derivatives of serine, glutamine, alanine, methionine, glycine, leucine, and valine.(1) The phenotype is variable with less than 20 patients described in the literature. Clinical findings range from asymptomatic to significant neurologic impairments including intellectual disability, seizures, sensorineural hearing loss, and behavioral features such as attention deficit hyperactivity disorder and autism.(2) According to a recent paper, the symptoms described in the literature vary widely, thus making the relationship between clinical symptomatology and ACY1D yet unclear.(3) For patients with a clinical suspicion of ACY1D, the biochemical diagnosis is established via elevated N-acetylated amino acids in urine. For confirmation, molecular genetic testing of the ACY1 gene is available; order CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-M9821N.

Useful For: Follow-up quantitation of abnormal organic acid elevations of N-acetylated amino acids, in particular N-acetylalanine, N-acetylglycine, N-acetylmethionine, and N-acetylglutamic acid Diagnosis of individuals with aminoacylase-1 deficiency Evaluating patients with neurologic and psychiatric symptoms of unknown etiology

Interpretation: When abnormal results are detected, a detailed interpretation is given including an overview of the results and of their significance; a correlation to available clinical information; elements

of differential diagnosis; recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis).

Reference Values:

N-acetylglycine: < or =15.00 mmol/mol creatinine
N-acetyl alanine: < or =10.00 mmol/mol creatinine
N-acetylglutamic acid: < or =20.00 mmol/mol creatinine
N-acetylmethionine: < or =5.00 mmol/mol creatinine

Clinical References: 1. van Coster R. Aminoacylase I deficiency. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Accessed October 17, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225896774 2. Alessandri MG, Milone R, Casalini C, et al. Four years follow up of ACY1 deficient patient and pedigree study. Brain and Dev. 2018;40(7):570-575 3. Smolka V, Friedecky D, Kolarova J, et al. Aminoacylase 1 deficiency: case report on three affected siblings. AME Case Rep. 2023;8:18. doi:10.21037/acr-23-46 4. Sass JO, Mohr V, Olbrich H, et al. Mutations in ACY1, the gene encoding aminoacylase 1, cause a novel inborn error of metabolism. Am J Hum Genet. 2006;78(3):401-409. doi:10.1086/500563

AIHL
609784

Aminoglycoside-Induced Hearing Loss, Targeted Variant Testing, Droplet Digital PCR, Varies

Clinical Information: Aminoglycosides (tobramycin, streptomycin, and gentamicin, etc) are a group of broad-spectrum antibiotics commonly prescribed for infections caused by Gram-negative bacteria. In the United States alone, approximately 4 million courses of aminoglycosides are administered each year with approximately 2% to 5% of patients treated developing clinically significant hearing loss. Mitochondrial gene RNR1 (MT-RNR1) variants m.1555A>G and m.1494C>T are the most common variants associated with aminoglycoside-induced ototoxicity. Hearing loss associated with aminoglycoside exposure can occur even after a single dose and may be bilateral, irreversible, and often severe to profound. Avoidance of aminoglycoside antibiotics reduces the risk of developing hearing loss for individuals carrying one of these 2 variants. The severity and onset of hearing loss in individuals with the associated pathogenic mitochondrial variants range from profound congenital deafness to mild to moderate late-onset hearing loss. Evidence demonstrates that this variance can often be explained by variant load in an individual. In contrast to variants in nuclear genes, which are present in either 0, 1, or 2 copies, mitochondrial variants can be present in any fraction of the total organelles, a phenomenon known as heteroplasmy. Penetrance of hearing loss without exposure to aminoglycosides is thought to be a function of the degree of heteroplasmy, with a correlation between higher fraction of altered mitochondria and higher penetrance. Hearing loss is believed to be 100% penetrant in homoplasmic individuals who receive aminoglycoside antibiotics.

Useful For: Identification of individuals who may be at risk for aminoglycoside-induced hearing loss (AIHL) Establishing a diagnosis of late-onset sensorineural hearing loss associated with aminoglycoside exposure Identifying mitochondrial variants associated with AIHL, allowing for predictive testing of at-risk family members

Interpretation: An interpretive report will be provided.

Reference Values:

An interpretive report will be provided.

Clinical References: 1. Gao Z, Chen Y, Guan MX: Mitochondrial DNA mutations associated with

aminoglycoside induced ototoxicity. J Otol. 2017 Mar;12(1):1-8 2. Krause KM, Serio AW, Kane TR, Connolly LE: Aminoglycosides: An overview. Cold Spring Harb Perspect Med. 2016 Jun 1;6(6):a027029 3. Qian Y, Guan MX: Interaction of aminoglycosides with human mitochondrial 12S rRNA carrying the deafness-associated mutation. Antimicrob Agents Chemother. 2009 Nov;53(11):4612-4618 4. Usami S, Nishio S: Nonsyndromic hearing loss and deafness, mitochondrial. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated June 14, 2018. Accessed March 15, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1422/

ALADW
31895

Aminolevulinic Acid Dehydratase, Washed Erythrocytes

Clinical Information: Porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. A defect in the second enzyme of this pathway causes 5-aminolevulinic acid (ALA) dehydratase (ALAD) deficiency porphyria (ADP). A marked deficiency of ALAD causes the accumulation and subsequent urinary excretion of large amounts of ALA. Urinary porphobilinogen remains essentially normal, which rules out other forms of acute porphyria. ADP is an autosomal recessive acute hepatic porphyria that produces neurologic symptoms similar to those seen in acute intermittent porphyria. Symptoms include acute abdominal pain, peripheral neuropathy, nausea, vomiting, constipation, and diarrhea. Respiratory impairment, seizures, and psychosis are possible during an acute period. ADP is extremely rare with only 8 cases described in the literature since 1979. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. Molecular confirmation is available; order CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify ALAD Gene List ID: IEMCP-D81317. See Porphyria (Acute) Testing Algorithm or call 800-533-1710 to discuss testing strategies.

Useful For: Confirmation of a diagnosis of aminolevulinic acid dehydratase deficiency porphyria using washed erythrocyte specimens This test is not useful for detecting lead intoxication.

Interpretation: Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:
Reference ranges have not been established for patients who are younger than 16 years.

> or =4.0 nmol/L/sec
3.5-3.9 nmol/L/sec (indeterminate)
<3.5 nmol/L/sec (diminished)

Clinical References: 1. Tortorelli S, Kloke K, Raymond K. Disorders of porphyrin metabolism. In: Dietzen DG, Bennett MJ, Wong ECC, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:307-324 2. Nuttall KL, Klee GG. Analytes of hemoglobin metabolism - porphyrins, iron, and bilirubin. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 5th ed. WB Saunders Company; 2001:584-607 3. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill, 2019. Accessed April 19, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225540906&bookid=2709 4. Lahiji AP, Anderson KE, Chan A. 5-Aminolevulinate dehydratase porphyria: Update on hepatic 5-aminolevulinic acid synthase induction and long-term response to hemin. Mol Genet Metab. 2020;131(4):418-423. doi:10.1016/j.ymgme.2020.10.011

ALAD
88924

Aminolevulinic Acid Dehydratase, Whole Blood

Clinical Information: Porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. A defect in the second enzyme of this pathway causes 5-aminolevulinic acid (ALA) dehydratase (ALAD) deficiency porphyria (ADP). A marked deficiency of ALAD causes the accumulation and subsequent urinary excretion of large amounts of ALA. Urinary porphobilinogen remains essentially normal, which rules out other forms of acute porphyria. ADP is an autosomal recessive acute hepatic porphyria that produces neurologic symptoms similar to those seen in acute intermittent porphyria. Symptoms include acute abdominal pain, peripheral neuropathy, nausea, vomiting, constipation, and diarrhea. Respiratory impairment, seizures, and psychosis are possible during an acute period. ADP is extremely rare with only 8 cases described in the literature since 1979. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. Molecular confirmation is available; order CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify ALAD Gene List ID: IEMCP-D81317. See Porphyria (Acute) Testing Algorithm or call 800-533-1710 to discuss testing strategies.

Useful For: Preferred confirmation test for the diagnosis of aminolevulinic acid dehydratase deficiency porphyria This test is not useful for detecting lead intoxication.

Interpretation: Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:
Reference ranges have not been established for patients who are younger than 16 years of age.

> or =4.0 nmol/L/sec
3.5-3.9 nmol/L/sec (indeterminate)
<3.5 nmol/L/sec (diminished)

Clinical References: 1. Tortorelli S, Kloke K, Raymond K. Disorders of porphyrin metabolism. In: Dietzen DG, Bennett MJ, Wong ECC, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:307-324 2. Nuttall KL, Klee GG. Analytes of hemoglobin metabolism-porphyrins, iron, and bilirubin. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 5th ed. WB Saunders Company; 2001:584-607 3. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill, 2019. Accessed April 19, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225540906&bookid=2709 4. Lahiji AP, Anderson KE, Chan A. 5-Aminolevulinate dehydratase porphyria: Update on hepatic 5-aminolevulinic acid synthase induction and long-term response to hemin. Mol Genet Metab. 2020;131(4):418-423. doi:10.1016/j.ymgme.2020.10.011

ALAUR
61547

Aminolevulinic Acid, Urine

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. For more information see The Heme Biosynthetic Pathway. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site

of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: aminolevulinic acid dehydratase deficiency porphyria (ADP), acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP, but it may be present in HCP and VP. The excretion of aminolevulinic acid (ALA) can be increased due to one of the inherited acute porphyrias or due to secondary inhibition of ALA dehydratase. Among the secondary causes, acute lead intoxication results in the greatest increases of aminolevulinic aciduria. Less significant elevations are seen in chronic lead intoxication, tyrosinemia type I, alcoholism, and pregnancy. Once the biochemical diagnosis of an acute porphyria is established, molecular genetic testing is available (APGP / Acute Porphyria Gene Panel, Varies), which allows for diagnosis of at-risk family members. For more information, see the following or call 800-533-1710 to discuss testing strategies: -The Heme Biosynthetic Pathway -Porphyria (Acute) Testing Algorithm -Porphyria (Cutaneous) Testing Algorithm

Useful For: Assisting in the differential diagnosis of the acute hepatic porphyrias

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
<1 year: < or =10 nmol/mL
1-17 years: < or =20 nmol/mL
> or =18 years: < or =15 nmol/mL

Clinical References:

AMIO
9247

Amiodarone, Serum

Clinical Information: Amiodarone is an antiarrhythmic agent used to treat life-threatening arrhythmias; it is typically categorized as a Class III drug (antiarrhythmic agents that are potassium channel blockers) but shows several mechanisms of action. The US Food and Drug Administration approved the use of amiodarone for recurrent ventricular fibrillation and recurrent hemodynamically unstable ventricular tachycardia only after demonstrating lack of response to other antiarrhythmics, but more recent studies have shown amiodarone to be the antiarrhythmic agent of choice for many situations, including atrial fibrillation.(1) Amiodarone can be administered orally or intravenously for cardiac rhythm control. It is approximately 95% protein bound in blood, with a volume of distribution of 60 L/kg. Amiodarone elimination is quite prolonged, with a half-life of 26-107 days for oral, chronic dosing. Cytochrome P450 (CYP) 3A4 converts amiodarone to its equally active metabolite, N-desethylamiodarone (DEA), which displays very similar pharmacokinetics and serum concentrations compared with the parent drug.(2) Current therapeutic ranges are based solely on amiodarone, but most individuals will have roughly equivalent concentrations of DEA at steady state.(3) Numerous side effects have been associated with amiodarone. The most common adverse effect is disruption of thyroid function (hypo- or hyperthyroidism) due to amiodarone's structural similarity to thyroid hormones. Neurological and gastrointestinal toxicities are concentration-dependent, whereas thyroid dysfunction, pulmonary fibrosis, and hepatotoxicity are more loosely linked to drug concentration. There is significant potential for drug interactions involving amiodarone, including several other cardioactive drugs (eg, digoxin,

verapamil, class I antiarrhythmics [sodium channel blockers]), warfarin, statins, and CYP3A4 substrates.

Useful For: Monitoring amiodarone therapy, especially when amiodarone is coadministered with other drugs that may interact Evaluating possible amiodarone toxicity Assessing patient compliance

Interpretation: Clinical effects generally require serum concentrations above 0.5 mcg/mL. Increased risk of toxicity is associated with amiodarone concentrations above 2.5 mcg/mL. Although therapeutic and toxic ranges are based only on the parent drug, the active metabolite N-desethylamiodarone should be present in similar concentrations to amiodarone.

Reference Values:
AMIODARONE
Trough Value
0.5-2.0 mcg/mL: Therapeutic concentration
>2.5 mcg/mL: Toxic concentration

DESETHYLAMIODARONE
No therapeutic range established for desethylamiodarone; activity and serum concentration are similar to parent drug.

Clinical References: 1. Goldschlager N, Epstein AE, Naccarelli GV, et al. A practical guide for clinicians who treat patients with amiodarone: 2007. Heart Rhythm. 2007;4(9):1250-1259 2. Klotz U. Antiarrhythmics: elimination and dosage considerations in hepatic impairment. Clin Pharmacokinet. 2007;46(12):985-996 3. Campbell TJ, Williams KM. Therapeutic drug monitoring: antiarrhythmic drugs. Br J Clin Pharmacol. 2001;52 Suppl1(Suppl 1):21S-34S 4. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

AMTRP 63506 Amitriptyline and Nortriptyline, Serum

Clinical Information: Amitriptyline is a tricyclic antidepressant that is metabolized to nortriptyline, which has similar pharmacologic activity. The relative blood levels of amitriptyline and nortriptyline are highly variable among patients. Amitriptyline is the drug of choice in treatment of depression when the side effect of mild sedation is desirable. Nortriptyline is used when its stimulatory side effect is considered to be of clinical advantage. Nortriptyline is unique among the antidepressants in that its blood level exhibits the classical therapeutic window effect, as blood concentrations above or below the therapeutic window correlate with poor clinical response. Thus, therapeutic monitoring to ensure that the blood level is within the therapeutic window is critical to accomplish successful treatment with this drug. Amitriptyline displays major cardiac toxicity when the combined serum level of amitriptyline and nortriptyline is above 500 ng/mL, characterized by QRS widening (intraventricular conduction delay), which leads to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations. Like amitriptyline, nortriptyline can cause major cardiac toxicity when the concentration is above 500 ng/mL, characterized by QRS widening, which leads to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations.

Useful For: Monitoring amitriptyline and nortriptyline serum concentrations during therapy Evaluating potential amitriptyline and nortriptyline toxicity May aid in evaluating patient compliance

Interpretation: Most individuals display optimal response to amitriptyline when combined serum levels of amitriptyline and nortriptyline are between 80 and 200 ng/mL. Risk of toxicity is increased with combined levels are above 500 ng/mL. Most individuals display optimal response to nortriptyline

with serum levels between 70 and 170 ng/mL. Risk of toxicity is increased with nortriptyline levels above 500 ng/mL. Some individuals may respond well outside of these ranges or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimens collected at trough (ie, immediately before the next dose).

Reference Values:
Amitriptyline and nortriptyline
Total therapeutic concentration: 80-200 ng/mL

Nortriptyline
Therapeutic concentration: 70-170 ng/mL
Note: Therapeutic ranges are for specimens collected at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

Clinical References: 1. Wille SM, Cooreman SG, Neels HM, Lambert WE. Relevant issues in the monitoring and the toxicology of antidepressants. Crit Rev Clin Lab Sci. 2008;45(1):25-89 2. Thanacoody HK, Thomas SHL. Antidepressant poisoning. Clin Med (Lond). 2003;3(2):114-118 3. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-01):9-62 4. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

NH3V
35130

Ammonia, Plasma

Clinical Information: Ammonia is a waste product of protein catabolism; it is potentially toxic to the central nervous system. Increased plasma ammonia may be indicative of hepatic encephalopathy, hepatic coma in terminal stages of liver cirrhosis, hepatic failure, acute and subacute liver necrosis, and Reye's syndrome. Hyperammonemia may also be found with increasing dietary protein intake. The major cause of hyperammonemia in infants includes inherited deficiencies of urea cycle enzymes, inherited metabolic disorders of organic acids and the dibasic amino acids lysine and ornithine, and severe liver disease.

Useful For: Assisting in the diagnosis of hepatic coma Investigating and monitoring treatment for inborn errors of metabolism Evaluating patients with advanced liver disease

Interpretation: Plasma ammonia concentrations do not correlate well with the degree of hepatic encephalopathy. Elevated ammonia concentration may also be found with increased dietary protein intake. Plasma ammonia concentrations in newborns younger than one week are elevated compared to adults. Values less than or equal to 82 mcmol/L have been observed.(1)

Reference Values:
< or =30 mcmol/L

Clinical References: 1. Madigan T, Block DR, Carey WA, et al: Proposed plasma ammonia reference intervals in a reference group of hospitalized term and preterm neonates. J App Lab Med. 2020 Mar 1;5(2):363-369 2. Rosenberg W: Liver disease. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1348-1397

AMMO
606643

Ammonium, 24 Hour, Urine

Clinical Information: The kidney regulates acid excretion and systemic acid base balance. Changing

the amount of ammonium in the urine is one important way the kidneys accomplish this task. Thus, measuring the urine ammonium level can provide understanding of the cause of an acid base disturbance in individual patients.(1-3) The urine ammonium level can also provide a lot of information about the daily acid production in a given patient. Since most of an individual's acid load comes from ingested protein, the urine ammonium is a good indicator of dietary protein intake. Urine ammonium measurements can be particularly helpful for the diagnosis and treatment of kidney stone patients: -High urine ammonium and low urinary pH suggest ongoing gastrointestinal losses. Such patients are at risk of uric acid and calcium oxalate stones. -Low urine ammonium and high urine pH suggest renal tubular acidosis. Such patients are at risk of calcium phosphate stones. -Patients with calcium oxalate and calcium phosphate stones are often treated with citrate to raise the urine citrate (a natural inhibitor of calcium oxalate and calcium phosphate crystal growth). However, citrate is metabolized to bicarbonate (a base), which can increase the urine pH. If the urine pH gets too high, the risk of calcium phosphate stones may have unintentionally been increased. Monitoring the urine ammonium concentration is one way to titrate the citrate dose and avoid this problem. A good starting citrate dose is about one-half of the urine ammonium excretion (in mEq of each). One can monitor the effect of this dose on urine ammonium, citrate, and pH values, and adjust the citrate dose based upon the response. A fall in urine ammonium should indicate whether the current citrate is enough to partially (but not completely) counteract the daily acid load of that given patient.(4)

Useful For: Diagnosis of the cause of acidosis Diagnosis and treatment of kidney stones

Interpretation: If a patient has acidosis and the amount of ammonium in the urine is low, this is suggestive of a renal tubular acidosis. If the amount of ammonium is high, this suggests that the kidneys are working normally and that there are other losses of bicarbonate in the body. Typically this implies gastrointestinal losses.

Reference Values:
15-56 mmol/24 hour
Reference values have not been established for patients <18 years and >77 years of age.
Reference values apply to 24 hour collections.

Clinical References: 1. Peonides A, Levin B, Young W: The renal excretion of hydrogen ions in infants and children. Arch Dis Child. 1965 Feb;40(209):33-39 2. Kamel KS, Briceno LF, Sanchez MI, et al: A new classification for renal defects in net acid excretion. Am J Kidney Dis. 1997 Jan;29(1):136-146 3. Madison LL, Seldin DW: Ammonia excretion and renal enzymatic adaptation in human subjects, as disclosed by administration of precursor amino acids. J Clin Invest .1958 Nov;37(11):1615-1627 4. Coe FL, Evan A, Worcester E: Pathophysiology-based treatment of idiopathic calcium kidney stones. Clin J Am Soc Nephrol. 2011 Aug;6(8):2083-2092

RAMBO
606709

Ammonium, Random, Urine

Clinical Information: The kidney regulates acid excretion and systemic acid base balance. Changing the amount of ammonium in the urine is one important way the kidneys accomplish this task. Thus, measuring the urine ammonium level can provide understanding of the cause of an acid base disturbance in individual patients.(1-3) The urine ammonium level can also provide a lot of information about the daily acid production in a given patient. Since most of an individual's acid load comes from ingested protein, the urine ammonium is a good indicator of dietary protein intake. Urine ammonium measurements can be particularly helpful for the diagnosis and treatment of kidney stone patients: -High urine ammonium and low urinary pH suggests ongoing gastrointestinal losses. Such patients are at risk of uric acid and calcium oxalate stones. -Low urine ammonium and high urine pH suggests renal tubular acidosis. Such patients are at risk of calcium phosphate stones. -Patients with calcium oxalate and calcium phosphate stones are often treated with citrate to raise the urine citrate (a natural inhibitor of

calcium oxalate and calcium phosphate crystal growth). However, citrate is metabolized to bicarbonate (a base), which can increase the urine pH. If the urine pH gets too high, the risk of calcium phosphate stones may have unintentionally been increased. Monitoring the urine ammonium concentration is one way to titrate the citrate dose and avoid this problem. A good starting citrate dose is about one-half of the urine ammonium excretion (in mEq of each). One can monitor the effect of this dose on urine ammonium, citrate, and pH values, and adjust the citrate dose based upon the response. A fall in urine ammonium should indicate whether the current citrate is enough to partially (but not completely) counteract the daily acid load of that given patient.(4)

Useful For: Diagnosis of the cause of acidosis using random urine specimens Diagnosis and treatment of kidney stones

Interpretation: If a patient has acidosis and the amount of ammonium in the urine is low, this is suggestive of a renal tubular acidosis. If the amount of ammonium is high, this suggests that the kidneys are working normally and that there are other losses of bicarbonate in the body. Typically this implies gastrointestinal losses.

Reference Values:
Random: 3-65 mmol/L
No reference values established for <18 years and >77 years of age.

Clinical References: 1. Peonides A, Levin B, Young W: The renal excretion of hydrogen ions in infants and children. Arch Dis Child. 1965 Feb;40(209):33-39 2. Kamel KS, Briceno LF, Sanchez MI, et al: A new classification for renal defects in net acid excretion. Am J Kidney Dis. 1997 Jan;29(1):136-146 3. Madison LL, Seldin DW: Ammonia excretion and renal enzymatic adaptation in human subjects, as disclosed by administration of precursor amino acids. J Clin Invest 1958. Nov;37(11):1615-1627 4. Coe FL, Evan A, Worcester E: Pathophysiology-Based Treatment of Idiopathic Calcium Kidney Stones. Clin J Am Soc Nephrol. 2011 Aug;6(8):2083-2092

AMOBS
8325

Amobarbital, Serum

Clinical Information: Amobarbital is an intermediate-acting barbiturate with hypnotic properties used in short-term treatment of insomnia and to reduce anxiety and provide sedation preoperatively.(1,2) Amobarbital is administered by intravenous infusion or intramuscular injection. The duration of its hypnotic effect is about 6 to 8 hours. The drug distributes throughout the body, with a volume of distribution of 0.9 to 1.4 L/kg, and about 59% of a dose is bound to plasma proteins. Metabolism takes place in the liver primarily via hepatic microsomal enzymes. Its half-life is about 15 to 40 hours (mean: 25 hours). Excretion occurs mainly in the urine.(2,3)

Useful For: Monitoring amobarbital therapy

Interpretation: Amobarbital concentrations above 10 mcg/mL have been associated with toxicity.

Reference Values:
Therapeutic concentration: 1.0-5.0 mcg/mL
Toxic concentration: >10.0 mcg/mL

Clinical References: 1. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:454-454.e484 2. Baselt RC. Disposition of toxic drugs and chemical in man. 12th ed. Biomedical Publications; 2020 3. Milone MC, Shaw LM. Therapeutic drugs and their management. In:

Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453 4. Mihic SJ, Mayfield J. Hypnotics and sedatives. In: Brunton LL, Knollmann BC, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 14th ed. McGraw-Hill Education; 2023

FAMOX
80450

Amoxapine (Asendin) and 8-Hydroxyamoxapine

Reference Values:

Amoxapine	No reference range provided	ng/mL
8-Hydroxyamoxapine	No reference range provided	ng/mL
Combined Total	200 – 400	ng/mL

AMOXY
82663

Amoxicillin, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to amoxicillin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive

5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FAMP
91171

Amphetamine, Serum or Plasma

Reference Values:
Reference Range: 10 – 100 ng/mL

AMPMX
62712

Amphetamine-Type Stimulants Confirmation, Chain of Custody, Meconium

Clinical Information: Several stimulants and hallucinogens chemically related to phenylethylamine are referred to collectively as the amphetamine-type stimulants (amphetamines). Generally, this refers to the prescription and illicit amphetamines including amphetamine; methamphetamine; 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy); 3,4-methylenedioxyamphetamine (MDA); and 3,4-methylenedioxyethylamphetamine (MDEA).(1) Methamphetamine has become a drug of choice among stimulant abusers because of its availability and ease of production. The metabolism of amphetamine consists of hydroxylation and deamination followed by conjugation with glucuronic acid. Methamphetamine is metabolized to amphetamine; both should be present in urine after methamphetamine use. Both MDMA and MDEA are metabolized to MDA.(1) The disposition of drug in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid.(2) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves to the colon by the 16th week of gestation.(3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure up to 5 months before birth, a longer historical measure than is possible by urinalysis.(2) Intrauterine drug exposure to amphetamines has been associated with maternal abruption, prematurity, and decreased growth parameters, such as low birthweight.(4) Some intrauterine amphetamine-exposed infants may develop hypertonia, tremors, and poor feeding and abnormal sleep patterns.(5) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting in utero drug exposure up to 5 months before birth Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

Interpretation: The presence of any of the following: amphetamine; methamphetamine; 3,4-methylenedioxyamphetamine; 3,4-methylenedioxymethamphetamine; or 3,4-methylenedioxyethylamphetamine at more than 20 ng/g is indicative of in utero exposure up to 5

months before birth.

Reference Values:
Negative

Positives are reported with a quantitative liquid chromatography tandem mass spectrometry (LC-MS/MS) result.
Cutoff concentrations for LC-MS/MS testing:
Amphetamine: 20 ng/g
Methamphetamine: 20 ng/g
3,4-Methylenedioxyamphetamine: 20 ng/g
3,4-Methylenedioxyethylamphetamine: 20 ng/g
3,4-Methylenedioxymethamphetamine: 20 ng/g

Clinical References: 1. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020 2. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz: Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989;115(3):474-477 3. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero: mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-56 4. Kwong TC, Ryan RM. Detection of intrauterine illicit drug exposure by newborn drug testing. National Academy of Clinical Biochemistry. Clin Chem. 1997;43(1):235-242 5. Dixon SD: Effects of transplacental exposure to cocaine and methamphetamine on the neonate. West J Med. 1989;150(4):436-442 6.Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

AMPHM
84371

Amphetamine-Type Stimulants Confirmation, Meconium

Clinical Information: Several stimulants and hallucinogens chemically related to phenylethylamine are referred to collectively as the amphetamine-type stimulants (amphetamines). Generally, this refers to the prescription and illicit amphetamines including amphetamine; methamphetamine; 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy); 3,4-methylenedioxyamphetamine (MDA); and 3,4-methylenedioxyethylamphetamine (MDEA).(1) Methamphetamine has become a drug of choice among stimulant abusers because of its availability and ease of production. The metabolism of amphetamine consists of hydroxylation and deamination followed by conjugation with glucuronic acid. Methamphetamine is metabolized to amphetamine; both should be present in urine after methamphetamine use. Both MDMA and MDEA are metabolized to MDA.(1) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(2) The first evidence of meconium in the fetal intestine appears at approximately the tenth to twelfth week of gestation, and slowly moves into the colon by the sixteenth week of gestation.(3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(2) Intrauterine drug exposure to amphetamines has been associated with maternal abruption, prematurity, and decreased growth parameters, such as low birthweight.(4) Some intrauterine amphetamine-exposed infants may develop hypertonia, tremors, and poor feeding and abnormal sleep patterns.(5)

Useful For: Detecting in utero exposure to amphetamine-type stimulants up to 5 months before birth

Interpretation: The presence of any of the following: amphetamine; methamphetamine; 3,4-methylenedioxyamphetamine; 3,4-methylenedioxymethamphetamine; or

3,4-methylenedioxyethylamphetamine at greater than 20 ng/g is indicative of in utero exposure up to 5 months before birth.

Reference Values:

Negative
Positives are reported with a quantitative liquid chromatography tandem mass spectrometry (LC-MS/MS) result.

Cutoff concentrations for LC-MS/MS testing:
Amphetamine: 20 ng/g
Methamphetamine: 20 ng/g
3,4-Methylenedioxyamphetamine: 20 ng/g
3,4-Methylenedioxyethylamphetamine: 20 ng/g
3,4-Methylenedioxymethamphetamine: 20 ng/g

Clinical References: 1. Baselt RC: Disposition of Toxic Drugs and Chemical in Man. 8th ed. Biochemical Publications; 2008:83-86; 947-952; 993-999 2. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz: Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989 Sep;115(3):474-477 3. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG: Meconium passage in utero: mechanisms, consequences, and management. Obstet Gynecol Surv. 2005 Jan;60(1):45-56 4. Kwong TC, Ryan RM: Detection of intrauterine illicit drug exposure by newborn drug testing. National Academy of Clinical Biochemistry. Clin Chem. 1997 Jan;43(1):235-242 5. Dixon SD: Effects of transplacental exposure to cocaine and methamphetamine on the neonate. West J Med. 1989 Apr;150(4):436-442

FASCC
75109

Amphetamines Analysis, Serum

Reference Values:

Reference Range:
Amphetamines: Cutoff: 50

Confirmation Threshold: 10 mg/mL

AMPHX
62711

Amphetamines Confirmation, Chain of Custody, Random, Urine

Clinical Information: Amphetamines are sympathomimetic amines that stimulate central nervous system activity and, in part, suppress the appetite. Phentermine, amphetamine, and methamphetamine are prescription drugs for weight loss. All other amphetamines are Class I (distribution prohibited) compounds. In addition to their medical use as anorectic drugs, they are used in the treatment of narcolepsy, attention-deficit disorder/attention-deficit hyperactivity disorder, and minimal brain dysfunction. Because of their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis. Chain-of-custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Confirming drug exposure involving amphetamines such as amphetamine and methamphetamine, phentermine, pseudoephedrine/ephedrine, methylenedioxymethamphetamine, and methylenedioxyamphetamine. Providing chain-of-custody for when the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by

demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of amphetamines in urine is a strong indicator that the patient has used these drugs within the past 3 days. Methamphetamine has a half-life of 9 to 24 hours and is metabolized by hepatic demethylation to amphetamines. Consequently, a sample containing methamphetamine usually also contains amphetamine. Amphetamine has a half-life of 4 to 24 hours. Amphetamine is not metabolized to methamphetamine; absence of methamphetamine in the presence of amphetamine indicates the primary drug of abuse is amphetamine. However, trace amounts of methamphetamine can be detected in amphetamine-based prescription drugs (eg, Adderall), but the concentrations are typically less than 1% of the amphetamine concentrations. 3,4-Methylenedioxymethamphetamine (Ecstasy, MDMA) is metabolized to 3,4-methylenedioxyamphetamine (MDA). Methylenedioxyethylamphetamine is also metabolized to MDA. The detection interval in urine for amphetamine type stimulants is typically to 3 to 5 days after last ingestion. This test will produce true-positive results for urine specimens collected from patients who are administered Adderall and Benzedrine (contain amphetamine); Desoxyn and Vicks Inhaler (contain methamphetamine); Selegiline, and famprofazone (metabolized to methamphetamine and amphetamine); and clobenzorex, fenethylline, fenproporex, and mefenorex, which are amphetamine pro-drugs and metabolized to amphetamine.

Reference Values:

Negative
Positive results are reported with a quantitative result.

Cutoff concentrations:

Immunoassay screen: 500 ng/mL

Liquid chromatography tandem mass spectrometry:
Amphetamine: 25 ng/mL
Methamphetamine: 25 ng/mL
Phentermine: 25 ng/mL
Methylenedioxyamphetamine: 25 ng/mL
Methylenedioxymethamphetamine: 25 ng/mL
Pseudoephedrine/ephedrine: 25 ng/mL reported as negative

Clinical References: 1. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 10th ed. Biomedical Publications; 2014 2. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 3. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:385

AMPHU
8257

Amphetamines Confirmation, Random, Urine

Clinical Information: Amphetamines are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Phentermine, amphetamine, and methamphetamine are prescription drugs for weight loss. All other amphetamines are Class I (distribution prohibited) compounds. In addition to their medical use as anorectic drugs, they are used in the treatment of narcolepsy, attention-deficit disorder/attention-deficit hyperactivity disorder and minimal brain dysfunction. Because of their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis.

Useful For: Confirming drug exposure involving amphetamines such as amphetamine and methamphetamine, phentermine, pseudoephedrine/ephedrine, methylenedioxyamphetamine (MDA), and methylenedioxymethamphetamine (MDMA)

Interpretation: The presence of amphetamines in urine is a strong indicator that the patient has used one of these drugs within the past 3 days. Methamphetamine has a half-life of 9 to 24 hours and is metabolized by hepatic demethylation to amphetamines. Consequently, a sample containing methamphetamine usually also contains amphetamine. Amphetamine has a half-life of 4 to 24 hours. Amphetamine is not metabolized to methamphetamine; absence of methamphetamine in the presence of amphetamine indicates the primary drug of abuse is amphetamine. However, trace amounts of methamphetamine can be detected in amphetamine-based prescription drugs (eg, Adderall), but the concentrations are typically less than 1% of the amphetamine concentrations. 3,4-Methylenedioxymethamphetamine (Ecstasy, MDMA) is metabolized to 3,4-methylenedioxyamphetamine (MDA). Methylenedioxyethylamphetamine (MDEA) is also metabolized to MDA. The detection interval in urine for amphetamine type stimulants is typically to 3 to 5 days after last ingestion. This test will produce true-positive results for urine specimens collected from patients who are administered Adderall and Benzedrine (contain amphetamine); Desoxyn and Vicks Inhaler (contain methamphetamine); Selegiline, and famprofazone (metabolized to methamphetamine and amphetamine); and clobenzorex, fenproporex, mefenorex, and fenethylline, which are amphetamine pro-drugs and metabolized to amphetamine.

Reference Values:

Negative

Positive results are reported with a quantitative result.

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Amphetamine: 25 ng/mL
Methamphetamine: 25 ng/mL
Phentermine: 25 ng/mL
Methylenedioxyamphetamine: 25 ng/mL
Methylenedioxymethamphetamine: 25 ng/mL
Pseudoephedrine/ephedrine: 25 ng/mL reported as negative

Clinical References: 1. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 10th ed. Biomedical Publications; 2014 2. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT eds Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

FCDU5 75780 Amphetamines, Umbilical Cord Tissue

Reference Values:

Reporting limit determined each analysis.

Units: ng/g

Only orderable as part of a profile-see FCDSU.

APHTS 618165 Amphiphysin Antibody Titer Assay, Serum

Clinical Information: Antineuronal autoantibodies specific for amphiphysin (a 128-kDa synaptic vesicle-associated protein) are found in a paraneoplastic context. These IgG antibodies were initially

described as a serological marker of paraneoplastic stiff-man syndrome associated with breast carcinoma. They are now more aptly recognized as a marker of autoimmune encephalomyeloneuritis, sensory neuronopathy, and assorted neuromyopathic disorders associated with small-cell lung carcinoma or breast carcinoma. Amphiphysin antibody is sometimes detected in patients with lung or breast carcinoma without evidence of neurological disease. Only 1 of 30 patients identified as seropositive for amphiphysin antibodies in the Mayo Clinic Neuroimmunology Laboratory exhibited any stiff-person phenomena (n=63: 39% women, 12% men). Only 10% of women (some with lung carcinoma) and 4% of men fulfilled diagnostic criteria for stiff-man syndrome. Overall, cancer was detected in 79.4% of seropositive patients (at last follow-up). Lung carcinoma (small cell) accounted for 61% of cancers and 35% had breast carcinoma (42% for women). Amphiphysin seropositivity implicates antineuronal autoimmunity as the basis for a variety of neurological presentations and focuses the patient's subsequent investigation to a search for breast carcinoma or small-cell lung carcinoma.

Useful For: Evaluating patients with recent onset of a subacute neurological disorder for which a paraneoplastic basis might be suspected, particularly if the patient has a previous history, risk factors, or family history of cancer, especially lung or breast cancer Reporting an end titer result from serum specimens

Interpretation: Positive results are consistent with neurologic autoimmunity, usually related to breast carcinoma or small-cell lung carcinoma.

Reference Values:

Only orderable as a reflex. For more information see:
-PAVAL / Paraneoplastic, Autoantibody Evaluation, Serum
-DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
-ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
-MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
-MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-SPPS / Stiff-Person Spectrum Disorders Evaluation, including Progressive Encephalomyelitis with Rigidity and Myoclonus, Serum
-AIAES / Axonal Neuropathy, Autoimmune/Paraneoplastic Evaluation, Serum

<1:240
Neuron-restricted patterns of IgG staining that do not fulfill criteria for amphiphysin antibody may be reported as "unclassified antineuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References: 1. Folli F, Solimena M, Cofiell R, et al: Autoantibodies to a 128-kd synaptic protein in three women with the stiff-man syndrome and breast cancer. N Engl J Med. 1993 Feb 25;328(8):546-551 2. Pittock SJ, Lucchinetti CF, Parisi JE, et al: Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol. 2005 Jul;58(1):96-107 3. McKeon A, Pittock SJ: Paraneoplastic encephalomyelopathies: pathology and mechanisms. Acta Neuropathol. 2011 Oct;122(4):381-400 4. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul 15;20(14):3862-3869

APHTC
618164

Amphiphysin Antibody Titer Assay, Spinal Fluid

Clinical Information: Antineuronal autoantibodies specific for amphiphysin (a 128-kDa synaptic vesicle-associated protein) are found in a paraneoplastic context. These IgG antibodies were initially described as a serological marker of paraneoplastic stiff-man syndrome associated with breast

carcinoma. They are now more aptly recognized as a marker of autoimmune encephalomyeloneuritis, sensory neuronopathy, and assorted neuromyopathic disorders associated with small-cell lung carcinoma or breast carcinoma. Only 1 of 30 patients identified as seropositive for amphiphysin antibodies in the Mayo Clinic Neuroimmunology Laboratory exhibited any stiff-person phenomena (n=63: 39% women, 12% men). Only 10% of women (some with lung carcinoma) and 4% of men fulfilled diagnostic criteria for stiff-man syndrome. Overall, cancer was detected in 79.4% of seropositive patients (at last follow-up). Lung carcinoma (small cell) accounted for 61% of cancers and 35% had breast carcinoma (42% for women). Amphiphysin seropositivity implicates antineuronal autoimmunity as the basis for a variety of neurological presentations and focuses the patient's subsequent investigation to a search for breast carcinoma or small-cell lung carcinoma.

Useful For: Evaluating patients with recent onset of a subacute neurological disorder for which a paraneoplastic basis might be suspected, particularly if the patient has a previous history, risk factors, or family history of cancer, especially lung or breast cancer Reporting an end titer result from cerebrospinal fluid specimens

Interpretation: Positive results are consistent with neurologic autoimmunity; usually related to breast carcinoma or small-cell lung carcinoma.

Reference Values:

Only orderable as a reflex. For more information see:
-DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-SPPC / Stiff-Person Spectrum Disorders Evaluation, including Progressive Encephalomyelitis with Rigidity and Myoclonus, Spinal Fluid

<1:2
Neuron-restricted patterns of IgG staining that do not fulfill criteria for amphiphysin antibody may be reported as "unclassified antineuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References: 1. Folli F, Solimena M, Cofiell R, et al: Autoantibodies to a 128-kd synaptic protein in three women with the stiff-man syndrome and breast cancer. N Engl J Med. 1993 Feb 25;328(8):546-551 2. Pittock SJ, Lucchinetti CF, Parisi JE, et al: Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol. 2005 Jul;58(1):96-107 3. McKeon A, Pittock SJ: Paraneoplastic encephalomyelopathies: pathology and mechanisms. Acta Neuropathol. 2011 Oct;122(4):381-400 4. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul 15;20(14):3862-3869

AMP
82664

Ampicillin, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants

and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to ampicillin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

AMBF
606595

Amylase, Body Fluid

Clinical Information: Pleural fluid: Amylase-rich pleural effusions are commonly associated with pancreatitis, esophageal rupture, malignancy, pneumonia, and liver cirrhosis.(1) Pleural fluid amylase measurement is not routinely indicated though may help to narrow the differential due to these causes. Results should be interpreted in conjunction with serum measurement usually as a ratio of pleural fluid to serum amylase. The ratio of pleural fluid to serum amylase in effusions caused by pancreatic disease is much higher (mean + or - SD = 18 + or - 6.3) versus non-pancreatic disease (4.8 + or - 1.3) (P = 0.003).(2) Isoform analysis revealed that pancreatic amylase is diagnostic of pancreatitis-related pleural effusions, whereas salivary amylase isoforms are more often associated with esophageal rupture and malignancy.(3) Peritoneal fluid: The digestive enzymes amylase and lipase can be measured in the identification of pancreatic fluid in the peritoneal cavity. Concentrations are expected to be elevated and at least several-fold times higher in fluid of pancreatic origin compared to simultaneous concentrations

in serum.(4) In contrast, amylase concentration in ascites of non-pancreatic origin was approximately half the plasma value.(5) Drain fluid: Amylase might be measured in a drain fluid to aid in the identification of internal pancreatic fistulas due to chronic pancreatitis or formation of a fistula after surgery.(6,7) Comparison to serum concentrations is recommended with elevations several-fold higher than blood being suggestive of the presence of pancreatic fluid in the drained cavity.

Useful For: Evaluation of patients with a pathological accumulation of fluid to determine whether pancreatic inflammation, pancreatic fistula, or esophageal rupture may be contributing Aiding in the diagnosis of pancreatitis

Interpretation: Peritoneal and drain fluid amylase activity in non-pancreatic peritoneal fluid is often less than or equal to the serum amylase activity. Ascites associated with pancreatitis typically has amylase activity at least 5-fold greater than serum.(1) Normal pleural fluid amylase activity is typically less than the upper limit of normal serum amylase and has a ratio of pleural fluid amylase to serum amylase ratio less than 1.0.(3) All Other Fluids: Body fluid amylase activity may become elevated due to the presence of pancreatitis, esophageal rupture, or amylase producing neoplasms. Results should be interpreted in conjunction with serum amylase and other clinical findings.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Burgess LJ. Biochemical analysis of pleural, peritoneal and pericardial effusions. Clin Chim Acta. 2004;343:61-84 2. Joseph J, Viney S, Beck P, Strange C, Sahn SA, Basran GS. A prospective study of amylase-rich pleural effusions with special reference to amylase isoenzyme analysis. Chest. 1992;102:1455-1459 3. Sahn SA. Getting the most from pleural fluid analysis. Respirology. 2012;17:270-277 4. Robert JH, Meyer P, Rohner A. Can serum and peritoneal amylase and lipase determinations help in the early prognosis of acute pancreatitis? Ann Surg. 1986;203:163-168 5. Runyon BA. Amylase levels in ascitic fluid. J Clin Gastroenterol. 1987;9(2):172-174 6. Lipsett PA, Cameron JL. Internal pancreatic fistula. Am J Surg. 1992;163(2):216-220 7. Kaman L, Behera A, Singh R, Katariya RN. Internal pancreatic fistulas with pancreatic ascites and pancreatic pleural effusions: recognition and management. ANZ J Surg. 2001;71(4):221-225 8. Nandakumar V, Dolan C, Baumann NA, Block DR. Effect of pH on the quantification of body fluid analytes for clinical diagnostic testing. Am J Clin Path. 2019;152(S1):S10-S11

AMISO
604930

Amylase, Isoenzymes, Serum

Clinical Information: The amylase enzymes are a group of hydrolases that degrade complex carbohydrates (starches) into simple sugars. The pancreas and salivary glands have amylase concentrations that are orders of magnitude greater than any other tissue. These two amylase isoenzymes, pancreatic and salivary, are present in serum. Pancreatic and salivary amylase isoenzymes can be measured in serum at physiologic concentrations (within the age-specific reference interval), and elevated concentrations indicate hyperamylasemia. Hyperamylasemia can result from either increased rate of release of amylase into blood or decreased metabolic clearance of the enzyme (ie, macroamylase). Routine amylase laboratory tests measure total amylase activity in serum and do not differentiate between amylase isoenzymes. Differentiation of amylase isoenzymes is useful in cases where amylase elevations are not thought to be from a pancreatic source. Pancreatic amylase may be elevated due to pancreatitis as well as other conditions in which pancreatic amylase is released (eg, cannulation of the pancreatic duct) or absorbed (eg, loss of bowel integrity) into the blood. Serum pancreatic amylase should always be interpreted in a context of total amylase to determine the relative contribution of salivary and pancreatic isoenzymes. Hyperamylasemia due to salivary amylase may occur when salivary gland disease is present. Salivary amylasemia may also be observed in conditions where there is no clinical evidence of salivary gland diseases, such as chronic alcoholism, postoperative states, lactic acidosis, anorexia nervosa or

bulimia, and malignant neoplasms that secrete amylase.

Useful For: Ruling out salivary amylase as the cause of elevated serum amylase

Interpretation: Increased concentrations of total amylase activity in conjunction with increased concentration of specific amylase isoenzymes may aid in differentiating the source of amylase (pancreatic versus salivary).

Reference Values:
AMYLASE, TOTAL
0-30 days: < or =6 U/L
31-182 days: 1-17 U/L
183-365 days: 6-44 U/L
1-3 years: 8-79 U/L
4-17 years: 21-110 U/L
> or =18 years: 28-100 U/L

AMYLASE, PANCREATIC
0-<24 months: < or =20 U/L
2-<18 years: 9-35 U/L
> or =18 years: 13-53 U/L

AMYLASE, SALIVARY
0-<18 years: Not established
> or =18 years: < or =86 U/L

Clinical References: 1. Panteghini M. Laboratory evaluation of pancreatic diseases. Biochimica Clinica. 2010;34(1):19-25 2. Rifai N, Horvath AR, Wittwer CT. Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics. 8th ed. Elsevier; 2018 3. Pieper-Bigelow C, Strocchi A, Levitt MD. Where does serum amylase come from and where does it go? Gastroenterol Clin North Am. 1990;19(4):793-810 4. Azzopardi E, Lloyd C, Teixeira SR, Conlan RS, Whitaker IS. Clinical applications of amylase: Novel perspectives. Surgery. 2016;160(1):26-37

AMLPC
60078

Amylase, Pancreatic Cyst Fluid

Clinical Information: Amylases are a group of hydrolases that degrade complex carbohydrates into fragments. Amylase is produced by the exocrine pancreas and the salivary glands to aid in the digestion of starch. It is also produced by the small intestine mucosa, ovaries, placenta, liver, and fallopian tubes. Measurement of amylase in pancreatic cyst fluid is often used in conjunction with tumor markers carcinoembryonic antigen, and CA19-9 as an aid in the differential diagnosis of pancreatic cysts lesions. Amylase seems to be particularly helpful in excluding pancreatic pseudocysts. A number of studies have demonstrated that amylase levels are typically very high, usually in the thousands in pseudocysts, therefore, low amylase values virtually exclude pseudocysts. Based on the evidence available, the American College of Gastroenterology practice guidelines for the Diagnosis and Management of Neoplastic Pancreatic Cysts suggest that an amylase cutoff value of 250 U/L is useful to exclude pseudocysts.

Useful For: Aiding in distinguishing between pseudocysts and other types of pancreatic cysts when used in conjunction with imaging studies, cytology, and other pancreatic cyst fluid tumor markers

Interpretation: A pancreatic cyst fluid amylase concentration of less than 250 U/L indicates a low risk of a pseudocyst and is more consistent with cystic neoplasms such as mucinous cystic neoplasms

(MCN), intraductal papillary mucinous neoplasm (IPMN), serous cystadenomas, cystic neuroendocrine tumor, and mucinous cystadenocarcinoma. High pancreatic cyst fluid amylase values are nonspecific and occur both in pseudocysts and some mucin-producing cystic neoplasms including MCN, IPMN, and mucinous cystadenocarcinoma. In-house studies showed that using a cutoff value of less than 250 U/L to exclude a pseudocyst has 94% sensitivity and 42% specificity. Cysts with amylase levels of less than 250 U/L included 69% of adenocarcinomas, 31% of intraductal papillary mucinous neoplasia, 55% of mucinous cystadenomas, 64% serous cystadenomas, and 6% of pseudocysts.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Snozek CL, Mascarenhas RC, O'Kane DJ. Use of cyst fluid CEA, CA19-9, and amylase for evaluation of pancreatic lesions. Clin Biochem. 2009;42(15):1585-1588 2. van der Waaij LA, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc. 2005;62(3):383-389 3. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG clinical guideline: Diagnosis and management of pancreatic cysts. Am J Gasroenterol. 2018;113(4):464-479 4. Brugge WR. Diagnosis and management of cystic lesions of the pancreas. J Gastrointest Oncol. 2015;6(4):375-388. doi:10.3978/j.issn.2078-6891.2015.057

AMS
8352

Amylase, Total, Serum

Clinical Information: The amylase enzymes are a group of hydrolases that degrade complex carbohydrates into fragments. Amylase is produced primarily by the exocrine pancreas where the enzyme is synthesized by the acinar cells and then secreted into the intestinal tract by way of the pancreatic duct system. Amylases also are produced by the salivary glands, small intestine mucosa, ovaries, placenta, liver, and fallopian tubes. Pancreatic and salivary isoenzymes are found in serum.

Useful For: Diagnosis and management of pancreatitis Evaluation of pancreatic function

Interpretation: In acute pancreatitis, a transient rise in serum amylase activity occurs within 2 to 12 hours of onset; levels return to normal by the third or fourth day. A 4- to 6-fold elevation of amylase activity above the reference limit is usual with the maximal levels obtained in 12 to 72 hours. However, a significant number of subjects show lesser elevations and sometimes none. The magnitude of the elevation of serum enzyme activity is not related to the severity of pancreatic involvement. Normalization is not necessarily a sign of resolution. In acute pancreatitis associated with hyperlipidemia, serum amylase activity may be spuriously normal; the amylasemia may be unmasked either by serial dilution of the serum or ultracentrifugation. A significant amount of serum amylase is excreted in the urine and, therefore, elevation of serum activity is reflected in the rise of urinary amylase activity. Urine amylase, as compared to serum amylase, appears to be more frequently elevated, reaches higher levels, and persists for longer periods. However, the receiver operator curves (ROC) of various serum and urine amylase assays demonstrated that all urine assays had poorer diagnostic utility than all serum assays. In quiescent chronic pancreatitis, both serum and urine activities are usually subnormal. Because it is produced by several organs, amylase is not a specific indicator of pancreatic function. Elevated levels also may be seen in a number of nonpancreatic disease processes including mumps, salivary duct obstruction, ectopic pregnancy, and intestinal obstruction/infarction.

Reference Values:
0-30 days: 0-6 U/L
31-182 days: 1-17 U/L
183-365 days: 6-44 U/L
1-3 years: 8-79 U/L
4-17 years: 21-110 U/L

> or =18 years: 28-100 U/L

Clinical References: 1. Soldin SJ: Pediatric Reference Ranges. 2nd ed AACC Press; 1997 2. Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018 3. Swaroop VS, Chari ST, Clain JE: Acute pancreatitis. JAMA. 2004;291:2865-2868 4. Azzopardi E, Lloyd C, Teixeira SR, Conlan, RS, Whitaker, IS: Clinical applications of amylase: Novel perspectives. Surgery. 2016;160(1):26-37

AAH
70349

Amyloid A (Hepatic) Immunostain, Technical Component Only

Clinical Information: Amyloid A (AA), also called serum AA, is an acute-phase protein. In the liver, AA is expressed on hepatocytes, although expression has been observed in adipocytes. AA can be used with a panel of immunohistochemical markers (beta-catenin, liver fatty acid binding protein, C-reactive protein, and glutamine synthetase) to distinguish hepatic adenoma from focal nodular hyperplasia and non-neoplastic liver. AA, along with C-reactive protein is overexpressed in inflammatory (type 3) hepatic adenoma and is not detectable in normal liver or in other adenoma types.

Useful For: Classification of hepatic adenomas This test is not useful for amyloid typing.

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. van Aalten SM, Verheij J, Terkivatan T, Dwarkasing RS, de Man RA, Ijzermans JN. Validation of a liver adenoma classification system in a tertiary referral centre: implications for clinical practice. J Hepatol. 2011;55(1):120-125 2. Bioulac-Sage P, Cubel G, Balabaud C, et al. Revisiting the pathology of resected benign hepatocellular nodules using new immunohistochemical markers. Semin Liver Dis. 2011;31(1):91-103 3. Bioulac-Sage P, Rebouissou S, Thomas C, et al. Hepatocellular adenoma subtype classification using molecular markers and immunohistochemistry. Hepatology. 2007;46(3):740-748 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FAMBT
75904

Amyloid Beta-Protein

Clinical Information: Amyloid B-Protein is a peptide that ranges in size from 28-43 amino acids. Most fragments have the same biological activity as the whole molecule. Amyloid B-Protein causes vascular and cerebral plaque formation. Insoluble fibrils of Amyloid B-Protein accumulate in adrenal blood vessels and in neutritic plaques. Occurrence of plaques are present in normal brain but in a much less dense degree as in Alzheimer's disease patients. Amyloid B-Protein is also found in elevated levels in patients with Down's Syndrome. Substance P has been found to counteract the effects of Amyloid B-Protein.

Reference Values:
20-80 pg/mL

AMYPI
70549

Amyloid P (SAP) Immunostain, Technical Component Only

Clinical Information: Amyloid P (SAP) is a serum protein that is generally incorporated into the extracellular deposits of all amyloid types. Immunohistochemical staining for SAP produces diffuse, extracellular staining in positive tissues, and colocalizes with Congo Red apple-green birefringence. All types of amyloid should be positive for SAP. Immunohistochemical classification of amyloid has been largely replaced by subtyping using tandem mass spectrometry analysis on formalin-fixed paraffin-embedded specimens, due to its superior sensitivity and specificity.

Useful For: Identification of amyloid deposits in tissue

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Jang B, Koh Y, Seo JW. Immunohistochemical classification of amyloid deposits in surgical pathology. Basic and Applied Pathology. 2009;2(1):1-8 2. Schonland SO, Hegenbart U, Bochtler T, et al. Immunohistochemistry in the classification of systemic forms of amyloidosis: a systematic investigation of 117 patients. Blood. 2012;119(2):488-493 3. Stewart CR, Haw A 3rd, Lopez R, et al. Serum amyloid P colocalizes with apolipoproteins in human atheroma: functional implications. J Lipid Res. 2007;48(10):2162-2171 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

APPI
70357

Amyloid Precursor Protein (APP) Immunostain, Technical Component Only

Clinical Information: Amyloid precursor protein (APP) is present in Alzheimer disease-associated plaques, large pyramidal cells as well as smaller neurons, astrocytes, and microglia. Histologic features of Alzheimer disease include the presence of abundant neurofibrillary, tangles, neuropil threads, and neuritic ("senile") plaques. The main component of senile plaque amyloid is a 39- to 42-amino acid segment referred to as beta amyloid, which is derived from APP.

Useful For: Aids in the identification of amyloid precursor protein present in Alzheimer disease

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Ahlgren S, Li GL, Olsson Y. Accumulation of beta-amyloid precursor protein and ubiquitin in axons after spinal cord trauma in humans: immunohistochemical observations on autopsy material. Acta Neuropathol. 1996;92(1):49-55 2. Craggs LJ, Yamamoto Y, Ihara M, et al. White matter pathology and disconnection in the frontal lobe in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Neuropathol Appl Neurobiol. 2014;40(5):591-602 3. Dermaut B, Kumar-Singh S, De Jonghe C, et al. Cerebral amyloid angiopathy is a pathogenic lesion in Alzheimer's disease due to a novel presenilin 1 mutation. Brain. 2001;124(Pt 12):2383-2392 4. Reichard RR, White CL 3rd, Hogan RN, Hladik CL, Dolinak D. Beta-amyloid precursor protein immunohistochemistry in the evaluation of pediatric traumatic optic nerve injury. Ophthalmology. 2004;111(4):822-827 5. Sawaguchi T, Franco P, Kadhim H, et al: Investigation into the

correlation in SIDS victims between Alzheimer precursor protein A4 in the brainstem and sleep apnea. Early Hum Dev. 2003;75 Suppl:S21-S30. 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

AMPIP
620247

Amyloid Protein Identification, Paraffin, Mass Spectrometry

Clinical Information: Amyloidosis is a group of hereditary and acquired diseases unified by extracellular tissue deposition of misfolded proteins resulting in end organ damage. Amyloidosis can be a systemic or localized disease. Although many cases of amyloidosis are hereditary, most are acquired as the result of an underlying monoclonal B-cell/plasma cell malignancy, as a phenomenon of aging, or as the result of long-standing chronic inflammation. Specific amyloid-related diseases are therefore associated with specific amyloid proteins. These include kappa or lambda immunoglobulin light chains (AL amyloid), transthyretin (ATTR amyloid), serum amyloid A (SAA amyloid), and other uncommon subtypes. Because treatment of patients with amyloidosis differs radically for the different amyloid subtypes, it is critically important to accurately identify the proteins that constitute the amyloid deposits. The basic diagnosis of amyloidosis is typically achieved by Congo red staining of paraffin-embedded tissue biopsy specimens obtained from diverse anatomic sites and demonstrating Congo red-positive, apple-green birefringent, amyloid deposits in the tissues. The next step is to definitively subtype the amyloid deposits. This test fulfills that need. It relies on laser microdissection of Congo red-positive amyloid deposits followed by analysis by liquid chromatography tandem mass spectrometry to accurately determine the identity of the proteins that constitute the amyloid.

Useful For: Definitive identification of amyloid proteins

Interpretation: An interpretation will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Theis JD, Dasari S, Vrana JA, Kurtin PJ, Dogan A. Shotgun-proteomics-based clinical testing for diagnosis and classification of amyloidosis. J Mass Spectrom. 2013;48(10):1067-1077 2. Said SM, Sethi S, Valeri AM, et al. Renal amyloidosis: origin and clinicopathologic correlations of 474 recent cases. Clin J Am Soc Nephrol. 2013;8(9):1515-1523 3. Dasari S, Theis JD, Vrana JA, et al. Amyloid typing by mass spectrometry in clinical practice: a comprehensive review of 16,175 samples. Mayo Clin Proc. 2020;95(9):1852-1864. doi:10.1016/j.mayocp.2020.06.029 4. Klein CJ, Vrana JA, Theis JD, et al. Mass spectrometric-based proteomic analysis of amyloid neuropathy type in nerve tissue. Arch Neurol. 2011;68(2):195-199 5. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR III, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009;114(24):4957-4959

TTRX
83674

Amyloidosis, Transthyretin-Associated Familial, Reflex, Blood

Clinical Information: The amyloidoses are a group of diseases that result from the abnormal deposition of amyloid in various tissues of the body. They have been classified into 3 major types: primary, secondary, and hereditary. The most common form of amyloidosis (AL) is a disease of the bone marrow called primary systemic AL (immunoglobulin light chain). Secondary AL usually occurs in tandem with chronic infectious or inflammatory diseases, such as rheumatoid arthritis, tuberculosis, or osteomyelitis. Familial or hereditary AL is the least common form. Determining the specific type of AL is imperative in order to provide both an accurate prognosis and appropriate therapies. Familial or

hereditary transthyretin AL is an autosomal dominant disorder caused by variants in the transthyretin gene (TTR). The resulting amino acid substitutions lead to a relatively unstable, amyloidogenic transthyretin (TTR) protein. Most individuals begin to exhibit clinical symptoms between the third and seventh decades of life. Affected individuals may present with a variety of symptoms including sensorimotor and autonomic neuropathy, vitreous opacities, cardiomyopathy, nephropathy, and gastrointestinal dysfunction. TTR-associated AL is progressive over a course of 5 to 15 years and usually ends in death from cardiac or kidney failure or malnutrition. Orthotopic liver transplantation is a treatment option for some patients who are diagnosed in early stages of the disease. Other treatment options include the use of TTR tetramer stabilizer medications and gene-silencing therapies (RNA interference/RNAi) approved for use in several countries including the United States. Mayo Clinic Laboratories recommends a testing strategy that includes both protein analysis by mass spectrometry (MS) and TTR gene analysis by DNA sequencing for patients in whom TTR-associated familial AL is suspected. The structure of TTR protein in plasma is first determined by MS. The presence of a disease-causing variant in the TTR gene leads to conformational changes in the TTR protein. This ultimately disrupts the stability of the mature TTR protein tetramer, leading to increased amounts of pro-amyloidogenic TTR monomers in the plasma of affected individuals. MS technology can identify the mass difference between wildtype TTR and variant TTR protein. Only the transthyretin (also known as prealbumin) is analyzed for amino acid substitutions. Other proteins involved in other less common forms of familial amyloidosis are not examined. If no alterations are detected, gene analysis will not be performed unless requested by the provider (ie, when the diagnosis is still strongly suspected; to rule out the possibility of a false-negative by MS). In all cases demonstrating a structural change by MS, DNA sequence analysis will be performed on the TTR gene to identify and characterize the observed alteration (disease-causing or benign variant). More than 90 variants that cause TTR-associated familial AL have now been identified within the TTR gene. Most of the variants described to date are single base pair changes that result in an amino acid substitution. Some of these variants correlate with the clinical presentation of AL. For predictive testing in cases where a familial variant is known, testing for the specific variant by DNA sequence analysis (FMTT / Familial Variant, Targeted Testing, Varies) is recommended. These assays do not detect alterations associated with non-TTR forms of familial AL. Therefore, it is important to first test an affected family member to determine if TTR is involved and to document a specific alteration in the family before testing at-risk individuals.

Useful For: Diagnosis of adult individuals suspected of having transthyretin-associated familial amyloidosis

Interpretation: The presence of a structural change in transthyretin (TTR) is suggestive of a gene variant that requires confirmation by DNA sequence analysis. A negative result by mass spectrometry does not rule out a TTR variant. Mass spectrometric (MS) results are falsely negative if the amino acid substitution does not produce a measurable mass shift for the transthyretin variant. Approximately 90% of the TTR variants are positive by MS (see Cautions). After identification of the variant at the DNA level, predictive testing for at-risk family members can be performed by molecular analysis (FMTT / Familial Variant, Targeted Testing, Varies).

Reference Values:
An interpretive report will be provided.

Clinical References:

ANAID
45010

Anaerobe Ident (Bill Only)

Reference Values:
This test is for Billing Purposes Only.
This is not an orderable test.

ISAN
45255

Anaerobe Identification by Sequencing (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

BATTA
80931

Anaerobe Suscep Battery (Bill Only)

Reference Values:
This test is for Billing Purposes Only.
This is not an orderable test.

SANA
45337

Anaerobe Suscep per Agent (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

ATPCO
614402

Anal ThinPrep Cytology with Human Papillomavirus (HPV) Co-Test, Varies

Clinical Information: Persistent infection with human papillomavirus (HPV) can cause anal cancer, with approximately 90% of all anal cancers being associated with HPV infection. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggests that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk (HR) for the development of cervical and anal cancer and precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all HPV-related cancers, while HPV-18 accounts for approximately 10% to 15% of HPV-related cancers.(1-3) Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected patients will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. DNA testing by real-time polymerase chain reaction (PCR) is a noninvasive method for determining the presence of anal HPV infection. Proper implementation of DNA testing for HPV may: 1. Increase the sensitivity of anal cancer detection 2. Reduce the need for unnecessary biopsy and treatment Recent data suggests that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging of patients who are at risk for cervical cancer and may be useful in cases of possible anal cancer. Detection of HR HPV DNA, especially genotypes 16 and 18, may assist in triaging patients and determining appropriate management strategies.

Useful For: Detection of malignant and premalignant changes Detection of high-risk (HR) genotypes associated with the development of anal cancer Individual genotyping of human papillomavirus (HPV)-16 and HPV-18, if present May aid in triaging men and women with positive HR-HPV but negative anal Papanicolaou (Pap) smear results The cobas HPV test is not recommended for evaluation of suspected sexual abuse.

Interpretation: Cytology: Suspicious or atypical results need further confirmation: clinical

observation, repeat cytology, or perhaps appropriate biopsy. Positive results should be confirmed by histologic examination of tissue before definitive therapy is instituted. Human papillomavirus: A positive result indicates the presence of human papillomavirus (HPV) DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. Management of abnormal results requires consideration of baseline risk of anal cancer and prior anal cytology and HPV results. For patients with an anal Papanicolaou (Pap) test result showing atypical squamous cells of undetermined significance (ASC-US) and who are positive for high-risk (HR) HPV, consider referral for anoscopy if clinically indicated. For men and women with a negative anal Pap test result but who are positive for HPV-16 or HPV-18, consider referral for anoscopy if clinically indicated. For men and women with a negative anal Pap smear, positive-HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and HR-HPV in 12 months.

Reference Values:

ANAL THINPREP CYTOLOGY

Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

HUMAN PAPILLOMAVIRUS (HPV)

Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Clinical References: 1. Swanson AA, Hartley C, Long ME, et al. Evaluation of high-risk human papillomavirus testing and anal cytology to detect high-grade anal intraepithelial neoplasia. J Am Soc Cytopathol. 2021;10(4):406-413. doi:10.1016/j.jasc.2021.03.007 2. Silva Dalla Libera L, Almeida de Carvalho KP, Enocencio Porto Ramos J, et al. Human papillomavirus and anal cancer: Prevalence, genotype distribution, and prognosis aspects from Midwestern region of Brazil. J Oncol. 2019;2019:6018269. Published 2019 Sep 18. doi:10.1155/2019/6018269 3. Wieland U, Kreuter A. Anal cancer risk: HPV-based cervical screening programmes. Lancet Infect Dis. 2019:19(8):799-800

ANAP
81157

Anaplasma phagocytophilum (Human Granulocytic Ehrlichiosis) Antibody, Serum

Clinical Information: Anaplasma phagocytophilum is an intracellular rickettsia-like bacterium that preferentially infects granulocytes and forms inclusion bodies, referred to as morulae. A phagocytophilum is transmitted by Ixodes species ticks, which also transmit Borrelia burgdorferi and Babesia species. Infection with A phagocytophilum is also referred to as human granulocytic anaplasmosis (HGA) or human granulocytic ehrlichiosis, and symptoms in otherwise healthy individuals are often mild and nonspecific, including fever, myalgia, arthralgia, and nausea. Clues to the diagnosis of anaplasmosis in a patient with an acute febrile illness after tick exposure include laboratory findings of leukopenia or thrombocytopenia and elevated liver enzymes. HGA is most prevalent in the upper Midwest and in other areas of the United States that are endemic for Lyme disease.

Useful For: As an adjunct in the diagnosis of human granulocytic ehrlichiosis (anaplasmosis) Seroepidemiological surveys of the prevalence of the infection in certain populations

Interpretation: A positive result of an immunofluorescence assay (IFA) test (titer > or =1:64) suggests current or previous infection with human granulocytic ehrlichiosis (anaplasmosis). In general, the higher the titer, the more likely it is that the patient has an active infection. Seroconversion may also be demonstrated by a significant increase in IFA titers. During the acute phase of the infection, serologic tests are often nonreactive, polymerase chain reaction (PCR) testing is available to aid in the diagnosis of these cases (see EPCRB / Ehrlichia/Anaplasma, Molecular Detection, PCR, Blood).

Reference Values:

<1:64
Reference values apply to all ages.

Clinical References: Center for Disease Control and Prevention (CDC): Tickborne Diseases of the United States: A Reference Manual for Healthcare Providers. 6th ed. US Department of Health and Human Services; 2022. Accessed May 10, 2024. Available at www.cdc.gov/ticks/tickbornediseases/TickborneDiseases-P.pdf

ALKOT 620405 Anaplastic Lymphoma Kinase (ALK [OTI1A4]) Immunostain, Technical Component Only

Clinical Information: A subset of anaplastic large-cell lymphomas show overexpression of anaplastic lymphoma kinase (ALK-1) protein, resulting from a translocation involving the ALK1 gene. The abnormal ALK-1 expression can be in a nuclear or cytoplasmic distribution. Overexpression of ALK-1 protein can also be useful in the diagnosis of inflammatory myofibroblastic tumor and ALK-positive histiocytosis. In normal tissue, ALK-1 expression is primarily limited to neurons and ganglion cells. This clone, OTI1A4, is not validated for use in lung adenocarcinoma.

Useful For: Identification of anaplastic lymphoma kinase overexpression Diagnosis of inflammatory myofibroblastic tumor and anaplastic large cell lymphoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

ALKD5 620966 Anaplastic Lymphoma Kinase (ALK[D5F3]) Immunostain, Technical Component Only

Clinical Information: A subset of anaplastic large-cell lymphomas shows overexpression of anaplastic lymphoma kinase (ALK-1) protein, resulting from a translocation involving the ALK1 gene. The abnormal ALK-1 expression can be in a nuclear or cytoplasmic distribution. Overexpression of ALK-1 protein is also useful in the diagnosis of lung adenocarcinoma and inflammatory myofibroblastic tumor. In normal tissue ALK-1 is negative.

Useful For: Identification of anaplastic lymphoma kinase overexpression Diagnosis of lung adenocarcinoma and inflammatory myofibroblastic tumor

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Hutarew G, Hauser-Kronberger C, Strasser F, Llenos IC, Dietze O. Immunohistochemistry as a screening tool for ALK rearrangement in NSCLC: evaluation of five different ALK antibody clones and ALK FISH. Histopathology. 2014;65:398-407 2. Stein H, Foss H, Durkop H, et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood. 2000;96(12):3681-3695 3. Yi ES, Boland JM, Maleszewski JJ, et al. Correlation of IHC and FISH for ALK gene rearrangement in non-small cell lung carcinoma: IHC score algorithm for FISH. J Thorac Oncol. 2011;6(3):459-465 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

ALKLC
615713

Anaplastic Lymphoma Kinase for Lung Cancer, Immunohistochemistry

Clinical Information: A subset of anaplastic large-cell lymphomas overexpresses anaplastic lymphoma kinase (ALK-1) protein, resulting from a translocation involving the ALK1 gene. The abnormal ALK-1 expression can be in a nuclear or cytoplasmic distribution. Overexpression of ALK-1 protein is also useful for targeted therapy in lung adenocarcinoma and in the diagnosis of inflammatory myofibroblastic tumor. In normal tissue ALK-1 is negative.

Useful For: Identification of anaplastic lymphoma kinase overexpression Diagnosis of inflammatory myofibroblastic tumor, anaplastic large-cell lymphoma, and for targeted therapy of lung adenocarcinoma

Interpretation: This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

Clinical References: 1. Hutarew G, Hauser-Kronberger C, Strasser F, Llenos IC, Dietze O: Immunohistochemistry as a screening tool for ALK rearrangement in NSCLC: evaluation of five different ALK antibody clones and ALK FISH. Histopathology. 2014 Sept;65(3):398-407 2. Stein H, Foss H, Durkop H, et al: CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood. 2000 Dec;96(12):3681-3695 3. Yi ES, Boland JM, Maleszewski JJ, et al: Correlation of IHC and FISH for ALK gene rearrangement in non-small cell lung carcinoma: IHC score algorithm for FISH. J Thorac Oncol. 2011 Mar;6(3):459-465

ANPAT
70318

Anatomic Pathology Consultation, Wet Tissue

Clinical Information: Mayo Clinic in Rochester, Minnesota is staffed by pathologists whose expertise and special interests cover the entirety of Pathology, from surgical pathology with all its respective subspecialty areas, to Hematopathology, Renal Pathology, and Dermatopathology. Consultation services are provided for difficult diagnostic problems. Consultation cases may be sent by a referring pathologist and directed to one of the pathologists who is an expert in the given area or directed more broadly to the subspecialty group. Cases are frequently shared and sometimes transferred between the pathologists, as deemed appropriate for the type of case or diagnostic problem encountered. Emphasis is placed on prompt and accurate results. Materials received are reviewed in conjunction with the clinical history provided, laboratory findings, radiographic findings (if applicable), and sending pathologist's report or letter. If additional special stains or studies are needed, the results are included in the final interpretive report. In some cases, electron microscopy and other special procedures are utilized as required. A variety of ancillary studies are available (eg, cytochemistry, immunohistochemistry, immunofluorescence, electron microscopy, mass spectrometry, cytogenetics, and molecular genetics) to aid in establishing a diagnosis. These ancillary studies are often expensive and labor intensive and are most efficiently utilized and interpreted in the context of the morphologic features. The goal is to provide

the highest possible level of diagnostic consultative service, while trying to balance optimal patient care with a cost-conscious approach to solving difficult diagnostic problems.

Useful For: Obtaining a rapid, expert opinion on unprocessed specimens (lung tissue for immunofluorescence, cardiac biopsies, enucleated eye specimens, iris, conjunctiva, cornea, and other small eye biopsies) referred by a pathologist This test is not useful for suspected hematologic disorders.

Interpretation: Results of the consultation are reported in a formal pathology report, which includes a description of ancillary test results (if applicable) and an interpretive comment. When the case is completed, results may be communicated by a phone call.

Reference Values:
An interpretive report will be provided.

Clinical References: Renshaw AA, Gould EW. Measuring the value of review of pathology material by a second pathologist. Am J Clin Pathol. 2006;125(5):737-739. doi:10.1309/6A0R-AX9K-CR8V-WCG4

ANCH
82345

Anchovy, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to anchovy Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

AREC 70358 Androgen Receptor Immunostain, Technical Component Only

Clinical Information: Androgen receptor binds testosterone and 5 alpha-dihydrotestosterone and mediates the biologic action of these sex hormones. It is normally expressed in a wide variety of tissues, including the epithelium and stromal cells of the prostate, endometrium, ovary, and breast. Cells of meningiomas and the pituitary gland may also be positive.

Useful For: Identification of tumors that express androgen receptor

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chen C, Yuan JP, Wei W, et al. Subtype classification for prediction of prognosis of breast cancer from a biomarker panel: correlations and indications. Int J Nanomedicine. 2014;9:1039-1048 2. Hobisch A, Culig Z, Radmayr C, Bartsch G, Klocker H, Hittmair A. Androgen receptor status of lymph node metastases from prostate cancer. Prostate. 1996;28(2):129-135 3. Park S, Koo J, Park HS, et al. Expression of androgen receptors in primary breast cancer. Ann Oncol. 2010;21(3):488-492 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FAGES 75656 Androstanediol Glucuronide (Endocrine Sciences)

Reference Values:

Age	Range
Prepubertal Children	Not Established
Adult Males	112-1046 ng/dL
Adult Females	11-249 ng/dL

ANST
9709

Androstenedione, Serum

Clinical Information: Androstenedione is secreted predominately by the adrenal gland and production is at least partly controlled by adrenocorticotropic hormone (ACTH). It is also produced independent of ACTH in the testes and ovaries from adrenal-secreted dehydroepiandrosterone sulfate (DHEA-S). Androstenedione is a crucial sex-steroid precursor. It lies at the convergence of the 2 biosynthetic pathways that lead from the progestins to the sex steroids, being derived either via: -C3-dehydrogenation of DHEA -Catalyzed by 3-beta-hydroxysteroid dehydrogenase-2 (adrenals and gonads) -17,20-lyase (CYP17A1)-mediated side-chain cleavage of 17-alpha-hydroxyprogesterone (OHPG) Androstenedione production during life mimics the pattern of other androgen precursors. Fetal serum concentrations increase throughout embryonal development and peak near birth at approximately young adult levels. Levels then fall rapidly during the first year of life to low prepubertal values. With the onset of adrenarche, androstenedione rises gradually, a process that accelerates with the onset of puberty, reaching adult levels around age 18. Adrenarche is a poorly understood phenomenon peculiar to higher primates that is characterized by a gradual rise in adrenal androgen production. It precedes puberty but is not causally linked to it. Early adrenarche is not associated with early puberty, or with any reduction in final height, or overt androgenization, and is generally regarded as a benign condition not requiring intervention. However, girls with early adrenarche may be at increased risk of polycystic ovarian syndrome as adults, and some boys may develop early penile enlargement. Elevated androstenedione levels can cause symptoms or signs of hyperandrogenism in women. Men are usually asymptomatic but through peripheral conversion of androgens to estrogens, can occasionally experience mild symptoms of estrogen excess, such as gynecomastia. Most mild-to-moderate elevations in androstenedione are idiopathic. However, pronounced elevations of androstenedione may be indicative of androgen-producing adrenal or gonadal tumors. In children, adrenal and gonadal tumors are uncommon, but many forms of congenital adrenal hyperplasia can increase serum androstenedione concentrations. Diagnosis always requires measurement of other androgen precursors (eg, OHPG, 17-alpha-hydroxypregnenolone, and DHEA-S) and cortisol, in addition to androstenedione. For more information see Steroid Pathways.

Useful For: Diagnosis and differential diagnosis of hyperandrogenism, in conjunction with measurements of other sex steroids Diagnosis of congenital adrenal hyperplasia (CAH), in conjunction with measurement of other androgenic precursors, particularly, 17-alpha-hydroxyprogesterone (OHPG), 17 alpha-hydroxypregnenolone, dehydroepiandrosterone sulfate (DHEA-S), and cortisol Monitoring CAH treatment, in conjunction with testosterone, OHPG, DHEA-S, and DHEA Diagnosis of premature adrenarche, in conjunction with measurement of follicle-stimulating hormone and luteinizing hormone as well as other adrenal and gonadal sex-steroids and their precursors

Interpretation: Elevated androstenedione levels indicate increased adrenal or gonadal androgen production. Mild elevations in adults are usually idiopathic or related to conditions, such as polycystic ovarian syndrome (PCOS) in women or use of androstenedione supplements in men and women. However, levels greater than or equal to 500 ng/dL can suggest the presence of an androgen-secreting adrenal or, less commonly, a gonadal tumor. Androstenedione levels are elevated in more than 90% of patients with benign androgen-producing adrenal tumors, usually well above 500 ng/dL. Most androgen-

secreting adrenal carcinomas also exhibit elevated androstenedione levels but more typically show relatively larger elevations in 17-alpha-hydroxyprogesterone (OHPG) and dehydroepiandrosterone sulfate (DHEA-S) than in androstenedione, as they have often lost the ability to produce downstream androgens. Most androgen-secreting gonadal tumors overproduce androstenedione, often to lesser degrees than adrenal tumors. They also overproduce testosterone. In men and in women with high baseline androgen levels (eg, PCOS), the respective elevations of androstenedione and testosterone may not be high enough to allow unequivocal diagnosis of androgen-producing gonadal tumors. In these cases, an elevation of the usual ratio of testosterone to androstenedione of 1, to a ratio of greater than 1.5, is a strong indicator of neoplastic androgen production. Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to 21-hydroxylase gene (CYP21A2) variants, the most common cause of CAH (>90% of cases), usually have very high levels of androstenedione, often 5- to 10-fold elevations. OHPG levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. In the much less common CYP11A1 variant, androstenedione levels are elevated to a similar extent as in the CYP21A2 variant, and cortisol is also low, but OHPG is only mildly, if at all, elevated. Also less common, 3-beta hydroxysteroid dehydrogenase (HSD) type 2 deficiency is characterized by low cortisol and substantial elevations in DHEA-S and 17-alpha hydroxypregnenolone, while androstenedione is either low, normal, or, rarely, very mildly elevated (as a consequence of peripheral tissue androstenedione production by 3-beta HSD-1). In the very rare STAR (steroidogenic acute regulatory protein) deficiency, all steroid hormone levels are low, and cholesterol is elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, OHPG, DHEA-S), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and their precursors, in particular progesterone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone, are increased. The goal of CAH treatment is normalization of cortisol levels and, ideally, also of sex-steroid levels. Traditionally, OHPG and urinary pregnanetriol or total ketosteroid excretion are measured to guide treatment, but these tests correlate only modestly with androgen levels. Therefore, androstenedione and testosterone should also be measured and used for treatment modifications. Normal prepubertal levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels up to 100 ng/dL are usually regarded as acceptable. Girls younger than 7 to 8 years of age and boys younger than 8 to 9 years of age who present with early development of pubic hair or, in boys, penile enlargement, may be suffering from either premature adrenarche or premature puberty, or both. Measurement of DHEA-S, DHEA, and androstenedione, alongside determination of sensitive estradiol, total and bioavailable or free testosterone, sex hormone binding globulin (SHBG), and luteinizing hormone/follicle-stimulating hormone levels will allow correct diagnosis in most cases. In premature adrenarche, only the adrenal androgens, chiefly DHEA-S, and to a lesser degree, androstenedione, will be above prepubertal levels, whereas early puberty will also show a fall in SHBG levels and variable elevations of gonadotropins and gonadal sex-steroids above the prepuberty reference range. For more information see Steroid Pathways.

Reference Values:

PEDIATRICS* Premature infants 26-28 weeks, day 4: 92-282 ng/dL 31-35 weeks, day 4: 80-446 ng/dL Full-term infants 1-7 days: 20-290 ng/dL 1 month-1 year:	**Age (Years)**	**Reference range (ng/dL)**
Stage I (prepubertal)		
Stage II	9.8-14.5	31-65
Stage III	10.7-15.4	50-100
Stage IV	11.8-16.2	48-140

Stage V	12.8-17.3	65-210
Females* Tanner stages	Age (Years)	Reference range (ng/dL)
Stage I (prepubertal)		
Stage II	9.2-13.7	42-100
Stage III	10.0-14.4	80-190
Stage IV	10.7-15.6	77-225
Stage V	11.8-18.6	80-240

Clinical References: 1. Bidlingmaier F, Wagner-Barnack M, Butenandt O, Knorr D. Plasma estrogens in childhood and puberty under physiologic and pathologic conditions. Pediatr Res. 1973;7(11):901-907. doi:10.1203/00006450-197311000-00006 2. Von Schnakenburg K, Bidlingmaier F, Knorr D. 17-hydroxyprogesterone, androstenedione, and testosterone in normal children and in prepubertal patients with congenital adrenal hyperplasia. Eur J Pediatr. 1980;133(3):259-267 3. Sciarra F, Tosti-Croce C, Toscano V. Androgen-secreting adrenal tumors. Minerva Endocrinol. 1995;20(1):63-68 4. Collett-Solberg P. Congenital adrenal hyperplasia: from genetics and biochemistry to clinical practice, part I. Clin Pediatr. 2001;40(1):1-16 5. Speiser PW, Azziz R, Baskin LS, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2010;95(9):4133-4160 6. Nordenstrom A, Falhammar H. Management of endocrine disease: Diagnosis and management of the patient with non-classic CAH due to 21-hydroxylase deficiency. Eur J Endocrinol. 2019;180(3):R127-R145 7. Young WF Jr. Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev. 1999;7(4):207-214 8. Young WF Jr. Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am. 1997;26(4):801-827 9. Wudy SA, Hartmann M, Svoboda M. Determination of 17-hydroxypregnenolone in plasma by stabile isotope dilution/benchtop liquid chromatography-tandem mass spectrometry. Horm Res. 2000;53(2):68-71 10. Therrell BL. Newborn screening for congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. 2001;30(1):15-30 11. Bachega TA, Billerbeck AE, Marcondes JA, Madureira G, Arnhold IJ, Mendonca BB. Influence of different genotypes on 17-hydroxyprogesterone levels in patients with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Clin Endocrinol. 2000;52(5):601-607 12. Kao PC, Machacek DA, Magera MJ, Lacey JM, Rinaldo P. Diagnosis of adrenal cortical dysfunction by liquid chromatography-tandem mass spectrometry. Ann Clin Lab Sci. 2001;31(2):199-204 13. Young WF Jr. Management approaches to adrenal incidentalomas. A view from Rochester, Minnesota. Endocrinol Metab Clin North Am. 2000;29(1):159-185 14. Ibanez L, DiMartino-Nardi J, Potau N, Saenger P. Premature adrenarche-normal variant or forerunner of adult disease? Endocr Rev. 2000;21(6):671-696 15. Allolio B, Arlt W. DHEA treatment: myth or reality? Trends Endocrinol Metab. 2002;13(7):288-294 16. Lin CL, Wu TJ, Machacek DA, Jiang NS, Kao PC. Urinary free cortisol and cortisone determined by high performance liquid chromatography in the diagnosis of Cushing's syndrome. J Clin Endocrinol Metab. 1997;82:151-155 17. Findling JW, Raff H. Diagnosis and differential diagnosis of Cushing's syndrome. Endocrinol Metab Clin North Am. 2001;30(3):729-747 18. Buchman Al. Side effects of corticosteroid therapy. J Clin Gastroenterol. 2001;33(4):289-297 18. Dodds HM, Taylor PJ, Cannell GR, Pond SM. A high-performance liquid chromatography-electrospray-tandem mass spectrometry analysis of cortisol and metabolites in placental perfusate. Anal Biochem. 1997;247(2):342-347 20. Cengiz H, Demirci T, Varim C, Cetin S. Establishing a new screening 17 hydroxyprogesterone cut-off value and evaluation of the reliability of the long intramuscular ACTH stimulation test in the diagnosis of nonclassical congenital adrenal hyperplasia. Eur Rev Med Pharmacol Sci. 2021;25(16):5235-5240. doi:10.26355/eurrev_202108_26537

AECDP
621547

Angioedema and Complement Disorders Gene Panel, Varies

Clinical Information: The complement system is an essential component of the innate immune system, which is present from birth and is responsible for immune mediation and responding to pathogens. Deficiency or dysregulation of the complement system can result in a wide spectrum of clinical presentations depending on the specific component that is impacted. Many complement

disorders are due to loss-of-function variants that result in recurrent or chronic bacterial infections and autoimmunity due to complement deficiencies. These disorders are mostly inherited in an autosomal recessive pattern. Deficiency of complement regulators may result in complement dysregulation (also known as primary immune regulatory disorder: PIRD) such as complement-mediated thrombotic microangiopathy (CM-TMA). For these disorders, order a different gene panel, AHUGP / Atypical Hemolytic Uremic Syndrome (aHUS)/Thrombotic Microangiopathy (TMA) /Complement 3 Glomerulopathy (C3G) Gene Panel, Varies. This gene panel is focused on complement component deficiencies. Early classical complement deficiencies (eg, C1, C2) typically present with susceptibility to encapsulated bacteria, such as Streptococcus pneumoniae or Haemophilus influenza type b, while C3 deficiency is associated with gram-negative bacteria including Neisseria meningitidis, Enterobacter aerogenes, and Escherichia coli. Individuals with deficiency of the late common pathway (eg, C5, C6, C7, C8, C9) or deficiency of complement factors D and B in the alternative complement pathway have increased susceptibility to bacterial infections, particularly Neisseria infections. In addition, patients with deficiency of the early classical components are at increased risk of autoimmune disorders, including systemic lupus erythematosus (SLE). In some individuals, deleterious variants in genes encoding complement inhibitors, such as CFH or CD46, may also be at increased risk of SLE and lupus nephritis. Individuals with C3 deficiency may also develop mesangiocapillary or membranoproliferative glomerulonephritis and kidney failure. Cluster of differentiation 55 (CD55), or complement decay-accelerating factor (DAF), is a cell surface complement regulator. CD55 deficiency is characterized by hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy, and is also known as CHAPLE syndrome. This is also an autosomal recessive disorder. For diseases with mainly gastrointestinal presentations, order EOIBD / Early Onset Monogenic Inflammatory Bowel Disease (IBD) Gene Panel, Varies. For diseases with mainly autoinflammatory presentations, order AUTOG / Autoinflammatory Disorders Gene Panel, Varies. Hereditary angioedema (HAE) is typically inherited in an autosomal dominant pattern and characterized by recurrent episodes of severe swelling of the upper airways, skin, or gastrointestinal tract. These episodes may last from 2 to 5 days and have minimal response to antihistamines, corticosteroids, and epinephrine. HAE is most frequently due to variants in the SERPING1 gene that encodes the C1-inhibitor (C1-INH). C1-INH functions in complement inhibition to prevent spontaneous activation but is also important in inhibition of proteases involved in the fibrinolytic, clotting, and kinin pathways. A subset of individuals with HAE has normal C1-INH, which is associated with variants in F12, KNG1, PLG, and ANGPT1. For a panel targeted to HAE with normal C1-INH, order GNANG / Hereditary Angioedema Focused Gene Panel, Next-Generation Sequencing, Varies.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an inherited complement disorder, including complement deficiency Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary angioedema, including those with absent or dysfunctional C1-inhibitor protein Establishing a diagnosis of a complement disorder or hereditary angioedema, allowing for appropriate management and surveillance for disease features based on the gene or variant involved Identifying variants within genes known to be associated with complement disorders and hereditary angioedema, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity:

2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507. doi:10.1007/s10875-022-01289-3 3. Mollah F, Tam S. Complement deficiency. In: StatPearls [Internet]. StatPearls Publishing; 2024. Updated March 13, 2023. Accessed March 28, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK557581/ 4. Costa-Reis P, Sullivan KE. Monogenic lupus: it's all new!. Curr Opin Immunol. 2017;49:87-95 5. Ozen A, Comrie WA, Ardy RC, et al. CD55 deficiency, early-onset protein-losing enteropathy, and thrombosis. N Engl J Med. 2017;377(1):52-61 6. Santacroce R, D'Andrea G, Maffione AB, Margaglione M, d'Apolito M. The genetics of hereditary angioedema: A review. J Clin Med. 2021;10(9):2023. Published 2021 May 9. doi:10.3390/jcm10092023

MASF 35859 Angiosarcoma, MYC (8q24) Amplification, FISH, Tissue

Clinical Information: Postradiation cutaneous angiosarcoma is a malignancy associated with very poor outcome and is consequently treated aggressively. Atypical vascular lesions are also associated with radiation therapy but are considered to be benign and do not require aggressive management. Therefore, the differentiation of these neoplasms is of considerable clinical importance. Postradiation cutaneous angiosarcomas often demonstrate high-level amplification of MYC, whereas reactive and benign vascular lesions do not show amplification of MYC.

Useful For: Identifying MYC amplification to aid in the differentiation of cutaneous angiosarcomas from atypical vascular lesions after radiotherapy

Interpretation: MYC will be clinically interpreted as positive, negative, or equivocal. The MYC locus is reported as amplified when the MYC:D8Z2 ratio is 2.0 or greater and demonstrates 6 or more copies of MYC. A MYC:D8Z2 ratio less than 2.0 or showing a ratio of 2.0 or greater with less than 6 copies of MYC is considered to lack amplification of MYC.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Mentzel T, Schildhaus H, Palmedo G, Buttner R, Kutzner H. Postradiation cutaneous angiosarcoma after treatment of breast carcinoma is characterized by MYC amplification in contrast to atypical vascular lesions after radiotherapy and control cases: clinicopathological, immunohistochemical and molecular analysis of 66 cases. Mod Pathol. 2012;25(1):75-85 2. Manner J, Radlwimmer B, Hohenberger P, et al. MYC high level gene amplification is a distinctive feature of angiosarcomas after irradiation or chronic lymphedema. Am J Pathol. 2010;176(1):34-39 3. WHO Classification of Tumours Editorial Board. Soft Tissue and Bone. 5th ed. IARC; 2020. World Health Organization Classification of Tumours. Vol 3

FACEC 57824 Angiotensin Converting Enzyme, CSF

Useful For: Support diagnosis of neurosarcoidosis. May be used to evaluate treatment response.

Reference Values:
0.0-2.5 U/L

ACE 603622 Angiotensin Converting Enzyme, Serum

Clinical Information: Angiotensin converting enzyme (ACE) is integral to the renin-angiotensin

system (RAS), which maintains blood pressure by regulation of fluid volume and vascular tension. Its peptidase action on the decapeptide angiotensinogen I results in the hydrolysis of a terminal histidyl leucine dipeptide and the formation of the octapeptide angiotensin II, a potent vasoconstrictor that increases blood pressure. ACE activity is increased in sarcoidosis, a systemic granulomatous disease that commonly affects the lungs. In sarcoidosis, ACE is thought to be produced by epithelioid cells and macrophages of the granuloma. ACE activity reflects the severity of sarcoidosis: 68% positivity in those with stage I sarcoidosis, 86% in stage II sarcoidosis, and 91% in stage III sarcoidosis. Other conditions such as Gaucher disease, leprosy, untreated hyperthyroidism, psoriasis, premature infants with respiratory distress syndrome, adults with amyloidosis, and histoplasmosis have been associated with increased serum ACE activity.

Useful For: Evaluation of patients with suspected sarcoidosis

Interpretation: An elevation in the level of serum angiotensin converting enzyme (ACE), along with radiographic evidence of infiltrates or adenopathy and organ biopsies showing noncaseating epithelial granulomas is suggestive of a diagnosis of sarcoidosis. Normal, healthy children and infants are known to have ACE activity levels greater than the adult reference interval.

Reference Values:
> or =18 years: 16-85 U/L
0-17 years: Angiotensin converting enzyme activity may be 20-50% higher in healthy children compared to healthy adults.

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Liebermann J: Elevation of serum angiotensin-converting-enzyme (ACE) level in sarcoidosis. Am J Med. 1975;59:365-372 2. Rodriguez GE, Shin BC, Abernathy RS, Kendig EL Jr: Serum angiotensin-converting enzyme activity in normal children and in those with sarcoidosis. J Pediatr. 1981;99:68-72 3. Personal observations from a Mayo pediatric normal range study using a manual method (Hana) 4. Maguire GA, Price CP: A continuous monitoring spectrophotometric method for the measurement of angiotensin-converting enzyme in human serum. Ann Clin Biochem. 1985;22:204-210 5. Allen DW, Rajagopal V: Other adjunctive drugs for coronary intervention: beta-blockers, calcium-channel blockers, and angiotensin-converting enzyme inhibitors. In: Tropol EJ, Teirstein P, eds. Textbook of Interventional Cardiology. 8th ed. Elsevier; 2020:214-222

FANG1 Angiotensin I, Plasma
75911

Clinical Information: Angiotensin I is a ten amino acid peptide formed by Renin cleavage of Angiotensinogen (Renin Substrate) I. Angiotensin I has little biological activity except that high levels cand stimulate Catecholamine production. It is metabolized to its biologically active byproduct Angiotensin II by Angiotensin Converting Enzyme (ACE). The formation of Angiotensin I is controlled by negative feedback of Angiotensin II and III on Renin release and by Aldosterone concentration. Levels of Angiotensin I are increased in many types of hypertension. Angiotensin I levels are used to determine Renin activity. Angiotensin I is excreted directly in the urine.

Reference Values:
Up to 25 pg/mL

Clinical References: 1. van Hooft IMS, Grobbee DE, Derkx FHM, et al. Renal Hemodynamics and the Renin-Angiotensin-Aldosterone System in Normotensive Subjects with Hypertensive and Normotensive Patients. N Engl J Med. 324:1305-1311, 1991 2. Oparia S and Haber E. The Renin-Angiotensin System. N Engl J Med. 291:389, 1974

ANISP
82857

Anisakis, Parasite, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to the Anisakis parasite Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ANSE
82487

Anise, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to Anise Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FANSE
57520

Annatto Seed (Bixa orellana) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 -0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

ANNEX 70355 Annexin-1 Immunostain, Technical Component Only

Clinical Information: Annexin-1 (annexin-A1) was identified by gene expression profiling studies of hairy cell leukemia. In the appropriate context, positivity for annexin A1 favors a diagnosis of hairy cell leukemia. Normal granulocytes and precursors also express annexin A1, serving as a positive internal control in bone marrow specimens.

Useful For: Classification of leukemias

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Falini B, Tiacci E, Liso A, et al. Simple diagnostic assay for hairy cell leukaemia by immunocytochemical detection of annexin A1 (ANXA1). Lancet. 2004;363(9424):1869-1870 2. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FABAA 75662 Anti-bestrophin Autoantibodies

Reference Values:
A final report will be provided.

AC1Q 621511 Anti-C1q Antibodies, IgG, Serum

Clinical Information: Anti-C1q antibodies have been found to be prevalent in hypocomplementemic urticarial vasculitis syndrome (also referred to as anti-C1Q vasculitis) as well as in some patients with systemic lupus erythematosus (SLE)1,2. These antibodies occur more frequently in lupus nephritis, particularly during active disease. The main target clinical diseases include SLE and anti-C1Q vasculitis. Anti-C1q antibodies may also be seen in infectious diseases such as HIV and hepatitis C.

Useful For: Evaluating patients with suspected anti-C1q vasculitis Predicting renal involvement in patients with systemic lupus erythematosus Detection of anti-C1q antibodies in serum

Interpretation: A positive result for Anti-C1q antibodies may support a diagnosis of anti-C1q vasculitis or renal involvement in patients with systemic lupus erythematosus in the appropriate clinical context. A negative result indicates no detectable IgG antibodies to C1q and does not rule out a diagnosis.

Reference Values:
<20 U/mL (Negative)
20-39 U/mL (Weak Positive)

40-80 U/mL (Moderate Positive)
>80 U/mL (Strong Positive)

Clinical References:

FACN1 Anti-cN-1A (NT5c1A) IBM
75620

Clinical Information: Anti-cN-1A autoantibodies in idiopathic inflammatory myopathy (IIM) patients appear to be disease-specific for sporadic Inclusion Body Myositis (sIBM) and are rarely detected in other autoimmune conditions. Anti-cN-1A autoantibodies have a moderate sensitivity, but their high specificity for sIBM may be helpful in the diagnosis of this infrequent and difficult-to-diagnose myopathy. This assay can augment and accelerate the suspected diagnosis of sIBM using sera where muscle biopsy is delayed and/or unfeasible.

Reference Values:
Reference Range: <20

Interpretation:
Negative: <20 units
Weak Positive: 20 - 39 units
Moderate Positive: 40 - 80 units
Strong Positive: >80 units

COL7 Anti-Collagen type VII, IgG Antibodies, Serum
616879

Clinical Information: Epidermolysis bullosa acquisita and certain other rare immunobullous diseases, including bullous lupus erythematosus, are caused by the development of IgG antibodies directed against collagen type VII, which lead to blisters and erosions that may heal with scarring. Circulating IgG autoantibodies against collagen type VII can be found in patient serum in these conditions.

Useful For: Initial screening test in the diagnosis of epidermolysis bullosa acquisita and other immunobullous diseases mediated by collagen VII

Interpretation: Antibodies to IgG collagen type VII have been shown to be present in patients with epidermolysis bullosa acquisita and certain other rare immunobullous diseases, including bullous lupus erythematosus

Reference Values:
Collagen type VII
<20 RU/mL (negative)
> or =20 RU/mL (positive)

Clinical References:

ADNAS Anti-DNase B Titer, Serum
80204

Clinical Information: A number of bacterial antigens have been identified in cultures of group A streptococci. These extracellular products are primarily enzymatic proteins and include streptolysin O,

streptokinase, hyaluronidase, deoxyribonucleases (DNases A, B, C, and D), and nicotinamide adenine nucleotidase. Infections by the group A streptococci are unique because they can be followed by serious nonpurulent complications of rheumatic fever and glomerulonephritis. Recent information suggests that rheumatic fever is associated with infection by certain rheumatogenic serotypes (M1, M3, M5, M6, M18, and M19), while glomerulonephritis follows infection by nephritogenic serotypes (M2, M12, M49, M57, M59, and M60). Glomerulonephritis and rheumatic fever occur following the infection, after a period of latency, during which the patient is asymptomatic. The latency period for glomerulonephritis is approximately 10 days, and the latency period for rheumatic fever is 20 days.

Useful For: Demonstration of acute or recent streptococcal infection using anti-DNase B titer

Interpretation: Elevated values are consistent with an antecedent infection by group A streptococci. Although the antistreptolysin O (ASO) test is quite reliable, performing the anti-DNase is justified for 2 primary reasons. First, the ASO response is not universal. Elevated ASO titers are found in the sera of about 85% of individuals with rheumatic fever; ASO titers remain normal in about 15% of individuals with the disease. The same holds true for other streptococcal antibody tests: a significant portion of individuals with normal antibody titers for 1 test will have elevated antibody titers for another test. Thus, the percentage of false-negative results can be reduced by performing 2 or more antibody tests. Second, skin infections, in contrast to throat infections, are associated with a poor ASO response. Patients with acute glomerulonephritis following skin infection (post-impetigo) have an attenuated immune response to streptolysin O. For such patients, performance of an alternative streptococcal antibody test, such as this assay, is recommended.

Reference Values:
<5 years: < or =250 U/mL
5-17 years < or =375 U/mL
> or =18 years: < or =300 U/mL

Clinical References: 1. Ayoub EM, Harden E. Immune response to streptococcal antigens: diagnostic methods. In: Rose NR, de Marco EC, Folds JD, et al, eds. Manual of Clinical and Laboratory Immunology. 5th ed. ASM Press; 1997 2. Anti-DNase B. Testing .com. Updated June 28, 2021. Accessed March 17, 2025. Available at www.testing.com/tests/anti-dnase-b/

FAEAB 91854 Anti-Enterocyte Antibodies

Reference Values:
IgG: Negative
IgA: Negative
IgM: Negative

AGNTS 43434 Anti-Glial/Neuronal Nuclear Antibody-Type 1 (AGNA-1) Titer, Serum

Clinical Information: Antiglial/neuronal nuclear autoantibody-type 1 (AGNA-1) is recognized clinically as a marker of a patient's immune response to a lung cancer that is usually limited in metastasis but manifests as an autoimmune neurological disorder. AGNA-1 is an IgG marker of an immune response to cancer (usually a small-cell lung carcinoma: SCLC) in patients presenting with a subacute, generally multifocal, paraneoplastic neurological disorder.(1-3) It binds to the nucleus, but not cytoplasm, of SCLC cell lines and, in the adult central nervous system, to nuclei in subsets of astrocytes and neurons, as well as ependyma. Its previous name was antineuronal nuclear antibody (ANNA)-4.(2)

The most common neurological presentations of patients who are positive for AGNA-1 are Lambert-Eaton myasthenic syndrome, sensorimotor or autonomic neuropathy, limbic encephalopathy, and ataxias. To date all 45 seropositive patients identified in the Mayo Clinic Neuroimmunology Laboratory have been smokers. SCLC was confirmed in more than 80% of cases. In 59% of patients, one or more identifiable coexisting paraneoplastic autoantibodies support the prediction of SCLC: P/Q-type Ca(++) channel antibody (41%) greater than N-type Ca(++) channel antibody, greater than collapsin response-mediator protein-5 (CRMP-5)-IgG greater than striational antibody equal to ANNA-1 greater than other antibodies.

Useful For: Reporting an end titer result from serum specimens Serological evaluation using serum specimens from patients who present with a subacute neurological disorder of undetermined etiology, especially those with risk factors for primary lung carcinoma Directing a focused search for cancer Investigating neurological symptoms that appear during, or after, cancer therapy, and are not explainable by metastasis Differentiating autoimmune neuropathies from neurotoxic effects of chemotherapy Monitoring the immune response of seropositive patients during cancer therapy Detecting early evidence of cancer recurrence in previously seropositive patients

Interpretation: A positive result confirms that the patient's subacute neurological disorder has an autoimmune basis and predicts with greater than 80% certainty that the patient has a lung carcinoma (usually small-cell lung carcinoma: SCLC), either new or recurrent, and confined to the chest. Fifteen percent of seropositive patients who are eventually proven to have SCLC additionally have an unrelated, often more obvious, cancer, either coexisting or by past history. Antiglial/neuronal nuclear autoantibody-type 1 (AGNA-1) has not been encountered in healthy subjects (n=170). Its onconeural antigen is the nuclear transcription factor Sox1.(3) IgG of this specifically has been reported detectable in 30% to 40% of patients with SCLC who lack neurological complications.(4)

Reference Values:

Only orderable as a reflex. For more information see:
-PAVAL / Paraneoplastic, Autoantibody Evaluation, Serum
-DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
-ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
-MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
-MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-AIAES / Axonal Neuropathy, Autoimmune/Paraneoplastic Evaluation, Serum

<1:240
Neuron-restricted patterns of IgG staining that do not fulfill criteria for anti-glial/neuronal nuclear antibody-type 1 may be reported as "unclassified anti-neuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References: 1. Graus F, Vincent A, Pozo-Rosich P, et al: Anti-glial nuclear antibody: marker of lung cancer-related paraneoplastic neurological syndromes. J Neuroimmunol. 2005 Aug;165(1-2):166-171 2. Lachance D, Kryzer TJ, Pittock SJ, et al: Anti-neuronal nuclear antibody type 4 (ANNA-4), a novel paraneoplastic marker of small-cell lung carcinoma (SCLC). Neurology. 2006;66 (Suppl 2):A340 3. Sabater L, Saiz A, Titulaer MG, et al: Sox 1 antibodies are markers of paraneoplastic Lambert-Eaton myasthenic syndrome. Neurology. 2007;68(Suppl 1):A290-A291 4. Gure AO, Stockert E, Scanlan MJ, et al: Serological identification of embryonic neural proteins as highly immunogenic tumor antigens in small cell lung cancer. Proc Natl Acad Sci USA. 2000 Apr 11;97(8):4198-4203 5. McKeon A, Pittock SJ: Paraneoplastic encephalomyelopathies: pathology and mechanisms. Acta Neuropathol. 2011 Oct;122(4):381-400 6. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul 15;20(14):3862-3869

AGNTC 43443 Anti-Glial/Neuronal Nuclear Antibody-Type 1 (AGNA-1) Titer, Spinal Fluid

Clinical Information: Anti-glial/neuronal nuclear autoantibody-type 1 (AGNA-1) is recognized clinically as a marker of a patient's immune response to a lung cancer that is usually limited in metastasis but manifests as an autoimmune neurological disorder. AGNA-1 is an IgG marker of an immune response to cancer (usually a small-cell lung carcinoma: SCLC) in patients presenting with a subacute, generally multifocal, paraneoplastic neurological disorder.(1-3) It binds to the nucleus, but not cytoplasm, of SCLC cell lines and, in the adult central nervous system, to nuclei in subsets of astrocytes and neurons, as well as ependyma. Its previous name was antineuronal nuclear antibody (ANNA)-4.(2) The most common neurological presentations of patients who are positive for AGNA-1 are Lambert-Eaton myasthenic syndrome, sensorimotor or autonomic neuropathy, limbic encephalopathy, and ataxias. To date, all 45 seropositive patients identified in the Mayo Clinic Neuroimmunology Laboratory have been smokers. SCLC was confirmed in more than 80% of cases. In 59% of patients, one or more identifiable coexisting paraneoplastic autoantibodies support the prediction of SCLC: P/Q-type Ca(++) channel antibody (41%) greater than collapsin response-mediator protein-5 (CRMP-5)-IgG equal to ANNA-1 greater than other antibodies.

Useful For: Reporting an end titer result from cerebrospinal fluid (CSF) specimens Serological evaluation using CSF specimens from patients who present with a subacute neurological disorder of undetermined etiology, especially those with risk factors for primary lung carcinoma Directing a focused search for cancer Investigating neurological symptoms that appear during, or after, cancer therapy and are not explainable by metastasis Differentiating autoimmune neuropathies from neurotoxic effects of chemotherapy Monitoring the immune response of seropositive patients during cancer therapy Detecting early evidence of cancer recurrence in previously seropositive patients

Interpretation: A positive result confirms that the patient's subacute neurological disorder has an autoimmune basis and predicts with greater than 80% certainty that the patient has a lung carcinoma (usually small-cell lung carcinoma: SCLC), either new or recurrent, and confined to the chest. Fifteen percent of seropositive patients who are eventually proven to have SCLC additionally have an unrelated, often more obvious, cancer, either coexisting or by past history. Anti-glial/neuronal nuclear autoantibody-type 1 (AGNA-1) has not been encountered in healthy subjects (n=170). Its onconeural antigen is the nuclear transcription factor Sox1.(2) IgG of this specifically has been reported detectable in 30% to 40% of patients with SCLC who lack neurological complications.(4)

Reference Values:

Only orderable as a reflex. For more information see:
-DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

<1:2

Neuron-restricted patterns of IgG staining that do not fulfill criteria for anti-glial/neuronal nuclear antibody-type 1 may be reported as "unclassified anti-neuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References: 1. Graus F, Vincent A, Pozo-Rosich P, et al: Anti-glial nuclear antibody: marker of lung cancer-related paraneoplastic neurological syndromes. J Neuroimmunol. 2005 Aug;165(1-2):166-171 2. Lachance D, Kryzer TJ, Pittock SJ, et al: Anti-neuronal nuclear antibody type 4 (ANNA-4), a novel paraneoplastic marker of small-cell lung carcinoma (SCLC). Neurology. 2006;66 (Suppl 2):A340 3. Sabater L, Saiz A, Titulaer MG, et al: Sox1 antibodies are markers of paraneoplastic

Lambert-Eaton myasthenic syndrome. Neurology. 2008 Mar 18;70(12):924-928 4. Gure AO, Stockert E, Scanlan MJ, et al: Serological identification of embryonic neural proteins as highly immunogenic tumor antigens in small cell lung cancer. Proc Natl Acad Sci USA. 2000 Apr 11;97(8):4198-4203 5. McKeon A, Pittock SJ: Paraneoplastic encephalomyelopathies: pathology and mechanisms. Acta Neuropathol. 2011 Oct;122(4):381-400 6. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul 15;20(14):3862-3869 7. Pittock SJ, Kryzer TJ, Lennon VA: Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. Ann Neurol. 2004 Nov;56(5):715-719

FANTI
57892

Anti-IgE

Clinical Information: This ELISA measures IgG antibodies specific for IgE. A result of normal indicates that the level of IgG anti-IgE antibodies is similar to that seen in a population of healthy individuals. A result of elevated indicates an increased level of IgG anti-IgE antibodies compared to healthy individuals. These autoantibodies have been implicated as a causative agent in autoimmune chronic urticaria and atopic dermatitis.

Reference Values:
Normal

FAMDA
75622

Anti-MDA-5 Ab (CADM-140)

Clinical Information: Anti-MDA5 antibodies are present in 7-35% of adult DM. Clinical features consist of absent or mild muscle symptoms (CADM), rapidly progressive ILD, specific mucocutaneous features of skin ulcerations and papules, oral ulcerations and arthritis.

Reference Values:
Reference Range: <20

Interpretation:
Negative: <20 units
Weak Positive: 20-39 units
Moderate Positive: 40-80 units
Strong Positive: >80 units

FFMI2
75591

Anti-Mi-2 Ab

Clinical Information:

Reference Values:
Negative

FCLNE
91321

Anti-Phosphatidylcholine Ab

Clinical Information: The anti-phospholipid syndrome (APS) is a disorder of recurrent vascular thrombosis associated with persistently positive anticardiolipin (aCL) or lupus anticoagulant tests. In patients with APS, anticardiolipin antibodies bind a variety of charged phospholipids, including phosphatidylethanolimine, as well as they do cardiolipin. Lupus patients also have high titers of

autoantibodies to various phospholipids, including phosphatidylethanolimine. Presentations of the syndrome include thrombosis of deep veins of the legs, as well as renal, hepatic, inferior vena cava or sagittal veins. Occlusion of the arterial circulation may be manifested as stroke, ischemic retinopathy, myocardial or bowel infarction, or peripheral gangrene. Thrombosis can occur in veins or arteries of any size. Recurrent pregnancy loss also appears to be the result of thrombosis within the placental vasculature. Anti-phospholipid antibody tests are supplemental tests and should not be used alone for diagnostic purposes. Diagnosis of anti-phospholipid syndrome must be made in conjunction with other clinical indications.

Reference Values:

Anti-Phosphatidylcholine IgA: <12.0 U/mL

Anti-Phosphatidylcholine IgG: <12.0 U/mL

Anti-Phosphatidylcholine IgM: <12.0 U/mL

Reference Range applies to Antiphosphatidylcholine IgA, IgG & IgM:

Normal	<12.0
Equivocal	12.0 – 18.0
Elevated	>18.0

FPHET
91322

Anti-Phosphatidylethanolamine Panel

Clinical Information: The anti-phospholipid syndrome (APS) is a disorder of recurrent vascular thrombosis associated with persistently positive anticardiolipin (aCL) or lupus anticoagulant tests. In patients with APS, anticardiolipin antibodies bind a variety of charged phospholipids, including phosphatidylethanolamine, as well as they do cardiolipin. Lupus patients also have high titers of autoantibodies to various phospholipids, including phosphatidylethanolamine. Presentations of the syndrome include thrombosis of deep veins of the legs, as well as renal, hepatic, inferior vena cava or sagittal veins. Occlusion of the arterial circulation may be manifested as a stroke, ishemic retinopathy, myocardial or bowel infarction, or peripheral gangrene. Thrombosis can occur in veins or arteries of any size. Recurrent pregnancy loss also appears to be the result of thrombosis within the placental vasculature. Anti-phosphatidyl antibody tests are supplemental tests and should not be used alone for diagnostic purposes. Diagnosis of anti-phospholipid syndrome must be made in conjunction with other clinical indications.

Reference Values:

Anti-Phosphatidylethanolamine IgA
<12.0 U/mL

Anti-Phosphatidylethanolamine IgG
<12.0 U/mL

Anti-Phosphatidylethanolamine IgM
<12.0 u/mL

Reference Range applies to Anti-Phosphatidylethanolamine IgA, IgG, & IgM
Normal: <12.0
Equivocal: 12.0-18.0
Elevated: >18.0

FAPMA
75623

Anti-PM/Scl-100 Ab

Clinical Information: The anti-PM/Scl-100 antibody is associated with younger age, calcinosis and has lower rates of gastrointestinal symptoms, ILD and pulmonary hypertension. There is also evidence of a possibly better survival compared to the presence of either anti-PM/Scl-75 or anti-Scl-70 antibodies.

Reference Values:
Reference Range: <20

Interpretation:
Negative: <20 units
Weak Positive: 20-39 units
Moderate Positive: 40-80 units
Strong Positive: >80 units

FARWB
57647

Anti-retinal autoantibodies follow up, WB

Reference Values:
A final report will be attached in MayoAccess.

FAS1A
75634

Anti-SAE1 Ab, IgG

Clinical Information: Anti-SAE 1 IgG autoantibody can be used to assist in the diagnoses and characterization of a subset of dermatomyositis (DM). It is highly specific for DM (>95%) and is present in 5-8% of the European DM population. Initial disease onset may consist of mild myopathic features with severe skin involvement; however, extensive myalgia and muscle disease with weakness can appear as the disease progresses. It is associated with dysphagia and systemic symptoms (i.e. fevers, weight loss, increased inflammatory markers). In one cohort, an association with ILD and cancer had been found.

Reference Values:
Reference Range: <20

Interpretation:
Negative: <20 units
Weak Positive: 20-39 units
Moderate Positive: 40-80 units
Strong Positive: >80 units

FFRFT
75624

Anti-Synthetase Profile

Clinical Information:

Reference Values:
Anti-PL-7 Ab, Anti-PL-12 Ab, Anti-EJ Ab, Anti-OJ Ab:
Reference Range: Negative

Interpretation for:
Anti-Jo-1 Ab:
Reference Range: <20

Negative: <20 units
Weak Positive: 20-39 units
Moderate Positive: 40-80 units
Strong Positive: >80 units

FATHO 75619 Anti-Th/To Ab

Clinical Information: The Th/To antibodies are present in 10-19% of patients with limited SSc, in 11% of patients with diffuse cutaneous SSc, and in 3% of patients with primary Raynaud's disease. Anti-Th/To antibody has been shown to be highly specific for patients with SSc.

Reference Values:
Negative

FAT1G 75632 Anti-TIF-1gamma Antibody

Clinical Information: Anti-TIF-1(P155) antibodies are present in 15-38% of adult DM and 20-30% in JDM. Highly associated with malignancy which is found in 50-75% of positive adult patients; 89% specificity and 78% sensitivity for diagnosing cancer associated DM; no cancer association in children.

Reference Values:

FAU3R 75631 Anti-U3 RNP Antibodies (Fibrillarin)

Clinical Information: The U3-RNP (Fibrillarin) particle is thought to participate in the first step of preribosomal RNA processing. Anti-U3 RNP antibodies have been shown to be highly specific for patients with SSc. Anti-Fibrillarin (U3 RNP) antibodies are highly specific for diffuse SSc with a sensitivity of 4-10%. They are associated with isolated pulmonary arterial hypertension, myositis, renal and cardiac manifestations of SSc. 15% of IIM, mostly found in scleroderma/myositis overlap. Found in 4-10% of Diffuse SSc, <2% in Limited SSc, associated with isolated PAH, myositis, cardiac and renal involvement. More prevalent in African-Americans.

Reference Values:
Negative

ABIDR 113389 Antibody Identification, Blood and Serum

Clinical Information: After exposure to foreign red blood cells (RBCs) via transfusion or pregnancy, some people form antibodies that are capable of the destruction of transfused RBCs or of fetal RBCs in utero. It is important to identify the antibody specificity to assess the antibody's capability of causing clinical harm and, if necessary, to avoid the antigen on transfused RBCs. Autoantibodies react against the patient's own RBCs as well as the majority of cells tested. Autoantibodies can be clinically benign or can hemolyze the patient's own RBCs, such as in cold agglutinin disease or autoimmune hemolytic anemia.

Useful For: Assessing positive pretransfusion antibody screens, transfusion reactions, hemolytic disease of the newborn, and autoimmune hemolytic anemias This test is not useful for monitoring the efficacy of Rh-immune globulin administration. This test is not useful for identifying antibodies

detected only at 4 degrees C or only after extended room temperature incubation.

Interpretation: Specificity of alloantibodies will be stated. The patient's red blood cells will be typed for absence of the corresponding antigens or as an aid to identification in complex cases. A consultation service is offered, at no charge, regarding the clinical relevance of red cell antibodies.

Reference Values:

Clinical References: Cohn CS, Delaney M, Johnson ST, Katz LM, Schwartz J, eds: Technical Manual. 21st ed. AABB; 2023

ABYSR
113387

Antibody Screen with Reflexed Antibody Identification, Blood

Clinical Information: Transfusion and pregnancy are the primary means of sensitization to red cell antigens. In a given population, 2% to 4% of the general population possess irregular red cell alloantibodies. Such antibodies may cause hemolytic disease of the newborn or hemolysis of transfused donor red blood cells.

Useful For: Detection of allo- or autoantibodies directed against red blood cell antigens in the settings of pretransfusion testing Evaluation of transfusion reactions Evaluation of hemolytic anemia

Interpretation: A positive result (antibody detected) necessitates antibody identification to establish the specificity and clinical significance of the antibody detected. Alloantibodies detected on pregnant Mayo Clinic-Rochester patients will be evaluated for the allo-antibody titer. If antibody reacts strongly, the titre test will be performed. Negative results indicate no antibody was detected.

Reference Values:
Negative
If positive, antibody identification will be performed.

Clinical References: Cohn CS, Delaney M, Johnson ST, Katz LM, Schwartz J, eds. Technical Manual. 21st ed. AABB; 2023

ABTIR
113390

Antibody Titer, Blood and Serum

Clinical Information: Some maternal IgG alloantibodies to red blood cell antigens will cross the placenta and cause hemolysis of antigen-positive fetal red blood cells. The resulting fetal anemia and hyperbilirubinemia can be harmful or possibly fatal to the newborn.

Useful For: Monitoring antibody levels during pregnancy to help assess the risk of hemolytic disease of the newborn This test is not useful for monitoring the efficacy of Rh-immune globulin administration.

Interpretation: The specificity of the maternal alloantibody will be stated. The titer result is the reciprocal of the highest dilution at which macroscopic agglutination (1+) is observed. If the antibody problem identified is not relevant in hemolytic disease of the newborn or if titrations are not helpful, the titer will be canceled and will be replaced by ABIDR / Antibody Identification, Blood and Serum. A consultation service is offered, at no charge, regarding the clinical relevance of red blood cell antibodies.

Reference Values:
Negative

If positive, result will be reported as the reciprocal of the highest dilution at with macroscopic agglutination (1+) is observed.

Clinical References: Cohn CS, Delaney M, Johnson ST, Katz LM, Schwartz J. eds: Technical Manual. 21st ed. AABB; 2023

ENAE
89035

Antibody to Extractable Nuclear Antigen Evaluation, Serum

Clinical Information: Antibodies to SS-A/Ro, SS-B/La, Smith (Sm), U1RNP (RNP68/A), Scl 70 and JO1 are associated with the presence of antinuclear antibodies (ANA) and useful in the evaluation of specific ANA-associated connective tissue diseases (CTD), ANA-CTD.(1) Due to their frequencies in ANA-CTD and the overlapping clinical presentations of these diseases, inclusion of these tests in a panel may be useful at initial evaluation of patients at-risk for certain CTD. The combined presence of antibodies to SS-A/Ro (Ro52 and Ro60) and anti-SS-B/La is highly suggestive of Sjogren syndrome.(2,3) Separate determination of anti-Ro52 and anti-Ro60 antibodies is preferred to combined SS-A/Ro in the evaluation of ANA-CTD as their differential presence maybe useful in risk stratification and prognosis of ANA-CTD patients.(4) The presence of anti-Sm antibodies are specific for systemic lupus erythematosus (SLE) and is included the classification criteria for disease.(5) Monospecific antibody reactivity to U1RNP may indicate a diagnosis of mixed connective tissue disease (MCTD).(6) However, anti-U1RNP antibodies may also be seen in patients with SLE, systemic sclerosis (SSc) and idiopathic inflammatory myopathies (IIM).(6,7) In addition, there exists diverse analytes for the detection U1RNP with differential correlations with MCTD, SLE, SSc, and IIM.(8) Anti-Scl 70 (topoisomerase 1) antibody is one of three autoantibodies included in the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for SSc.(9). It is generally associated with diffuse cutaneous SSc clinical manifestations including interstitial lung disease with poor prognostic outcomes.(10) Lastly, antibodies to JO1, is a member of the amino acyl-tRNA synthetase family of enzymes is suggestive of diagnosis of IIM, specifically anti-synthetase syndrome and is included in the 2017 EULAR/ACR classification for IIM.(11) For more information, see the individual test codes.

Useful For: Evaluating patients with clinical features suggestive of antinuclear antibody (ANA) associated connective tissue disease. May also be indicated in patients who test negative for ANA and have features of Sjogren syndrome and idiopathic inflammatory myopathies

Interpretation: A positive antibody result in the appropriate clinical context maybe suggestive of connective tissue disease. For more information, see the individual test codes.

Reference Values:
SS-A/Ro ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

SS-B/La ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Sm ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

RNP ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Scl 70 ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Jo 1 ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References:

FADDS 57772 Antidepressant Drug Screen, Qualitative

Reference Values:
Antidepressant screen includes the analysis for:
Amytriptyline, Clomipramine and Desmethylclomipramine, Cyclobenzaprine, Desipramine, Doxepin and Desmethyldoxepin, Fluoxetine and Norfluoxetine, Imipramine, Maprotiline, Nortriptyline, Paroxetine, Protriptyline, Sertraline and Desmethylsertraline, Trimipramine.

FASQN 57740 Antidepressant Drug Screen, Ur, Quantitative

Reference Values:
Antidepressant screen includes the analysis for: amitriptyline, clomipramine and desmethylclomipramine, cyclobenzaprine, desipramine, doxepin and desmethldoxepin, fluoxetine and norfluoxetine, imipramine, maprotiline, nortriptyline, paroxetine, protriptyline, sertraline and desmethylsertraline, trimipramine.

AHPRU 618553 Antihypertension Panel, Random, Urine

Clinical Information: Adherence to antihypertensive medication dose and frequency is important for adequate hypertension control. Not taking medications as prescribed is a common and underappreciated cause of resistant hypertension. It can be challenging to suspect and discern medication nonadherence from history alone. This urine assay includes drug targets that are commonly prescribed for hypertension and allows for an objective assessment of whether a patient has taken a prescribed medication in the previous twenty-four hours. If not, a healthcare professional can explore the reason for noncompliance with the patient in a targeted fashion. If there are issues with patient tolerance of a given medication not previously appreciated, alternative regimens can be considered. This targeted information can also help avoid over prescription of additional medications and related complications. This test can also be used as a screen to detect nonprescribed use of common diuretics.

Useful For: Aid in the management of hypertension, especially treatment resistant hypertension Monitoring compliance in individuals prescribed antihypertensive drug therapy As a screen for to detect nonprescribed use of common diuretics

Interpretation: Antihypertensive medications are reported as either detected or not detected, specific concentrations are not quantified. This test measures urine concentrations of 7 alpha-thiomethylspironolactone, a major active metabolite of spironolactone. Detection of this metabolite indicates recent intake of spironolactone and can be used to assess patient compliance with spironolactone therapy.

Reference Values:
Not detected: These drugs should not be present in untreated individuals.

Cutoff concentrations:
Amlodipine: 400 ng/mL
Atenolol: 800 ng/mL
Bumetanide: 40 ng/mL
Carvedilol: 40 ng/mL
Chlorthalidone: 4 ng/mL
Clonidine: 40 ng/mL
Furosemide: 4 ng/mL
Hydralazine: 400 ng/mL
Hydrochlorothiazide: 10 ng/mL
Labetalol: 40 ng/mL
Lisinopril: 1000 ng/mL
Losartan: 4 ng/mL
Metoprolol: 40 ng/mL
7-alpha-Thiomethylspironolactone: 10 ng/mL
Terazosin: 4 ng/mL
Torsemide: 40 ng/mL

Clinical References: 1. Gupta P, Patel P, Strauch B, et al. Biochemical screening for nonadherence is associated with blood pressure reduction and improvement in adherence. Hypertension. 2017;70(5):1042-1048. doi:10.1161/Hypertensionaha 2. Jung O, Gechter JL, Wunder C, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. J Hypertens. 2013;31(4):766-774. doi:10.1097/HJH.0b013e32835e2286 3. Tomaszewski M, White C, Patel P, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. Heart. 2014;100(11):855-861. doi:10.1136/heartjnl-2013-305063 4. Peeters LEJ, Kappers MHW, Boersma E, et al. The effect of combining therapeutic drug monitoring of antihypertensive drugs with personalised feedback on adherence and resistant hypertension: the (RHYME-RCT) trial protocol of a multi-centre randomised controlled trial. BMC Cardiovasc Disord. 2023;23(1):87. doi:10.1186/s12872-023-03114-0

MMLYP
81602

Antimicrobial Susceptibility Panel, Yeast, Varies

Clinical Information: Candida species are the fourth leading cause of nosocomial infections and are frequent causes of community-acquired infections. Antifungal susceptibility testing may aid in the management of patients with invasive infections due to Candida species or patients who appear to be experiencing therapeutic failure. The Clinical Laboratory Standards Institute has approved the use of a broth microdilution method for determining the susceptibility of Candida species.

Useful For: Determining in vitro quantitative antifungal susceptibility (minimum inhibitory concentration) of non-fastidious yeast As an aid in the management of certain circumstances, such as: -Refractory oropharyngeal infections due to Candida species in patients who appear to be experiencing therapeutic failure with standard agents at standard doses -Invasive infections due to Candida species when the utility of azole antifungal agents is uncertain (eg, when the infection is due to a non-Candida

albicans organism)

Interpretation: The Clinical and Laboratory Standards Institute method, breakpoints, and interpretive criteria are used.

Reference Values:
Results reported in mcg/mL

Clinical References: Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1-e50

MMLRG 81601 Antimicrobial Susceptibility, Acid-Fast Bacilli, Rapidly Growing, Varies

Clinical Information: There are more than 100 species of rapidly growing mycobacteria and many are significant human pathogens (eg, Mycobacterium abscessus, Mycobacterium chelonae, Mycobacterium fortuitum). Rapidly growing mycobacteria cause a variety of infections including pulmonary infections, skin and soft tissue infections, and disseminated disease. Antimicrobial susceptibility testing of clinically significant rapidly growing mycobacteria is important to help guide patient care. Antimicrobials tested in this assay are amikacin, cefoxitin, ciprofloxacin, clarithromycin, clofazimine, doxycycline, imipenem, linezolid, moxifloxacin, tigecycline, tobramycin, and trimethoprim/sulfamethoxazole.

Useful For: Determination of susceptibility of rapidly growing mycobacteria to the antimicrobial agents on the test panel

Interpretation: Results are reported as the minimum inhibitory concentration in micrograms/mL. Interpretive criteria (susceptible, intermediate, or resistant) are reported according the Clinical and Laboratory Standards Institute guidelines.

Reference Values:
Interpretive criteria and reporting guidelines are followed using the Clinical Laboratory Standards Institute (CLSI) M24S document.

Clinical References: 1. Brown-Elliott BA, Pilley JV. Rapidly growing mycobacteria. Microbiol Spectr. 2017;5(1):1-19 2. Apiwattankul N, Flynn PM, Hayden RT, Adderson EE. Infections caused by rapidly growing mycobacteria spp in children and adolescents with cancer. J Pediatric Infect Dis Soc. 2015;4(2):104-113 3. Kasperbauer SH, De Groote MA. The treatment of rapidly growing mycobacterial infections. Clin Chest Med. 2015;36(1):67-78

MMLSG 34805 Antimicrobial Susceptibility, Acid-Fast Bacilli, Slowly Growing, Varies

Clinical Information: The slowly growing nontuberculous mycobacteria are associated with a variety of infections including pulmonary, extra-pulmonary, and disseminated disease. Slowly growing mycobacteria differ from the rapidly growing mycobacteria and Mycobacterium tuberculosis complex by their growth rates, metabolic properties, and antimicrobial susceptibility profiles. The antimicrobial susceptibility profile of an organism within this group varies depending on the species and is performed

according to the Clinical and Laboratory Standards Institute (CLSI) guideline for slowly growing mycobacteria.(1,2) The extremely fastidious slowly growing mycobacteria (Mycobacterium genavense and Mycobacterium haemophilum) will not be tested. Mycobacterium malmoense can be difficult to grow in the test medium so some isolates may not be amenable to testing. Mycobacterium xenopi requires incubation at a higher temperature and may require extended incubation times. Mycobacterium gordonae is frequently encountered in the environment and in clinical laboratories but is almost always considered nonpathogenic; therefore, antimicrobial susceptibility testing for M gordonae is performed by specific request only.

Useful For: Determination of resistance of slowly growing mycobacteria to antimicrobial agents

Interpretation: Results are reported as the minimum inhibitory concentration in micrograms/mL.

Reference Values:
Interpretive criteria and reporting guidelines are followed using the Clinical Laboratory Standards Institute (CLSI) M24S document.

Clinical References: 1. CLSI: Susceptibility Testing of Mycobacteria, Nocardia spp., and Other Aerobic Actinomycetes. 3rd ed. CLSI standard M24. Clinical and Laboratory Standards Institute; 2018 2. CLSI: Performance Standards for Susceptibility Testing of Mycobacteria, Nocardia spp., and Other Aerobic Actinomycetes. CLSI supplement M62. Clinical and Laboratory Standards Institute; 2018 3. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Eur Respir J. 2020;56(1):2000535. doi:10.1183/13993003.00535-2020 4. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: An official ATS/ERS/ESCMID/IDSA clinical practice guideline. Clin Infect Dis. 2020;71(4):e1-e36. doi:10.1093/cid/ciaa241 5. Griffith DE, Winthrop KL. You gotta make me see, what does it mean to have an MIC?. Chest. 2021;159(2):462-464. doi:10.1016/j.chest.2020.11.007 6. Schon T, Chryssanthou E. Minimum inhibitory concentration distributions for Mycobacterium avium complex-towards evidence-based susceptibility breakpoints. Int J Infect Dis. 2017;55:122-124. doi:10.1016/j.ijid.2016.12.027

ZMMLS
8073

Antimicrobial Susceptibility, Aerobic Bacteria, Varies

Clinical Information: Antimicrobial susceptibility testing (AST) determines the minimal inhibitory concentration (MIC) of antimicrobial agents. The MIC is a measurement of the activity of an antimicrobial agent against an organism. It is defined as the lowest concentration of an antimicrobial agent that inhibits growth of the microorganism. Clinical breakpoints are derived from a number of data including: -The pharmacokinetics/pharmacodynamics of an antimicrobial agent -The MIC distribution of a large number of isolates -Clinical outcome data for a patient population treated with the antimicrobial of interest Antimicrobial susceptibility testing should be performed on pure culture isolates of pathogenic bacteria (or those potentially pathogenic in special situations) grown from specimens that have been appropriately collected so as not to confuse clinically significant isolates with normal or contaminating microbiota. Susceptibility testing is indicated for any organism that contributes to an infectious process warranting antimicrobial chemotherapy if its susceptibility cannot be reliably predicted from the organism's identity. The MIC obtained during AST is helpful in indicating the concentration of antimicrobial agent required at the site of infection necessary to inhibit the infecting organism. For each organism-antimicrobial agent combination, the Clinical and Laboratory Standards Institute and/or the European Committee on Antimicrobial Susceptibility Testing provides interpretive criteria for determining whether the MIC should be interpreted as susceptible, susceptible dose dependent, intermediate, nonsusceptible, resistant, or epidemiological cutoff value if applicable.

Useful For: Determining the in vitro susceptibility of aerobic bacteria involved in human infections

Interpretation: A "susceptible" category result and a low minimum inhibitory concentration value indicate in vitro susceptibility of the organism to the antimicrobial tested. Refer to Reference Values for interpretation of various antimicrobial susceptibility interpretive categories (ie, susceptible, susceptible-dose dependent, intermediate, nonsusceptible, resistant, or epidemiological cutoff value).

Reference Values:
Susceptibility results are reported as minimal inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as clinical breakpoints) are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, or nonsusceptible according to breakpoint setting organizations, either the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST), as applicable.

In some instances, an interpretive category cannot be provided based on available data; therefore, the following comment will be included on the report: There are no established interpretive guidelines for agents reported without interpretations.

For information regarding CLSI and EUCAST susceptibility interpretations, see Susceptibility Interpretative Category Definitions.

Clinical References: 1. Jorgensen JH, Ferraro MJ. Antimicrobial susceptibility testing: a review of general principles and contemporary practices. Clin Infect Dis. 2009;49(11):1749-1755 2. Jenkins SG, Schuetz AN. Current concepts in laboratory testing to guide antimicrobial therapy. Mayo Clin Proc. 2012;87(3):290-308 3. Procop GW, Church DL, Hall GS, et al: Antimicrobial susceptibility testing. In: Koneman's Color Atlas and Textbook of Diagnostic Microbiology. 7th ed. Wolters Kluwer Health; 2017:1074-1171

MMLSA 56031 Antimicrobial Susceptibility, Anaerobic Bacteria, Minimal Inhibitory Concentration, Varies

Clinical Information: Anaerobic bacteria are the greatest component of the human body's normal bacterial flora. Anaerobic bacteria colonize the skin, oral cavity, and genitourinary and lower gastrointestinal tracts and generally do not cause infection. Their presence is important for vitamin and other nutrient absorption and in preventing infection with disease-causing bacteria. When usual skin and mucosal barriers are compromised, in an anaerobic environment, these bacteria can behave as pathogens. Typical anaerobic infections include periodontitis, abdominal or pelvic abscesses, endometritis, pelvic inflammatory disease, aspiration pneumonia, empyema and lung abscesses, sinusitis, brain abscesses, gas gangrene, and other soft tissue infections. Anaerobic bacteria grow aggressively in the body under anaerobic conditions and may possess a variety of virulence factors, including capsules and extracellular enzymes. They also can develop resistance to antimicrobials by producing beta-lactamase and other modifying enzymes, and by alterations in membrane permeability and structure of penicillin-binding proteins. Susceptibility testing results are useful to clinicians because anaerobic bacteria are a significant cause of human infection, and they are often resistant to commonly used antimicrobials. Bacteroides and Parabacteroides species produce beta-lactamases. Ertapenem, metronidazole, and clindamycin are generally effective agents, although resistance to clindamycin, and occasionally ertapenem, is increasing. The minimal inhibitory concentration (MIC) obtained during antimicrobial susceptibility testing is helpful in indicating the concentration of antimicrobial agent required at the site of infection necessary to inhibit the infecting organism. For each organism-antimicrobial agent combination, the Clinical and Laboratory Standards Institute and/or the European Committee on Antimicrobial Susceptibility Testing provides interpretive criteria for determining whether the MIC should be interpreted as susceptible, susceptible dose dependent, intermediate, nonsusceptible, resistant, or epidemiological cutoff value.

Useful For: Determining the in vitro susceptibility on isolates of anaerobic bacteria involved in human

infections Directing antimicrobial therapy for anaerobic bacterial infections

Interpretation: In vitro susceptibility does not guarantee clinical response. Therefore, the decision to treat with a particular agent should not be based solely on the antimicrobial susceptibility testing result. Refrigeration may result in decreased viability of anaerobic organisms.

Reference Values:
Susceptibility results are reported as minimal inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as clinical breakpoints) are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, or nonsusceptible according to breakpoint setting organizations, either the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST), as applicable.

In some instances, an interpretive category cannot be provided based on available data; therefore, the following comment will be included on the report: There are no established interpretive guidelines for agents reported without interpretations.

For information regarding CLSI and EUCAST susceptibility interpretations, see Susceptibility Interpretative Category Definitions.

Clinical References: 1. Rosenblatt JE, Brook I. Clinical relevance of susceptibility testing of anaerobic bacteria. Clin Infect Dis. 1993;16(Suppl 4):S446-S448 2. Jenkins SG, Schuetz AN. Current concepts in laboratory testing to guide antimicrobial therapy. Mayo Clin Proc. 2012;87(3):290-308 3. Schuetz AN, Carpenter DE. Susceptibility test methods: anaerobic bacteria. In: Carroll KC, Pfaller MA, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:1377-1397 4. Jenkins SG, Schuetz AN. Current concepts in laboratory testing to guide antimicrobial therapy. Mayo Clin Proc. 2012;87(3):290-308

TB1LN 35994 Antimicrobial Susceptibility, Mycobacterium tuberculosis Complex, First Line, Varies

Clinical Information: Initial treatment regimens for Mycobacterium tuberculosis complex often include isoniazid, rifampin, ethambutol, and pyrazinamide. Susceptibility testing of M tuberculosis complex isolates against these antimycobacterial agents is a key component of patient management. The Clinical Laboratory Standards Institute (CLSI) provides consensus protocols for the methods, antimycobacterial agents, and critical concentrations of each agent to be tested to permit standardized interpretation of M tuberculosis complex susceptibility test results. This test uses an US Food and Drug Administration cleared commercial system for rapid broth susceptibility testing of M tuberculosis complex and assesses resistance to antimycobacterial drugs at the CLSI-recommended critical concentrations.

Useful For: Susceptibility testing of Mycobacterium tuberculosis complex isolates growing in pure culture.

Interpretation: Mycobacterium tuberculosis complex isolates are reported as susceptible or resistant to the aforementioned drugs at the critical concentrations. Some experts believe that patients infected with strains exhibiting resistance to low levels of isoniazid but not exhibiting resistance to high levels may benefit from continuing therapy with this agent. A specialist in the treatment of tuberculosis should be consulted concerning the appropriate therapeutic regimen and dosages.

Reference Values:

Results are reported as susceptible or resistant.

Clinical References: 1. Nahid P, Mase SR, Migliori GB, et al. Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline [published correction appears in Am J Respir Crit Care Med. 2020 Feb 15;201(4):500-501 2. Clinical and Laboratory Standards Institute (CLSI). Susceptibility Testing of Mycobacteria, Nocardia spp., and Other Aerobic Actinomycetes. 3rd ed. CLSI standard M24. CLSI; 2018 3. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Susceptibility Testing of Mycobacteria, Nocardia spp., and Other Aerobic Actinomycetes. 2nd ed. CLSI supplement M24S. CLSI; 2023

MMLNS
82019

Antimicrobial Susceptibility, Nocardia species and other Aerobic Actinomycetes, Varies

Clinical Information: Nocardia species and other aerobic actinomycetes can cause significant disease, often in immunocompromised patients. Clinical presentation can include, but is not limited to, pneumonia, skin abscess, bacteremia, brain abscess, eye infection, and joint infection. Antimicrobial susceptibility testing may aid with selection of appropriate antimicrobial agents for patient care.

Useful For: Determining the resistance of species of Nocardia and other aerobic actinomycetes to antimicrobial agents. This test is not useful for determining resistance of aerobic actinomycetes species of the following genera: Actinoallomurus, Actinocatenispora, Actinoplanes, Aeromicrobium, Croceifilum, Hazenella, Intrasporangium, Kineosphaera, Kitasatospora, Kribella, Kutzneria, Laceyella, Marinactinospora, Microbispora, Micromonospora, Nocardioides (not Nocardia), Phycicoccus, Piscicoccus, Prauserella, Risungbinella, Saccharothrix, Sphaerimonospora, Spirillospora, Streptosporangium, Terracoccus, or Thermoactinomyces.

Interpretation: Interpretive values for susceptibility testing of Nocardia species using a broth microdilution method are included in the report, as appropriate. For Rhodococcus equi, the interpretive values for vancomycin and rifampin will also be included. See Reference Values for additional information.

Reference Values:
Interpretive criteria and reporting guidelines are followed using the Clinical Laboratory Standards Institute (CLSI) M24S document.

Clinical References: 1. Duggal SD, Chugh TD. Nocardiosis: A neglected disease. Med Princ Pract. 2020;29(6):514-523. doi:10.1159/000508717 2. Conville PS, Brown-Elliott BA, Smith T, Zelazny AM. The complexities of Nocardia taxonomy and identification. J Clin Microbiol. 2017;56(1):e01419-17

AMH1
608824

Antimullerian Hormone, Serum

Clinical Information: Antimullerian hormone (AMH), also known as Mullerian-inhibiting substance, is a dimeric glycoprotein hormone belonging to the transforming growth factor-beta family. It is produced by Sertoli cells of the testis in male patients and by ovarian granulosa cells in female patients. Expression during male fetal development prevents the Mullerian ducts from developing into the uterus, resulting in development of the male reproductive tract. In the absence of AMH, the Mullerian ducts and structures develop into the female reproductive tract. AMH serum concentrations are elevated in boys under 2 years old and then progressively decrease until puberty when there is a sharp decline. In female individuals, serum AMH concentrations are very low at birth, peaking after puberty, and decrease progressively thereafter with age, eventually becoming undetectable at menopause. Because of the gender differences in

AMH concentrations, its changes in circulating concentrations with sexual development, and its specificity for Sertoli and granulosa cells, AMH measurement has utility in the assessment of gender, gonadal function, fertility, and as a gonadal tumor marker. In female individuals, AMH is considered an ovarian reserve marker. It correlates with the primordial follicle pool, has an inverse correlation with chronologic age, predicts ovarian response in assisted reproductive therapy, and has been suggested to be predictive of the timing of the onset of menopause. In contrast to other markers of ovarian reserve that show significant fluctuations during the menstrual cycle, serum AMH concentrations have been shown to be relatively stable. Women with higher concentrations of AMH have a better response to ovarian stimulation and tend to produce more retrievable oocytes than women with low or undetectable AMH. Women at risk of ovarian hyperstimulation syndrome after gonadotropin administration can have significantly elevated AMH concentrations. Polycystic ovarian syndrome can elevate serum AMH concentrations, because it is associated with the presence of large numbers of small follicles. AMH measurements are commonly used to evaluate testicular presence and function in infants with intersex conditions or ambiguous genitalia and to distinguish between cryptorchidism and anorchia in male infants. Serum AMH concentrations are increased in some individuals with ovarian granulosa cell tumors, which comprise approximately 10% of ovarian tumors. AMH, along with related tests including inhibin A and B (INHA / Inhibin A, Tumor Marker, Serum; INHB / Inhibin B, Serum; INHAB / Inhibin A and B, Tumor Marker, Serum), estradiol (EEST / Estradiol, Serum), and cancer antigen 125 (CA25 / Cancer Antigen 125 [CA 125], Serum), can be useful for diagnosing and monitoring these individuals.

Useful For: Assessing ovarian status, including ovarian reserve and responsiveness, as part of an evaluation for infertility and assisted reproduction protocols Assessment of menopausal status, including premature ovarian failure Evaluation of infants with ambiguous genitalia and other intersex conditions Evaluating testicular function in infants and children Monitoring individuals with antimullerian hormone-secreting ovarian granulosa cell tumors

Interpretation: Menopausal women or women with premature ovarian failure of any cause, including after cancer chemotherapy, have very low anti-Mullerian hormone (AMH) levels. While the optimal AMH concentrations for predicting response to in vitro fertilization are still being established, it is accepted that AMH concentrations in the perimenopausal to menopausal range indicate minimal to absent ovarian reserve. Depending on patient age, ovarian stimulation is likely to fail in such individuals. AMH may be used as a surrogate to antral follicle count (AFC) at day 2 to 4 of the menstrual cycle to determine ovarian reserve. Women with an AFC greater than 15 are identified as having high ovarian reserve. In this context, a Roche AMH concentration greater than 1.77 ng/mL at day 2 to 4 of the menstrual cycle identified women with an AFC greater than 15 with 88.3% sensitivity and 68.3% specificity.(1) Controlled ovarian stimulation (COS) with exogenous gonadotropin is an essential step of in vitro fertilization protocols. Using the Roche AMH assay, a cut-off of 2.10 ng/mL is correlated with the response categories in women undergoing COS using a gonadotropin-releasing hormone antagonist protocol. A 2.10 ng/mL cutoff provided reliable prediction of hyperresponse to COS.(2) Sensitivity for the detection of hyperresponsive individuals was 81.3%, and the negative predictive value for ruling out hyperresponse was 96.6%. The 2.10 ng/mL cutoff identified 88.9% of individuals with a poor response.(2) In individuals with polycystic ovarian syndrome, AMH concentrations may be 2- to 5-fold higher than age-appropriate reference range values. Such high levels predict anovulatory and irregular cycles. In children with intersex conditions, an AMH result above the normal female range is predictive of the presence of testicular tissue, while an undetectable value suggests its absence. In boys suspected of cryptorchidism, a measurable AMH concentration is predictive of undescended testes, while an undetectable value is highly suggestive of anorchia or functional failure. Klinefelter syndrome is characterized by accelerated germ cell depletion and occurs in approximately 10% to 12% of men presenting with nonobstructive azoospermia. In these patients, serum AMH concentrations are within the reference interval until puberty, and thereafter, AMH concentrations decline to abnormally low or undetectable levels. Pubertal delay and congenital hypogonadotropic hypogonadism (HH) share the same clinical manifestation of delayed sexual maturation in prepubertal boys. Levels of gonadotropin and testosterone are very low in prepubertal boys and, therefore, have little clinical significance; thus, AMH measurements are useful in the

differential diagnosis of pubertal delay and congenital HH. In individuals with congenital HH, AMH concentrations are abnormally low, while in pubertal delay, AMH concentrations will be within the prepubertal reference interval. Granulosa cell tumors of the ovary may secrete AMH, inhibin A, and inhibin B. Elevated levels of any of these markers can indicate the presence of such a neoplasm in a woman with an ovarian mass. Levels should fall with successful treatment. Rising levels indicate tumor recurrence or progression.

Reference Values:

Males
<2 years: 18-283 ng/mL
2-12 years: 8.9-109 ng/mL
>12 years: <13 ng/mL

Females
<3 years: 0.11-4.2 ng/mL
3-6 years: 0.21-4.9 ng/mL
7-11 years: 0.36-5.9 ng/mL
12-14 years: 0.49-6.9 ng/mL
15-19 years: 0.62-7.8 ng/mL
20-24 years: 1.2-12 ng/mL
25-29 years: 0.89-9.9 ng/mL
30-34 years: 0.58-8.1 ng/mL
35-39 years: 0.15-7.5 ng/mL
40-44 years: 0.03-5.5 ng/mL
45-50 years: <2.6 ng/mL
51-55 years: <0.88 ng/mL
>55 years: <0.03 ng/mL

Clinical References: 1. Jacobs MH, Reuter LM, Baker VL, et al. A multicentre evaluation of the Elecsys anti-Mullerian hormone immunoassay for prediction of antral follicle count. Reprod Biomed Online. 2019;38(5):845-852 2. Anckaert E, Denk B, He Y, Torrance HL, Broekmans F, Hund M. Evaluation of the Elecsys anti-Mullerian hormone assay for the prediction of hyper-response to controlled ovarian stimulation with a gonadotrophin-releasing hormone antagonist protocol. Eur J Obstet Gynecol Reprod Biol. 2019;236:133-138 3. Bedenk J, Vrtacnik-Bokal E, Virant-Klun I. The role of anti-Mullerian hormone (AMH) in ovarian disease and infertility. J Assist Reprod Genet. 2020;37(1):89-100 4. Xu HY, Zhang HX, Xiao Z, Qiao J, Li R. Regulation of anti-Mullerian hormone (AMH) in males and the associations of serum AMH with the disorders of male fertility. Asian J Androl. 2019;21(2):109-114 5. Grinspon RP, Bergada I, Rey RA. Male hypogonadism and disorders of sex development. Front Endocrinol (Lausanne). 2020;11:211. Published 2020 April 15 6. Kanakatti Shankar R, Dowlut-McElroy T, Dauber A, Gomez-Lobo V. Clinical utility of anti-Mullerian hormone in pediatrics. J Clin Endocrinol Metab. 2022;107(2):309-323. doi:10.1210/clinem/dgab687 7. Saint Paul LP, Debruyne D, Bernard D, Mock DM, and Defer GL. Pharmacokinetics and pharmacodynamics of MD1003 (high-dose biotin) in the treatment of progressive multiple sclerosis. Expert Opin Drug Metab Toxicol. 2016;12:3,327-344 8. Grimsey P, Frey N, Bendig G,et al: Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. J Pharmacokinet Pharmacodyn. 2017;2(4),247-256

AN2TS
43432

Antineuronal Nuclear Antibody Type 2 (ANNA-2) Titer, Serum

Clinical Information: Antineuronal nuclear autoantibody type 2 (ANNA-2), also known as anti-Ri, is an IgG serologic marker of paraneoplastic neurologic autoimmunity and reflects an immune response to neuronal antigens expressed in certain breast, lung, or gynecologic cancers. These carcinomas are often occult, with patients presenting with unexplained signs of neurologic dysfunction. ANNA-2 is far less

common than ANNA-1. It is one of the rarest paraneoplastic antibodies encountered in the Mayo Clinic Neuroimmunology Laboratory. Patients who are seropositive for ANNA-2 usually present to a neurologist with signs of midbrain, brain stem, cerebellar, or spinal cord dysfunction. Some have sensorimotor neuropathy. Ocular opsoclonus-myoclonus, laryngospasm, or jaw-opening dystonia may be prominent. Peripheral neuropathic sign and symptoms may occur. These often reflect coexisting autoimmunity to other onconeural proteins (eg, ANNA-1, collapsin response-mediator protein-5 [CRMP-5], calcium channels); coexisting paraneoplastic autoantibodies are found in 73% of cases. ANNA-2-positive patients are female in 64% of cases. Most have a primary carcinoma of breast or lung; gynecologic cancer is less frequent. Treatment of the cancer can lead to progressive reduction in ANNA-2 titer and stabilization or striking improvement of the neurologic disorder. ANNA-2 is not detected in serum or spinal fluid of healthy individuals. It is found in less than 2% of patients who have small-cell lung carcinoma without evidence of neurologic dysfunction. ANNA-2 is identified by an indirect immunofluorescence assay. It characteristically stains neurons in the central nervous system and spares neurons in the peripheral nervous system. ANNA-2 is also identifiable by neuronal Western blot characteristics.

Useful For: Investigating middle-aged or older patients who present with unexplainable signs of midbrain/cerebellar/brain stem disorder and/or myelopathy, especially women with a previous history of breast cancer, and both sexes if there is a history of tobacco abuse or passive exposure Investigating a smoker presenting with 1 or more elements of encephalomyeloradiculoneuropathy as a part of PAVAL / Paraneoplastic, Autoantibody Evaluation, Serum Reporting an end titer result from serum specimens

Interpretation: Detection of antineuronal nuclear autoantibodies type 2 (ANNA) in serum or spinal fluid of patients with a clinically unexplainable neurologic disorder: -Identifies the neurologic problem as autoimmune and almost certainly paraneoplastic -Prompts a search for underlying malignancy (breast, lung, or gynecologic) -Leads to early treatment of cancer and consideration of immunosuppressant therapy

Reference Values:

Only orderable as a reflex. For more information see:
-PAVAL / Paraneoplastic, Autoantibody Evaluation, Serum
-DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
-ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
-MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
-MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum

<1:240
Neuron-restricted patterns of IgG staining that do not fulfill criteria for antineuronal nuclear antibody type 2 may be reported as "unclassified antineuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References: 1. Kiers L, Altermatt HJ, Lennon VA: Paraneoplastic anti-neuronal nuclear IgG autoantibodies (type 1) localize antigen in small cell lung carcinoma. Mayo Clin Proc. 1991 Dec;66(12):1209-1216 2. Lennon VA: Paraneoplastic autoantibodies: the case for a descriptive generic nomenclature. Neurology. 1994 Dec;44(12):2236-2240 3. Lennon VA, Kryzer TJ, Griesmann GE, et al: Calcium-channel antibodies in the Lambert-Eaton syndrome and other paraneoplastic syndromes. N Engl J Med. 1995 Jun 1;332(22):1467-1474 4. Chan KH, Vernino S, Lennon VA: ANNA-3 anti-neuronal nuclear antibody: marker of lung cancer-related autoimmunity. Ann Neurol. 2001 Sep;50(3):301-311 5. Pittock SJ, Lucchinetti CF, Lennon VA: Anti-neuronal nuclear autoantibody-type 2: paraneoplastic accompaniments. Ann Neurol. 2003 May;53(5):580-587 6. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul 15;20(14):3862-3869 7. Vernino S, Lennon VA: New Purkinje cell antibody (PCA-2): marker of lung cancer-related neurological autoimmunity. Ann Neurol. 2000 Mar;47(3):297-305

AN2TC
43441

Antineuronal Nuclear Antibody Type 2 (ANNA-2) Titer, Spinal Fluid

Clinical Information: Antineuronal nuclear autoantibody type 2 (ANNA-2), also known as anti-Ri, is an IgG serologic marker of paraneoplastic neurologic autoimmunity and reflects an immune response to neuronal antigens expressed in certain breast, lung, or gynecologic cancers. These carcinomas are often occult, with the patients presenting with unexplained signs of neurologic dysfunction. ANNA-2 is far less common than ANNA-1. It is one of the rarest paraneoplastic antibodies encountered in the Mayo Clinic Neuroimmunology Laboratory. Patients who are seropositive for ANNA-2 usually present to a neurologist with signs of midbrain, brain stem, cerebellar, or spinal cord dysfunction. Some have sensorimotor neuropathy. Ocular opsoclonus-myoclonus, laryngospasm, or jaw-opening dystonia may be prominent. Peripheral neuropathic signs and symptoms may occur. These often reflect coexisting autoimmunity to other onconeural proteins (eg, ANNA-1, collapsin response-mediator protein-5 [CRMP-5], calcium channels); coexisting paraneoplastic autoantibodies are found in 73% of cases. ANNA-2 positive patients are female in 64% of cases. Most have a primary carcinoma of breast or lung; gynecologic cancer is less frequent. Treatment of the cancer can lead to progressive reduction in ANNA-2 titer and stabilization or striking improvement of the neurologic disorder. ANNA-2 is not detected in serum or spinal fluid of healthy individuals. It is found in fewer than 2% of patients who have small-cell lung carcinoma without evidence of neurologic dysfunction. ANNA-2 is identified by an indirect immunofluorescence assay. It characteristically stains neurons in the central nervous system and spares neurons in the peripheral nervous system. ANNA-2 is also identifiable by neuronal Western blot characteristics.

Useful For: Investigating middle-aged or older patients who present with unexplainable signs of midbrain/cerebellar/brain stem disorder and/or myelopathy, especially women with a previous history of breast cancer, and both sexes if there is a history of tobacco abuse or passive exposure Reporting an end titer result from cerebrospinal fluid specimens

Interpretation: Detection of antineuronal nuclear autoantibodies type 2 (ANNA-2) in serum or spinal fluid of patients with a clinically unexplainable neurologic disorder: -Identifies the neurologic problem as autoimmune and almost certainly paraneoplastic -Prompts a search for underlying malignancy (breast, lung, or gynecologic) -Leads to early treatment of cancer and consideration of immunosuppressant therapy

Reference Values:
Only orderable as a reflex. For more information see:
-DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

<1:2
Neuron-restricted patterns of IgG staining that do not fulfill criteria for antineuronal nuclear antibody type 2 may be reported as "unclassified antineuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References: 1. Kiers L, Altermatt HJ, Lennon VA: Paraneoplastic anti-neuronal nuclear IgG autoantibodies (type 1) localize antigen in small cell lung carcinoma. Mayo Clin Proc. 1991 Dec;66(12):1209-1216 2. Lennon VA: Paraneoplastic autoantibodies: the case for a descriptive generic nomenclature. Neurology. 1994 Dec;44(12):2236-2240 3. Lennon VA, Kryzer TJ, Griesmann GE, et al: Calcium-channel antibodies in the Lambert-Eaton syndrome and other paraneoplastic syndromes. N Engl J Med. 1995 Jun 1;332(22):1467-1474 4. Chan KH, Vernino S, Lennon VA: ANNA-3 anti-neuronal nuclear antibody: marker of lung cancer-related autoimmunity. Ann Neurol. 2001 Sep;50(3):301-311 5.

Pittock SJ, Lucchinetti CF, Lennon VA: Anti-neuronal nuclear autoantibody-type 2: paraneoplastic accompaniments. Ann Neurol. 2003 May;53(5):580-587 6. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul 15;20(14):3862-3869

AN3TS 43433 Antineuronal Nuclear Antibody Type 3 (ANNA-3) Titer, Serum

Clinical Information: Antineuronal nuclear autoantibodies (ANNA) are recognized clinically as markers of a patient's immune response to specific cancers (paraneoplastic autoantibodies). In 1985, an antineuronal nuclear autoantibody (now known as ANNA-1 or anti-Hu)(1) was described as a serological accompaniment of subacute sensory neuropathy related to small-cell lung carcinoma (SCLC). ANNA-1 was subsequently recognized as an IgG marker for a spectrum of encephalomyeloradiculoneuropathy (including gastrointestinal dysmotilities) related to SCLC,(2) childhood neuroblastoma, and thymoma. The second antineuronal nuclear antibody to be recognized (known as ANNA-2 or anti-Ri) is an IgG marker of neurological autoimmunity related to SCLC and breast carcinoma.(3) ANNA-3 is an IgG marker of an immune response to SCLC in patients presenting with a subacute, usually multifocal, paraneoplastic neurologic disorder.(4) Paraneoplastic sensorimotor neuropathy, cerebellar ataxia, and limbic encephalopathy are the most common presentations. However, an ANNA-3-positive patient may present with any element of an encephalomyeloradiculoneuropathy. Other autoantibody markers of immune responses to SCLC include amphiphysin, collapsin response-mediated protein-5 (CRMP-5) IgG, Purkinje cell antibody type 2 (PCA-2), antiglial neuronal nuclear antibody (AGNA-1), voltage-gated calcium channel (P/Q-type) and potassium channel (VGKC) antibodies and muscle acetylcholine receptor antibodies.

Useful For: Evaluating patients who present with a subacute neurological disorder of undetermined etiology and have risk factors for primary lung carcinoma Reporting an end titer result from serum specimens

Interpretation: A positive result confirms that a patient's subacute neurological disorder has an autoimmune basis and predicts with 90% certainty that the patient has an aerodigestive carcinoma, usually a small-cell lung carcinoma (SCLC) that is new or recurrent and confined to the chest. Fifteen percent of patients who are eventually proven to have small-cell carcinoma have an unrelated often more obvious cancer, either coexisting or in the past. Antineuronal nuclear antibody type 3 (ANNA-3) has not yet been encountered in healthy subjects (n=100) or patients with lung carcinoma without a neurological accompaniment (n=100) or with other cancers (n=300).

Reference Values:

Only orderable as a reflex. For more information see:
-PAVAL / Paraneoplastic, Autoantibody Evaluation, Serum
-DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
-ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
-MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
-AIAES / Axonal Neuropathy, Autoimmune/Paraneoplastic Evaluation, Serum
-MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum

<1:240

Neuron-restricted patterns of IgG staining that do not fulfill criteria for antineuronal nuclear antibody type 3 may be reported as "unclassified anti-neuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References: 1. Graus F, Cordon-Cardo C, Posner JB: Neuronal antinuclear antibody in sensory neuropathy from lung cancer. Neurology. 1985 Apr;35(4):538-543 2. Lucchinetti CF, Kimmel

DW, Lennon VA: Paraneoplastic and oncologic profile of patients seropositive for type 1 antineuronal nuclear autoantibodies. Neurology. 1998 Mar;50(3):652-657 3. Vernino S, Eggenberger ER, Rogers LR, Lennon VA: Paraneoplastic neurological autoimmunity associated with ANNA-1 autoantibody and thymoma. Neurology. 2002 Sep 24;59(6):929-932 4. Pittock SJ, Lucchinetti CF, Lennon VA: Anti-neuronal nuclear autoantibody-type 2: paraneoplastic accompaniments. Ann Neurol. 2003 May;53(5):580-587 5. Chan KH, Vernino S, Lennon VA: ANNA-3 anti-neuronal nuclear antibody: marker of lung cancer-related autoimmunity. Ann Neurol 2001 September;50(3):301-311 6. Pittock SJ, Kryzer TJ, Lennon VA: Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. Ann Neurol. 2004 Nov;56(5):715-719 7. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul 15;20(14):3862-3869

AN3TC
43442

Antineuronal Nuclear Antibody Type 3 (ANNA-3) Titer, Spinal Fluid

Clinical Information: Antineuronal nuclear autoantibodies (ANNA) are recognized clinically as markers of a patient's immune response to specific cancers (paraneoplastic autoantibodies). In 1985, an antineuronal nuclear autoantibody (now known as ANNA-1 or anti-Hu)(1) was described as a serological accompaniment of subacute sensory neuropathy related to small-cell lung carcinoma (SCLC). ANNA-1 was subsequently recognized as an IgG marker for a spectrum of encephalomyeloradiculoneuropathy (including gastrointestinal dysmotilities) related to SCLC,(2) childhood neuroblastoma, and thymoma. The second antineuronal nuclear antibody to be recognized (known as ANNA-2 or anti-Ri) is an IgG marker of neurological autoimmunity related to SCLC and breast carcinoma.(3) ANNA-3 is an IgG marker of an immune response to SCLC in patients presenting with a subacute, usually multifocal, paraneoplastic neurologic disorder.(4) Paraneoplastic sensorimotor neuropathy, cerebellar ataxia, and limbic encephalopathy are the most common presentations. However, an ANNA-3-positive patient may present with any element of an encephalomyeloradiculoneuropathy. Other autoantibody markers of immune responses to SCLC include amphiphysin, collapsin response-mediated protein-5 (CRMP-5) IgG, Purkinje cell antibody type 2 (PCA-2), antiglial nuclear antibody, calcium channel antibodies (P/Q-type), and muscle acetylcholine receptor antibodies.

Useful For: Evaluating patients who present with a subacute neurological disorder of undetermined etiology and have risk factors for primary lung carcinoma Reporting an end titer result from cerebrospinal fluid specimens

Interpretation: A positive result confirms that a patient's subacute neurological disorder has an autoimmune basis and predicts with 90% certainty that the patient has an aerodigestive carcinoma, usually a small-cell lung carcinoma (SCLC) that is new or recurrent and confined to the chest. Fifteen percent of patients who are eventually proven to have small-cell carcinoma have an unrelated often more obvious cancer, either coexisting or in the past. Antineuronal nuclear autoantibody type 3 (ANNA-3) has not yet been encountered in healthy subjects (n=100) or patients with lung carcinoma without a neurological accompaniment (n=100) or with other cancers (n=300).

Reference Values:

Only orderable as a reflex. For more information see:
-DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

<1:2
Neuron-restricted patterns of IgG staining that do not fulfill criteria for antineuronal nuclear antibody

type 3 may be reported as "unclassified antineuronal IgG. "Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References: 1. Graus F, Cordon-Cardo C, Posner JB: Neuronal antinuclear antibody in sensory neuropathy from lung cancer. Neurology. 1985 April;35(4):538-543 2. Lucchinetti CF, Kimmel DW, Lennon VA: Paraneoplastic and oncologic profile of patients seropositive for type 1 antineuronal nuclear autoantibodies. Neurology. 1998 Mar;50(3):652-657 3. Vernino S, Eggenberger ER, Rogers LR, Lennon VA: Paraneoplastic neurological autoimmunity associated with ANNA-1 autoantibody and thymoma. Neurology. 2002 Sep 24;59(6):929-932 4. Pittock SJ, Lucchinetti CF, Lennon VA: Anti-neuronal nuclear autoantibody-type 2: paraneoplastic accompaniments. Ann Neurol. 2003 May;53(5):580-587 5. Chan KH, Vernino S, Lennon VA: ANNA-3 anti-neuronal nuclear antibody: marker of lung cancer-related autoimmunity. Ann Neurol. 2001 Sep;50(3):301-311 6. Pittock SJ, Kryzer TJ, Lennon VA: Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. Ann Neurol. 2004 Nov;56(5):715-719 7. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul 15;20(14):3862-3869

AN1TS
43431

Antineuronal Nuclear Antibody-Type 1 (ANNA-1) Titer, Serum

Clinical Information: A spectrum of paraneoplastic neurologic disorders (often multifocal) is found with antineuronal nuclear antibody type 1 (ANNA-1), also known as anti-Hu. Most frequent are neuropathies: mixed sensorimotor, pure sensory, predominantly autonomic, and least commonly, predominantly motor. Other manifestations include limbic encephalitis, subacute cerebellar degeneration, myelopathy, or radiculopathy. Small-cell lung carcinoma (SCLC) is almost always present, although difficult to find. Extrapulmonary primary small-cell carcinoma thymoma or neuroblastoma is rarely encountered as the pertinent neoplasm. Whole body positron emission tomography (PET) scanning is justifiable in seropositive patients when no cancer is found. ANNA-1 antibody is an extremely valuable marker of paraneoplastic intestinal dysmotilities associated with SCLC, ranging from gastroparesis to pseudo-obstruction. In this context it may be accompanied by muscle or ganglionic acetylcholine receptor (AChR) antibody, voltage-gated potassium channel antibody, striational antibody, glutamic acid decarboxylase 65 (GAD65) antibody, or thyroid or gastric parietal cell antibodies. ANNA-1 antibody is uncommon in patients with SCLC without a neuropathy, including patients with Lambert-Eaton myasthenic syndrome or pure cerebellar ataxia. ANNA-1 has been encountered in children with intestinal dysmotility, cerebellar ataxia, brain stem encephalitis, and myeloneuropathy with and without evident cancer (neuroblastoma).

Useful For: Diagnosis of paraneoplastic autoimmune neuropathies, encephalomyeloradiculopathies, related neurologic disorders, and intestinal pseudo-obstruction/dysmotility associated with small-cell lung carcinoma Reporting an end titer result from serum specimens This test alone should not be used as a general screening test for carcinoma of the lung.

Interpretation: This autoantibody is rarely found in adult patients without asbestos exposure, or a long history of tobacco use or passive exposure. Sixty-six percent of seropositive patients are female; small-cell lung carcinoma (SCLC) has been confirmed in 83% of those with adequate follow-up. In 15% with confirmed SCLC, an unrelated and more obvious primary malignancy coexists with SCLC. Antineuronal nuclear antibody type 1 is found before SCLC is diagnosed in 55% of cases. Positron emission tomography (PET) scanning, magnetic resonance imaging of the chest, and transesophageal ultrasound sometimes reveal malignant adenopathy when computerized tomography is negative. An extrapulmonary primary small cell carcinoma should be considered, especially in nonsmoking patients (eg, skin, larynx, tongue, breast, cervix, ovary, prostate, endocrine, or pancreas). Autopsy sometimes reveals SCLC in patients who lack evidence of tumor in life.

Reference Values:

Only orderable as a reflex. For more information see:
-AIAES / Axonal Neuropathy, Autoimmune/Paraneoplastic Evaluation, Serum
-DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
-DYS2 / Dysautonomia, Autoimmune/Paraneoplastic Evaluation, Serum
-ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
-GID2 / Gastrointestinal Dysmotility, Autoimmune/Paraneoplastic Evaluation, Serum
-MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
-PAVAL / Paraneoplastic, Autoantibody Evaluation, Serum
-PCDES / Pediatric Autoimmune Encephalopathy/CNS Disorder Evaluation, Serum

<1:240
Neuron-restricted patterns of IgG staining that do not fulfill criteria for antineuronal nuclear antibody type 1 may be reported as "unclassified anti-neuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References: 1. Lucchinetti CF, Kimmel DW, Lennon VA. Paraneoplastic and oncologic profile of patients seropositive for type 1 antineuronal nuclear autoantibodies. Neurology. 1998;50(3):652-657 2. Vernino S, Eggenberger ER, Rogers LR, Lennon VA. Paraneoplastic neurological autoimmunity associated with ANNA-1 autoantibody and thymoma. Neurology. 2002;59(6):929-932 3. Pranzatelli MR, McGee NR. Neuroimmunology of OMS and ANNA-1/anti-Hu paraneoplastic syndromes in a child with neuroblastoma. Neurol Neuroimmunol Neuroinflamm. 2017;5(2):e433. doi:10.1212/NXI.0000000000000433 4. Horta ES, Lennon VA, Lachance DH, et al. Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014;20(14):3862-3869

AN1TC 43440 Antineuronal Nuclear Antibody-Type 1 (ANNA-1) Titer, Spinal Fluid

Clinical Information: A spectrum of paraneoplastic neurologic disorders is found with antineuronal nuclear antibody type1 (ANNA-1), also known as anti-Hu. Most frequent are neuropathies: mixed sensorimotor, pure sensory, predominantly autonomic, and least commonly, predominantly motor. Other manifestations include limbic encephalitis, subacute cerebellar degeneration, myelopathy, or radiculopathy. Small-cell lung carcinoma (SCLC) is almost always present, although difficult to find. Thymoma or neuroblastoma are encountered rarely as the pertinent neoplasm. ANNA-1 antibody is an extremely valuable marker of paraneoplastic intestinal dysmotilities associated with SCLC, ranging from gastroparesis to pseudo-obstruction. ANNA-1 antibody is uncommon in patients with SCLC without a neuropathy, including patients with Lambert-Eaton myasthenic syndrome or pure cerebellar ataxia. ANNA-1 has been encountered in children with intestinal dysmotility, cerebellar ataxia, brain stem encephalitis, and myeloneuropathy with and without evident cancer (neuroblastoma).

Useful For: Diagnosis of paraneoplastic autoimmune neuropathies, encephalomyeloradiculopathies, related neurologic disorders, and intestinal pseudo-obstruction/dysmotility associated with small-cell lung carcinoma Reporting an end titer result from cerebrospinal fluid specimens This test alone should not be used as a general screening test for carcinoma of the lung.

Interpretation: This autoantibody is rarely found in adult patients without asbestos exposure, or a long history of tobacco use or passive exposure. Sixty-six percent of seropositive patients are female; small-cell lung carcinoma (SCLC) has been confirmed in 83% of those with adequate follow-up. In 15% of patients with confirmed SCLC, an unrelated and more obvious primary malignancy coexists with SCLC. Antineuronal nuclear antibody type 1 is found before SCLC is diagnosed in 55% of cases. Positron emission tomography (PET) scanning, magnetic resonance imaging of the chest, and transesophageal

ultrasound sometimes reveal malignant adenopathy when computed tomography is negative. An extra pulmonary primary small-cell carcinoma (eg, skin, larynx, tongue, breast, cervix, prostate, endocrine, or pancreas) should be considered, especially in nonsmoking patients. Autopsy sometimes reveals SCLC in patients who lack evidence of tumor in life.

Reference Values:

Only orderable as a reflex. For more information see:
-DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-PCDEC / Pediatric Autoimmune Encephalopathy/CNS Disorder Evaluation, Spinal Fluid

<1:2
Neuron-restricted patterns of IgG staining that do not fulfill criteria for antineuronal nuclear antibody type 1 may be reported as "unclassified antineuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References: 1. Lucchinetti CF, Kimmel DW, Lennon VA: Paraneoplastic and oncological and profiles of patients seropositive for type 1 antineuronal nuclear autoantibodies. Neurology. 1998 Mar;50(3):652-657 2. Vernino S, Eggenberger ER, Rogers LR, Lennon VA: Paraneoplastic neurological autoimmunity associated with ANNA-1 autoantibody and thymoma. Neurology. 2002 Sep 24;59(6):929-932 3. Pranzatelli MR, McGee NR. Neuroimmunology of OMS and ANNA-1/anti-Hu paraneoplastic syndromes in a child with neuroblastoma. Neurol Neuroimmunol Neuroinflamm. 2017 Dec 22;5(2):e433. doi: 10.1212/NXI.0000000000000433 4. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul 15;20(14):3862-3869

VASC
83012

Antineutrophil Cytoplasmic Antibodies Vasculitis Panel, Serum

Clinical Information: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides are characterized by a pauci-immune inflammation within the walls of small blood vessels.(1) There are 3 specific diseases which are identified as ANCA-associated vasculitides: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The serological hallmark of these disorders is the presence of ANCA, which are antibodies that bind to cytoplasmic antigens found in the granules of neutrophils.(2) Patients with GPA frequently have antibodies specific for proteinase 3 (PR3), while individuals with MPA or EGPA are more likely to have antibodies that bind to myeloperoxidase (MPO). The presence of PR3-ANCA and MPO-ANCA can be detected using antigen-specific immunoassays or indirect immunofluorescence (IIF). IIF is typically performed using ethanol-fixed neutrophils. Using this substrate, anti-PR3 antibodies produce a granular cytoplasmic-staining pattern, which is referred to as cANCA. In comparison, due to an artefact that is a result of the fixation process, anti-MPO antibodies display a perinuclear pattern (pANCA). Patients with suspected ANCA-associated vasculitis should be evaluated for the presence of PR3-ANCA, MPO-ANCA and ANCA by IIF. A consensus guideline published in 2017 recommends that patients with possible GPA or MPA be tested for PR3-ANCA and MPO-ANCA using antigen-specific immunoassays.(3) ANCA by IIF should then be used in cases where there is a high degree of suspicion for GPA or MPA, but the PR3-ANCA and MPO-ANCA testing is negative. To improve specificity of the testing, this guideline also suggests that ANCA be used in situations where a low-positive PR3-ANCA or MPO-ANCA level is detected. The classification criteria for MPA, GPA, and EGPA published by the American College of Rheumatology and the European Alliance of Associations for Rheumatology include PR3-ANCA and MPO-ANCA detected by either antigen-specific

immunoassay or IIF.(4-6) These classification criteria incorporate serological ANCA testing along with clinical symptoms, imaging, and biopsy results to determine a score that allows for the classification of the various ANCA-associated vasculitides.

Useful For: Evaluating patients with clinical features of anti-neutrophil cytoplasmic antibody-associated vasculitis, specifically granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis

Interpretation: Positive results for proteinase 3 anti-neutrophil cytoplasmic antibodies (ANCA) by antigen-specific immunoassay and cytoplasmic ANCA by indirect immunofluorescence are consistent with the diagnosis of granulomatosis with polyangiitis, in patients with the appropriate clinical presentation. Positive results for myeloperoxidase-ANCA by antigen-specific immunoassay and perinuclear ANCA by indirect immunofluorescence are consistent with the diagnosis of microscopic polyangiitis or eosinophilic granulomatosis with polyangiitis, in patients with the appropriate clinical presentation.

Reference Values:
MYELOPEROXIDASE ANTIBODIES, IgG
<0.4 U (negative)
0.4-0.9 U (equivocal)
> or =1.0 U (positive)
Reference values apply to all ages.

PROTEINASE 3 ANTIBODIES, IgG
<0.4 U (negative)
0.4-0.9 U (equivocal)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References: 1. Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. Nat Rev Dis Primers. 2020;6(1):71 2. Ramponi G, Folci M, De Santis M, et al. The biology, pathogenetic role, clinical implications, and open issues of serum anti-neutrophil cytoplasmic antibodies. Autoimmun Rev. 2021;20(3):102759 3. Bossuyt X, Cohen Tervaert JW, Arimura Y, et al. Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol. 2017;13(11):683-692 4. Suppiah R, Robson JC, Grayson PC, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. Ann Rheum Dis. 2022;81(3):321-326. doi:10.1136/annrheumdis-2021-221796 5. Robson JC, Grayson PC, Ponte C, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. Ann Rheum Dis. 2022;81(3):315-320. doi:10.1136/annrheumdis-2021-221795 6. Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. Ann Rheum Dis. 2022;81(3):309-314. doi:10.1136/annrheumdis-2021-221794

ANA2
9026

Antinuclear Antibodies (ANA), Serum

Clinical Information: Measurement of antinuclear antibodies (ANAs) in serum is the most commonly performed screening test for patients suspected of having a systemic autoimmune rheumatic disease (SARD), also referred to as connective tissue disease.(1) ANAs occur in patients with various autoimmune diseases, both systemic and organ specific, but they are particularly common in SARDs, which include systemic lupus erythematosus (SLE), discoid lupus erythematosus, drug-induced lupus

erythematosus, mixed connective tissue disease (MCTD), Sjogren syndrome (SjS), systemic sclerosis, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia), and idiopathic inflammatory myopathies. Antinuclear antibodies can be detected by different technologies, including indirect immunofluorescence assay (IFA) and solid phase assays, such as enzyme immunoassays and multiplex bead immunoassays. In a study performed in the Mayo Clinic Antibody Immunology Laboratory, no significant differences were demonstrated between ANA IFA and ANA enzyme-linked immunosorbent assay (ELISA) for a cohort of patients with connective tissue disease consisting predominantly of patients with SLE, SjS, and MCTD. Weakly positive ANA ELISA results were not a strong indicator of SARD in this laboratory cohort. The likelihood of finding an autoantibody to a specific extractable nuclear antigen including double-stranded DNA on a second-order testing increased directly with the level of ANA: 88% of sera that had detectable autoantibodies on second-order testing had an ANA level greater than 3.0 U.(2) Overall, an ANA ELISA result of greater than or equal to 3.0 U was demonstrated as the optimal cutoff for CTDC / Connective Tissue Disease Cascade, Serum. This algorithm is intended to evaluate patients with common connective tissue diseases such as SLE, SjS, and MCTD. For more information see Connective Tissue Disease Cascade.

Useful For: Evaluating patients at-risk for antinuclear antibodies-associated systemic autoimmune rheumatic disease particularly systemic lupus erythematosus, Sjogren syndrome, and mixed connective tissue disease

Interpretation: A large number of healthy individuals have weakly-positive (1.1-2.9 U) antinuclear antibody (ANA) enzyme-linked immunosorbent assay (ELISA) results, many of which are likely to be clinical false-positive results; therefore, second-order testing of all positive ANA yields a very low percentage of positive results to extractable nuclear antigens including double-stranded (ds) DNA.(2) Positive ANA results greater than 3.0 U are associated with the presence of detectable autoantibodies to specific extractable nuclear antigens (SM, SS-A, SS-B, Sm/RNP or RNP 68 and RNP A, Jo-1, Scl-70) including dsDNA.

Reference Values:
Negative: < or =1.0 U
Weakly positive: 1.1-2.9 U
Positive: 3.0-5.9 U
Strongly positive: > or =6.0 U
Reference values apply to all ages.

Clinical References: 1. Agmon-Levin N, Damoiseaux J, Kallenberg C, et al. International recommendations for the assessment of autoantibodies to cellular antigens referred to as anti-nuclear antibodies. Ann Rheum Dis. 2014;73(1):17-23. doi:10.1136/annrheumdis-2013-203863 2. Deng X, Peters B, Ettore MW, et al. Utility of antinuclear antibody screening by various methods in a clinical laboratory patient cohort: J Appl Lab Med. 2016;1(1):36-46. doi:10.1373/jalm.2016.020172 3. Sparchez M, Delean D, Samasca G, Miu N, Sparchez Z. Antinuclear antibody screening by ELISA and IF techniques: discrepant results in juvenile idiopathic arthritis but consistency in childhood systemic lupus erythematous. Clin Rheumatol. 2014;33(5):643-647. doi:10.1007/s10067-014-2529-y 4. Bossuyt X, De Langhe E, Borghi MO, Meroni PL. Understanding and interpreting antinuclear antibody tests in systemic rheumatic diseases. Nat Rev Rheumatol. 2020;16(12):715-726. doi:10.1038/s41584-020-00522-w 5. Bossuyt X, Claessens J, De Langhe E, et al. Antinuclear antibodies by indirect immunofluorescence and solid phase assays. Ann Rheum Dis. 2020;79(6):e65. doi:10.1136/annrheumdis-2019-215443 6. Alsaed OS, Alamlih LI, Al-Radideh O, Chandra P, Alemadi S, Al-Allaf AW. Clinical utility of ANA-ELISA vs ANA-immunofluorescence in connective tissue diseases. Sci Rep. 2021;11(1):8229. doi:10.1038/s41598-021-87366-w

NAIFA
65161

Antinuclear Antibodies, HEp-2 Substrate, IgG, Serum

Clinical Information:

Useful For: Evaluation of patients suspected of having systemic autoimmune rheumatic disease (ANA-associated rheumatic diseases or connective tissue disease) or organ-specific autoimmune diseases such as autoimmune liver diseases

Interpretation:

Reference Values:
<1:80 (Negative)

Clinical References: 1. Agmon-Levin N, Damoiseaux J, Kallenberg C, et al. International recommendations for the assessment of autoantibodies to cellular antigens referred to as anti-nuclear antibodies. Ann Rheum Dis. 2014;73:17-23 2. Chan EK, Damoiseaux J, Gabriel Carballo O, et al. Report of the First International Consensus on Standardized Nomenclature of Antinuclear Antibody HEp-2 Cell Patterns 2014-2015. Front Immunol. 2015;6:412 3. Bossuyt X, De Langhe E, Borghi MO, Meroni PL. Understanding and interpreting antinuclear antibody tests in systemic rheumatic diseases. Nat Rev Rheumatol. 2020;16:715-726 4. International Consensus on ANA Patterns. Nomenclature and Classification Tree. ICAP; 2021 Accessed August 13, 2021. Available at www.anapatterns.org/trees.php 5. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67:145-172 6. Younossi ZM, Bernstein D, Shiffman ML, et al. Diagnosis and management of primary biliary cholangitis. Am J Gastroenterol. 2019;114:48-63 7. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol. 2019;71:1400-1412 8. Naides SJ, Genzen JR, Abel G, Bashleben C, Ansari MQ. Antinuclear antibodies testing method variability: A survey of participants in the College of American Pathologists' Proficiency Testing Program. J Rheumatol. 2020;47:1768-1773 9. Van Hoovels L, Broeders S, Chan EKL, et al. Current laboratory and clinical practices in reporting and interpreting anti-nuclear antibody indirect immunofluorescence (ANA IIF) patterns: results of an international survey. Auto Immun Highlights. 2020;11:17 10. Tebo AE, Schmidt RL, Kadkhoda K, et al. The antinuclear antibody HEp-2 indirect immunofluorescence assay: a survey of laboratory performance, pattern recognition and interpretation. Auto Immun Highlights. 2021;12:14 11. Choi MY, Clarke AE, ST Pierre Y, et al. Antinuclear antibody-negative systemic lupus erythematosus in an international inception cohort. Arthritis Care Res. 2019;71:893-902 12. Nandjwada SL, Peterson LK, Mayes MD, et al. Ethnic differences in autoantibody diversity and hierarchy: More clues from a US cohort of patients with systemic sclerosis. J Rheumatol. 2016;43:1816-1824

ASO
80205

Antistrep-O Titer, Serum

Clinical Information: A number of bacterial antigens have been identified in cultures of group A streptococci. These extracellular products are primarily enzymatic proteins and include streptolysin O, streptokinase, hyaluronidase, deoxyribonucleases (DNases A, B, C, and D), and nicotinamide adenine nucleotidase. Infections by the group A streptococci are unique because they can be followed by serious nonpurulent complications of rheumatic fever and glomerulonephritis. Recent information suggests that rheumatic fever is associated with infection by certain rheumatogenic serotypes (M1, M3, M5, M6, M18, and M19), while glomerulonephritis follows infection by nephritogenic serotypes (M2, M12, M49, M57, M59, and M60). Glomerulonephritis and rheumatic fever occur following the infection, after a period of latency, during which the patient is asymptomatic. The latency period for glomerulonephritis is approximately 10 days, and the latency period for rheumatic fever is 20 days.

Useful For: Demonstration of acute or recent streptococcal infection

Interpretation: Elevated values are consistent with an antecedent infection by group A streptococci.

Reference Values:
<5 years: < or =70 IU/mL
5-17 years: < or =640 IU/mL
> or =18 years: < or =530 IU/mL

Clinical References: 1. Ayoub EM, Harden E. Immune response to streptococcal antigens: diagnostic methods. In: Rose NR, de Marco EC, Folds JD, et al, eds. Manual of Clinical and Laboratory Immunology. 5th ed. ASM Press; 1997 2. Antistreptolysin O (ASO). Testing.com; Updated July 24, 2020. Accessed March 18, 2025. Available at www.testing.com/tests/antistreptolysin-o-aso/

ATTF
9030

Antithrombin Activity, Plasma

Clinical Information: Antithrombin is a member of the serine protease inhibitor (serpin) superfamily. It is the principal plasma anticoagulant serpin mediating inactivation of serine protease procoagulant enzymes, chiefly thrombin and coagulation factors Xa and IXa.(1) Heparin and certain other naturally occurring glycosaminoglycans markedly enhance the anticoagulant activity of antithrombins (approximately 1000-fold) by providing a template to catalyze formation of covalently bonded, inactive complexes of serine protease and antithrombin that are subsequently cleared from circulation. Antithrombin is the mediator of anticoagulant activity of heparin. The antithrombin gene on chromosome 1 encodes a glycoprotein with a molecular weight of approximately 58,000 Da that is synthesized in the liver and is present in a relatively high plasma concentration (approximately 2.3 mcmol/L). The biological half-life of antithrombin is 2 to 3 days. Hereditary antithrombin deficiency, a relatively rare autosomal dominant disorder, produces a thrombotic diathesis (thrombophilia). Individuals with hereditary antithrombin deficiency are usually heterozygous with plasma antithrombin activity results of approximately 40% to 70%. These patients primarily manifest with venous thromboembolism (deep vein thrombosis and pulmonary embolism) with the potential of development as early as adolescence or younger adulthood. More than 100 different genetic alterations have been identified throughout the gene producing either the more common type I defects (low antithrombin activity and antigen) or the rarer type II defects (dysfunctional protein with low activity and normal antigen).(2) Homozygous antithrombin deficiency appears to be incompatible with life. The incidence of hereditary antithrombin deficiency is approximately 1:2000 to 1:3000 in general populations, although minor deficiency (antithrombin activity =70%-75%) may be more frequent (approximately 1:350-650). In populations with venous thrombophilia, approximately 1% to 2% of individuals have antithrombin deficiency. Among the recognized hereditary thrombophilic disorders (including deficiencies of proteins C and S, as well as activated protein C -resistance [factor V Leiden variant]), antithrombin deficiency may have the highest phenotypic penetrance (greater risk of venous thromboembolism). Arterial thrombosis (eg, stroke, myocardial infarction) has occasionally been reported in association with hereditary antithrombin deficiency. Hereditary deficiency of antithrombin activity can also occur because of defective glycosylation of this protein in individuals with carbohydrate-deficient glycoprotein syndromes (CDGS).(3) Antithrombin activity assessment may be useful as an adjunct in the diagnosis and management of CDGS. Acquired deficiency of antithrombin is much more common than hereditary deficiency. Acquired deficiency can occur due to: -Heparin therapy (catalysis of antithrombin consumption) -Intravascular coagulation and fibrinolysis, disseminated intravascular coagulation, or other consumptive coagulopathies -Liver disease (decreased synthesis and/or increased consumption) or with nephritic syndrome (urinary protein loss) -L-asparaginase chemotherapy (decreased synthesis) -Other conditions(1) In general, the clinical implications (thrombotic risk) of antithrombin deficiency in these disorders are not well defined, although antithrombin replacement in severe disseminated intravascular coagulation/intravascular coagulation and fibrinolysis is being evaluated.(4) Assay of antithrombin activity may be of diagnostic or prognostic value in some acquired deficiency states.

Useful For: Diagnosis of antithrombin deficiency, acquired or congenital Monitoring treatment of antithrombin deficiency disorders, including infusion of antithrombin therapeutic concentrate

Interpretation: Antithrombin deficiencies due to inherited causes are much less common than those due to acquired causes (see Clinical Information). Diagnosis of hereditary deficiency requires clinical correlation, with the prospect of repeat testing (including antithrombin antigen assay), and family studies (with appropriate counseling). DNA-based diagnostic testing may be helpful, see GNANT / Antithrombin Deficiency, SERPINC1 Gene, Next-Generation Sequencing, Varies. The clinical significance (thrombotic risk) of acquired antithrombin deficiency is not well established, but accumulating information suggests possible benefit of antithrombin replacement therapy in carefully selected situations.(4) Antithrombin deficiency, acquired or congenital, may contribute to the phenomenon of "heparin therapy resistance" (requirement of larger heparin doses than expected for achievement of therapeutic anticoagulation responses). However, it may more often have other pathophysiology, such as "acute-phase" elevation of coagulation factor VIII or plasma heparin-binding proteins. Increased antithrombin activity is of unknown hemostatic significance. Direct factor Xa inhibitors, rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) may falsely elevate the antithrombin activity and mask a diagnosis of antithrombin deficiency.

Reference Values:
Normal values: 80-130%
Normal, full-term newborn infants have lower levels (> or =35-40%) that reach normal values by age 90 days. Premature infants (30-36 weeks gestation) have lower levels that reach normal values by age 180 days.

Clinical References: 1. Lane DA, Olds RJ, Thein SL. Antithrombin and its deficiency. In: Bloom AL, Forbes CD, Thomas DP, eds. Haemostasis and Thrombosis. 3rd ed. Churchill Livingstone; 1994:655-670 2. Lane DA, Bayston T, Olds RJ, et al. Antithrombin mutation database: 2nd (1997) update. For the Plasma Coagulation Inhibitors Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haesmostasis. Thromb Haemost. 1997;77(1):197-211 3. Young G, Dricsoll MC. Coagulation abnormalities in the carbohydrate-deficient glycoprotein syndrome: case report and review of the literature. Am J Hematol. 1999;60(1):66-69. doi:10.1002/(sici)1096-8652(199901)60:1<66:aid-ajh11>3.0.co;2-d 4. Mammen EF. Antithrombin: its physiological importance and role in DIC. Semin Thromb Haemost. 1998;24(1):19-25. doi:10.1055/s-2007-995819 5. Yohe S, Olson J. Thrombophilia: Assays and Interpretation. In: Kottke-Marchant Wiley K, ed. Laboratory Hematology Practice. Blackwell Publishing; 2012:492-508 6. Favaloro EJ and Lippi G. eds. Hemostasis and Thrombosis: Methods and Protocols. 1st ed. Humana Press; 2017

AATTF
614506

Antithrombin Activity, with Reflex to Antithrombin Antigen, Plasma

Clinical Information: Antithrombin is a member of the serine protease inhibitor (serpin) superfamily. It is the principal plasma anticoagulant serpin mediating inactivation of serine protease procoagulant enzymes, chiefly thrombin and coagulation factors Xa and IXa.(1) Heparin and certain other naturally occurring glycosaminoglycans markedly enhance the anticoagulant activity of antithrombins (approximately 1000-fold) by providing a template to catalyze formation of covalently bonded, inactive complexes of serine protease and antithrombin that are subsequently cleared from circulation. Antithrombin is the mediator of anticoagulant activity of heparin. The antithrombin gene on chromosome 1 encodes a glycoprotein with a molecular weight of approximately 58,000 D, which is synthesized in the liver and is present in a relatively high plasma concentration (approximately 2.3 mcmol/L). The biological half-life of antithrombin is 2 to 3 days. Hereditary antithrombin deficiency, a relatively rare autosomal dominant disorder, produces a thrombotic diathesis (thrombophilia). Individuals with hereditary antithrombin deficiency are usually heterozygous with plasma antithrombin activity results of

approximately 40% to 70%. These patients primarily manifest with venous thromboembolism (deep vein thrombosis and pulmonary embolism) with the potential of development as early as adolescence or younger adulthood. More than 100 different alterations have been identified throughout the gene producing either the more common type I defects (low antithrombin activity and antigen) or the rarer type II defects (dysfunctional protein with low activity and normal antigen).(2) Homozygous antithrombin deficiency appears to be incompatible with life. The incidence of hereditary antithrombin deficiency is approximately 1:2000 to 1:3000 in general populations, although minor deficiency (antithrombin activity =70%-75%) may be more frequent (approximately 1:350-650). In populations with venous thrombophilia, approximately 1% to 2% of individuals have antithrombin deficiency. Among the recognized hereditary thrombophilic disorders (including deficiencies of proteins C and S, as well as activated protein C -resistance [factor V Leiden variant]), antithrombin deficiency may have the highest phenotypic penetrance (greater risk of venous thromboembolism). Arterial thrombosis (eg, stroke, myocardial infarction) has occasionally been reported in association with hereditary antithrombin deficiency. Hereditary deficiency of antithrombin activity can also occur because of defective glycosylation of this protein in individuals with carbohydrate-deficient glycoprotein syndromes (CDGS).(3) Antithrombin activity assessment may be useful as an adjunct in the diagnosis and management of CDGS. Acquired deficiency of antithrombin is much more common than hereditary deficiency. Acquired deficiency can occur due to: -Heparin therapy (catalysis of antithrombin consumption) -Intravascular coagulation and fibrinolysis (ICF), or disseminated intravascular coagulation (DIC), and other consumptive coagulopathies -Liver disease (decreased synthesis and/or increased consumption) or with nephritic syndrome (urinary protein loss) -L-asparaginase chemotherapy (decreased synthesis) -Other conditions(1) In general, the clinical implications (thrombotic risk) of antithrombin deficiency in these disorders are not well defined, although antithrombin replacement in severe disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) is being evaluated.(4) Assay of antithrombin activity may be of diagnostic or prognostic value in some acquired deficiency states.

Useful For: Diagnosis of antithrombin deficiency, acquired or congenital

Interpretation: Antithrombin deficiencies due to inherited causes are much less common than those due to acquired causes (see Clinical Information). Diagnosis of hereditary deficiency requires clinical correlation, with the prospect of repeat testing (including antithrombin antigen assay), and family studies (with appropriate counseling). DNA-based diagnostic testing may be helpful, see GNANT / Antithrombin Deficiency, SERPINC1 Gene, Next-Generation Sequencing, Varies. The clinical significance (thrombotic risk) of acquired antithrombin deficiency is not well established, but accumulating information suggests possible benefit of antithrombin replacement therapy in carefully selected situations.(4) Antithrombin deficiency, acquired or congenital, may contribute to the phenomenon of "heparin therapy resistance" (requirement of larger heparin doses than expected for achievement of therapeutic anticoagulation responses). However, it may more often have other pathophysiology, such as "acute-phase" elevation of coagulation factor VIII or plasma heparin-binding proteins. Increased antithrombin activity is of unknown hemostatic significance. Direct factor Xa inhibitors, rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) may falsely elevate the antithrombin activity and mask a diagnosis of antithrombin deficiency.

Reference Values:

Normal values:
80%-130%

Normal, full-term newborn infants have lower levels (> or =35%-40%) that reach normal values by 90 days of age. Premature infants (30-36 weeks gestation) have lower levels that reach normal values by 180 days of age.

Clinical References: 1. Lane DA, Olds RJ, Thein SL. Antithrombin and its deficiency. In: Bloom AL, Forbes CD, Thomas DP, eds. Haemostasis and Thrombosis. 3rd ed. Churchill Livingstone;

1994:655-670 2. Lane DA, Bayston T, Olds RJ, et al. Antithrombin mutation database: 2nd (1997) update. For the Plasma Coagulation Inhibitors Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haesmostasis. Thromb Haemost. 1997;77(1):197-211 3. Young G, Dricsoll MC. Coagulation abnormalities in the carbohydrate-deficient glycoprotein syndrome: case report and review of the literature. Am J Hematol. 1999;60(1):66-69. doi: 10.1002/(sici)1096-8652(199901)60:1<66:aid-ajh11>3.0.co;2-d 4. Mammen EF. Antithrombin: its physiological importance and role in DIC. Semin Thromb Haemost. 1998;24(1):19-25. doi: 10.1055/s-2007-995819 5. Yohe S, Olson J. Thrombophilia: Assays and Interpretation. In: Kottke-Marchant Wiley K, ed. Laboratory Hematology Practice. Blackwell Publishing; 2012:492-508 6. Van Cott EM, Orlando C, Moore GW, et al. Recommendations for clinical laboratory testing for antithrombin deficiency; Communication from the SSC of the ISTH. J Thromb Haemost. 2020;18(1):17-22. doi:10.1111/jth.14648

ATTI
9031

Antithrombin Antigen, Plasma

Clinical Information: Antithrombin is a member of the serine protease inhibitor (serpin) superfamily. It is the principal plasma anticoagulant serpin mediating inactivation of serine protease procoagulant enzymes, chiefly thrombin and coagulation factors Xa and IXa.(1) Heparin and certain other naturally occurring glycosaminoglycans markedly enhance antithrombin's anticoagulant activity (approximately 1000-fold) by providing a template to catalyze formation of covalently bonded, inactive complexes of serine protease and antithrombin that are subsequently cleared from circulation. Antithrombin is the mediator of heparin's anticoagulant activity. The antithrombin gene on chromosome 1 encodes a glycoprotein of approximately 58,000 Da that is synthesized in the liver and is present in a relatively high plasma concentration (approximately 2.3 mcmol/L). The biological half-life of antithrombin is 2 to 3 days. Hereditary antithrombin deficiency, a relatively rare, autosomal dominant disorder, produces a thrombotic diathesis (thrombophilia). Individuals with hereditary antithrombin deficiency are usually heterozygous with plasma antithrombin activity results of approximately 40% to 70%. These patients primarily manifest with venous thromboembolism (deep vein thrombosis and pulmonary embolism), with the potential of development as early as adolescence or younger adulthood. More than 100 different variants have been identified throughout the gene, producing either the more common type I defects (low antithrombin activity and antigen) or the rarer type II defects (dysfunctional protein with low activity and normal antigen).(2) Homozygous antithrombin deficiency appears to be incompatible with life. The incidence of hereditary antithrombin deficiency is approximately 1:2000 to 1:3000 in general populations, although minor deficiency (antithrombin activity =70% to 75%) may be more frequent (approximately 1:350 to 1:650). In populations with venous thrombophilia, approximately 1% to 2% have antithrombin deficiency. Among the recognized hereditary thrombophilic disorders (including deficiencies of proteins C and S, as well as activated protein C-resistance [factor V Leiden variant]), antithrombin deficiency may have the highest phenotypic penetrance (greater risk of venous thromboembolism). Arterial thrombosis (eg, stroke, myocardial infarction) has occasionally been reported in association with hereditary antithrombin deficiency. Hereditary deficiency of antithrombin activity can also occur because of defective glycosylation of this protein in individuals with carbohydrate-deficient glycoprotein syndromes (CDGS).(3) Antithrombin activity assessment may be useful as an adjunct in the diagnosis and management of CDGS. Acquired deficiency of antithrombin is much more common than hereditary deficiency. Acquired deficiency can occur due to: -Heparin therapy (catalysis of antithrombin consumption) -Intravascular coagulation and fibrinolysis (ICF) or disseminated intravascular coagulation (DIC), and other consumptive coagulopathies -Liver disease (decreased synthesis and/or increased consumption) -Nephrotic syndrome (urinary protein loss) -L-asparaginase chemotherapy (decreased synthesis) -Other conditions(1) In general, the clinical implications (thrombotic risk) of antithrombin deficiency in these disorders are not well defined, although antithrombin replacement in severe DIC/IFC is being evaluated.(4) Assay of antithrombin activity may be of diagnostic or prognostic value in some acquired deficiency states.

Useful For: Assessing abnormal results of the antithrombin activity assay (ATTF / Antithrombin

Activity, Plasma), the recommended primary (screening) antithrombin assay Diagnosing antithrombin deficiency, acquired or congenital, in conjunction with measurement of antithrombin activity An adjunct in the diagnosis and management of carbohydrate-deficient glycoprotein syndromes

Interpretation: Hereditary antithrombin deficiency is much less common than acquired deficiency. Diagnosis of hereditary deficiency requires clinical correlation, testing of both antithrombin activity and antithrombin antigen, and may be aided by repeated testing and by family studies. DNA-based diagnostic testing may be helpful but is generally not readily available. Acquired antithrombin deficiency may occur in association with a number of conditions (see Clinical Information). The clinical significance (thrombotic risk) of acquired antithrombin deficiency is not well established, but accumulating information suggests possible benefit of antithrombin replacement therapy in carefully selected situations.(4) Increased antithrombin activity has no definite clinical significance.

Reference Values:
Adults: 80-120%
Normal, full-term newborn infants may have decreased levels (> or =35-40%) that reach adult levels by 180 days postnatal.*
Healthy, premature infants (30-36 weeks gestation) may have decreased levels that reach adult levels by 180 days postnatal.*
*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing.

Clinical References: 1. Bock SC. Antithrombin III and heparin cofactor II. In: Colman RW, Hirsh J, Marder VJ, et al, eds. Hemostasis and Thrombosis. 4th ed. Lippencott Williams and Wilkins; 2001:321-333 2. Viazzer H. Hereditary and acquired antithrombin deficiency. Semin Thromb Hemost. 1999;25(3):257-263 3. Conrad J. Antithrombin activity and antigen. In: Laboratory Techniques in Thrombosis-A Manual. 2nd ed. Kluwer Academic Publishers; 1999:121-128 4. Lane DA, Bayston T, Olds RJ, et al. Antithrombin mutation database: 2nd (1997) update. For the Plasma Coagulation Inhibitors Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost. 1997;77(1):197-211 5. Van Cott EM, Orlando C, Moore GW, et al. Recommendations for clinical laboratory testing for antithrombin deficiency; Communication from the SSC of the ISTH. J Thromb Haemost. 2020;18(1):17-22

GNANT
619005

Antithrombin Deficiency, SERPINC1 Gene, Next-Generation Sequencing, Varies

Clinical Information: Antithrombin (AT) deficiency is a rare hereditary blood clotting disorder (thrombophilia) associated with germline variants in the SERPINC1 gene. It is inherited in an autosomal dominant manner with variable penetrance; both men and women may be affected. The prevalence varies widely, with estimates between 1 in 500 to 1 in 5000 individuals.(1-3) AT deficiency is characterized by defects in the concentration or function of AT, a natural anticoagulant in blood plasma. It leads to the highest risk of venous thromboembolism among the known inherited thrombophilias. In some cases, patients have resistance to heparin therapy. Affected women have a particularly elevated risk for pregnancy-related complications, including thromboembolic events during pregnancy and after delivery, as well as fetal loss.(4-7) Acquired (nongenetic) AT deficiency is more common than inherited AT deficiency and should be excluded prior to genetic testing. Causes of acquired AT deficiency include liver disease, acute thrombosis, heparin therapy, nephrotic syndrome, disseminated intravascular coagulation, and chemotherapeutic agents, such an L-asparaginase.(4,8) The British Society for Haematology provides guidelines regarding diagnosis, management, and laboratory testing for individuals with hereditary thrombophilias including AT deficiency.(9)

Useful For: Evaluating antithrombin AT deficiency in patients with a personal or family history

suggestive of this hereditary thrombophilia Confirming an AT deficiency diagnosis with the identification of a known or suspected disease-causing alteration in the SERPINC1 gene, particularly in patients with borderline low AT activity levels Determining the disease-causing alteration within the SERPINC1 gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of AT deficiency Prognosis and risk assessment based on the genotype-phenotype correlations Ascertaining the variant status of family members related to an individual with a confirmed SERPINC1 variant for the purposes of informing clinical management and genetic counseling Evaluating individuals with apparent heparin resistance This test is not intended for prenatal diagnosis.

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(10) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Tait RC, Walker ID, Perry DJ, et al: Prevalence of antithrombin deficiency in the healthy population. Br J Haematol. 1994 May;87(1):106-112 2. Wells PS, Blajchman MA, Henderson P, et al: Prevalence of antithrombin deficiency in healthy blood donors: a cross-sectional study. Am J Hematol. 1994 Apr;45(4):321-324 3. Thaler E, Lechner K: Antithrombin III deficiency and thromboembolism. Clin Haematol. 1981 Jun;10(2):369-390 4. Patnaik MM, Moll S. Inherited Antithrombin deficiency: a review. Haemophilia. 2008 Nov;14(6):1229-1239 5. Blajchamn MA, Austin RC, Fernandez-Rachubinski F, Sheffield WP: Molecular basis of inherited human antithrombin deficiency. Blood. 1992 Nov 1;80(9):2159-2171 6. Bauer KA, Nguyen-Cao TM, Spears JB: Issues in the diagnosis and management of hereditary antithrombin deficiency. Ann Pharmacother. 2016 Sep;50(9):758-767 7. Rogenhofer N, Bohlmann MK, Beuter-Winkler P, et al: Prevention, management and extent of adverse pregnancy outcomes in women with hereditary antithrombin deficiency. Ann Hematol. 2014 Mar;93(3):385-392 8. Corral J, de la Morena-Barrio ME, Vicente V: The genetics of antithrombin. Thromb Res. 2018 Sep;169:23-29 9. Arachchillage DJ, Mackillop L, Chandratheva A, et al: Thrombophilia testing: A British Society for Haematology guideline. Br J Haematol. 2022 Aug;198(3):443-458 10. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

AATTA
621379

Antithrombin Summary Interpretation

Clinical Information: Antithrombin is a member of the serine protease inhibitor (serpin) superfamily. It is the principal plasma anticoagulant serpin mediating inactivation of serine protease procoagulant enzymes, chiefly thrombin and coagulation factors Xa and IXa.(1) Heparin and certain other naturally occurring glycosaminoglycans markedly enhance the anticoagulant activity of antithrombins (approximately 1000-fold) by providing a template to catalyze formation of covalently bonded, inactive complexes of serine protease and antithrombin that are subsequently cleared from circulation. Antithrombin is the mediator of anticoagulant activity of heparin. The antithrombin gene on chromosome 1 encodes a glycoprotein with a molecular weight of approximately 58,000 D, which is synthesized in the liver and is present in a relatively high plasma concentration (approximately 2.3 mcmol/L). The biological half-life of antithrombin is 2 to 3 days. Hereditary antithrombin deficiency, a relatively rare autosomal dominant disorder, produces a thrombotic diathesis (thrombophilia). Individuals with hereditary antithrombin deficiency are usually heterozygous with plasma antithrombin activity results of approximately 40% to 70%. These patients primarily manifest with venous thromboembolism (deep vein thrombosis and pulmonary embolism) with the potential of development as early as adolescence or

younger adulthood. More than 100 different alterations have been identified throughout the gene producing either the more common type I defects (low antithrombin activity and antigen) or the rarer type II defects (dysfunctional protein with low activity and normal antigen).(2) Homozygous antithrombin deficiency appears to be incompatible with life. The incidence of hereditary antithrombin deficiency is approximately 1:2000 to 1:3000 in general populations, although minor deficiency (antithrombin activity =70%-75%) may be more frequent (approximately 1:350-650). In populations with venous thrombophilia, approximately 1% to 2% of individuals have antithrombin deficiency. Among the recognized hereditary thrombophilic disorders (including deficiencies of proteins C and S, as well as activated protein C-resistance [factor V Leiden variant]), antithrombin deficiency may have the highest phenotypic penetrance (greater risk of venous thromboembolism). Arterial thrombosis (eg, stroke, myocardial infarction) has occasionally been reported in association with hereditary antithrombin deficiency. Hereditary deficiency of antithrombin activity can also occur because of defective glycosylation of this protein in individuals with carbohydrate-deficient glycoprotein syndromes (CDGS).(3) Antithrombin activity assessment may be useful as an adjunct in the diagnosis and management of CDGS. Acquired deficiency of antithrombin is much more common than hereditary deficiency. Acquired deficiency can occur due to: -Heparin therapy (catalysis of antithrombin consumption) -Intravascular coagulation and fibrinolysis (ICF) or disseminated intravascular coagulation (DIC), and other consumptive coagulopathies -Liver disease (decreased synthesis and/or increased consumption) or with nephritic syndrome (urinary protein loss) -L-asparaginase chemotherapy (decreased synthesis) -Other conditions(1) In general, the clinical implications (thrombotic risk) of antithrombin deficiency in these disorders are not well defined, although antithrombin replacement in severe disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) is being evaluated.(4) Assay of antithrombin activity may be of diagnostic or prognostic value in some acquired deficiency states.

Useful For: Diagnosis of antithrombin deficiency, acquired or congenital Monitoring treatment of antithrombin deficiency disorders, including infusion of antithrombin therapeutic concentrate

Interpretation: Antithrombin deficiencies due to inherited causes are much less common than those due to acquired causes (see Clinical Information). Diagnosis of hereditary deficiency requires clinical correlation, with the prospect of repeat testing (including antithrombin antigen assay), and family studies (with appropriate counseling). DNA-based diagnostic testing may be helpful, see GNANT / Antithrombin Deficiency, SERPINC1 Gene, Next-Generation Sequencing, Varies. The clinical significance (thrombotic risk) of acquired antithrombin deficiency is not well established, but accumulating information suggests possible benefit of antithrombin replacement therapy in carefully selected situations.(4) Antithrombin deficiency, acquired or congenital, may contribute to the phenomenon of "heparin therapy resistance" (requirement of larger heparin doses than expected for achievement of therapeutic anticoagulation responses). However, it may more often have other pathophysiology, such as "acute-phase" elevation of coagulation factor VIII or plasma heparin-binding proteins. Increased antithrombin activity is of unknown hemostatic significance. Direct factor Xa inhibitors, rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) may falsely elevate the antithrombin activity and mask a diagnosis of antithrombin deficiency.

Reference Values:
Only orderable as a reflex. For more information see AATTF / Antithrombin Activity, with Reflex to Antithrombin Antigen, Plasma.

An interpretive report will be provided.

Clinical References: 1. Lane DA, Olds RJ, Thein SL. Antithrombin and its deficiency. In: Bloom AL, Forbes CD, Thomas DP, eds. Haemostasis and Thrombosis. 3rd ed. Churchill Livingstone; 1994:655-670 2. Lane DA, Bayston T, Olds RJ, et al. Antithrombin mutation database: 2nd (1997) update. For the Plasma Coagulation Inhibitors Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haesmostasis. Thromb Haemost.

1997;77(1):197-211 3. Young G, Dricsoll MC. Coagulation abnormalities in the carbohydrate-deficient glycoprotein syndrome: case report and review of the literature. Am J Hematol. 1999;60(1):66-69. doi:10.1002/(sici)1096-8652(199901)60:1<66::aid-ajh11>3.0.co;2-d 4. Mammen EF. Antithrombin: its physiological importance and role in DIC. Semin Thromb Haemost. 1998;24(1):19-25. doi:10.1055/s-2007-995819 5. Yohe S, Olson J. Thrombophilia: Assays and Interpretation. In: Kottke-Marchant Wiley K, ed. Laboratory Hematology Practice. Blackwell Publishing; 2012:492-508 6. Van Cott EM, Orlando C, Moore GW, et al. Recommendations for clinical laboratory testing for antithrombin deficiency; Communication from the SSC of the ISTH. J Thromb Haemost. 2020;18(1):17-22. doi:10.1111/jth.14648

APIXA
65848

Apixaban, Anti-Xa, Plasma

Clinical Information: Apixaban, an oral anticoagulant that directly inhibits factor Xa, has been approved by the US Food and Drug Administration for prophylaxis of thrombosis in atrial fibrillation and surgical patients and treatment of venous thromboembolism (VTE). Unlike warfarin, it does not require routine therapeutic monitoring. However, in selected clinical situations, measurement of drug level would be useful (eg, renal insufficiency, assessment of compliance, periprocedural measurement of drug concentration, suspected overdose, advanced age, and extremes of body weight). Table. Predicted Apixaban Steady-State Exposure Concentrations(1) Dosage Apixaban C-min (ng/mL) trough plasma concentration (predose) Apixaban C-max (ng/mL) peak plasma concentration (2-4 hours postdose) Prevention of VTE: elective hip or knee replacement surgery 2.5 mg twice daily 51 (23-109) 77 (41-146) Prevention of stroke and systemic embolism: NVAF 2.5 mg twice daily 79 (34-162) 123 (69-221) 5 mg twice daily 103 (41-230) 171 (91-321) Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTE) 2.5 mg twice daily 32 (11-90) 67 (30-153) 5 mg twice daily 63 (22-177) 132 (59-302) 10 mg twice daily 120 (41-335) 251 (111-572) Median (5th-95th percentile) Abbreviations not previously defined: Nonvalvular atrial fibrillation (NVAF) Deep vein thrombosis (DVT) Pulmonary embolism (PE)

Useful For: Measuring apixaban concentration in selected clinical situations (eg, renal insufficiency, assessment of compliance, periprocedural measurement of drug concentration, suspected overdose, advanced age, and extremes of body weight)

Interpretation: The lower limit of detection of this assay is 10 ng/mL. Therapeutic reference ranges have not been established. See Clinical Information for peak and trough drug concentrations observed from clinical trials.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Eliquis (apixaban). Package insert. Bristol-Meyers Squibb Company; Revised 11/2019 2. Hurst KV, O'Callaghan JM, Handa A. Quick reference guide to apixaban. Vasc Health Risk Manag. 2017;13:263-267 3. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patient with atrial fibrillation. N Engl J Med. 2011;365(11):981-992 4. Frost C, Nepal S, Wang J, et al. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. Br J Clin Pharmocol. 2013;76:(5):776-786 5. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799-808 6. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373(25):2413-2424 7. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost. 2016;14(6):1308-1313

FAPIX
75395

Apixaban, Plasma

Interpretation: In a study of 1691 patients taking apixaban, doses ranging from 2.5 mg twice a day to 20 mg once a day, apixaban plasma concentrations ranged from 1 to 933 ng/mL, with a median value of 105 ng/mL.

Reference Values:
Reporting limit determined each analysis.

Mean peak plasma concentrations of apixaban following a single oral administration of 5, 10, 25, or 50 mg oral tablets are as follows:

5 mg: 104.7 ng/mL (range, 79.7 to 129.7)
10 mg: 176.3 ng/mL (range, 134.3 to 218.3)
25 mg: 365.1 ng/mL (range, 348.1 to 382.1)
50 mg: 685.2 ng/mL (range, 663.2 to 707.2)

APOL1
605251

APOL1 Genotype, Varies

Clinical Information: The APOL1 gene encodes apolipoprotein L-1, a serum apolipoprotein bound to high-density lipoprotein (HDL) particles. Two alleles, commonly called G1 and G2, have been associated with increased risk for development or progression of nondiabetic chronic kidney diseases (CKD), including HIV-associated nephropathy (HIVAN) and focal segmental glomerulosclerosis (FSGS) with collapsing features.(1-4) The APOL1 (NM_001136540.1) G1 allele is a haplotype consisting of 2 missense variants: c.1024A>G (p.Ser342Gly) and c.1152T>G (p.Ile384Met). The G2 allele is comprised of a 6 base pair deletion that results in the deletion of 2 amino acids: c.1164_1169del (p.Asn388_Tyr389del). The G1 and G2 alleles are thought to be in complete linkage disequilibrium, meaning when both the G1 and G2 alleles are detected, they are on opposite chromosomes.(1) The risk for chronic kidney disease is only increased when 2 risk alleles are present (ie, genotypes G1/G1, G2/G2, or G1/G2), following an autosomal recessive pattern of inheritance.(1) Individuals with 2 risk alleles and nondiabetic CKD can be described as having APOL1-associated nephropathy. Individuals with one risk allele or no risk alleles do not appear to be at an increased risk for APOL1-associated nephropathy. The G1 and G2 risk alleles are enriched in individuals of African ancestry. Population studies show that in individuals of African descent, the G1 and G2 alleles occur at a frequency of 20% to 22.5% and 13% to 15%, respectively.(5-6) Importantly, it is estimated that 10% to 15% of individuals of African descent have 2 risk alleles.(5-6) The high frequency of the G1 and G2 alleles in this population is likely due to the protective effect these alleles confer against Trypanosoma brucei ganbiense and Trypanosoma brucei rhodesiense, which are parasites that causes trypanosomiasis, a disease endemic to Africa.(1) The G1 and G2 alleles are extremely rare or absent in individuals not of recent African descent (eg, European and Asian descent).(1,5) For this reason, increased risk associated with the G1 and G2 alleles has only been stratified in populations of recent African ancestry, and it remains unclear if similar risk effects associated with these APOL1 risk genotypes are applicable to individuals without African ancestry. Currently, there are no guidelines for clinical management of individuals with APOL1 risk genotypes and there are no specific treatments for APOL1-associated nephropathy.(7) However, several clinical trials are underway studying potential treatments.(8) Additionally, there currently is limited guidance on genetic testing strategies for APOL1 risk genotypes.(9) One consensus statement suggests APOL1 genotyping should be considered "in all patients of African ancestry with kidney disease and in any patient with kidney disease and a family member with a confirmed APOL1 high-risk genotype."(7) Evidence exists that the donor APOL1 genotype may impact both donor and recipient outcomes of kidney allografts. Previous studies have shown that donor kidneys from individuals with 2 risk alleles were more likely to fail after transplantation when compared to donor kidneys from individuals with one or no risk alleles.(10-11) Another study suggests that living donors with two risk alleles may be at an increased risk for reduced

kidney function following kidney donation.(12) Recent literature suggests that recipients with 2 APOL1 high risk alleles may have lower graft survival one year after transplantation; however, additional research is required.(13-14) A prospective, large scale study to assess kidney allograft survival from donors with recent African ancestry based on donor and recipient APOL1 genotypes is currently ongoing.(15) Based on presently available data, guidelines advise that an individual's APOL1 genotype alone should not determine eligibility for donation or receipt of kidney allografts.(16)

Useful For:

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

APOAB
607593

Apolipoprotein A1 and B, Serum

Clinical Information: Apolipoprotein B (ApoB) is the primary protein component of low-density lipoprotein (LDL). Apolipoprotein A1 (ApoA1) is the primary protein component of high-density lipoprotein (HDL). Elevated ApoB and decreased ApoA1 are associated with increased risk of cardiovascular disease. Multiple studies have reported that ApoB and ApoA1 are more strongly associated with cardiovascular disease than the corresponding lipoprotein cholesterol fraction (see APOA1 / Apolipoprotein A1, Serum and APOLB / Apolipoprotein B, Serum). ApoB is present in all atherogenic lipoproteins including LDL, Lp(a), intermediate-density lipoprotein (IDL), and very low-density lipoprotein (VLDL) remnants. ApoA1 is the nucleating protein around which HDL forms during reverse cholesterol transport. The ApoB:ApoA1 ratio represents the balance between atherogenic and antiatherogenic lipoproteins. Several large prospective studies have shown that the ApoB:ApoA1 ratio performs as well, and often better, than traditional lipids as an indicator of risk.(1-3)

Useful For: Assessment of cardiovascular risk Follow-up studies in individuals with basic lipid measures inconsistent with risk factors or clinical presentation Definitive studies of cardiac risk factors in individuals with significant family histories of coronary artery disease or other increased risk factors

Interpretation: Elevated apolipoprotein B (ApoB) confers increased risk of atherosclerotic cardiovascular disease, even in a context of acceptable LDL cholesterol concentrations. Extremely low values of ApoB (<48 mg/dL) are related to malabsorption of food lipids and can lead to polyneuropathy. Reduced apolipoprotein A1 (ApoA1) confers an increased risk of coronary artery disease. Extremely low ApoA1 (<20 mg/dL) is suggestive of liver disease or a genetic disorder. Elevated ApoB:ApoA1 ratio confers increased risk of atherosclerotic cardiovascular disease, independently of LDL and HDL cholesterol concentrations.

Reference Values:

Males Age	Apolipoprotein A (mg/dL)	Apolipoprotein B (mg/dL)	Apolipoprotein B/A1 ratio
	Not established	Not established	Not established
2-17 years	Low: 120	Acceptable: or =110	
>18 years	> or =120	Desirable: or =140	Lower Risk: 0.9

Females Age	Apolipoprotein A (mg/dL)	Apolipoprotein B (mg/dL)	Apolipoprotein B/A1 ratio
	Not established	Not established	Not established
2-17 years	Low: 120	Acceptable: or =110	
>18 years	> or =140	Desirable: or =140	Lower Risk: 0.8

Clinical References: 1. Reiner Z, Catapano AL, De Backer G, et al: ESC/EAS Guidelines for the management of dyslipidaemias: The task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011;32(14):1769-1818 2. McQueen MJ, Hawken S, Wang X, et al: Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. Lancet 2008;372:224-233 3. Thompson A, Danesh J: Associations between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease: a literature-based meta-analysis of prospective studies. J Intern Med 2006;259:481-492 4. Jacobson TA, Ito MK, Maki KC, et al: National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1-executive summary. J Clin Lipidol 2014 Sep-Oct;8(5):473-488 5. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011 Dec;128 Suppl 5:S213-S256

APOA1
607591

Apolipoprotein A1, Serum

Clinical Information: Apolipoprotein A1 (ApoA1) is the primary protein associated with high-density lipoprotein (HDL) particles, and plays a central role in reverse cholesterol transport.(1) HDL cholesterol (HDL-C) and ApoA1 concentrations are inversely related to the risk for coronary artery disease (CAD).(2) There are a variable number of ApoA1 proteins per HDL particle. Therefore, ApoA1 is not a 1:1 surrogate marker for HDL particles. Similarly, the number of ApoA1 proteins and the amount of cholesterol contained in HDL particles is highly variable. This heterogeneity has led to unique clinical findings related to ApoA1 compared with HDL-C. Increased ApoA1 concentrations are more strongly associated with a reduction in risk of a first myocardial infarction than HDL-C concentrations.(3) Low concentrations of ApoA1, but not HDL-C, are predictive of preclinical atherosclerosis as assed by computed tomography estimated coronary artery calcium (CAC) scoring.(4) Increased ApoA1, but not HDL-C concentrations, are associated with reduced cardiovascular events among statin-treated patients, even when LDL-C <50 mg/dL.(5) In statin-treated patients, patients whose ApoA1 increased while on treatment were at lower risk than those whose ApoA1 did not increase.

Useful For: Evaluating risk for atherosclerotic cardiovascular disease Aiding in the detection of Tangier disease

Interpretation: Low levels of apolipoprotein A1 (ApoA1) confer increased risk of atherosclerotic cardiovascular disease. ApoA1 below 25 mg/dL may aid in the detection of a genetic disorder such as Tangier disease. ApoA1 is often interpreted as a ratio with apolipoprotein B (ApoB).

Reference Values:

Males Age	Apolipoprotein A (mg/dL)
	Not established
2-17 years	Low: 120
>18 years	> or =120
Females Age	Apolipoprotein A (mg/dL)
	Not established
2-17 years	Low: 120
>18 years	> or =140

Clinical References: 1. Sorci-Thomas MG, Thomas MJ: Why Targeting HDL Should Work as a Therapeutic Tool, but Has Not. J Cardiovasc. Pharmacol 2013;62:239-246 2. Di Angelantonio E, Sarwar N, Perry P, et al: Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. JAMA 2009;302:1993-2000 3. McQueen MJ, Hawken S, Wang X, et al: Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case control study. Lancet 2008;372:224-233 4. Sung KC, Wild SH, Byrne CD: Controlling for apolipoprotein A-I concentrations changes the inverse direction of the relationship between high HDL-C concentration and a measure of pre-clinical atherosclerosis. Atherosclerosis 2013;231:181-186 5. Boekholdt SM, Arsenault BJ, Hovingh GK, et.al: Levels and Changes of HDL Cholesterol and Apolipoprotein A-I in Relation to Risk of Cardiovascular Events Among Statin-Treated Patients: A Meta-Analysis. Circulation 2013;128:1504-1512

APOLB
614544

Apolipoprotein B, Serum

Clinical Information: Apolipoprotein B (ApoB) is the primary protein component of low-density lipoprotein (LDL). LDL contains a variable amount of cholesterol, but each LDL contains exactly one ApoB protein. Therefore, ApoB is a more reliable indicator of circulating LDL compared to LDL cholesterol (LDL-C). ApoB has been demonstrated to perform equally with LDL particles measured by nuclear magnetic resonance spectroscopy.(1) ApoB is strongly associated with increased risk of developing cardiovascular disease (CVD) and often outperforms LDL-C at predicting risk of coronary heart disease.(2-4) Patients with acceptable non-high-density lipoprotein cholesterol (HDL-C) or LDL-C but elevated ApoB remain at higher risk of developing CVD; conversely, patients with acceptably low ApoB but moderate non-HDL-C or LDL-C elevations are at a reduced risk for CVD.(5,6) Finally, in 7 different placebo-controlled randomized clinical trials, on-statin reduction of ApoB was more closely related to CVD risk reduction than non-HDL-C or LDL-C.(7)

Useful For: Assessment of cardiovascular risk Follow-up studies in individuals with basic lipid measures inconsistent with risk factors or clinical presentation Definitive studies of cardiac risk factors in individuals with significant family histories of coronary artery disease or other increased risk factors Confirmation of suspected abetalipoproteinemia or hypobetalipoproteinemia

Interpretation: Elevated apolipoprotein B (ApoB) confers increased risk of coronary artery disease. ApoB can be used as a therapeutic target analogous to non-HDL-C and LDL-C. Extremely low values of ApoB (<48 mg/dL) are related to malabsorption of food lipids and can lead to polyneuropathy.

Reference Values:
Less than 2 years: Not established

2-17 years:
Acceptable: <90 mg/dL
Borderline high: 90-109 mg/dL
High: > or =110 mg/dL

Greater than 18 years:
Desirable: <90 mg/dL
Above Desirable: 90-99 mg/dL
Borderline high: 100-119 mg/dL
High: 120-139 mg/dL
Very high: > or =140 mg/dL

Clinical References: 1. Cole TG, Contois JH, Csako G, et al. Association of apolipoprotein B and nuclear magnetic resonance spectroscopy-derived LDL particle number with outcomes in 25 clinical studies: assessment by the AACC Lipoprotein and Vascular Diseases Division Working Group on best practices. Clin Chem. 2013;59(8):752-770 2. Sierra-Johnson J, Fisher RM, Romero-Corral A, et al. Concentration of apolipoprotein B is comparable with the apolipoprotein B/apolipoprotein A-I ratio and better than routine clinical lipid measurements in predicting coronary heart disease mortality: findings from a multi-ethnic US population. Eur Heart J. 2009;30(6):710-717 3. Steffen BT, Guan W, Remaley AT, et al. Use of lipoprotein particle measures for assessing coronary heart disease risk Post-American Heart Association / American College of Cardiology Guidelines: The Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol. 2015;35(2):448-454 4. Thompson A, Danesh J. Associations between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease: a literature-based meta-analysis of prospective studies. J Intern Med. 2006;259(5):481-492 5. Mora S, Buring JE, Ridker PM. Discordance of low-density lipoprotein (LDL) cholesterol with alternative LDL-related measures and future coronary events. Circulation. 2014;129(5):553-561 6. Pencina MJ, D'Agostino RB, Zdrojewski T, et al. Apolipoprotein B improves risk assessment of future coronary heart disease in the Framingham Heart Study beyond LDL-C and non-HDL-C. Eur J Prev Cardiol. 2015;22(10):1321-7. doi: 10.1177/2047487315569411 7. Thanassoulis G, Williams K, Ye K, et al. Relations of change in plasma levels of LDL-C, non-HDL-C and apoB with risk reduction from statin therapy: a meta-analysis of randomized trials. J Am Heart Assoc. 2014;3(2):e000759 8. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1-executive summary. J Clin Lipidol. 2014;8(5):473-488 9. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128 Suppl 5:S213-S256 10. Contois JH, McConnell JP, Sethi AA, et al. Apolipoprotein B and Cardiovascular Disease Risk: Position Statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. Clinical Chemistry. 2009:55:3:407-419

APOEG
35358

Apolipoprotein E Genotyping, Blood

Clinical Information:

Useful For: Determining the specific apolipoprotein E (APOE) genotypes in individuals with type III hyperlipoproteinemia Determining the specific APOE genotypes that may increase risk for amyloid related imaging abnormalities in individuals being treated for Alzheimer disease with B-amyloid-targeting antibodies APOE genotyping has been used to assess susceptibility for Alzheimer disease. However, the use of APOE analysis for predictive testing for Alzheimer disease is not currently recommended by the American College of Medical Genetics due to limited clinical utility and poor predictive value.

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Smelt AH, de Beer F. Apolipoprotein E and familial dysbetalipoproteinemia: Clinical, biochemical, and genetic aspects. Semin Vasc Med. 2004;4(3):249-257 2. Utermann G. Morgagni lecture: genetic polymorphism of apolipoprotein E-impact on plasma lipoprotein metabolism. In: Crepaldi G, Tiengo A, Baggio G, eds. Diabetes, Obesity and Hyperlipidemias 3: Proceedings of the 4th European Symposium on Metabolism. 1985. Elsevier; 1-28 3. Elosua R, Ordovas JM, Cupples LA, et al. Association of APOE genotype with carotid atherosclerosis in men and women: the Framingham Heart Study. J Lipid Res. 2004;45(10):1868-1875 4. Poirier J, Davignon J, Bouthillier D, et al. Apolipoprotein E polymorphism and Alzheimer's disease. Lancet. 1993;342(8873):697-699 5. Farrer L, Cupples A, Haines J, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. JAMA. 1997;278(16):1349-1356 6. Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. 2011;13(6):597-605 7. American College of Medical Genetics and Genomics: Five things physicians and patients should question. Choosing Wisely; 2015. Updated July 1, 2021. Accessed January 16, 2025. Available at www.choosingwisely.org/societies/american-college-of-medical-genetics-and-genomics/ 8. Filippi M, Cecchetti G, Spinelli EG, Vezzulli P, Falini A, Agosta F. Amyloid-Related Imaging Abnormalities and Beta-Amyloid-Targeting Antibodies: A Systematic Review. JAMA Neurol. 2022;79(3):291-304 9. LEQEMBI (lecanemab-irmb injection, for intravenous use). Package insert: Eisai Inc; Revised 07/2023. Available at www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s001lbl.pdf 10. KISUNLA (donanemab-azbt injection, for intravenous use). Package insert: Eli Lilly and Company; Revised 07/2024. Available at www.accessdata.fda.gov/drugsatfda_docs/label/2024/761248s000lbl.pdf 11. Kane M. Lecanemab Therapy and APOE Genotype. In: Pratt VM, Scott SA, Pirmohamed M, et al, eds. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012. Updated August 12, 2024. Accessed January 16, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK605938/ 12. Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2023;10(3):362-377. doi:10.14283/jpad.2023.30 13. Belloy ME, Andrews SJ, Le Guen Y, et al. APOE genotype and Alzheimer disease risk across age, sex, and population ancestry. JAMA Neurol. 2023;80(12):1284-1294. doi:10.1001/jamaneurol.2023.3599

FAPLG
57629

Apple IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

APPL
82712

Apple, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to apples Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

APR
82835

Apricot, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an

allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to apricots Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ARBOP
83267

Arbovirus Antibody Panel, IgG and IgM, Serum

Clinical Information: California (LaCrosse) Virus: California (LaCrosse) virus is a member of the Bunyaviridae family and is one of the arthropod-borne encephalitides. It is transmitted by various Aedes and Culex mosquitoes and is found in such intermediate hosts as the rabbit, squirrel, chipmunk, and field mouse. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children less than 15 years, usually from rural areas. The incubation period is estimated to be 7 days, and acute illness lasts 10 days or less in most instances. Typically, the first

symptoms are nonspecific, lasting 1 to 3 days, and are followed by the appearance of central nervous system (CNS) signs and symptoms such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those over 18 years. The most important sequela of California virus encephalitis is epilepsy, which occurs in about 10% of children; almost always in patients who have had seizures during the acute illness. A few patients (estimated 2%) have persistent paresis. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (no more than 2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas. Eastern Equine Encephalitis: Eastern equine encephalitis (EEE) is within the alphavirus group. It is a low prevalence cause of human disease in the eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when humans may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. CNS involvement is demonstrated in only a minority of infected individuals, it is more abrupt and more severe than with other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70%. St. Louis Encephalitis: Areas of outbreaks of St. Louis encephalitis (SLE) since 1933 have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence occurs in summer and early autumn. Disease onset is characterized by generalized malaise, fever, chills, headache, drowsiness, nausea, and sore throat or cough, followed in 1 to 4 days by meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Western Equine Encephalitis: The virus that causes Western equine encephalitis (WEE) is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. In infants and children, the onset may be more abrupt than for adults. WEE should be suspected in any case of febrile CNS disease from an endemic area. Infants are highly susceptible to CNS disease, with about 20% of cases under 1 year. There is an excess of males with WEE clinical encephalitis, averaging about twice the number of infections detected in females. After recovery from the acute disease, patients may require from several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at higher risk of permanent brain damage after recovery than adults.

Useful For: Aiding the diagnosis of arboviral encephalitis (California [LaCrosse], St. Louis, Eastern equine, and Western equine encephalitis)

Interpretation: In patients infected with these or related viruses, IgM class antibody is reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. A single serum specimen IgG of 1:10 or greater indicates exposure to the virus. A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicates recent infection. In the United States, it is unusual for any patient to show positive reactions to more than 1 of the arboviral antigens, although Western equine encephalitis and Eastern equine encephalitis antigens will show a noticeable cross-reactivity.

Reference Values:

CALIFORNIA VIRUS (La CROSSE) ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

EASTERN EQUINE ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

ST. LOUIS ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

WESTERN EQUINE ENCEPHALITIS
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

Clinical References: 1. Gonzalez-Scarano F, Nathanson N. Bunyaviruses. In: Fields BN, Knipe DM, eds. Fields Virology. Vol 1. 2nd ed. Raven Press; 1990:1195-1228 2. Donat JF, Rhodes KH, Groover RV, Smith TF. Etiology and outcome in 42 children with acute nonbacterial meningoencephalitis. Mayo Clin Proc. 1980;55(3):156-160 3. Tsai TF. Arboviruses. In: Murray PR, Baron EJ, Pfaller MA, et al, eds. Manual of Clinical Microbiology. 7th ed. American Society for Microbiology; 1999:1107-1124 4. Calisher CH. Medically important arboviruses of the United States and Canada. Clin Microbiol Rev. 1994;7(1):89-116 5. Dolin R. California encephalitis, hantavirus pulmonary syndrome, hantavirus hemorrhagic fever with renal syndrome, and bunyavirus hemorrhagic fevers. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2169-2176

ABOPC
83897

Arbovirus Antibody Panel, IgG and IgM, Spinal Fluid

Clinical Information: California (LaCrosse) Virus: California (LaCrosse) virus is a member of the Bunyaviridae family, and it is one of the arthropod-borne encephalitides. It is transmitted by various Aedes and Culex mosquitoes and is found in such intermediate hosts as rabbits, squirrels, chipmunks, and field mice. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children and adolescents younger than 15 years, usually from rural areas. The incubation period is estimated to be 7 days, and acute illness lasts 10 days or less in most instances. Typically, the first symptoms are nonspecific, lasting 1 to 3 days, and are followed by the appearance of central nervous system (CNS) signs and symptoms, such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those older than 18 years. The most important sequela of California virus encephalitis is epilepsy, which occurs in about 10% of children; almost always in patients who have had seizures during the acute illness. An estimated 2% of patients have persistent paresis. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas. Eastern Equine Encephalitis: Eastern equine encephalitis (EEE) is within the alphavirus group. It is a low-prevalence cause of human disease in the eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when humans may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. CNS involvement is demonstrated in only a minority of infected individuals and is more abrupt and more severe than with other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70%. St Louis Encephalitis: Areas or outbreaks of St Louis encephalitis since 1933 have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence occurs in summer and early autumn. Disease onset is characterized by generalized malaise, fever, chills, headache, drowsiness, nausea, and sore throat or

cough, followed in 1 to 4 days by meningeal and neurologic signs. The severity of illness increases with advancing age; persons older than 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Western Equine Encephalitis: The virus that causes Western equine encephalitis (WEE) is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. In infants and children, the onset may be more abrupt than for adults. WEE should be suspected in any case of febrile CNS disease from an endemic area. Infants are highly susceptible to CNS disease, with about 20% of cases in patients younger than 1 year. There is an excess of male patients with WEE clinical encephalitis, averaging about twice the number of infections detected in female patients. After recovery from the acute disease, patients may require from several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at a higher risk of permanent brain damage after recovery than adults.

Interpretation: Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system (CNS) infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

Reference Values:
CALIFORNIA VIRUS (La CROSSE) ENCEPHALITIS ANTIBODY
IgG: <1:1
IgM: <1:1
Reference values apply to all ages.

EASTERN EQUINE ENCEPHALITIS ANTIBODY
IgG: <1:1
IgM: <1:1
Reference values apply to all ages.

ST. LOUIS ENCEPHALITIS ANTIBODY
IgG: <1:1
IgM: <1:1
Reference values apply to all ages.

WESTERN EQUINE ENCEPHALITIS
IgG: <1:1
IgM: <1:1
Reference values apply to all ages.

Clinical References: Piantadosi A, Kanjilal S. Diagnostic approach for arboviral infections in the United States. J Clin Microbiol. 2020;58(12):e01926-19. doi:10.1128/JCM.01926-19

ARGIN
70359

Arginase-1 Immunostain, Technical Component Only

Clinical Information: Arginase-1 is a urea cycle metalloenzyme specifically expressed in hepatocytes. This protein serves as a marker in the identification and differentiation of hepatocellular

carcinoma within the context of an antibody panel.

Useful For: Identification and differentiation of hepatocellular carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Radwan NA, Ahmed NS. The diagnostic value of arginase-1 immunostaining in differentiating hepatocellular carcinoma from metastatic carcinoma and cholangiocarcinoma as compared to HepPar-1. Diagn Pathol. 2012;7:149 2. Timek DT, Shi J, Liu H, Lin F. Arginase-1, HepPar-1, and Glypican-3 are the most effective panel of markers in distinguishing hepatocellular carcinoma from metastatic tumor on fine-needle aspiration specimens. Am J Clin Pathol. 2012;138(2):203-210 3. Fujiwara M, Kwok S, Yano H, Pai RK. Arginase-1 is a more sensitive marker of hepatic differentiation than HepPar-1 and glypican-3 in fine-needle aspiration biopsies. Cancer Cytopathol. 2012;120(4):230-237 4. Yan BC, Gong C, Song J, et al. Arginase-1: a new immunohistochemical marker of hepatocytes and hepatocellular neoplasms. Am J Surg Pathol. 2010;34(8):1147-1154 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FARI
57112

Aripiprazole (Abilify)

Reference Values:
Units: ng/mL

Expected steady state plasma levels in patients receiving recommended daily dosages: 109.0 - 585.0 ng/mL

ARVGG
617127

Arrhythmogenic Cardiomyopathy Gene Panel, Varies

Clinical Information: The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by either inherited, genetic factors or by nongenetic (acquired) causes such as infection or inflammation.(1) When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Arrhythmogenic cardiomyopathy (ACM) is characterized by the presence of arrhythmogenic cardiac muscle in the absence of ischemic, hypertensive, or valvular cardiac disease. Arrhythmogenic right ventricular cardiomyopathy (ARVC), the most well-defined form of ACM, is characterized by breakdown of the myocardium and replacement of right ventricular muscle tissue with fibrofatty tissue, resulting in an increased risk of arrhythmia and sudden death. In some cases, there may also be left ventricular involvement. The prevalence of ARVC (genetic and acquired) is estimated to be 1 in 2000 to 1 in 5000 in the general population.(2) The clinical presentation of ACM can be variable, even within the same family. Overt symptoms such as palpitations, ventricular arrythmias, structural heart changes, and sudden cardiac arrest typically manifest in adulthood, but more subtle symptoms may be present in childhood.(2) Additionally, ACM may be apparently asymptomatic in some individuals, but can cause sudden, life-threatening arrhythmias, increasing the risk of sudden cardiac death.(1) Hereditary forms of ACM primarily follow an autosomal dominant pattern of inheritance. Rarely, ACM may be present as a feature of an autosomal recessive condition (eg, Naxos syndrome, Carvajal syndrome, or myofibrillar myopathy).(1) Cardiomyopathy in combination with

cardiac arrhythmia is also common in the X-linked condition Emery-Dreifuss muscular dystrophy.(3)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of a hereditary form of arrhythmogenic cardiomyopathy Establishing a diagnosis of a hereditary form of arrhythmogenic cardiomyopathy

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(4) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Towbin JA, McKenna WJ, Abrams DJ, et al: 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. Heart Rhythm. 2019 Nov;16(11):e301-e372. doi: 10.1016/j.hrthm.2019.05.007 2. Corrado D, Link MS, Calkins H: Arrhythmogenic right ventricular cardiomyopathy. N Engl J Med. 2017 Jan;376(1):61-72. doi: 10.1056/NEJMra1509267 3. Bonne G, Leturcq F, Ben Yaou R: Emery-Dreifuss Muscular Dystrophy. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated August 15, 2019. Accessed July 14, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1436/ 4. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

ASOU 608890 Arsenic Occupational Exposure, Random, Urine

Clinical Information: Arsenic (As) is a naturally occurring element that is widely distributed in the Earth's crust. Arsenic is classified chemically as a metalloid, having both metal and nonmetal properties. Elemental arsenic is a steel gray solid material. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As[3+]/As[III]) and arsenate (As[5+]/As[V]). Inorganic As(V) is readily reduced to inorganic As(III), which is then primarily broken down to the less toxic methylated metabolites monomethylarsonic acid and, subsequently, dimethylarsinic acid. In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate, and monosodium methylarsenate, are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are added to other metals to form metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, from fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be

introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days.

ASUOE
608895

Arsenic Occupational Exposure, with Reflex, Random, Urine

Useful For: Preferred screening test for detection of occupational exposure to arsenic in random urine specimens

Clinical Information: Arsenic (As) is a naturally occurring element that is widely distributed in the Earth's crust. Arsenic is classified chemically as a metalloid, having both metal and nonmetal properties. Elemental arsenic is a steel gray solid material. However, arsenic is usually found in the environment combined with other elements, such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As[3+]/As[III]) and arsenate (As[5+]/As[V]). Inorganic As(V) is readily reduced to inorganic As(III), which is then primarily broken down to the less toxic methylated metabolites, monomethylarsonic acid and, subsequently, dimethylarsinic acid. In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate, and monosodium methylarsenate, are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are added to other metals to form metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, from fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning, including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days.

Interpretation: Mayo Clinic uses the American Conference of Governmental Industrial Hygienists biological exposure index (BEI) as the reference value. The BEI is the sum of all the toxic species (inorganic arsenic plus methylated arsenic metabolites). Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total

arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is a toxic form (eg, inorganic and methylated arsenic forms) or a relatively nontoxic organic form (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, As[III] and As[V]) are found in the urine shortly after ingestion, whereas the less toxic methylated forms, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA), are the species that predominate longer than 24 hours after ingestion. In general, urinary As[III] and As[V] concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. This test can determine if a patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health.

Reference Values:

ARSENIC
Biological Exposure Indices (BEI): <35 mcg/L at end of work week

CREATININE
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are less than 18 years of age.

Clinical References: 1. Fillol CC, Dor F, Labat L, et al. Urinary arsenic concentrations and speciation in residents living in an area with naturally contaminated soils. Sci Total Environ. 20101;408(5):1190-1194 2. Caldwell KL, Jones RL, Verdon CP, Jarrett JM, Caudill SP, Osterloh JD. Levels of urinary total and speciated arsenic in the US population: National Health and Nutrition Examination Survey 2003-2004. J Expo Sci Environ Epidemiol. 2009;19(1):59-68 3. Agency for Toxic Substances and Disease Registry: Toxicological profile for arsenic. US Department of Health and Human Services; August 2007. Available at www.atsdr.cdc.gov/ToxProfiles/tp2.pdf 4. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44 5. Keil DE, Berger-Ritchie J, McMillin GA. Testing for toxic elements: A focus on arsenic, cadmium, lead, and mercury. Lab Med. 2011;42(12):735-742. doi:10.1309/LMYKGU05BEPE7IAW 6. Navas-Acien A, Francesconi KA, Silbergeld EK, Guallar E. Seafood intake and urine concentrations of total arsenic, dimethylarsinate and arsenobetaine in the US population. Environ Res. 2011;111(1):110-118 doi:10.1016/j.envres.2010.10.009 7. Tchounwou PB, Yedjou CG, Udensi UK, et al. State of the science review of the health effects of inorganic arsenic: Perspectives for future research. Environ Toxicol. 2019;34(2):188-202 doi:10.1002/tox.22673

SPASU
609383

Arsenic Speciation, 24 Hour, Urine

Clinical Information: Arsenic (As) exists in a number of different forms; some are toxic, while others are not. The toxic inorganic forms are arsenite (As[3+], As[III]) and arsenate (As[5+], As[V]), and their partially detoxified metabolites are monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). As(III) is more toxic than As(V), and both are more toxic than MMA and DMA. The biologic half-life of inorganic arsenic is 4 to 6 hours, while the biologic half-life of the methylated metabolites is 20 to 30 hours. Target organs of As(III)-induced effects are the heart, gastrointestinal tract, skin and other epithelial tissues, kidney, and nervous system. Inorganic arsenic is carcinogenic to humans. Symptoms of chronic poisoning, called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Nontoxic, organic forms of arsenic are present in many foods. Arsenobetaine and arsenocholine are the 2 most common forms of organic arsenic found in food. The most common foods that contain significant concentrations of organic arsenic are shellfish and other predators in the seafood chain (cod, haddock, etc). Some meats, such as meats from chickens that have been fed seafood remnants, may also contain the organic

forms of arsenic. Following ingestion of arsenobetaine and arsenocholine, these compounds undergo rapid kidney clearance to become concentrated in the urine. Organic arsenic is completely excreted within 1 to 2 days after ingestion, and there are no residual toxic metabolites. The biologic half-life of organic arsenic is 4 to 6 hours. For reporting purposes, the concentrations of the inorganic forms (As[III] and As[V]) along with the methylated forms (MMA and DMA) will be summed and reported together as 'inorganic' arsenic. This is consistent with how the biological exposure index reference range is reported.

Useful For: Diagnosing arsenic intoxication using 24-hour urine specimens

Reference Values:
TOXIC ARSENIC
<35 mcg/L
Reference values apply to all ages.

Arsenic Speciation Interpretive Information:
The toxic arsenic concentration represents the sum of the inorganic and methylated arsenic species. The reference value for toxic arsenic is <35 mcg/L. This value is based on the American Conference of Governmental Industrial Hygienists (ACGIH) Biological Exposure Index (BEI), which does not include the non-toxic organic arsenic.

Clinical References: 1. Caldwell KL, Jones RL, Verdon CP, Jarrett JM, Caudill SP, Osterloh JD. Levels of urinary total and speciated arsenic in the US population: National Health and Nutrition Examination Survey 2003-2004. J Expo Sci Environ Epidemiol. 2009;19(1):59-68. doi:10.1038/jes.2008.32 2. Agency for Toxic Substances and Disease Registry. Toxicological profile for arsenic. US Department of Health and Human Services. 2007. Available at www.atsdr.cdc.gov/ToxProfiles/tp2.pdf 3. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

SPAS
607691

Arsenic Speciation, Random, Urine

Clinical Information: Arsenic (As) exists in a number of different forms; some are toxic, while others are not. The toxic inorganic forms are arsenite (As[3+], As[III]) and arsenate (As[5+], As[V]), and their partially detoxified metabolites are monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). As(III) is more toxic than As(V) and both are more toxic than MMA and DMA. As(III) is more toxic than As(V), and both are more toxic than MMA and DMA. The biologic half-life of inorganic arsenic is 4 to 6 hours, while the biologic half-life of the methylated metabolites is 20 to 30 hours. Target organs of As(III)-induced effects are the heart, gastrointestinal tract, skin and other epithelial tissues, kidney, and nervous system. Inorganic arsenic is carcinogenic to humans. Symptoms of chronic poisoning, called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Nontoxic, organic forms of arsenic are present in many foods. Arsenobetaine and arsenocholine are the 2 most common forms of organic arsenic found in food. The most common foods that contain significant concentrations of organic arsenic are shellfish and other predators in the seafood chain (cod, haddock, etc). Some meats, such as meats from chickens that have been fed seafood remnants, may also contain the organic forms of arsenic. Following ingestion of arsenobetaine and arsenocholine, these compounds undergo rapid kidney clearance to become concentrated in the urine. Organic arsenic is completely excreted within 1 to 2 days after ingestion, and there are no residual toxic metabolites. The biologic half-life of organic arsenic is 4 to 6 hours. For reporting purposes, the concentrations of the inorganic forms (As[III] and As[V]) along with the methylated forms (MMA and DMA) will be summed and reported together as 'Inorganic' arsenic. This is consistent with how the biological exposure index reference range is reported.

Useful For: Diagnosing arsenic intoxication using random urine specimens

Interpretation: The quantitative reference range for fractionated arsenic applies only to the inorganic forms. Concentrations of 20 mcg inorganic arsenic per liter or higher are considered toxic. There is no limit to the normal range for the organic forms of arsenic since they are not considered toxic and are normally present after consumption of certain food types. For example, a typical finding in a urine specimen with total 24-hour excretion of arsenic of 350 mcg/24 hr would be that more than 95% is present as the organic species from a dietary source, and less than 5% is present as the inorganic species. This would be interpreted as indicating the elevated total arsenic was due to ingestion of the nontoxic form of arsenic, usually found in seafood. A normal value for blood arsenic does not exclude a finding of elevated urine inorganic arsenic, due to the very short half-life of blood arsenic.

Reference Values:
TOXIC ARSENIC
<35 mcg/L
Reference values apply to all ages.

Arsenic Speciation Interpretive Information:
The toxic arsenic concentration represents the sum of the inorganic and methylated arsenic species. The reference value for toxic arsenic is <35 mcg/L. This value is based on the ACGIH Biological Exposure Index (BEI), which does not include the nontoxic organic arsenic.

Clinical References: 1. Caldwell KL, Jones RL, Verdon CP, Jarrett JM, Caudill SP, Osterloh JD. Levels of urinary total and speciated arsenic in the US population: National Health and Nutrition Examination Survey 2003-2004. J Expo Sci Environ Epidemiol. 2009;19(1):59-68. doi:10.1038/jes.2008.32 2. Agency for Toxic Substances and Disease Registry. Toxicological profile for arsenic. US Department of Health and Human Services. 2007. Available at www.atsdr.cdc.gov/ToxProfiles/tp2.pdf 3. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

ASU24
48537

Arsenic with Reflex, 24 Hour, Urine

Clinical Information: Arsenic (As) is a naturally occurring element that is widely distributed in the Earth's crust. Arsenic is classified chemically as a metalloid, having both metal and nonmetal properties. Elemental arsenic is a steel gray solid material. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As[3+]/As[III]) and arsenate (As[5+]/As[V]). Inorganic As(V) is readily reduced to inorganic As(III), which is then primarily broken down to the less toxic methylated metabolites monomethylarsonic acid and, subsequently, dimethylarsinic acid. In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate, and monosodium methylarsenate, are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are added to other metals to form metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the

greatest amounts of arsenic, for fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning, including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days.

Useful For: Preferred screening test for detection of arsenic exposure using 24-hour urine specimens

Interpretation: Physiologically, arsenic exists in toxic and nontoxic forms. The total arsenic concentration reflects all arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is a toxic form (eg, inorganic and methylated forms) or a relatively nontoxic organic form (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, As[III] and As[V]) are found in the urine shortly after ingestion, whereas the less toxic methylated forms (monomethylarsonic acid [MMA], dimethylarsinic acid [DMA]) are the species that predominate longer than 24 hours after ingestion. In general, urinary As(III) and As(V) concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. After a seafood meal (seafood generally contains the nontoxic, organic form of arsenic (eg, arsenobetaine), the urine output of arsenic may increase to over 300 mcg/24 h, after which it will decline. This test can determine if the patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health.

Reference Values:
0-17 years: Not established
> or =18 years: <35 mcg/24 h

Clinical References: 1. Fillol CC, Dor F, Labat L, et al. Urinary arsenic concentrations and speciation in residents living in an area with naturally contaminated soils. Sci Total Environ. 2010;408(5):1190-1194 2. Caldwell K, Jones R, Verdon C, et al. Levels of urinary total and speciated arsenic in the US population: National Health and Nutrition Examination Survey 2003-2004. J Expo Sci Environ Epidemiol. 2009;19(1):59-68 3. Agency for Toxic Substances and Disease Registry: Toxicological profile for arsenic. US Department of Health and Human Services. Updated August 2007. Accessed December 26, 2024. Available at www.atsdr.cdc.gov/ToxProfiles/tp2.pdf 4. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44 5. Keil DE, Berger-Ritchie J, McMillin GA. Testing for toxic elements: A focus on arsenic, cadmium, lead, and mercury. Lab Med. 2011;42(12):735-742 6. Navas-Acien A, Francesconi KA, Silbergeld EK, Guallar E. Seafood intake and urine concentrations of total arsenic, dimethylarsinate and arsenobetaine in the US population. Environ Res. 2011;111(1):110-8. doi:10.1016/j.envres.2010.10.009 7. Tchounwou PB, Yedjou CG, Udensi UK, et al. State of the science review of the health effects of inorganic arsenic: Perspectives for future research. Environ Toxicol. 2019;34(2):188-202. doi:10.1002/tox.22673

ASB
8645

Arsenic, Blood

Clinical Information: Arsenic (As) exists in a number of toxic and nontoxic forms. The toxic forms are the inorganic species As(5+), also denoted as As(V), the more toxic As(3+), also known as As(III), and their partially detoxified metabolites, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). Detoxification occurs in the liver as As(3+) is oxidized to As(5+) and then methylated to MMA and DMA. As a result of these detoxification steps, As(3+) and As(5+) are found in the urine shortly after ingestion, whereas MMA and DMA are the species that predominate more than 24 hours after ingestion. Blood concentrations of arsenic are elevated for a short time after exposure, after which arsenic rapidly disappears into tissues because of its affinity for tissue proteins. The body treats arsenic like phosphate, incorporating it wherever phosphate would be incorporated. Arsenic "disappears" into the normal body pool of phosphate and is excreted at the same rate as phosphate (excretion half-life of 12 days). The half-life of inorganic arsenic in blood is 4 to 6 hours, and the half-life of the methylated metabolites is 20 to 30 hours. Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure but will only be detected immediately after exposure. Arsenic is not likely to be detected in blood specimens drawn more than 2 days after exposure because it has become integrated into nonvascular tissues. Consequently, blood is not a good specimen to screen for arsenic, although periodic blood levels can be determined to follow the effectiveness of therapy. Urine is the preferred specimen for assessment of arsenic exposure. A wide range of signs and symptoms may be seen in acute arsenic poisoning, including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic (abdominal pain), diarrhea, and paresthesias of the hands and feet can occur.

Useful For: Detecting acute or very recent arsenic exposure Monitoring the effectiveness of therapy This test is not useful for evaluation of chronic arsenic exposure.

Interpretation: Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure. Absorbed arsenic is rapidly distributed into tissue storage sites with a blood half-life of less than 6 hours. Unless a blood specimen is drawn within 2 days of exposure, arsenic is not likely to be detected in a blood specimen.

Reference Values:
<13 ng/mL
Reference values apply to all ages.

Clinical References: 1. Hall M, Chen Y, Ahsan H, et al. Blood arsenic as a biomarker of arsenic exposure: results from a prospective study. Toxicology. 2006;225(2-3):225-233 2. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

ASHA
8651

Arsenic, Hair

Clinical Information: Arsenic circulating in the blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in hair is higher than in other tissues. Arsenic binds to keratin at the time of exposure, "trapping" the arsenic in hair. Therefore, hair analysis for arsenic is not only used to document that an exposure occurred, but when it occurred. Hair collected from the nape of the neck can be used to document recent exposure. Axillary or pubic hair is used to document long-term (6 months-1 year) exposure.

Useful For: Detection of nonacute arsenic exposure in hair specimens

Interpretation: Hair grows at a rate of approximately 0.5 inch/month. Hair keratin synthesized today will protrude through the skin in approximately 1 week. Thus, a hair specimen collected at the skin level represents exposure of 1 week ago, 1 inch distally from the skin represents exposure 2 months ago, etc. Hair arsenic levels above 1.00 mcg/g dry weight may indicate excessive exposure. It is normal for some arsenic to be present in hair, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure, which was the cause of death.

Reference Values:
0-15 years: Not established
> or =16 years: <1.0 mcg/g of hair

Clinical References: 1. Sthiannopkao S, Kim K-W, Cho KH, et al. Arsenic levels in human hair, Kandal Province, Cambodia: The influences of groundwater arsenic, consumption period, age and gender. Applied Geochemistry 2010;25:81-90 2. Pearse DC, Dowling K, Gerson AR, et al. Arsenic microdistribution and speciation in toenail clippings of children living in a historic gold mining area. Sci Total Environ 2010;408:2590-2599 3. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

ASNA
89848

Arsenic, Nails

Clinical Information: Arsenic circulating in the blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in nails is higher than in other tissues. Several weeks after exposure, transverse white striae, called Mees' lines, may appear in the fingernails.

Useful For: Detection of nonacute arsenic exposure in nail specimens

Interpretation: Nails grow at a rate of approximately 0.1 inch/month. Nail keratin synthesized today will grow to the distal end in approximately 6 months. Thus, a nail specimen collected at the distal end represents exposure of 6 months ago. Nail arsenic above 1.0 mcg/g dry weight may indicate excessive exposure. It is normal for some arsenic to be present in nails, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair or nail arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure, which was the cause of death.

Reference Values:
0-15 years: Not established
> or =16 years: <1.0 mcg/g of nails

Clinical References: 1.Hindmarsh JT, McCurdy RF. Clinical and environmental aspects of arsenic toxicity. Crit Rev Clin Lab Sci 1986;23(4):315-347 2.Strathmann FG, Blum LM: Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

ASCU
608900

Arsenic/Creatinine Ratio, Urine

Clinical Information: Arsenic (As) is a naturally occurring element that is widely distributed in the Earth's crust. Arsenic is classified chemically as a metalloid, having both metal and nonmetal properties. Elemental arsenic is a steel gray solid material. However, arsenic is usually found in the environment combined with other elements, such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As[3+]/AsIII) and arsenate (As[5+]/As[V]). Inorganic As(V) is readily reduced to inorganic As(III), which is then primarily broken down to the less toxic methylated metabolites, monomethylarsonic acid (MMA) and, subsequently, dimethylarsinic acid (DMA). In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate, and monosodium methylarsenate, are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are added to other metals to form metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, from fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning, including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days.

Useful For: Screening for arsenic exposure using random urine specimens

Interpretation: Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is the toxic forms (eg, inorganic and methylated forms) or the relatively nontoxic organic forms (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, As[III] and As[V]) are found in the urine shortly after ingestion, whereas the less toxic methylated forms monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA), are the species that predominate longer than 24 hours after ingestion. In general, urinary As[III] and As[V] concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. This test can determine if a patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health.

Reference Values:
Only orderable as part of profile. For more information see:
-ASUCR / Arsenic/Creatinine Ratio, with Reflex, Random, Urine

-HMUCR / Heavy Metal/Creatinine Ratio, with Reflex, Random, Urine

0-17 years: Not established
> or =18 years: <24 mcg/g creatinine

Clinical References: 1. Fillol CC, Dor F, Labat L, et al. Urinary arsenic concentrations and speciation in residents living in an area with naturally contaminated soils. Sci Total Environ. 2010;408(5):1190-1194. doi:10.1016/j.scitotenv.2009.11.046 2. Caldwell KL, Jones RL, Verdon CP, Jarrett JM, Caudill SP, Osterloh JD: Levels of urinary total and speciated arsenic in the US population: National Health and Nutrition Examination Survey 2003-2004. J Expo Sci Environ Epidemiol. 2009;19(1):59-68. doi:10.1038/jes.2008.32 3. Agency for Toxic Substances and Disease Registry: Toxicological profile for arsenic. US Department of Health and Human Services; 2007. Available at www.atsdr.cdc.gov/ToxProfiles/tp2.pdf 4. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44 5. Keil DE, Berger-Ritchie J, McMillin GA. Testing for toxic elements: A focus on arsenic, cadmium, lead, and mercury. Lab Med. 2011; 42(12):735-742. doi:10.1309/LMYKGU05BEPE7IAW 6. Navas-Acien A, Francesconi KA, Silbergeld EK, Guallar E. Seafood intake and urine concentrations of total arsenic, dimethylarsinate and arsenobetaine in the US population. Environ Res. 2011;111(1):110-118. doi:10.1016/j.envres.2010.10.009 7. Tchounwou PB, Yedjou CG, Udensi UK, et al. State of the science review of the health effects of inorganic arsenic: Perspectives for future research. Environ Toxicol. 2019;34(2):188-202. doi:10.1002/tox.22673

ASUCR
608905

Arsenic/Creatinine, Ratio, with Reflex, Random, Urine

Clinical Information: Arsenic (As) is a naturally occurring element that is widely distributed in the Earth's crust. Arsenic is classified chemically as a metalloid, having both metal and nonmetal properties. Elemental arsenic is a steel gray solid material. However, arsenic is usually found in the environment combined with other elements, such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As[3+]/As[III]) and arsenate (As[5+]/As[V]). Inorganic As(V) is readily reduced to inorganic As(III), which is then primarily broken down to the less toxic methylated metabolites, monomethylarsonic acid and, subsequently, dimethylarsinic acid. In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate, and monosodium methylarsenate are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are added to other metals to form metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, from fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal

tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days.

Useful For: Preferred screening test for detection of arsenic exposure using random urine specimens

Interpretation: Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is a toxic form (eg, inorganic and methylated forms) or a relatively nontoxic organic form (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, As[III] and As[V]) are found in the urine shortly after ingestion, whereas the less toxic methylated forms, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) are the species that predominate longer than 24 hours after ingestion. In general, urinary As(III) and As(V) concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. This test can determine if a patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health.

Reference Values:
ARSENIC/CREATININE:
0-17 years: Not established
> or =18 years: <24 mcg/g creatinine

CREATININE:
> or =18 years: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Fillol CC, Dor F, Labat L, et al. Urinary arsenic concentrations and speciation in residents living in an area with naturally contaminated soils. Sci Total Environ. 20101;408(5):1190-1194 2. Caldwell KL, Jones RL, Verdon CP, Jarrett JM, Caudill SP, Osterloh JD. Levels of urinary total and speciated arsenic in the US population: National Health and Nutrition Examination Survey 2003-2004. J Expo Sci Environ Epidemiol. 2009;19(1):59-68 3. Agency for Toxic Substances and Disease Registry: Toxicological profile for arsenic. US Department of Health and Human Services. August 2007. Available at www.atsdr.cdc.gov/ToxProfiles/tp2.pdf 4. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44 5. Keil DE, Berger-Ritchie J, McMillin GA. Testing for toxic elements: A focus on arsenic, cadmium, lead, and mercury. Lab Med. 2011;42(12):735-742. doi:10.1309/LMYKGU05BEPE7IAW 6. Navas-Acien A, Francesconi KA, Silbergeld EK, Guallar E. Seafood intake and urine concentrations of total arsenic, dimethylarsinate and arsenobetaine in the US population. Environ Res. 2011;111(1):110-118 doi:10.1016/j.envres.2010.10.009 7. Tchounwou PB, Yedjou CG, Udensi UK, et al. State of the science review of the health effects of inorganic arsenic: Perspectives for future research. Environ Toxicol. 2019;34(2):188-202 doi:10.1002/tox.22673

FART
57913

Artichoke (Cynara scolymus) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong

Positive

Reference Values:
<0.35 kU/L

ARSU
8777

Arylsulfatase A, 24 Hour, Urine

Clinical Information: Metachromatic leukodystrophy (MLD) is a lysosomal storage disorder caused by a deficiency of the arylsulfatase A (ARSA) enzyme, which leads to the accumulation of sulfatides (both galactosyl and lactosyl sulfatide) in the white matter of the central nervous system, the peripheral nervous system, and to a lesser extent, in visceral organs including the kidney and gallbladder. Cells that produce myelin are especially affected causing the characteristic leukodystrophy seen in MLD. Patients with MLD excrete excessive amounts of sulfatides in their urine. The 3 clinical forms of MLD are late-infantile, juvenile, and adult, depending on age of onset. All forms result in progressive neurologic changes and leukodystrophy demonstrated on magnetic resonance imaging. Late-infantile MLD is the most common (50%-60% of cases) and usually presents before 30 months of age with hypotonia, clumsiness, diminished reflexes, and slurred speech. Progressive neurodegeneration occurs and, unless successfully treated, most patients do not survive past childhood. Juvenile MLD (20%-30% of cases) is characterized by onset between 30 months to 16 years. Presenting features are behavior problems, declining school performance, clumsiness, and slurred speech. Neurodegeneration occurs at a somewhat slower and more variable rate than the late-infantile form. Adult MLD (15%-20% of cases) has an onset after puberty and can be as late as the fourth or fifth decade. Presenting features are often behavior and personality changes, including psychiatric symptoms. Clumsiness, neurologic symptoms, and seizures are also common. The disease course has variable progression and may occur over 2 to 3 decades. Metachromatic leukodystrophy is an autosomal recessive disorder caused by disease-causing variants in the ARSA gene. This disorder is distinct from conditions caused by deficiencies of arylsulfatase B (Maroteaux-Lamy disease) and arylsulfatase C (steroid sulfatase deficiency). Saposin B deficiency is a rare autosomal recessive disorder with symptoms that mimic MLD; however, the ARSA enzyme level is normal. Like MLD, patients with saposin B deficiency can also excrete excessive amounts of sulfatides in their urine. Individuals with multiple sulfatase deficiency, which is clinically distinct from MLD, will also have deficiency of arylsulfatase A, however, other sulfatase enzymes will also be deficient. Individuals with "pseudodeficiency" of ARSA have very low levels of ARSA activity but are otherwise healthy. Pseudodeficiency has been found among patients with other unrelated neurologic conditions as well as among the general population, therefore a diagnosis of MLD cannot be based upon reduced ARSA activity alone. To confirm a diagnosis, additional studies such as molecular genetic testing of ARSA (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-WHFH2K), urinary excretion of sulfatides (CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine), or, less commonly, histological analysis for metachromatic lipid deposits in nervous system tissue are recommended. Current treatment options for MLD depend on the clinical stage and presence of neurologic symptoms. Early diagnosis is extremely important to improve clinical outcomes. Allogenic hematopoietic stem cell transplant (HSCT) can treat symptoms related to the central nervous system in pre- and very early-symptomatic juvenile- or adult-onset MLD. Recently, autologous hematopoietic stem cell-based gene therapy has been approved in the United States and elsewhere for individuals with presymptomatic late-infantile MLD, presymptomatic juvenile MLD, or early-symptomatic juvenile MLD with maintained ability to walk and before the onset of cognitive decline.

Useful For: Detection of arylsulfatase A deficiency using urine specimens This test is not suitable for carrier detection.

Interpretation: Reduced levels of arylsulfatase A are seen in patients with metachromatic leukodystrophy (MLD). Individuals with pseudodeficiency of arylsulfatase A can have results in the affected range but are otherwise unaffected with MLD. Abnormal results should be confirmed using

CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine. If molecular confirmation is desired, consider molecular genetic testing of ARSA (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-WHFH2K).

Reference Values:

> or =19 nmol/h/mL

Note: Results from this assay may not reflect carrier status because of individual variation of arylsulfatase A enzyme levels. Low normal values may be due to the presence of pseudodeficiency or carrier alleles. Patients with these depressed levels may be phenotypically normal.

Clinical References: 1. Gieselmann V, Ingeborg KM: Metachromatic leukodystrophy. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed June 9, 2025. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225546629 2. Gomez-Ospina N. Arylsulfatase A deficiency. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews[Internet]. University of Washington, Seattle; 2006.Updated April 25, 2024. Accessed June 9, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1130/ 3. Fumagalli F, Zambon AA, Rancoita PMV, et al. Metachromatic leukodystrophy: A single-center longitudinal study of 45 patients. J Inherit Metab Dis. 2021;44(5):1151-1164. doi:10.1002/jimd.12388 4. Laugwitz L, Mechtler TP, Janzen N, et al. Newborn screening and presymptomatic treatment of metachromatic leukodystrophy. N Engl J Med. 2024; 391(13): 1256-1258. doi:10.1056/NEJMc2407165

ARSAB
623012

Arylsulfatase A, Blood Spot

Clinical Information: Metachromatic leukodystrophy (MLD) is a lysosomal disorder caused by a deficiency of the enzyme arylsulfatase A (ARSA), which leads to the accumulation of sulfatides (both galactosyl and lactosyl sulfatide) in the white matter of the central nervous system, the peripheral nervous system, and, to a lesser extent, in visceral organs including the kidney and gallbladder. Cells that produce myelin are especially affected causing the characteristic leukodystrophy seen in MLD. Patients with MLD excrete excessive amounts of sulfatides in their urine. The 3 clinical forms of MLD are late-infantile, juvenile, and adult, depending on age of onset. All forms result in progressive neurologic changes and leukodystrophy demonstrated on magnetic resonance imaging. To date, late-infantile MLD is most commonly diagnosed (50%-60% of cases) and usually presents before 30 months of age with hypotonia, clumsiness, diminished reflexes, and dysarthric speech. Progressive neurodegeneration occurs and, unless successfully treated, most patients do not survive past childhood. Juvenile MLD (20%-30% of cases) is characterized by onset between 30 months to 16 years old. Presenting features are behavior problems, declining school performance, clumsiness, and slurred speech. Neurodegeneration occurs at a somewhat slower and more variable rate than the late-infantile form. Adult MLD (15%-20% of cases) has an onset after puberty and can be as late as the fourth or fifth decade. Presenting features are often behavior and personality changes, including psychiatric symptoms. Clumsiness, neurologic symptoms, and seizures are also common. The disease course has variable progression and may occur over 2 to 3 decades. Metachromatic leukodystrophy is an autosomal recessive disorder caused by disease-causing variants in the ARSA gene. This disorder is distinct from conditions caused by deficiencies of arylsulfatase B (Maroteaux-Lamy disease) and arylsulfatase C (steroid sulfatase deficiency). Saposin B deficiency is a rare autosomal recessive disorder with symptoms that mimic MLD; however, ARSA activity is not deficient. Like MLD, patients with saposin B deficiency can excrete excessive amounts of sulfatides in their urine. Individuals with multiple sulfatase deficiency, which is clinically distinct from MLD, will also have deficiency of ARSA, however, other sulfatase enzymes will also be deficient. Individuals with "pseudodeficiency" of ARSA have very low levels of ARSA activity but are otherwise healthy. Pseudodeficiency has been found among patients with other unrelated neurologic conditions as well as among the general population, therefore a diagnosis of MLD cannot be based upon reduced ARSA activity alone. To confirm a diagnosis, additional studies, such as molecular genetic testing of ARSA (CGPH / Custom Gene Panel,

Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-WHFH2K), urinary excretion of sulfatides (CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine), and/or histological analysis for metachromatic lipid deposits in nervous system tissue are recommended. While sulfatides appear to be elevated in newborn dried blood spots and is used as a primary newborn screening test, the utility of sulfatide analysis in dried blood spots outside of newborn screening has not been determined. Current treatment options for MLD depend on the clinical stage and presence of neurologic symptoms. Allogenic hematopoietic stem cell transplant can treat symptoms related to the central nervous system in pre- and very early-symptomatic juvenile- or adult-onset MLD. Recently, autologous hematopoietic stem cell-based gene therapy has been approved in the U.S. and elsewhere for individuals with presymptomatic late-infantile MLD, presymptomatic juvenile MLD, or early-symptomatic juvenile MLD with maintained ability to walk and before the onset of cognitive decline. Early diagnosis is extremely important to achieve optimal outcomes, especially for patients with late-infantile and early juvenile MLD. Therefore, newborn screening for MLD has been proposed and has recently been implemented in Norway, Austria, and parts of Germany. The approach entails measurement of sulfatides in the newborns dried blood spot followed by measurement of ARSA activity as a second-tier test when sulfatides are elevated. In the United States, New York is the first state to provide routine newborn screening for MLD.

Useful For: Second-tier newborn screening test for metachromatic leukodystrophy (MLD) when sulfatides are elevated Enzymatic test for detection of arylsulfatase A deficiency This test is not suitable for carrier detection.

Interpretation: Reduced levels of arylsulfatase A (ARSA) are seen in patients with metachromatic leukodystrophy (MLD); however, some patients with MLD may have normal results by this method. Individuals with pseudodeficiency of ARSA can have results in the affected range but are otherwise unaffected with MLD. Reduced levels of ARSA are also possible when samples have been left at room temperature after drying. Abnormal results and/or clinical suspicion should be confirmed using CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine and molecular genetic testing of ARSA (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-WHFH2K).

Reference Values:
Normal: > or =0.100 mmol/mL/hr

Clinical References: 1. Gomez-Ospina N. Arylsulfatase A deficiency. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1993-2025. Updated April 25, 2024. Accessed June 4, 2025. Available from: www.ncbi.nlm.nih.gov/books/NBK1130/ 2. Fumagalli F, Calbi V, Natali Sora MG, et al. Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access. Lancet. 2022;399(10322):372-383. doi:10.1016/S0140-6736(21)02017-1 3. Fumagalli F, Zambon AA, Rancoita PMV, et al. Metachromatic leukodystrophy: A single-center longitudinal study of 45 patients. J Inherit Metab Dis. 2021;44(5):1151-1164. doi:10.1002/jimd.12388 4. Laugwitz L, Mechtler TP, Janzen N, et al. Newborn screening and presymptomatic treatment of metachromatic leukodystrophy. N Engl J Med. 2024;391(13):1256-1258. doi:10.1056/NEJMc2407165

ARSAW 8779 Arylsulfatase A, Leukocytes

Clinical Information: Metachromatic leukodystrophy (MLD) is a lysosomal storage disorder caused by a deficiency of the enzyme arylsulfatase A (ARSA), which leads to the accumulation of sulfatides (both galactosyl and lactosyl sulfatide) in the white matter of the central nervous system, the peripheral nervous system, and, to a lesser extent, in visceral organs including the kidney and gallbladder. Cells that produce myelin are especially affected causing the characteristic leukodystrophy seen in MLD. Patients

with MLD excrete excessive amounts of sulfatides in their urine. The 3 clinical forms of MLD are late-infantile, juvenile, and adult, depending on age of onset. All forms result in progressive neurologic changes and leukodystrophy demonstrated on magnetic resonance imaging. Late-infantile MLD is the most common (50%-60% of cases) and usually presents before 30 months of age with hypotonia, clumsiness, diminished reflexes, and slurred speech. Progressive neurodegeneration occurs and, unless successfully treated, most patients do not survive past childhood. Juvenile MLD (20%-30% of cases) is characterized by onset between 30 months to 16 years old. Presenting features are behavior problems, declining school performance, clumsiness, and slurred speech. Neurodegeneration occurs at a somewhat slower and more variable rate than the late-infantile form. Adult MLD (15%-20% of cases) has an onset after puberty and can be as late as the fourth or fifth decade. Presenting features are often behavior and personality changes, including psychiatric symptoms. Clumsiness, neurologic symptoms, and seizures are also common. The disease course has variable progression and may occur over 2 to 3 decades. Metachromatic leukodystrophy is an autosomal recessive disorder caused by disease-causing variants in the ARSA gene. This disorder is distinct from conditions caused by deficiencies of arylsulfatase B (Maroteaux-Lamy disease) and arylsulfatase C (steroid sulfatase deficiency). Saposin B deficiency is a rare autosomal recessive disorder with symptoms that mimic MLD; however, the ARSA enzyme level is normal. Like MLD, patients with saposin B deficiency can excrete excessive amounts of sulfatides in their urine. Individuals with multiple sulfatase deficiency, which is clinically distinct from MLD, will also have deficiency of arylsulfatase A, however, other sulfatase enzymes will also be deficient. Individuals with "pseudodeficiency" of ARSA have very low levels of ARSA activity but are otherwise healthy. Pseudodeficiency has been found among patients with other unrelated neurologic conditions as well as among the general population, therefore a diagnosis of MLD cannot be based upon reduced ARSA activity alone. To confirm a diagnosis, additional studies, such as molecular genetic testing of ARSA (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-WHFH2K), urinary excretion of sulfatides (CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine), or, less commonly, histological analysis for metachromatic lipid deposits in nervous system tissue are recommended. Current treatment options for MLD depend on the clinical stage and presence of neurologic symptoms. Early diagnosis is extremely important to improve clinical outcomes. Allogenic hematopoietic stem cell transplant (HSCT) can treat symptoms related to the central nervous system in pre- and very early-symptomatic juvenile- or adult-onset MLD. Recently, autologous hematopoietic stem cell-based gene therapy has been approved in the United States and elsewhere for individuals with presymptomatic late-infantile MLD, presymptomatic juvenile MLD, or early-symptomatic juvenile MLD with maintained ability to walk and before the onset of cognitive decline.

Useful For: Preferred enzymatic test for detection of arylsulfatase A deficiency This test is not suitable for carrier detection.

Interpretation: Reduced levels of arylsulfatase A are seen in patients with metachromatic leukodystrophy (MLD), however some patients with MLD may have normal results by this method. Individuals with pseudodeficiency of arylsulfatase A can have results in the affected range but are otherwise unaffected with MLD. Abnormal results and/or clinical suspicion should be confirmed using CTSU / Ceramide Trihexosides and Sulfatides, Random, Urine. If molecular confirmation is desired, consider molecular genetic testing of ARSA (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-WHFH2K).

Reference Values:
> or =62 nmol/h/mg

Note: Results from this assay may not reflect carrier status because of individual variation of arylsulfatase A enzyme levels. Low normal values may be due to the presence of pseudodeficiency or carrier alleles. Patients with these depressed levels may be phenotypically normal.

Clinical References: 1. Gieselmann V, Ingeborg KM: Metachromatic leukodystrophy. In: Valle

D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed June 9, 2025. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225546629 2. Gomez-Ospina N. Arylsulfatase A deficiency. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews[Internet]. University of Washington, Seattle; 2006.Updated April 25,2024. Accessed June 9, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1130/ 3. Fumagalli F, Zambon AA, Rancoita PMV, et al. Metachromatic leukodystrophy: A single-center longitudinal study of 45 patients. J Inherit Metab Dis. 2021;44(5):1151-1164. doi:10.1002/jimd.12388 4. Laugwitz L, Mechtler TP, Janzen N, et al. Newborn screening and presymptomatic treatment of metachromatic leukodystrophy. N Engl J Med. 2024; 391(13): 1256-1258. doi:10.1056/NEJMc2407165

ARSBB
616834

Arylsulfatase B, Blood Spot

Clinical Information: Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome) is an autosomal recessive lysosomal disorder caused by the deficiency of N-acetylgalactosamine 4-sulfatase, also known as arylsulfatase B (ARSB) leading to the accumulation of dermatan sulfate. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, and degenerative joint disease. Other clinical features may include facial dysmorphism, hepatosplenomegaly, corneal clouding, and cardiac disease. Intelligence is usually normal. Rapidly progressing forms have an early onset of symptoms, significantly elevated GAGs, and can lead to death before the second or third decades. A more slowly progressing form has a later onset, milder skeletal manifestations, smaller elevations of GAGs, and typically a longer lifespan. Treatment options include hematopoietic stem cell transplantation and/or enzyme replacement therapy. The differential diagnosis of ARSB deficiency should include multiple sulfatase deficiency and mucolipidosis II (I-Cell disease), however both conditions present with developmental delays that make them clinically different from MPS VI. The symptoms of MSD mimic metachromatic leukodystrophy (MLD) as well as the mucopolysaccharidoses and can include developmental delay, neurologic regression, dysmorphic facies, dysostosis multiplex, organomegaly, ichthyosis, and chondroplasia punctata. If MSD is suspected, testing of an additional sulfatase enzyme, such as arylsulfatase A (ARSAW/ Arylsulfatase A, Leukocytes) in MLD, can help determine if multiple sulfatases are deficient. I-cell disease is characterized by congenital or early infantile manifestations including coarse facial features, short stature, skeletal anomalies, cardio- and hepatomegaly, and developmental delays. This is a progressive disorder and death typically occurs in the first decade of life. Additional testing including hydrolase enzymes in serum, such as hexosaminidase A in Tay-Sach disease (NAGS/ Hexosaminidase A and Total Hexosaminidase, Serum) is recommended if a diagnosis of I-cell is suspected. A diagnostic workup for MPS includes glycosaminoglycan (GAG) determination in urine (MPSQU / Mucopolysaccharides Quantitative, Random, Urine) or blood (MPSBS / Mucopolysaccharidosis, Blood Spot, or MPSER / Mucopolysaccharidosis, Serum) and molecular genetic analysis of the relevant gene. For MPS VI, molecular analysis of the ARSB gene (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-QQF7DP) allows for detection of disease-causing variant in affected patients and subsequent carrier detection in relatives.

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidosis type VI (MPS VI, Maroteaux-Lamy syndrome) This test is not useful for carrier detection for MPS VI

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular genetic analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
>0.90 nmol/mL/hour

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The Mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 14, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ, Ballabio A. Multiple Sulfatase Deficiency and the Nature of the Sulfatase Family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 14, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546905

ARSBW
616835

Arylsulfatase B, Leukocytes

Clinical Information: Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome) is an autosomal recessive lysosomal disorder caused by the deficiency of N-acetylgalactosamine 4-sulfatase, also known as arylsulfatase B (ARSB) leading to the accumulation of dermatan sulfate. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, and degenerative joint disease. Other clinical features may include facial dysmorphism, hepatosplenomegaly, corneal clouding, and cardiac disease. Intelligence is usually normal. Rapidly progressing forms have an early onset of symptoms, significantly elevated GAGs, and can lead to death before the second or third decades. A more slowly progressing form has a later onset, milder skeletal manifestations, smaller elevations of GAGs, and typically a longer lifespan. Treatment options include hematopoietic stem cell transplantation and/or enzyme replacement therapy. The differential diagnosis of ARSB deficiency should include multiple sulfatase deficiency and mucolipidosis II (I-Cell disease), however both conditions present with developmental delays that make them clinically different from MPS VI. The symptoms of MSD mimic metachromatic leukodystrophy (MLD) as well as the mucopolysaccharidoses and can include developmental delay, neurologic regression, dysmorphic facies, dysostosis multiplex, organomegaly, ichthyosis, and chondroplasia punctata. If MSD is suspected, testing of an additional sulfatase enzyme, such as arylsulfatase A (ARSAW/ Arylsulfatase A, Leukocytes) in MLD, can help determine if multiple sulfatases are deficient. I-cell disease is characterized by congenital or early infantile manifestations including coarse facial features, short stature, skeletal anomalies, cardio- and hepatomegaly, and developmental delays. This is a progressive disorder and death typically occurs in the first decade of life. Additional testing including hydrolase enzymes in serum, such as hexosaminidase A in Tay-Sach disease (NAGS/ Hexosaminidase A and Total Hexosaminidase, Serum) is recommended if a diagnosis of I-cell is suspected. A diagnostic workup for MPS includes glycosaminoglycan (GAG) determination in urine (MPSQU / Mucopolysaccharides Quantitative, Random, Urine) or blood (MPSBS / Mucopolysaccharidosis, Blood Spot, or MPSER / Mucopolysaccharidosis, Serum) and molecular genetic analysis of the relevant gene. For MPS VI, molecular analysis of the ARSB gene (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-QQF7DP) allows for detection of disease-causing variant in affected patients and subsequent carrier detection in relatives.

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidosis type VI (MPS VI, Maroteaux-Lamy syndrome) in whole blood specimens This test is not useful for carrier detection.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements

of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
>0.34 nmol/hour/mg protein

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 14, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ, Ballabio A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 14, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546905

ASCRI
82764

Ascaris, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Ascaris worms Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

VITC
42362

Ascorbic Acid (Vitamin C), Plasma

Clinical Information: Vitamin C, also known as L-ascorbic acid or simply ascorbic acid, is a water-soluble vitamin that is naturally present in some foods, added to others, and available as a dietary supplement. Humans, unlike most animals, are unable to synthesize vitamin C endogenously, so it is an essential dietary component. Vitamin C is required for the enzymatic amidation of neuropeptides, production of adrenal cortical steroid hormones, promotion of the conversion of tropocollagen to collagen, and metabolism of tyrosine and folate. It also plays a role in lipid and vitamin metabolism and is a powerful reducing agent or antioxidant. Specific actions include activation of detoxifying enzymes in the liver; antioxidation, interception and destruction of free radicals; preservation and restoration of the antioxidant potential of vitamin E; and blockage of the formation of carcinogenic nitrosamines. In addition, vitamin C appears to function in a variety of other metabolic processes in which its role has not been well characterized. Prolonged deficiency of vitamin C leads to the development of scurvy, a disease characterized by an inability to form adequate intercellular substance in connective tissues. This results in the formation of swollen, ulcerative lesions in the gums, mouth, and other tissues that are structurally weakened. Early symptoms may include weakness, easy fatigue and listlessness, as well as shortness of breath, and aching joints, bones, and muscles. The need for vitamin C can be increased by the use of aspirin, oral contraceptives, tetracycline, and a variety of other medications. Psychological stress and advancing age also tend to increase the need for vitamin C. Among older adults, lack of fresh fruit and vegetables often adds vitamin C depletion to the inherently increased need, with development of near-scurvy status.

Useful For: Identifying vitamin C deficiency

Interpretation: Values below 0.2 mg/dL indicate significant deficiency. Values greater than or equal to 0.2 mg/dL and less than 0.4 mg/dL are consistent with a moderate risk of deficiency due to inadequate tissue stores. Values of 0.4 to 2.0 mg/dL indicate adequate supply. The actual level at which vitamin C is excessive has not been defined. Values above 3.0 mg/dL are suggestive of excess intake. Whether vitamin C in excess is indeed toxic continues to be uncertain. However, limited observations suggest that this condition may induce uricosuria and, in individuals with glucose-6-phosphate dehydrogenase deficiency, may induce increased red blood cell fragility.

Reference Values:
0.4-2.0 mg/dL

Clinical References:

ASPAR
82478

Asparagus, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to asparagus Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus

MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

AST
8360

Aspartate Aminotransferase (AST) (GOT), Serum

Clinical Information: Aspartate aminotransferase (AST) is found in high concentrations in liver, heart, skeletal muscle, and kidney. AST is present in both cytoplasm and mitochondria of cells. In cases involving mild tissue injury, the predominant form of AST is that from the cytoplasm. Severe tissue damage results in more of the mitochondrial enzyme being released. High levels of AST can be found in cases such as myocardial infarction, acute liver cell damage, viral hepatitis, and carbon tetrachloride poisoning. Slight to moderate elevation of AST is seen in muscular dystrophy, dermatomyositis, acute pancreatitis, and crushed muscle injuries.

Useful For: Diagnosing and monitoring liver disease, particularly diseases resulting in a destruction of hepatocytes

Interpretation: Elevated aspartate aminotransferase (AST) values are seen in parenchymal liver diseases characterized by a destruction of hepatocytes. Values are typically at least 10 times above the normal range. Levels may reach values as high as 100 times the upper reference limit, although 20- to 50-fold elevations are most frequently encountered. In infectious hepatitis and other inflammatory conditions affecting the liver, alanine aminotransferase (ALT) is characteristically as high as or higher than AST, and the ALT:AST ratio, which normally and in other condition is less than 1, becomes greater than unity. AST levels are usually elevated before clinical signs and symptoms of disease appear. Five- to 10-fold elevations of both AST and ALT occur in patients with primary or metastatic carcinoma of the liver, with AST usually being higher than ALT, but levels are often normal in the early stages of malignant infiltration of the liver. Elevations of ALT activity persist longer than do those of AST activity. Elevated AST values may also be seen in disorders affecting the heart, skeletal muscle, and kidney.

Reference Values:
Males
0-11 months: not established
1-13 years: 8-60 U/L
> or =14 years: 8-48 U/L
Females
0-11 months: not established
1-13 years: 8-50 U/L
> or =14 years: 8-43 U/L

Clinical References: Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. Philadelphia, WB Saunders Company, 1994

FASPE
57947

Aspen (Populus tremuloides) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

ASPAG
84356

Aspergillus (Galactomannan) Antigen, Serum

Clinical Information: Invasive aspergillosis (IA) is a severe infection that occurs in patients with prolonged neutropenia, following transplantation, or in conjunction with aggressive immunosuppressive regimens (eg, prolonged corticosteroid usage, chemotherapy). The incidence of IA is reported to vary from 5% to 20% depending on the patient population. IA has an extremely high mortality rate of 50% to 80% due in part to the rapid progression of the infection (ie, 1-2 weeks from onset to death). Approximately 30% of cases remain undiagnosed and untreated at death. Definitive diagnosis of IA requires histopathological evidence of deep-tissue invasion or a positive culture. This evidence is often difficult to obtain due to the critically ill nature of the patient and the fact that severe thrombocytopenia often precludes the use of invasive procedures to obtain a quality specimen. The sensitivity of culture in this setting is low, reportedly ranging from 30% to 60% for bronchoalveolar lavage fluid. Accordingly, the diagnosis is often based on nonspecific clinical symptoms (unexplained fever, cough, chest pain, dyspnea) in conjunction with radiologic evidence (computed tomography scan); a definitive diagnosis is often not established before fungal proliferation becomes overwhelming and refractory to therapy. Recently, a serologic assay was approved by the US Food and Drug Administration for the detection of galactomannan, a molecule found in the cell wall of Aspergillus species. Serum galactomannan can often be detected a mean of 7 to 14 days before other diagnostic clues become apparent, and monitoring of galactomannan can potentially allow initiation of preemptive antifungal therapy before life-threatening infection occurs.

Useful For: Aiding in the diagnosis of invasive aspergillosis Assessing response to therapy

Interpretation: A positive result supports a diagnosis of invasive aspergillosis (IA). Positive results should be considered in conjunction with other diagnostic procedures, such as microbiologic culture, histological examination of biopsy specimens, and radiographic evidence. See Cautions. A negative result does not rule out the diagnosis of IA. Repeat testing is recommended if the result is negative but IA is clinically suspected. Patients at risk of IA should have a baseline serum tested and should be monitored twice a week for increasing galactomannan antigen levels. Galactomannan antigen levels may be useful in the assessment of therapeutic response. Antigen levels decline in response to antimicrobial therapy.

Reference Values:
<0.5 index
Reference values apply to all ages.

Clinical References: 1. Schroeder I, Dichtl K, Liebchen U, et al. Digestive enzymes of fungal origin as a relevant cause of false positive Aspergillus antigen testing in intensive care unit patients. Infection. 2021;49(2):241-248. doi:10.1007/s15010-020-01506-4 2. Maertens J, Verhaegen J, Lagrou K, Boogaerts M. Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: a prospective evaluation. Blood. 2001;97(6):1604-1610 3. Pinel C, Fricker-Hidalgo H, Lebeau B, et al. Detection of circulating Aspergillus fumigatus galactomannan: value and limits of the Platelia test for diagnosing invasive aspergillosis. J Clin Microbiol. 2003;41(5):2184-2186 4. Swanink CM, Meis JF, Rijs AJ, Donnelly JP, Verweij PE. Specificity of a sandwich enzyme-linked immunosorbent assay for detecting Aspergillus galactomannan. J Clin Microbiol. 1997;35(1):257-260 5. Ansorg R, van den Boom R, Rath PM. Detection of Aspergillus galactomannan antigen in foods and antibiotics. Mycoses. 1997;40(9-10):353-357 6. Connolly P, Durkin M, Wheat LJ, et al. Rapid diagnosis of systemic and invasive mycoses. Clinical Microbiology Newsletter. 2007;29(1):1-5 7. Thompson GR, Patterson TF. Aspergillus species. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3103-3116

FASAB
75571

Aspergillus Antibodies, Quantitative, DID

Reference Values:

Aspergillus fumigatus	Neg: <1:1
Aspergillus flavus	Neg: <1:1
Aspergillus niger	Neg: <1:1

ASPBA
61009

Aspergillus Antigen, Bronchoalveolar Lavage

Clinical Information: Invasive aspergillosis (IA) is a severe infection that occurs in patients with prolonged neutropenia following transplantation or in conjunction with aggressive immunosuppressive regimens (eg, prolonged corticosteroid use, chemotherapy). The incidence of IA is reported to vary from 5% to 20% depending on the patient population. IA has an extremely high mortality rate of 50% to 80%, due in part to the rapid progression of the infection (ie, 1-2 weeks from onset to death). Approximately 30% of cases remain undiagnosed and untreated at death. Definitive diagnosis of IA requires histopathological evidence of deep-tissue invasion or a positive culture. This evidence is often difficult to obtain due to the critically ill nature of the patient and the fact that severe thrombocytopenia often precludes the use of invasive procedures to obtain a quality specimen. The sensitivity of culture in this setting is low, reportedly ranging from 30% to 60% for bronchoalveolar lavage (BAL) fluid. Accordingly, the diagnosis is often based on nonspecific clinical symptoms (unexplained fever, cough, chest pain, dyspnea) in conjunction with radiologic evidence (computed tomography scan); a definitive diagnosis is often not established before fungal proliferation becomes overwhelming and refractory to therapy. Recently, a serologic assay was approved by the US Food and Drug Administration for the detection of galactomannan, a molecule found in the cell wall of Aspergillus species. Serum galactomannan (Aspergillus antigen) can often be detected a mean of 7 to 14 days before other diagnostic clues become apparent, and monitoring of Aspergillus antigen can potentially allow initiation of preemptive antifungal therapy before life-threatening infection occurs. The clinical utility of Aspergillus antigen testing in BAL specimens as an early prognostic indicator of IA has recently been assessed. These studies demonstrated equivalent or higher sensitivity compared to detection of Aspergillus antigen in serum.(1-4) This assay may be useful in the assessment of therapeutic response as antigen levels typically decline in response to effective antimicrobial therapy.

Useful For: Aiding in the diagnosis of invasive aspergillosis using bronchoalveolar lavage specimens
Assessing response to therapy

Interpretation: A positive result in bronchoalveolar lavage (BAL) fluid supports a diagnosis of invasive, pulmonary aspergillosis. Positive results should be considered in conjunction with other diagnostic procedures, such as microbiologic culture, histological examination of biopsy specimens, and radiographic evidence (see Cautions). A negative result in BAL fluid does not rule out the diagnosis of invasive aspergillosis (IA). Patients at risk of IA should be monitored twice a week for Aspergillus antigen levels in serum until determined to be clinically unnecessary. Aspergillus antigen levels typically decline in response to effective antimicrobial therapy.

Reference Values:
<0.5 Index

Clinical References: 1. Park SY, Lee SO, Choi SH, et al. Aspergillus galactomannan antigen assay in bronchoalveolar lavage fluid for diagnosis of invasive pulmonary aspergillosis. J Infect. 2010;61(6):492-498 2. Husain S, Clancy CJ, Nguyen MH, et al. Performance characteristics of the platelia aspergillus enzyme immunoassay for detection of Aspergillus galactomannan antigen in bronchoalveolar lavage fluid. Clin Vaccine Immunol. 2008;15(12):1760-1763 3. Meersseman W, Lagrou K, Maertens J, et al. Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. Am J Respir Crit Care Med. 2008;177(1):27-34 4. Becker MJ, Lugtenburg EJ, Cornelissen JJ, Van Der Schee C, Hoogsteden HC, De Marie S. Galactomannan

detection in computerized tomography-based bronchoalveolar lavage fluid and serum in haematological patients at risk for invasive pulmonary aspergillosis. Br J Haematol. 2003;121(3):448-457 5. Schroeder I, Dichtl K, Liebchen U, et al. Digestive enzymes of fungal origin as a relevant cause of false positive Aspergillus antigen testing in intensive care unit patients. Infection. 2021;49(2):241-248. doi:10.1007/s15010-020-01506-4 6. Xavier MO, Pasqualotto AC, Cardoso ICE, Severo LC. Cross-reactivity of Paracoccidioides brasiliensis, Histoplasma capsulatum, and Cryptococcus species in the commercial Platelia Aspergillus enzyme immunoassay. Clin Vaccine Immunol. 2009;16(1):132-133 7. Thompson GR, Patterson TF: Aspergillus species. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3103-3116

FAFE
57910

Aspergillus flavus IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

ASP
82911

Aspergillus fumigatus, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Aspergillus fumigatus Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SASP
9678

Aspergillus fumigatus, IgG Antibodies, Serum

Clinical Information: Hypersensitivity pneumonitis (HP) is a type of interstitial lung disease caused by an immune-mediated response to inhaled environmental antigens.(1) Patients with HP commonly display symptoms of cough, dyspnea, and midinspiratory squeaks. Patients may present with an acute onset of symptoms (within hours of antigen exposure) or a chronic onset (which may occur over a course of weeks to months). The nature of an individual's disease course will be affected by several factors, including quantity of inhaled antigen, intensity/frequency of exposure, and genetic background. The epidemiology of HP is also challenging to understand, as incidence and prevalence of the disease varies with geographic areas, climate, and local customs. While the immunopathogenesis of HP is not completely understood, it is presumed to involve both type III and type IV hypersensitivity reactions, with the type III reaction characterized by the presence of IgG antibodies specific for the inciting antigen.(2,3) Clinical practice guidelines for HP include a diagnostic algorithm which focuses on exposure identification, imaging evaluation, and bronchoalveolar lavage/histopathology.(4) In patients with clinical, pathological and imaging results consistent with HP, identification of causative exposure is important, as a significant part of treatment is antigen avoidance. There are many antigens, both organic and inorganic, that have been associated with the development of HP.(2,3) Causative organic antigens include a wide array of bacteria, mycobacteria, fungi, and animal proteins. Aspergillus fumigatus is a fungus found in locations with high humidity, including soil, greenhouses, and compost heaps. It is ubiquitous and may even be found in household dust. In patients diagnosed with HP, evaluation for antigen-specific IgG antibodies, in conjunction with known environmental exposures, can help to document the causative exposure for an individual. However, IgG testing is only useful as supportive information for the diagnosis of HP; a positive result only indicates sensitization to the antigen and a negative result does not exclude the possibility that a patient with HP may be sensitized to another antigen.

Useful For: Evaluation of patients suspected of having hypersensitivity pneumonitis (HP) induced by exposure to Aspergillus fumigatus Evaluation of patients suspected of having HP who have documented environmental exposures to high-humidity environments

Interpretation: Positive results for IgG antibodies to Aspergillus fumigatus, in patients with signs and symptoms of hypersensitivity pneumonitis, may be consistent with sensitization to this fungus.

Reference Values:
<4 years: Not established
> or =4 years: < or =102 mg/L

Clinical References:

FASPG
75681

Aspergillus IgG Precipitins Panel

Interpretation: The gel diffusion method was used to test this patients serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and immunological sensitization. The clinical significance varies, depending on the history and symptoms.

Reference Values:
Negative

ASPG
86324

Aspergillus niger, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Aspergillus niger Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ADMA
607697

Asymmetric Dimethylarginine, Plasma

Clinical Information: Asymmetric dimethylarginine (ADMA) is an independent risk factor for major adverse cardiovascular events.(1-7) ADMA inhibits nitric oxide (NO) synthesis and is elevated in diseases related to endothelial dysfunction including hypertension, hyperlipidemia, and type II diabetes mellitus. Elevation in ADMA and subsequent NO synthesis inhibition leads to vasoconstriction, reduced peripheral blood flow, and reduced cardiac output. Elevated plasma ADMA confers a 4- to 6-fold increased risk of subsequent cardiovascular events or mortality among patients with acute coronary syndrome,(3) unstable angina,(4) type II diabetes mellitus,(5) end-stage renal disease,(6) coronary heart disease,(7) and peripheral artery disease.(1) Baseline ADMA remained a significant risk factor of adverse events even after adjusting for low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides, creatinine, and high-sensitivity C-reactive protein. Plasma ADMA concentrations are lowered by rosuvastatin and atorvastatin, but not simvastatin in patients with hypercholesterolemia.(8) Addition of vildagliptin (Galvus) to metformin significantly reduced ADMA concentrations among patients with type II diabetes mellitus.(9)

Useful For: Assessing the likelihood of future coronary events in patients with coronary heart disease, type II diabetes mellitus, or kidney disease Prompting intervention and assessing improvements among subjects with elevated ADMA and hypercholesterolemia or type II diabetes mellitus

Interpretation: In patients with preexisting coronary conditions or at high risk for coronary events (diabetes, renal insufficiency), asymmetric dimethylarginine levels in the upper tertile, above 112 ng/mL, confer an increased risk for future coronary events.

Reference Values:
> or =18 years: 63-137 ng/mL
Reference values have not been established for patients who are <18 years of age

Clinical References: 1. Chu R, Yu D, Chu J, et al. Prognostic efficacy of circulating asymmetric dimtheylarginine in patients with peripheral arterial disease: A meta-analysis of prospective cohort studies. Vascular. 2018;26:322-330 2. Schulze F, Lenzen H, Hanefeld C, et al. Asymmetric

dimethylarginine is an independent risk factor for coronary heart disease: results from the multicenter Coronary Artery Risk Determination investigating the Influence of ADMA Concentration (CARDIAC) study. Am Heart J. 2006;152(3):493.e1-8 3. Cavusoglu E, Ruwende C, Chopra V, et al. Relationship of baseline plasma ADMA levels to cardiovascular outcomes at 2 years in men with acute coronary syndrome referred for coronary angiography. Coron Artery Dis. 2009;20:112-117 4. Krempl TK, Maas R, Sydow K, et al. Elevation of asymmetric dimethylarginine in patients with unstable angina and recurrent cardiovascular events. Eur Heart J. 2005;26:1846-1851 5. Cavusoglu E, Ruwende C, Chopra V, et al. Relation of baseline plasma ADMA levels to cardiovascular morbidity and mortality at two years in men with diabetes mellitus referred for coronary angiography. Atherosclerosis. 2010;210(1):226-231 6. Abedini S, Meinitzer A, Holme I, et al. Asymmetrical dimethylarginine is associated with renal and cardiovascular outcomes and all-cause mortality in renal transplant recipients. Kidney Int. 2010;77(1):44-50 7. Valkonen VP, Paiva H, Salonen JT, et al. Risk of acute coronary events and serum concentration of asymmetrical dimethylarginine. Lancet. 2001;358:2127-2128 8. Kurtoglu E, Sevket B, Sincer I, et al. Comparison of effects of Rosuvastatin versus Atorvastatin treatment on plasma levels of asymmetric dimethylarginine in patients with hyperlipidemia having coronary artery disease. Angiology. 2014;65:788-793 9. Cakirca M, Karatoprak C, Zorlu M, et al. Effect of vildagliptin add-on treatment to metformin on plasma asymmetric dimethylarginine in type 2 diabetes mellitus patients. Drug Des Devel Ther. 2014;8:239-243 10. Ravani P, Tripepi G, Malberti F, et al. Asymmetrical dimethylarginine predicts progression to dialysis and death in patients with chronic kidney disease: a competing risks modeling approach. J Am Soc Nephrol. 2005;16:2449-2455 11. Elesber AA, Solomon H, Lennon RJ, et al. Coronary endothelial dysfunction is associated with erectile dysfunction and elevated asymmetric dimethylarginine in patients with early atherosclerosis. Eur Heart J. 2006;27(7):824-31

ATRX
70360

ATRX Immunostain, Technical Component Only

Clinical Information: This test is intended to identify the presence of adenosine triphosphate (ATP)-dependent helicase ATRX, X-linked helicase II (ATRX) protein. ATRX is produced by most mitotically active normal cells and can be useful in the distinction of differentiated from undifferentiated neoplasms.

Useful For: Distinguishing differentiated from undifferentiated neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Wiestler B, Capper D, Holland-Letz T, et al. ATRX loss refines the classification of anaplastic gliomas and identifies a subgroup of IDH mutant astrocytic tumors with better prognosis. Acta Neuropathol. 2013;126(3):443-451 2. De La Fuente R, Baumann C, Viveiros MM. Role of ATRX in chromatin structure and function: implications for chromosome instability and human disease. Reproduction. 2011;142(2):221-234 3. Zhang J, Francois R, Iyer R, Seshadri M, Zajac-Kaye M, Hochwald SN. Current understanding of the molecular biology of pancreatic neuroendocrine tumors. J Natl Cancer Inst. 2013;105(14):1005-1017 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

AHUGP
618016

Atypical Hemolytic Uremic Syndrome (aHUS)/Thrombotic Microangiopathy (TMA) /Complement 3 Glomerulopathy (C3G)

Gene Panel, Varies

Clinical Information: Thrombotic microangiopathy (TMA) is a pathologic condition characterized by abnormalities in the walls of small blood vessels (arterioles and capillaries) that result in microvascular thrombosis. Typically, they feature microangiopathic hemolytic anemia (MAHA) and thrombocytopenia, but these features may not be apparent in kidney-limited disease. Laboratory findings may include anemia, thrombocytopenia, presence of schistocytes on peripheral smear, elevated lactate dehydrogenase, and elevated serum creatinine.(1,2) The main categories of TMA include complement-mediated thrombotic microangiopathy (CM-TMA; also known as atypical hemolytic syndrome [aHUS]), thrombotic thrombocytopenic purpura (TTP), Shiga toxin-mediated hemolytic uremic syndrome, and drug-induced TMA. Due to the overlapping clinical features, laboratory testing is useful in differentiated these disorders.(3) CM-TMA (aHUS) is a well-recognized disease entity characterized by complement activation in the microvasculature. Abnormalities of the alternate pathway of complement, which may be inherited (genetic) or acquired, underlie both the sporadic and familial forms of the disease and are identified in approximately 60% of patients.(3,4) Unlike many other monogenic disorders of the immune system, multiple hits may be required for disease manifestation, which may include a trigger event (transplantation, pregnancy, malignant hypertension, autoimmune disorders, sepsis, malignancy, etc) and one or more contributing genetic variants or risk haplotypes in the alternate pathway complement genes.(3) Individuals with genetic CM-TMA (aHUS) may experience relapse even after complete recovery following the presenting episode. TTP is a rare clinical entity but is important to diagnose properly since it is associated with very high mortality (90%) if untreated. Mortality can be reduced by early plasma exchange. Congenital TTP is due to genetic defects in the ADAMTS13 gene, while acquired TTP is related to autoantibodies against ADAMTS13, which reduces function. While TTP was initially characterized by thrombocytopenia, MAHA, fluctuating neurological signs, kidney failure and fever, not all of these features may be present in the manifestation of the disease.(1,2) The hereditary form of CM-TMA is characterized by the presence of disease-causing variants in one or more of the genes known to be associated with aHUS, irrespective of familial history, or when two or more members of the same family are affected by the disease at least 6 months apart and exposure to a common triggering infectious agent has been excluded.(3) A patient may have both genetic variants in the alternative complement pathway and autoantibodies. While genetic testing may be used during the diagnostic work-up, the presence of disease-causing variants may also alter recurrence risk and impact decisions related to continuation of anti-complement therapy after resolution of symptoms. Complement 3 glomerulopathies (C3G) include dense deposit disease and C3 glomerulonephritis and are characterized by C3 deposition within the glomeruli. In these disorders, the activity of the C3 convertase is increased by C3 nephritic factors, which are antibodies that stabilize the convertase, or loss of complement regulator activity, which may be due to genetic variants, autoantibodies, or other immunoglobulins. C3G may be preceded by an upper respiratory tract infection in some cases. Patients typically have proteinuria or hematuria and may present with variable kidney impairment. In addition to medical therapy, patients may be treated with kidney transplantation; however, disease recurrence and graft loss may occur. It is important to note that while TMA and C3G are associated with complement dysregulation, disease-causing variants in these genes may also result in complement deficiency, which is associated with recurrent infections with encapsulated pathogens or connective tissue diseases with no evidence of aHUS/TMA.(5) Two risk alleles associated with increased susceptibility to aHUS/TMA and variants in C5 associated with poor response to anticomplement therapy are also included on this panel to aid in risk assessment: -CFH-H3 Risk Haplotype: The variants that comprise this risk haplotype are common in the general population, but in the context of additional pathogenic genetic and environmental factors, the presence of this risk haplotype is associated with an increased risk for development or progression of atypical hemolytic uremic syndrome. (6) -MCP/CD46 Risk Haplotype: The variants that comprise this risk haplotype are common in the general population, but in the context of additional pathogenic genetic and environmental factors, the presence of this risk haplotype is associated with an increased risk for development or progression of atypical hemolytic uremic syndrome.6) -C5 Genotype: Two variants, p.Arg885His and p.Arg885Cys, have been associated with poor response to eculizumab.(7)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of atypical hemolytic uremic syndrome (aHUS), thrombotic microangiopathy (TMA), or complement 3 glomerulopathy (C3G) Establishing a diagnosis of genetic aHUS, TMA, or C3G and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying variants in genes encoding complement alternate pathway components and specific coagulation pathway genes known to be associated with increased risk for aHUS, TMA, and C3G allowing for predictive testing of at-risk family members Providing genetic information that may be considered when making treatment decisions, including duration of therapy and recurrence risk, as well as consideration of transplantation

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. George JN, Nester CM: Syndromes of thrombotic microangiopathy. N Engl J Med. 2014 Aug 14;371(7):1654-1666 2. Go RS, Winters JL, Leung N, et al: Thrombotic microangiopathy care pathway: A consensus statement for the Mayo Clinic Complement Alternative Pathway-Thrombotic Microangiopathy (CAP-TMA) Disease-Oriented Group. Mayo Clin Proc. 2016 Sep;91(9):1189-1211 3. Noris M, Bresin E, Mele C, Remuzzi G: Genetic atypical hemolytic-uremic syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2007. Updated September 23, 2021. Accessed June 7, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1367/ 4. Kavanagh D, Goodship TH. Atypical hemolytic uremic syndrome, genetic basis, and clinical manifestations. Hematology Am Soc Hematol Educ Program. 2011:15-20. doi: 10.1182/asheducation-2011.1.15 5. Picard C, Gaspar HB, Al-Herz W, et al: International Union of Immunological Societies: 2017 Primary Immunodeficiency Disease Committee report on inborn errors of immunity. J Clin Immunol. 2018 Jan;38(1):96-128 6. Bernabeu-Herrero ME, Jimenez-Alcazar M, Anter J, et al. Complement factor H, FHR-3 and FHR-1 variants associate in an extended haplotype conferring increased risk of atypical hemolytic uremic syndrome. Mol Immunol. 2015;67(2 Pt B):276-286. doi: 10.1016/j.molimm.2015.06.021 7. Nishimura J, Yamamoto M, Hayashi S, et al. Genetic variants in C5 and poor response to eculizumab. N Engl J Med. 2014 Feb 13;370(7):632-639 doi: 10.1056/NEJMoa1311084 8. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424.

AHUSD 64881 Atypical Hemolytic Uremic Syndrome Complement Panel, Serum and Plasma

Clinical Information: Individuals presenting with thrombotic microangiopathies (TMA) require clinical testing to identify the underlying cause. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are both acute syndromes with many overlapping clinical features. Reduced levels of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motives, member 13) activity is associated with TTP and is one laboratory feature that distinguishes TTP from HUS. HUS can also have a number of causes; one of the rarer forms of disease is caused by defects in the alternative pathway of the complement system, so called atypical-HUS (aHUS). Patients with defective alternative pathway regulation can benefit from biologics that suppress the complement system. The purpose of this panel is to aid in the differential diagnosis of TMA. The suggested approach is to rule-out other causes of TMA first, since aHUS is one of the rarer causes of TMA. Additionally, the assays can be

used in the setting of membranoproliferative glomerulonephritis (MPGN) and can help distinguish between immune-complex mediated or complement-mediated kidney disease. MPGN mediated by immune-complexes are ones resulting from infectious processes, autoimmune diseases, or monoclonal gammopathies; whereas complement-mediated MPGN can be subdivided in C3 glomerulonephritis and dense deposit disease, based on electron microscopy of the kidney biopsy histological findings. Despite phenotypic differences, these glomerular diseases share dysfunction of the alternative pathway as the defining pathophysiology.

Useful For: Detecting deficiencies in the alternative pathway that can cause atypical-hemolytic uremic syndrome, dense deposit disease, and C3 glomerulonephritis A second-tier test that aids in the differential diagnosis of thrombotic microangiopathies

Interpretation: An interpretive report will be included.

Reference Values:

FACTOR B COMPLEMENT ANTIGEN
15.2-42.3 mg/dL

SC5b-9 COMPLEMENT
< or =250 ng/mL

FACTOR H COMPLEMENT ANTIGEN
18.5 to 40.8 mg/dL

CBb COMPLEMENT ACTIVATION FRAGMENT
< or =1.6 mcg/mL

COMPLEMENT C4
14-40 mg/dL

COMPLEMENT C3
75-175 mg/dL

ALTERNATIVE COMPLEMENT, PATHWAY (AH50) FUNCTIONAL
> or =46% Normal

COMPLEMENT, TOTAL
30-75 U/mL

Clinical References: 1. Daha MR. Role of complement in innate immunity and infections. Crit Rev Immunol. 2010;30(1):47-52. doi:10.1615/critrevimmunol.v30.i1.30 2. Prohaszka Z, Varga L, Fust G. The use of "real-time" complement analysis to differentiate atypical haemolytic uraemic syndrome from other forms of thrombotic microangiopathies. Br J Haematol. 2012;158(3):424-425. doi:10.1111/j.1365-2141.2012.09168.x 3. Cataland SR, Holers VM, Geyer S, Yang S, Wu HM. Biomarkers of terminal complement activation confirm the diagnosis of aHUS and differentiate aHUS from TTP. Blood. 2014;123(24):3733-3738. doi:10.1182/blood-2013-12-547067 4. Go RS, Winters JL, Leung N, et al. Thrombotic microangiopathy care pathway: A consensus statement for the Mayo Clinic Complement Alternative Pathway-Thrombotic Microangiopathy (CAP-TMA) Disease-Oriented Group. Mayo Clin Proc. 2016;91(9):1189-1211. doi:10.1016/j.mayocp.2016.05.015 5. Willrich MAV, Andreguetto BD, Sridharan M, et al. The impact of eculizumab on routine complement assays. J Immunol Methods. 2018;460:63-71. doi:10.1016/j.jim.2018.06.010

AHLP
619372

AudioloGene Hearing Loss Panel, Varies

Clinical Information: Hereditary hearing loss encompasses a heterogeneous group of syndromic and nonsyndromic conditions. A comprehensive diagnostic genetic test is useful to help determine a molecular etiology for hearing loss and, therefore, identify other organ systems that may be involved, establish long-term prognosis, and ascertain the inheritance pattern and recurrence risk within a family. Individuals with syndromic hearing loss typically have other organ or organ system involvement and may have malformations of the external ear. Individuals with nonsyndromic hearing loss may have abnormalities of the middle ear or inner ear but typically do not have visible abnormalities of the external ear. Additionally, they often do not have additional organ system involvement or other related medical problems. In developed countries, approximately 50% to 60% of individuals with congenital hearing loss have a genetic etiology. Of those, approximately 70% of individuals have a nonsyndromic condition, and the remaining 30% have one of over 400 syndromes involving hearing loss. Of the individuals with nonsyndromic hearing loss, at least three-quarters have an autosomal recessive condition, approximately 25% of whom have variants in the GJB2 or GJB6 genes.(1)

Useful For: Establishing a diagnosis of a syndromic or nonsyndromic hereditary hearing loss disorder Identifying variants within genes known to be associated with hereditary hearing loss, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(2,3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Sloan-Heggen CM, Bierer AO, Shearer AE, et al: Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss. Hum Genet. 2016 Apr;135(4):441-450 2. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 3. Oza AM, DiStefano MT, Hemphill SE, et al: Expert specification of the ACMG/AMP variant interpretation guidelines for genetic hearing loss. Hum Mutat. 2018 Nov;39(11):1593-1613 4. Alford RL, Arnos KS, Fox M, et al: American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss. Genet Med. 2014 Apr;16(4):347-355 5. DiStefano MT, Hemphill SE, Oza AM, et al: ClinGen expert clinical validity curation of 164 hearing loss gene-disease pairs. Genet Med. 2019 Oct;21(10):2239-2247 6. Morton CC, Nance WE: Newborn hearing screening-a silent revolution. N Engl J Med. 2006 May 18;354(20):2151-2164 7. Shearer AE, Hildebrand MS, Smith RJH: Hereditary hearing loss and deafness overview. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated July 27, 2017. Accessed October 25, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1434/

AUPU
82855

Aureobasidium pullulans, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In

individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Aureobasidium pullulans Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

APIN
82803

Australian Pine, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins)

followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to the Australian pine Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ALDG2
619516

Autoimmune Liver Disease Panel, Serum

Clinical Information: Autoimmune liver diseases result from damage to hepatocytes or cholangiocytes caused by an inflammatory immune reaction. Included within this disease group are autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC).(1) In some cases, patients with these diseases may present asymptomatically, with increases in various liver enzymes being identified incidentally during an unrelated clinical evaluation. On the other end of the spectrum are patients who present with clinical evidence of liver disease, including fatigue, hepatomegaly, ascites, esophageal varices, and jaundice. Diagnosis of an autoimmune liver disease first requires that other etiologies of liver injury, including viral, drug, and metabolic causes, be excluded. In some situations, a liver biopsy may be indicated. For those patients in whom an autoimmune liver disease is suspected, autoantibody serology testing may be considered. These assays include markers that may support a diagnosis of an autoimmune liver disease, specifically AIH or PBC. Unfortunately, there are no known autoantibodies specific for PSC that are useful as diagnostic markers.(1) Patients with AIH may be

positive for smooth muscle antibodies (SMA) and/or antinuclear antibodies (ANA).(2) SMA are generally identified by indirect immunofluorescence using a smooth muscle substrate. The antigen specificity of SMA in the context of AIH has been identified as filamentous-acting (F-actin). SMA and F-actin antibodies with liver histology and thorough clinical evaluation are useful in the evaluation of patients with suspected autoimmune hepatitis.(3) SMA have a specificity of 80% to 90% for AIH, although the sensitivity is only in the range of 70% to 80%. In contrast, ANA, although relatively sensitive for AIH, lack specificity, being associated with a variety of autoimmune diseases.(4) Both SMA and ANA, along with other lab markers and biopsy evaluation, are included in the international diagnostic criteria for AIH.(5) In association with chronic cholestasis after exclusion of known causes of liver disease, antimitochondrial antibodies (AMA) are strongly suggestive of a diagnosis of PBC.(6) AMA have a variable prevalence in other autoimmune diseases that can also be found in some apparently healthy individuals.(7,8) AMA are found in more than 90% of patients with PBC, with a specificity of greater than 95%. AMA are included in the clinical practice guidelines for PBC, which were developed through an international collaborative effort.(9) For more information see First-Line Screening for Autoimmune Liver Disease Algorithm.

Useful For: Evaluating patients with suspected autoimmune liver disease, specifically autoimmune hepatitis or primary biliary cholangitis Evaluating patients with liver disease of unknown etiology

Interpretation: The presence of smooth muscle antibodies (SMA) or antinuclear antibodies (ANA) is consistent with a diagnosis of chronic autoimmune hepatitis, in patients with clinical or laboratory evidence of hepatocellular damage. A positive result for antimitochondrial antibodies (AMA) of M2 specificity in the setting of chronic cholestasis after exclusion of other causes of liver disease is highly suggestive of primary biliary cholangitis. Negative results for SMA, ANA, or AMA does not exclude a diagnosis of an autoimmune liver disease. This test is not useful for indicating the stage or prognosis of the disease or for monitoring the course of disease.

Reference Values:

MITOCHONDRIAL ANTIBODIES (M2)
Negative: <0.1 Units
Borderline: 0.1-0.3 Units
Weakly positive: 0.4-0.9 Units
Positive: > or =1.0 Units
Reference values apply to all ages.

ANTINUCLEAR ANTIBODIES
Negative: <1:80

SMOOTH MUSCLE ANTIBODIES
Negative
If positive, results are titered.
Reference values apply to all ages.

Clinical References: 1. Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D: The clinical usage and definition of autoantibodies in immune-mediated liver disease: A comprehensive overview. J Autoimmun. 2018 Dec;95:144-158. doi: 10.1016/j.jaut.2018.10.0046 2. Mieli-Vergani G, Vergani D, Czaja AJ, et al: Autoimmune hepatitis. Nat Rev Dis Primers. 2018 Apr 12;4:18017 3. Invernizzi P, Lleo A, Podda M: Interpreting serological tests in diagnosing autoimmune liver diseases. Sem Liver Dis. 2007 May;27(2):161-172 4. Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D: Serology in autoimmune hepatitis: A clinical-practice approach. Eur J Intern Med. 2018 Feb;48:35-43 5. Hennes EM, Zeniya M, Czaja AJ, et al: Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatol. 2008 Jul;48(1):169-176 6. Muratori L, Granito A, Muratori P, Pappas G, Bianchi FB: Antimitochondrial antibodies and other antibodies in primary biliary cirrhosis: diagnostic and prognostic value. Clin Liver Dis. 2008 May;12(2):261-276 7. Colapietro F, Lleo A, Generali E: Antimitochondrial antibodies: From

bench to bedside. Clin Rev Allergy Immunol. 2022 Oct:63(2):166-177. doi: 10.1007/s12016-021-08904-y 8. Leung PSC, Choi J, Yang G, Woo E, Kenny TP, Gershwin ME: A contemporary perspective on the molecular characteristics of mitochondrial autoantigens and diagnosis in primary biliary cholangitis. Expert Rev Mol Diagn. 2016 Jun;16(6):697-705. doi: 10.1586/14737159.2016.1164038 9. European Association for the Study of the Liver: EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017 Jul;67(1):145-172

ALPSG
619746

Autoimmune Lymphoproliferative Syndrome (ALPS) Gene Panel, Varies

Clinical Information: Autoimmune lymphoproliferative syndrome (ALPS) is a complex clinical disorder of dysregulated lymphocyte homeostasis characterized by chronic nonmalignant lymphoproliferative disease, splenomegaly, lymphadenopathy, and autoimmunity (mainly autoimmune cytopenias), with an increased susceptibility to lymphomas. Typically, ALPS is diagnosed by childhood or young adulthood. Lymphoproliferation and autoimmunity are usually the first presentations. Lymphomas (Hodgkin and non-Hodgkin) can occur at any age but are usually late complications. ALPS is reported worldwide in various racial and ethnic backgrounds but affects more men than women (approximately 2.2 affected men per 1.6 affected women). Laboratory investigations showed that ALPS patients have an increase in a normally rare population of T cells (typically <1%) that are alpha beta T-cell receptor-positive, as well as negative for both CD4 and CD8 coreceptors (double-negative T cells). In addition, there are elevated peripheral blood interleukin (IL)-10, IL-18, vitamin B12, and soluble FAS ligand (FASL) levels. Defective FAS-mediated apoptosis on in vitro assays is another main characteristic of ALPS. Genetic defects in the apoptosis (programmed cell death) pathway have been determined for most cases of ALPS. Apoptosis plays a role in normal immune homeostasis by limiting lymphocyte accumulation and autoimmune reactivity. The interaction of the surface receptor CD95 (FAS) and its ligand (FASL or CD95L) triggers the apoptotic pathway in lymphocytes. Germline variants in CD95 (FAS) are the most common cause (60%-75%) of ALPS (ALPS-FAS), followed by somatic mutations in CD95 (ALPS-sFAS). Variants in CD95L (ALPS-FASL), CASP10 (ALPS-CAS10), and others are rare causes. Currently, up to 20% of patients do not have an identifiable genetic variant (ALPS-U). All these forms present with the main clinical features of ALPS, but there are differences in the results of laboratory tests used to evaluate ALPS patients. Genotype-phenotype correlations are noted in ALPS-FAS, which is the only form common enough for these studies. Both mono- and bi-allelic variants in FAS can cause disease. Dominant negative, haploinsufficient mechanisms are invoked to explain the disease mechanism. It appears that biallelic disease-causing FAS variants cause a more severe clinical phenotype than the monoallelic forms. Lymphomas are mostly associated with disease-causing variants in the intracellular domain of FAS. Penetrance of the clinical phenotype is reduced and varies based on the location and type of causative variant (30%-90%). The latest diagnostic criteria for ALPS were published in 2010.(1) A definitive diagnosis is based on the presence of both required criteria and one primary accessory criterion. A probable diagnosis is based on the presence of both required criteria plus one secondary accessory criterion. Several other diseases can present with an ALPS-like phenotype, including other inborn errors of immunity, like CTLA4 deficiency (also known as CTLA4 haploinsufficiency or CTLA4 haploinsufficiency with autoimmune infiltration [CHAI]) and LRBA (lipopolysaccharide-responsive and beige-like anchor protein) deficiency, gain-of-function variants in STAT3 and CARD11 genes, as well as conditions like Evans syndrome (a combination of autoimmune hemolytic anemia and autoimmune thrombocytopenic purpura) and malignant conditions like Hodgkin disease and large granular lymphocyte leukemias. Genes associated with several ALPS-like disorders are also included on this panel.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of autoimmune lymphoproliferative syndrome (ALPS) or related disorders Establishing a diagnosis of ALPS or a related disorder, allowing for appropriate management and surveillance for disease features based on the gene or variant involved Identifying variants within genes known to be associated with ALPS or a related disorder, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(2) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Oliveira JB, Bleesing JJ, Dianzani U, et al: Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH International Workshop. Blood. 2010 Oct 7;116(14):e35-40 2. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 3. Consonni F, Gambineri E, Favre C: ALPS, FAS, and beyond: from inborn errors of immunity to acquired immunodeficiencies. Ann Hematol. 2022 Mar;101(3):469-484. doi: 10.1007/s00277-022-04761-7 4. Lopez-Nevado M, Gonzalez-Granado LI, Ruiz-Garcia R, et al: Primary immune regulatory disorders with an autoimmune lymphoproliferative syndrome-like phenotype: Immunologic evaluation, early diagnosis and management. Front Immunol. 2021 Aug 10;12:671755. doi:10.3389/fimmu.2021.671755 5. Molnar E, Radwan N, Kovacs G, et al: Key diagnostic markers for autoimmune lymphoproliferative syndrome with molecular genetic diagnosis. Blood. 2020 Oct 22;136(17):1933-1945. doi: 10.1182/blood.2020005486 6. Price S, Shaw PA, Seitz A, et al: Natural history of autoimmune lymphoproliferative syndrome associated with FAS gene mutations. Blood. 2014 Mar 27;123(13):1989-1999. doi: 10.1182/blood-2013-10-535393

FARP
75446

Autoimmune Retinopathy Panel by Immunoblot (ARP)

Reference Values:
A final report will be provided.

AUTOG
620092

Autoinflammatory Disorders Gene Panel, Varies

Clinical Information: Systemic autoinflammatory disorders result from dysregulation of the innate immune system and are characterized by a hyperinflammatory state with elevated acute phase reactants. These disorders may present at any age, but symptoms often begin in childhood with unexplained fever that may be accompanied by a rash. While these features can mimic infections or hematological neoplasias, the inflammatory lesions are noncancerous and sterile. Additional features may be present and highly variable, depending on the organ or organs impacted by cytokine amplification loops and sterile inflammation. Symptoms may involve the gastrointestinal (GI) tract (eg, serositis, abdominal pain, early-onset inflammatory bowel disease), bone, eyes (eg, uveitis), musculoskeletal system (eg, arthritis and arthralgias), central nervous system (eg, meningitis), or other tissues. Some autoinflammatory disorders are also associated with an increased risk of developing amyloid A (AA) amyloidosis. These disorders include familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), cryopyrin-associated autoinflammatory syndrome (CAPS), and hyper-IgD syndrome/mevalonate kinase deficiency (HIDS/MKD). Autoinflammatory disorders are classified by molecular pathogenesis or clinical features. Pathophysiologic classification is based on the pathway or cytokine that drives disease, such as interleukin (IL)-1, interferon, nuclear factor kappa B, and IL-18. Disease classification based on clinical features often focuses on skin involvement or fever duration and frequency. Age of onset, triggers, and additional organ system involvement are also used to classify these disorders and aid clinical diagnosis. The genetic basis of many heritable autoinflammatory disorders has been identified. Autoinflammatory disorders may be

inherited in an autosomal recessive, autosomal dominant, or X-linked manner. Disease-causing variants may also arise de novo. The inheritance pattern appears more complicated for some disorders. For example, FMF is typically inherited in an autosomal recessive manner. However, some affected individuals appear to have only one disease-causing alteration. For other autoinflammatory disorders, cases of digenic and oligogenic inheritance have also been described. Inheritance may also be multifactorial, requiring an environmental component along with low-penetrance variants. One example is Yao syndrome, a recently described clinical entity characterized by recurrent fever, dermatitis, inflammatory arthritis, and GI symptoms in most affected individuals. While some variants in NOD2 have been reported in association with Yao syndrome, they are relatively common among the general population. They may confer an increased risk for developing Yao syndrome but are not diagnostic and appear insufficient to cause disease by themselves. Some disorders such as PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis) syndrome, systemic juvenile idiopathic arthritis, adult-onset Still disease, and Behcet disease have significant phenotypic overlap with monogenic autoinflammatory conditions, but a genetic cause of these disorders has not been identified. Finally, several examples of post-zygotic (mosaic or somatic) genetic alterations causing autoinflammatory disorders have been described. While it may be possible to identify mosaic variants, this test is primarily intended for the identification of germline variants and the diagnosis of inherited monogenic autoinflammatory disorders. Determining the underlying genetic cause of an autoinflammatory condition may help guide treatment decisions. For example, colchicine is an effective therapy for many patients with FMF, but some patients may not respond. Instead, these individuals, and others affected by a subset of autoinflammatory disorders, may respond to IL-1 blocking therapies. Anakinra, rilonacept, and canakinumab are several examples of medications that target IL-1. However, another subset of autoinflammatory disorders is not responsive to IL-1 blockade, such as proteasome-associated autoinflammatory syndromes (PRAAS), CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy), deficiency of IL-36 receptor antagonist, and CAMPS (CARD14-mediated psoriasis). Medications that target other components of the IL-1 pathway are under development. In addition, medications that target other pathways (eg, anti-tumor necrosis factor, anti-IL-6, and JAK-inhibitors) have demonstrated efficacy in some patients.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an inherited autoinflammatory disorder Establishing a diagnosis of a monogenic autoinflammatory disorder, allowing for appropriate management and surveillance for disease features based on the gene or variant involved Identifying variants within genes known to be associated with monogenic autoinflammatory disorders, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Hashkes PJ, Laxer RM, Simon A. Textbook of Autoinflammation. Springer Nature; 2019 3. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507 4. Rood JE, Behrens EM. Inherited autoinflammatory syndromes. Annu Rev Pathol. 2022;17:227-249 5. Gutierrez MJ, Lapidus SK. Systemic autoinflammatory diseases. Rheum Dis Clin North Am. 2022;48(1):371-395 6. Broderick L, Hoffman HM. IL-1 and autoinflammatory disease: biology, pathogenesis and therapeutic targeting. Nat Rev Rheumatol. 2022;18(8):448-463

FAVCG
57690

Avocado IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

AVOC
82812

Avocado, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to avocados Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive

5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

AIAES
606974

Axonal Neuropathy, Autoimmune/Paraneoplastic Evaluation, Serum

Clinical Information: Neuropathy patients have variable sensory disturbance (loss or exaggerated sensation) with pain, weakness, and autonomic involvements such as sweat abnormalities, gastrointestinal dysfunction, and lightheadedness on standing. These symptoms result from injury to the distal nerves, roots, ganglia, or their gathering points (nerve plexus in the thighs and arms). Patients may have symmetric or asymmetric involvements of the extremities, trunk, and head, including extraocular muscles. Subacute onsets and asymmetric involvements favor inflammatory or immune causes over inherited or metabolic forms. Depending on the specific inflammatory or immune mediated causes other parts of the nervous system may also be affected (brain, cerebellum, spinal cord). In the evaluation of patients with immune-mediated autoantibody neuropathies, nerve conduction studies and needle electromyography can help to classify the neuropathy as either primary axonal, primary demyelinating, or mixed axonal and demyelinating. This evaluation focuses on persons with primary axonal forms. Well established neuronal autoantibodies responsible for axonal neuropathies include antineuronal nuclear antibody (ANNA1 and 3), Purkinje cytoplasmic antibody (PCA1 and 2), amphiphysin antibody, collapsin response mediator protein 5 (CRMP5) antibody, leucine-rich glioma inactivated 1 protein (LGI1) antibody, and contactin-associated response protein 2 (CASPR2) antibody. Other autoantibodies have preliminary evidence to support their association with neuropathy, including antiglial nuclear antibody (AGNA), antineuronal nuclear antibody type 2 (ANNA2), and glial fibrillary acidic protein (GFAP) antibody. A patient's humoral and cellular immune response leads to the neurological syndrome. This may be related to an underlying cancer or unidentified antigen trigger. If related to cancer, it may be a new or recurrent malignancy, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeural proteins found in the plasma membrane, cytoplasm, and nucleus of neurons, glia, or muscle are generated in this immune response and serve as serological markers of paraneoplastic autoimmunity. Cancers recognized in this context most commonly are small-cell lung carcinoma, thymoma, ovarian (or related Mullerian) carcinoma, breast carcinoma, and Hodgkin lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin lymphoma, and chondroblastoma. This evaluation focuses on those antibodies with known associations with varied forms of peripheral axonal neuropathy. Seropositive patients usually present with subacute neurological symptoms of radiculopathy; plexopathy; or sensory, sensorimotor, or autonomic neuropathy, with or without a neuromuscular transmission disorder, such as neuromuscular hyperexcitability. Other peripheral manifestations include cranial neuropathies, especially loss of vision, hearing, smell, or taste. Commonly beyond the peripheral manifestation are encephalopathy, seizures, cerebellar ataxia, and myelopathy. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Sensorimotor neuropathy and cerebellar ataxia are common presentations, but the clinical picture in some patients is dominated by striking gastrointestinal dysmotility and limbic encephalopathy. Some patients may present with mostly pain and have a limited small fiber neuropathy with or without autonomic symptoms. Cancer risk factors include previous or family history of cancer, history of smoking, or social or environmental exposure to carcinogens.

Useful For: Evaluation of patients who present with a subacute neurological disorder of undetermined etiology, especially those with known risk factors for cancer Directing a focused search for cancer

Investigating neurological symptoms that appear during, or after, cancer therapy and are not explainable by metastasis Differentiating autoimmune neuropathies from neurotoxic effects of chemotherapy Detecting early evidence of cancer recurrence in previously seropositive patients

Interpretation: Antibodies directed at onconeural proteins shared by neurons, glia, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy individuals and are usually accompanied by subacute neurological signs and symptoms. Several autoantibodies have a syndromic association, but no autoantibody predicts a specific neurological syndrome. More than one paraneoplastic autoantibody may be detected and associated with specific cancers.

Reference Values:

Test ID	Reporting name	Methodology	Reference value
AIAEI	Autoimmune Axonal Interp, S	Medical interpretation	NA
AGN1S	Anti-Glial Nuclear Ab, Type 1	IFA	Negative
AMPHS	Amphiphysin Ab, S	IFA	Negative
ANN1S	ANNA-1, S	IFA	Negative
ANN3S	ANNA-3, S	IFA	Negative
APBIS	AP3B2 IFA, S	IFA	Negative
CRMWS	CRMP-5-IgG Western Blot, S	WB	Negative
CS2CS	CASPR2-IgG CBA, S	CBA	Negative
IG5CS	IgLON5 CBA, S	CBA	Negative
LG1CS	LGI1-IgG CBA, S	CBA	Negative
NIFIS	NIF IFA, S	IFA	Negative
PCAB2	PCA-2, S	IFA	Negative
PCABP	PCA-1, S	IFA	Negative
GFAIS	GFAP IFA, S	IFA	Negative
Reflex Information: Test ID	Reporting name	Methodology	Reference value
AGNBS	AGNA-1 Immunoblot, S	IB	Negative
AGNTS	AGNA-1 Titer, S	IFA	
AINCS	Alpha Internexin CBA, S	CBA	Negative
AMIBS	Amphiphysin Immunoblot, S	IB	Negative
AN1BS	ANNA-1 Immunoblot, S	IB	Negative
AN1TS	ANNA-1 Titer, S	IFA	
AN2BS	ANNA-2 Immunoblot, S	IB	Negative
AN3TS	ANNA-3 Titer, S	IFA	
APBCS	AP3B2 CBA, S	CBA	Negative

APBTS	AP3B2 IFA Titer, S	IFA	
APHTS	Amphiphysin Ab Titer, S	IFA	
CRMTS	CRMP-5-IgG Titer, S	IFA	
GFACS	GFAP CBA, S	CBA	Negative
GFATS	GFAP IFA Titer, S	IFA	
IG5TS	IgLON5 IFA Titer, S	IFA	
NFHCS	NIF Heavy Chain CBA, S	CBA	Negative
NFLCS	NIF Light Chain CBA, S	CBA	Negative
NIFTS	NIF IFA Titer, S	IFA	
PC1BS	PCA-1 Immunoblot, S	IB	Negative
PC1TS	PCA-1 Titer, S	IFA	
PC2TS	PCA-2 Titer, S	IFA	

Clinical References: 1. Klein CJ. Autoimmune-mediated peripheral neuropathies and autoimmune pain. In: Pittock SJ, Vincent A, eds. Autoimmune Neurology. Elsevier; 2016:417-446. Aminoff MJ, Boller F, Swaab DF, eds. Handbook of Clinical Neurology; vol 133 2. Cutsforth-Gregory JK, McKeon A, Coon EA, et al. Ganglionic antibody level as a predictor of severity of autonomic failure. Mayo Clin Proc. 2018;93(10):1440-1447 3. Wei YC, Huang CC, Liu CH, Kuo HC, Lin JJ. Peripheral neuropathy in limbic encephalitis with anti-glutamate receptor antibodies: Case report and systematic literature review. Brain Behav. 2017;7(9):e00779 4. Lucchinetti CF, Kimmel DW, Lennon VA. Paraneoplastic and oncologic profiles of patients seropositive for type 1 antineuronal nuclear autoantibodies. Neurology. 1998;50(3):652-657. doi:10.1212/wnl.50.3.652 5. Pittock SJ, Lucchinetti CF, Lennon VA. Anti-neuronal nuclear autoantibody type 2: paraneoplastic accompaniments. Ann Neurol. 2003;53(5):580-587 6. Chan KH, Vernino S, Lennon VA. ANNA-3 anti-neuronal nuclear antibody: marker of lung cancer-related autoimmunity. Ann Neurol. 2001;50(3):301-311 7. Dubey D, Lennon VA, Gadoth A, et al. Autoimmune CRMP5 neuropathy phenotype and outcome defined from 105 cases. Neurology. 2018;90(2):e103-e110 8. Gadoth A, Pittock SJ, Dubey D, et al. Expanded phenotypes and outcomes among 256 LGI1/CASPR2-IgG-positive patients. Ann Neurol. 2017;82(1):79-92 9. Honnorat J, Trouillas P, Thivolet C, Aguera M, Belin MF. Autoantibodies to glutamate decarboxylase in a patient with cerebellar cortical atrophy, peripheral neuropathy, and slow eye movements. Arch Neurol. 1995;52(5):462-468 10. McKeon A, Tracy JA. GAD65 neurological autoimmunity. Muscle Nerve. 2017;56(1):15-27 11. Bradshaw MJ, Haluska P, McKeon A, Klein CJ. Multifocal neuropathy as the presenting symptom of Purkinje cell cytoplasmic autoantibody-1. Muscle Nerve. 2013;48:827-831 12. Pittock SJ, Lucchinetti CF, Parisi JE, et al. Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol. 2005;58(1):96-107

FAZAT
91934

Azathioprine (Imuran) as 6-Mercaptopurine

Reference Values:
Units: ng/mL

Azathioprine is measured as the metabolite, 6-mercaptopurine. Therapeutic and toxic ranges have not been established. Usual therapeutic doses produce 6-mercaptopurine serum concentrations of less than 1000 ng/ml.

CTNBT
616499

B-Catenin Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information: Desmoid-type fibromatosis is a locally invasive soft tissue tumor. The histological diagnosis of desmoid-type fibromatosis is challenging. Mutations in exon 3 of the beta-catenin (CTNNB1) gene have been identified in 50% to 87% of desmoid-type fibromatosis, including T41A (121 A>G), S45P (133 T>C), and S45F (134 C>T), but not in other soft tissue tumors. Patients harboring beta-catenin mutations may have a higher recurrence rate compared to the patients with wildtype beta-catenin. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for common somatic mutations in the beta-catenin gene known to be associated with desmoid-type fibromatosis. The results of this test can be useful for supporting a diagnosis of desmoid-type fibromatosis and predicting prognosis.

Useful For: Distinguishing desmoid-type fibromatosis from other soft tissue tumors by assessing gene targets within the beta-catenin (CTNNB1) gene

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al: Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. Lazar AJ, Tuvin D, Hajibashi S, et al: Specific mutations in the beta-catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoid tumors. Am J Pathol. 2008;173(5):1518-1527 4. Amary MF, Pauwels P, Meulemans E, et al: Detection of beta-catenin mutations in paraffin-embedded sporadic desmoid-type fibromatosis by mutation-specific restriction enzyme digestion (MSRED): an ancillary diagnostic tool. Am J Surg Pathol. 2007;31(9):1299-1309 5. Domont J, Salas S, Lacroix L, et al: High frequency of beta-catenin heterozygous mutations in extra-abdominal fibromatosis: a potential molecular tool for disease management. Br J Cancer. 2010;102(6):1032-1036

COGBF
113530

B-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Children's Oncology Group Enrollment Testing, FISH, Varies

Clinical Information: In the United States, the incidence of acute lymphoblastic leukemia (ALL) is roughly 6000 new cases per year (as of 2019). ALL accounts for approximately 70% of all childhood leukemia cases (ages 0-19 years), making it the most common type of childhood cancer. Approximately 85% of pediatric cases of ALL are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). It has a peak incidence at 2 to 5 years of age. The incidence decreases with increasing age, before increasing again at around 50 years of age. ALL is slightly more common in male patients than female patients. There is an increased incidence of ALL in individuals with Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, X-linked agammaglobulinemia, and severe combined immunodeficiency. The overall cure rate for ALL in children is about 90% and about 45% to 60% of adults have long-term disease-free survival. CRLF2/IGH rearrangements are more commonly observed in patients with Down syndrome or of Hispanic descent. Specific genetic abnormalities are identified in the majority of cases of B-ALL, either by conventional chromosome studies or fluorescence in situ hybridization (FISH) studies. For more than 25 years, the Mayo Clinic Genomics Laboratory has served

as a Children's Oncology Group (COG) accredited laboratory for the performance of cytogenetic testing in pediatric patients being considered for enrollment in COG clinical trials and research. The laboratory is highly equipped to perform the time sensitive and critical cytogenetic testing necessary to assign risk stratification and facilitate enrollment in COG protocols. Each of the B-ALL genetic subgroups is important to detect and can be critical prognostic markers. The decision for early transplantation may be made if t(9;22)(q34;q11.2), MLL (KMT2A) translocations, RUNX1 duplication/amplification (iAMP21) or a hypodiploid clone is identified. In contrast, if the ETV6/RUNX1 fusion is detected by FISH or hyperdiploidy is identified by chromosome studies, the patient has a favorable prognosis and transplantation is rarely considered. A newly recognized World Health Organization entity BCR-ABL1-like ALL, also known as Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL), is increasing in importance due to the poor prognosis seen in pediatric, adolescent, and young adult ALL. Common features of this entity involve rearrangements with tyrosine kinase genes involving the following genes: ABL2, PDGFRB, JAK2, ABL1, CRLF2, and P2RY8. Deletion of IKZF1 often accompanies this entity. Some patients who have failed conventional therapies have demonstrated favorable responses to targeted therapies in clinical trials when rearrangements involving these specific gene regions have been identified. Evaluation of the MYC gene region is included in all diagnostic B-ALL panels to evaluate for Burkitt lymphoma. If a positive result is obtained, additional testing for the BCL2 and BCL6 gene regions will be performed. Metaphase FISH confirmation of classic translocations that are cryptic and not visually detectable by chromosome analysis [ie, t(12;21) associated with ETV6/RUNX1 fusion] is performed, as required by COG, and is included as part of the electronic case submission by the Mayo Clinic Genomics Laboratory to COG for central review. Additional cytogenetic techniques such as chromosomal microarray (CMAH / Chromosomal Microarray, Hematologic Disorders, Varies) may be helpful to resolve questions related to ploidy (hyperdiploid clone vs doubled hypodiploid clone) or to resolve certain clonal structural rearrangements such as the presence or absence of intra-chromosomal amplification of chromosome 21 (iAMP21). A summary of the characteristic chromosome abnormalities identified in B-ALL is listed in the following table. Table. Common Chromosome Abnormalities in B-cell Acute Lymphoblastic Leukemia Leukemia type Cytogenetic change Typical demographic Risk category B-cell acute lymphoblastic leukemia t(12;21)(p13;q22), ETV6(TEL)/RUNX1(AML1) Pediatric Favorable Hyperdiploidy Pediatric Favorable t(1;19)(q23;p13.3), PBX1/TCF3 Pediatric Intermediate t(9;22)(q34;q11.2), BCR/ABL1 Pediatric/adult Unfavorable iAMP21, RUNX1 Pediatric Unfavorable del(9p), CDKN2A(p16) All ages Unknown t(11q23;var), MLL All ages Unfavorable t(4;11)(q21;q23), AFF1(AF4)/MLL All ages Unfavorable t(6 ;11)(q27;q23), MLLT4(AFDN)/MLL All ages Unfavorable t(9;11)(p22;q23), MLLT3(AF9)/MLL All ages Unfavorable t(10;11)(p12;q23), MLLT10/MLL All ages Unfavorable t(11;19)(q23;p13.1), MLL/ELL All ages Unfavorable t(11;19)(q23;p13.3), MLL/MLLT1(ENL) All ages Unfavorable t(14q32;var), IGH All ages Variable t(X;14)(p22;q32)/t(Y;14)(p11;q32), CRLF2/IGH Adolescent/young adult Unfavorable t(Xp22.33;var) or t(Yp11.32;var), CRLF2 All ages Unfavorable t(Xp22.3;var) or t(Yp11.32;var), P2RY8 All ages Unfavorable -17/17p-, TP53 All ages Unfavorable t(8q24.1;var), MYC Pediatric/ adolescent/ young adult Complex karyotype (> or =4 abnormalities) Adult Unfavorable Low hypodiploidy/near triploidy Adult Unfavorable Near-haploid/hypodiploid All ages Unfavorable 7p-, IKZF1 All ages Unfavorable in absence of ERG deletion Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) t(1q25;var), ABL2 Pediatric/ adolescent/ young adult Unfavorable t(5q32;var), PDGFRB t(9p24.1;var), JAK2 t(9q34;var), ABL1 t(Xp22.33;var) or t(Yp11.32;var), CRLF2 t(Xp22.33;var) or t(Yp11.32;var), P2RY8

Useful For: Evaluation of pediatric bone marrow and peripheral blood specimens by fluorescence in situ hybridization probe analysis for classic rearrangements and chromosomal copy number changes associated with B-cell acute lymphoblastic leukemia/lymphoma (B-ALL) and Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) in patients being considered for enrollment in Children's Oncology Group (COG) clinical trials and research protocols As an adjunct to conventional chromosome studies in performed in pediatric patients with B-ALL and Ph-like ALL being considered for enrollment in COG protocols

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds

the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Moorman AV, Harrison CJ, Buck GAN, et al: Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood. 2007 Apr 15;109(8):3189-3197 2. Moorman AV: The clinical relevance of chromosomal and genetic abnormalities in B-cell precursor acute lymphoblastic leukemia. Blood Rev. 2012 May;26(3):123-135 3. Roberts KG, Li Y, Payne-Turner D, et al: Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med. 2014 Sep 11;371(11):1005-1015 4. Mullighan CG: The genomic landscape of acute lymphoblastic leukemia in children and young adults. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):174-180. doi: 10.1182/asheducation-2014.1.174 5. Swerdlow SH, Campo E, Harris NL, et al, eds: WHO Classification of Tumours. Vol 2. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017

BALAF
609537

B-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), FISH, Adult, Varies

Clinical Information: In the United States, the incidence of B-lymphoblastic leukemia/lymphoma (B-ALL/LBL) is roughly 6000 new cases per year, or approximately 1 in 50,000. B-ALL/LBL accounts for approximately 70% of all childhood leukemia cases (ages 0 to 19 years), making it the most common type of childhood cancer. It has a peak incidence at 2 to 5 years of age. This incidence decreases with age before increasing again at around 50 years of age. B-ALL/LBL is slightly more common in male patients than female patients. There is also an increased incidence of B-ALL/LBL in individuals with genetic conditions such as Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, Li-Fraumeni syndrome, X-linked agammaglobulinemia, and severe combined immunodeficiency. The overall cure rate for B-ALL/LBL in children is approximately 90%, and about 45% to 60% of adults have long-term disease-free survival. Of note, CRLF2::IGH fusion is more commonly observed in patients with Down syndrome or of Hispanic descent. Specific cytogenetic abnormalities are identified in the majority of cases of B-ALL/LBL, by conventional chromosome studies and/or fluorescence in situ hybridization (FISH) studies. B-ALL genetic subgroups are important to detect and can be critical prognostic markers. For example, a decision for early transplantation may be made if BCR::ABL1 fusion, KMT2A rearrangement, iAMP21, or a hypodiploid clone is identified. In contrast, if ETV6::RUNX1 fusion or hyperdiploidy is identified, the patient has a more favorable prognosis and transplantation is rarely initially considered. A newly recognized World Health Organization entity called BCR-ABL1-like ALL, also known as Philadelphia chromosome-like acute lymphoblastic leukemia, is increasing in importance due to the poor prognosis seen in pediatric, adolescent, and young adult ALL. Common features of this entity involve rearrangements with tyrosine kinase genes involving the following genes: ABL2, PDGFRB, JAK2, ABL1, CRLF2, and P2RY8, as well as deletions involving IKZF1. Patients who have failed conventional therapies have demonstrated favorable responses to targeted therapies when rearrangements involving these specific gene regions have been identified. Evaluation of the MYC gene region is included in all diagnostic pediatric B-ALL panels to evaluate for Burkitt lymphoma. If a positive result is obtained, additional testing for the BCL2 and BCL6 gene regions may be considered. Per National Comprehensive Cancer Network guidelines, a combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients with B-ALL/lymphoblastic lymphoma (LBL). Additional cytogenetic techniques such as chromosomal microarray (CMAH / Chromosomal Microarray, Hematologic Disorders, Varies) may be helpful to resolve questions related to ploidy (hyperdiploid clone vs doubled hypodiploid clone) or to

resolve certain clonal structural rearrangements such as the presence or absence of intra-chromosomal amplification of chromosome 21 (iAMP21). A summary of the characteristic chromosome abnormalities identified in B-ALL is listed in the following table. Table. Common Chromosome Abnormalities in B-cell Acute Lymphoblastic Leukemia Leukemia type Cytogenetic change Typical demographic Risk category B-acute lymphoblastic leukemia t(12;21)(p13;q22), ETV6::RUNX1 Pediatric Favorable Hyperdiploidy Pediatric Favorable t(1;19)(q23;p13.3), PBX1::TCF3 Pediatric Intermediate to favorable t(9;22)(q34;q11.2), BCR::ABL1 All ages Unfavorable iAMP21, RUNX1 Pediatric Unfavorable del(9p), CDKN2A All ages Unknown t(11q23;var), MLL rearrangement All ages Unfavorable t(4;11)(q21;q23), AFF1::MLL All ages Unfavorable t(6;11)(q27;q23), MLLT4(AFDN)::MLL All ages Unfavorable t(9;11)(p22;q23), MLLT3::MLL All ages Unfavorable t(10;11)(p12;q23), MLLT10::MLL All ages Unfavorable t(11;19)(q23;p13.1), MLL::ELL All ages Unfavorable t(11;19)(q23;p13.3), MLL::MLLT1 All ages Unfavorable t(14q32;var), IGH rearrangement All ages Variable t(X;14)(p22;q32)/t(Y;14)(p11;q32), CRLF2::IGH Adolescent/ young adult Unfavorable t(Xp22.33;var) or t(Yp11.32;var), CRLF2 rearrangement All ages Unfavorable t(Xp22.33;var) or t(Yp11.32;var), P2RY8 rearrangement All ages Unfavorable -17/17p-, TP53 All ages Unfavorable t(8q24.2;var), MYC rearrangement *representing Burkitt or other mature B-cell lymphoma Pediatric/ adolescent/ young adult Complex karyotype (> or =4 abnormalities) Adult Unfavorable Low hypodiploidy/near triploidy Adult Unfavorable Near-haploid/hypodiploid All ages Unfavorable del(7p) IKZF1 All ages Unfavorable in absence of ERG deletion Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) t(1q25;var), ABL2 Pediatric/ adolescent/ young adult Unfavorable t(5q32;var), PDGFRB t(9p24.1;var), JAK2 t(9q34;var), ABL1 t(Xp22.33;var) or t(Yp11.32;var), CRLF2 t(Xp22.33;var) or t(Yp11.32;var), P2RY8

Useful For: Detecting, at diagnosis, recurrent common chromosome abnormalities associated with B-cell acute lymphoblastic leukemia/lymphoma (B-ALL/LBL) and Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) in adult patients As an adjunct to conventional chromosome studies in patients with B-ALL/LBL Evaluating specimens in which chromosome studies are unsuccessful This test should not be used to screen for residual B-ALL/LBL.

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. The absence of an abnormal clone does not rule out the presence of an acute B-cell lymphoblastic leukemia/lymphoma or another neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Moorman AV, Harrison CJ, Buck GA, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood. 2007;109(8):3189-3197. doi:10.1182/blood-2006-10-051912 2. Moorman AV. The clinical relevance of chromosomal and genetic abnormalities in B-cell precursor acute lymphoblastic leukemia. Blood Rev. 2012;26:123-135. doi:10.1016/j.blre.2012.01.001 3. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med. 2014;371(11):1005-1015. doi:10.1056/NEJMoa1403088 4. Mullighan CG. The genomic landscape of acute lymphoblastic leukemia in children and young adults. Hematology Am Soc Hematol Educ Program. 2014;2014(1):174-180. doi:10.1182/asheducation-2014.1.174 5. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours. Vol 2.

BALPF 609547 B-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Pediatric, FISH, Varies

Clinical Information: In the United States, the incidence of B-lymphoblastic leukemia/lymphoma (B-ALL/LBL) is roughly 6000 new cases per year or approximately 1 in 50,000. B-ALL/LBL accounts for approximately 70% of all childhood leukemia cases (ages 0 to 19 years), making it the most common type of childhood cancer. It has a peak incidence at 2 to 5 years of age. This incidence decreases with age before increasing again at around 50 years of age. B-ALL/LBL is slightly more common in male patients than female patients. There is also an increased incidence of B-ALL/LBL in individuals with genetic conditions such as Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, Li-Fraumeni syndrome, X-linked agammaglobulinemia, and severe combined immunodeficiency. The overall cure rate for B-ALL/LBL in children is approximately 90%, and about 45% to 60% of adults have long-term disease-free survival. Of note, CRLF2::IGH fusion is more commonly observed in patients with Down syndrome or of Hispanic descent. Specific cytogenetic abnormalities are identified in the majority of cases of B-ALL/LBL, by conventional chromosome studies or fluorescence in situ hybridization (FISH) studies. B-ALL genetic subgroups are important to detect and can be critical prognostic markers. For example, a decision for early transplantation may be made if BCR::ABL1 fusion, KMT2A rearrangement, iAMP21, or a hypodiploid clone is identified. In contrast, if the ETV6::RUNX1 fusion or hyperdiploidy is identified, the patient has a more favorable prognosis and transplantation is rarely initially considered. A newly recognized World Health Organization entity called BCR-ABL1-like ALL, also known as Philadelphia chromosome-like acute lymphoblastic leukemia, is increasing in importance due to the poor prognosis seen in pediatric, adolescent, and young adult ALL. Common features of this entity involve rearrangements with tyrosine kinase genes involving the following genes: ABL2, PDGFRB, JAK2, ABL1, CRLF2, and P2RY8, as well as deletions involving IKZF1. Patients who have failed conventional therapies have demonstrated favorable responses to targeted therapies when rearrangements involving these specific gene regions have been identified. Evaluation of the MYC gene region is included in all diagnostic B-ALL panels to evaluate for Burkitt lymphoma. If a positive result is obtained, additional testing for the BCL2 and BCL6 gene regions may be considered. Per National Comprehensive Cancer Network guidelines, a combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients with B-ALL/lymphoblastic lymphoma (LBL). Additional cytogenetic techniques such as chromosomal microarray (CMAH / Chromosomal Microarray, Hematologic Disorders, Varies) may be helpful to resolve questions related to ploidy (hyperdiploid clone vs doubled hypodiploid clone) or to resolve certain clonal structural rearrangements such as the presence or absence of intra-chromosomal amplification of chromosome 21 (iAMP21). A summary of the characteristic chromosome abnormalities identified in B-ALL is listed in the following table. Table. Common Chromosome Abnormalities in B-cell Acute Lymphoblastic Leukemia Leukemia type Cytogenetic change Typical demographic Risk category B-acute lymphoblastic leukemia t(12;21)(p13;q22), ETV6::RUNX1 Pediatric Favorable Hyperdiploidy Pediatric Favorable t(1;19)(q23;p13.3), PBX1::TCF3 Pediatric Intermediate to favorable t(9;22)(q34;q11.2), BCR::ABL1 All ages Unfavorable iAMP21, RUNX1 Pediatric Unfavorable del(9p), CDKN2A All ages Unknown t(11q23;var), MLL rearrangement All ages Unfavorable t(4;11)(q21;q23), AFF1::MLL All ages Unfavorable t(6;11)(q27;q23), MLLT4(AFDN)::MLL All ages Unfavorable t(9;11)(p22;q23), MLLT3::MLL All ages Unfavorable t(10;11)(p12;q23), MLLT10::MLL All ages Unfavorable t(11;19)(q23;p13.1), MLL::ELL All ages Unfavorable t(11;19)(q23;p13.3), MLL::MLLT1 All ages Unfavorable t(14q32;var), IGH rearrangement All ages Variable t(X;14)(p22;q32)/t(Y;14)(p11;q32), CRLF2::IGH Adolescent/ young adult Unfavorable t(Xp22.33;var) or t(Yp11.32;var), CRLF2 rearrangement All ages Unfavorable t(Xp22.33;var) or t(Yp11.32;var), P2RY8 rearrangement All ages Unfavorable -17/17p-, TP53 All ages Unfavorable t(8q24.2;var), MYC rearrangement *representing Burkitt or other mature B-cell lymphoma Pediatric/ adolescent/ young adult Complex karyotype (> or =4 abnormalities) Adult Unfavorable Low hypodiploidy/near triploidy Adult Unfavorable Near-haploid/hypodiploid All ages Unfavorable del(7p) IKZF1 All ages Unfavorable in absence of ERG deletion Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) t(1q25;var), ABL2 Pediatric/ adolescent/ young adult Unfavorable t(5q32;var), PDGFRB t(9p24.1;var), JAK2 t(9q34;var), ABL1 t(Xp22.33;var) or t(Yp11.32;var), CRLF2 t(Xp22.33;var) or t(Yp11.32;var), P2RY8

Useful For: Detecting, at diagnosis, recurrent common chromosome abnormalities associated with B-

cell acute lymphoblastic leukemia/lymphoma (B-ALL/LBL) and Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) in pediatric patients As an adjunct to conventional chromosome studies for pediatric patients with B-ALL/LBL Evaluating specimens in which chromosome studies are unsuccessful This test should not be used to screen for residual B-ALL/LBL.

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. The absence of an abnormal clone does not rule out the presence of an acute B-cell lymphoblastic leukemia/lymphoma or another neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Moorman AV, Harrison CJ, Buck GA, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood. 2007;109(8):3189-3197 2. Moorman AV. The clinical relevance of chromosomal and genetic abnormalities in B-cell precursor acute lymphoblastic leukemia. Blood Rev. 2012;26:123-135 3. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med. 2014;371(11):1005-1015 4. Mullighan CG. The genomic landscape of acute lymphoblastic leukemia in children and young adults. Hematology Am Soc Hematol Educ Program. 2014;2014(1):174-180 5. Swerdlow SH, Campo E, Harris NL, et al, eds: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours. Vol 2.

BALMF 614215 B-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Specified FISH, Varies

Clinical Information:

Useful For: Detecting a neoplastic clone associated with recurrent common chromosome abnormalities associated with B-cell acute lymphoblastic leukemia/lymphoma (B-ALL/LBL) and Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) using client specified probes As an adjunct to conventional chromosome studies in patients with B-ALL/LBL Evaluating specimens in which chromosome studies are unsuccessful This test should not be used to screen for residual B-ALL/LBL.

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. The absence of an abnormal clone does not rule out the presence of an acute B-cell lymphoblastic leukemia/lymphoma or another neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Moorman AV, Harrison CJ, Buck GA, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood. 2007;109(8):3189-3197. doi:10.1182/blood-2006-10-051912 2. Moorman AV. The clinical relevance of chromosomal and genetic abnormalities in B-cell precursor acute lymphoblastic leukemia. Blood Rev. 2012;26(3):123-135. doi:10.1016/j.blre.2012.01.001 3. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med. 2014;371(11):1005-1015. doi:10.1056/NEJMoa1403088 4. Mullighan CG. The genomic landscape of acute lymphoblastic leukemia in children and young adults. Hematology Am Soc Hematol Educ

Program. 2014;2014(1):174-180. doi:10.1182/asheducation-2014.1.174 5. Arber DA, Orazi A, Hasserjian R, et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405. doi:10.1182/blood-2016-03-643544

BCELL
620106

B-Cell and Antibody Deficiency Gene Panel, Varies

Clinical Information: Primary B-cell disorders and humoral immunodeficiencies are characterized by an insufficient number of B cells or the impaired functioning or differentiation of B cells. B-cell disorders account for approximately half to two-thirds of all genetic primary immunodeficiency disorders (PIDD). They may result in a decrease or dysfunction of one or more isotypes of immunoglobulin, leading to increased susceptibility to infection, particularly bacterial infections, such as sinopulmonary infections, gastrointestinal infections, otitis, skin infections, and conjunctivitis. In the absence of infection, patients may be asymptomatic and, thus, difficult to diagnose. In addition, primary B-cell disorders may result in lymphoproliferative disorders or be associated with autoimmune (AI) manifestations, including AI cytopenias, AI endocrine disorders, and AI enteropathy. Primary immunodeficiency disorders that are primarily antibody deficiencies fall into four main categories: 1. Agammaglobulinemias, which are characterized by severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells 2. Common variable immunodeficiency (CVID)-like diseases that are characterized by severe reduction in at least two serum immunoglobulin isotypes with normal or low number of B cells 3. Hyper-IgM syndromes, which are characterized by severe reduction in serum IgG and IgA with normal or elevated IgM and normal numbers of B cells 4. A mixed group of isotype, light chain, or functional antibody deficiencies generally with normal numbers of B cells In addition, there are several PIDD that also have an associated T-cell or other cellular immunodeficiency as well as B-cell defects. Agammaglobulinemia typically presents in the first few years of life with recurrent bacterial infections, a severe life-threatening bacterial infection (ie, meningitis, sepsis), and decreased lymphoid tissue (ie, small adenoids, tonsils, and lymph nodes in X-linked agammaglobulinemia, due to Bruton tyrosine kinase [BTK] gene variants). Inheritance can be either X-linked (eg, due to variants in BTK), autosomal dominant (eg, TCF3, TOP2B), or autosomal recessive (eg, IGHM, CD79A, CD79B, IGLL1, BLNK, and PIK3R1). Common variable immunodeficiency (CVID) is the most common adult humoral immunodeficiency disorder with an incidence of approximately 1:10,000 to 1:50,000. CVID may present with frequent and unusual infections during early childhood, adolescence, or adulthood. As per current diagnostic criteria, CVID is not considered in children younger than 4 years. In addition, a significant proportion of patients may have autoimmune or inflammatory manifestations, enlarged lymphoid tissues, granulomas, and an increased susceptibility to cancer. These patients typically have normal numbers of B cells (<5% of CVID patients have <1% B cells, which is due to early B-cell defects) but have impaired terminal differentiation, resulting in decreased levels of IgG and IgA, with or without a decrease in IgM. Over two-thirds of patients have quantitative defects in switched memory B cells. Some patients may also have quantitative and functional T-cell defects or natural killer (NK) cell deficiency. Patients with decreased naive T-cell numbers are considered to have late-onset combined immunodeficiency. Genetic variants have been identified in several genes, including ICOS, TNFRSF13B (TACI), CD19, TNFRSF13C (BAFFR), MS4A1 (CD20), CR2 (CD21), CD81, LRBA, NFKB2, and IKZF1 (IKAROS) in a subset of CVID patients. However, most of these patients have unknown genetic defects and may have oligogenic or polygenic causes of disease. Hyper IgM syndrome is characterized by an inability to switch from the production of IgM-type antibodies to IgG, IgA, or IgE isotypes. The condition is most often caused by variants in CD40LG, but variants in other genes (eg, CD40, AICDA, PI3KCD, UNG) have also been reported to cause disease. Patients with CD40L and CD40 deficiency tend to present with severe opportunistic infections more reminiscent of a cellular immunodeficiency and, therefore, may also be considered as combined immunodeficiencies. Selective antibody deficiencies may occur when a patient is either lacking a specific immunoglobulin isotype (eg, selective IgA deficiency or IgG deficiency) or a specific vaccine antibody response (impaired pneumococcal polysaccharide responsiveness). Selective deficiencies may be due to variants in genes encoding immunoglobulin heavy or light chains. Selective IgA deficiency (sIgAD) is the most common PIDD with an incidence of

1:200 to 1:1000, depending on the cohort studied. Most patients with sIgAD are asymptomatic though some may have frequent infections. There is also a higher incidence of celiac disease in this group. Most patients with selective antibody deficiencies are treated if they have frequent infections in addition to impaired vaccine antibody responses. Some patients with sIgAD may have autoantibodies to IgA.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an inherited primary B-cell disorder or humoral immunodeficiency Establishing a diagnosis of a primary B-cell disorder or humoral immunodeficiency, allowing for appropriate management and surveillance for disease features based on the gene or variant involved Identifying variants within genes known to be associated with primary B-cell disorders or humoral immunodeficiencies, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507. doi:10.1007/s10875-022-01289-3 3. Smith T, Cunningham-Rundles C. Primary B-cell immunodeficiencies. Hum Immunol. 2019;80(6):351-362. doi:10.1016/j.humimm.2018.10.015 4. Peng XP, Caballero-Oteyza A, Grimbacher B. Common variable immunodeficiency: more pathways than roads to Rome. Annu Rev Pathol. 2023;18:283-310. doi:10.1146/annurev-pathmechdis-031521-024229 5. Wang LA, Abbott JK. "Common variable immunodeficiency: Challenges for diagnosis". J Immunol Methods. 2022;509:113342. doi:10.1016/j.jim.2022.113342 6. Ramirez NJ, Posadas-Cantera S, Caballero-Oteyza A, Camacho-Ordonez N, Grimbacher B. There is no gene for CVID - novel monogenetic causes for primary antibody deficiency. Curr Opin Immunol. 2021;72:176-185. doi:10.1016/j.coi.2021.05.010 7. Cardenas-Morales M, Hernandez-Trujillo VP. Agammaglobulinemia: from X-linked to autosomal forms of disease. Clin Rev Allergy Immunol. 2022;63(1):22-35. doi:10.1007/s12016-021-08870-5 8. Jhamnani RD, Nunes-Santos CJ, Bergerson J, Rosenzweig SD. Class-switch recombination (CSR)/dyper-IgM (HIGM) syndromes and phosphoinositide 3-kinase (PI3K) defects. Front Immunol. 2018;9:2172. doi:10.3389/fimmu.2018.02172 9. de la Morena MT. Clinical phenotypes of hyper-IgM syndromes. J Allergy Clin Immunol Pract. 2016;4(6):1023-1036. doi:10.1016/j.jaip.2016.09.013 10. Yazdani R, Fekrvand S, Shahkarami S, et al. The hyper IgM syndromes: Epidemiology, pathogenesis, clinical manifestations, diagnosis and management. Clin Immunol. 2019;198:19-30. doi:10.1016/j.clim.2018.11.007 11. Bousfiha A, Moundir A, Tangye SG, et al. The 2022 update of IUIS phenotypical classification for human inborn errors of immunity. J Clin Immunol. 2022;42(7):1508-1520. doi:10.1007/s10875-022-01352-z

CD40
89009

B-Cell CD40 Expression by Flow Cytometry, Blood

Clinical Information: The adaptive immune response includes both cell-mediated (mediated by T cells and natural killer [NK] cells) and humoral (mediated by B cells) immunity. After antigen recognition and maturation in secondary lymphoid organs, some antigen-specific B cells terminally differentiate into antibody-secreting plasma cells. Decreased numbers or aberrant function of B cells result in humoral immune deficiency states with increased susceptibility to infections, and these may be either primary

(genetic) or secondary immunodeficiencies. Secondary causes include medications, malignancies, infections, and autoimmune disorders (this does not cause immunodeficiency with increased infection). CD40 is a member of the tumor necrosis factor receptor superfamily, expressed on a wide range of cell types including B cells, macrophages, and dendritic cells.(1) CD40 is the receptor for CD40 ligand (CD40LG), a molecule predominantly expressed by activated CD4+ T cells. CD40/CD40LG interaction is involved in the formation of memory B lymphocytes and promotes immunoglobulin (Ig) isotype switching.(1) CD40LG expression in T cells requires cellular activation, while CD40 is constitutively expressed on the surface of B cells and other antigen-presenting cells. Hyperimmunoglobulin M (hyper-IgM or HIGM) syndrome is a rare primary immunodeficiency characterized by increased or normal levels of IgM with low IgG and/or IgA.(2) Patients with hyper-IgM syndromes may have genetic variants in 1 of several known genes. Some of these genes are CD40LG, CD40, AICDA (activation-induced cytidine deaminase), UNG (uracil DNA glycosylase), and IKBKG (inhibitor of kappa light polypeptide gene enhancer in B cells, kinase gamma; also known as NEMO).(2) Not all cases of hyper-IgM syndrome fit into these known genetic defects. Variants in CD40LG and IKBKG are inherited in an X-linked fashion, while variants in the other 3 genes are autosomal recessive in inheritance. Elevated IgM is only one of the features of NEMO deficiency and therefore, it is no longer classified exclusively with the hyper-IgM syndromes. Distinguishing between the different forms of hyper-IgM syndrome is very important because of differing prognoses. CD40 and CD40LG deficiency are among the more severe forms, which typically manifest in infancy or early childhood, and are characterized by an increased susceptibility to opportunistic pathogens (eg, Pneumocystis carinii, Cryptosporidium, and Toxoplasma gondii).(3) CD40 deficiency, also known as hyper-IgM type 3 (HIGM3), accounts for less than 1% of hyper-IgM syndromes. Flow cytometry analysis usually shows a complete lack of CD40 expression on the B cells of these patients.(4) Intravenous injection with IgG is the treatment of choice along with immune reconstitution with hematopoietic cell transplantation. Most CD40-deficient patients have been diagnosed before age 1. Consequently, when used in the context of HIGM3, this test is only indicated in children (for diagnosis). In the case of CD40L deficiency, this test can be used for male patients or in female patients of child-bearing age (to identify carriers). A larger age spectrum has been reported with CD40L deficiency, ranging from infancy to early adulthood.

Useful For: Evaluating patients for hyper-IgM type 3 (HIGM3) syndrome due to defects in CD40, typically seen in patients less than 10 years Assessing B-cell immune competence in other clinical contexts, including autoimmunity, malignancy, and transplantation

Interpretation: This assay is qualitative; CD40 expression is reported as present (normal) or absent (abnormal). Normal B cells express surface CD40 on the majority of cells. Hyper-IgM (HIGM3) syndrome patients typically do not express CD40 on the surface of B cells. Genotyping of CD40 is required for a definite diagnosis of HIGM3. Call 800-533-1710 for ordering assistance.

Reference Values:
Present (normal)

Clinical References: 1. Bishop GA, Hostager BS. The CD40-CD154 interaction in B cell-T cell liaisons. Cytokine Growth Factor Rev. 2003;14(3-4):297-309 2. Lee WI, Torgerson TR, Schumacher MJ, et al. Molecular analysis of a large cohort of patients with hyper immunoglobulin M (IgM) syndrome. Blood. 2005;105(5):1881-1890 3. Kutukculer N, Moratto D, Aydinok Y, et al. Disseminated cryptosporidium infection in an infant with hyper-IgM syndrome caused by CD40 deficiency. J Pediatr. 2003;142(2):194-196 4.Banday AZ, Nisar R, Patra PK et al. Clinical and immunological features, genetic variants, and outcomes of patients with CD40 Deficiency J Clin Immunol. 2023;44(1):17. doi:10.1007/s10875-023-01633-1. 5. Yazdani R, Fekrvand S, Shahkarami S, et al. The hyper IgM syndromes: Epidemiology, pathogenesis, clinical manifestations, diagnosis and management. Clin Immunol. 2019;198:19-30. doi:10.1016/j.clim.2018.11.007

BALLM
608251

B-Cell Lymphoblastic Leukemia Monitoring, Minimal Residual Disease Detection, Flow Cytometry, Varies

Clinical Information: B-cell acute lymphoblastic leukemia (B-ALL) is a neoplasm of precursor cells (lymphoblasts) committed to B-cell lineage. B-ALL is the most common acute leukemia in children and adolescents and can also occur in adults. Patients with B-ALL typically present with a high blast count in the peripheral blood and bone marrow replacement with the disease. The diagnosis of B-ALL is based on a combination of morphologic features showing primarily small blasts with open chromatin and high N:C ratio, and an immunophenotype showing immaturity (CD34 and/or TdT expression) associated with B-cell lineage markers (CD19, CD22, and CD79a). New therapeutic approaches in B-ALL have been increasingly successful. One of the most important predictors of the disease relapse is the ability to detect minimal residual disease (MRD) in the bone marrow specimens following induction phase of the therapy (day 28). Immunophenotyping studies are necessary as morphologic features are not sufficient to detect MRD. The absence of MRD (at 0.002% sensitivity) is an important prognostic indicator in these patients. This test may also be used to establish an immunophenotypic fingerprint of tumor cells at diagnosis to monitor MRD in these patients after treatments or allogeneic stem cell transplant.

Useful For: Aids in monitoring a previously confirmed diagnosis of B-cell acute lymphoblastic leukemia

Interpretation: An interpretive report for the presence or absence of B-cell acute lymphoblastic leukemia (B-ALL) minimal residual disease (MRD) is provided. Patients who have detectable MRD by this assay are considered to have residual/recurrent B-ALL.

Reference Values:
An interpretive report will be provided.
This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist for every case.

Clinical References: 1. Bader P, Kreyenberg H, Henze GHR, et al. Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group. J Clin Oncol. 2009;27(3):377-384 2. Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood. 2008;111(12):5477-5485 3. Borowitz MJ, Pullen DJ, Winick N, Martin PL, Bowman WP, Camitta B. Comparison of diagnostic and relapse flow cytometry phenotypes in childhood acute lymphoblastic leukemia: implications for residual disease detection: a report from the children's oncology group. Cytometry B Clin Cytom. 2005;68(1):18-24 4. Campana D. Role of minimal residual disease monitoring in adult and pediatric acute lymphoblastic leukemia. Hematol Oncol Clin North Am. 2009;23(5):1083-1098 5. Chen W, Karadikar NJ, McKenna RW, Kroft SH. Stability of leukemia-associated immunophenotypes in precursor B-lymphoblastic leukemia/lymphoma: a single institution experience. Am J Clin Pathol. 2007;127(1):39-46 6. Coustan-Smith E, Ribeiro RC, Stow P, et al. A simplified flow cytometric assay identifies children with acute lymphoblastic leukemia who have a superior clinical outcome. Blood. 2006;108(1):97-102 7. Coustan-Smith E, Sancho J, Behm FG, et al. Prognostic importance of measuring early clearance of leukemic cells by flow cytometry in childhood acute lymphoblastic leukemia. Blood. 2002;100(1):52-58 8. Guillaume N, Penther D, Vaida I, et al. CD66c expression in B-cell lymphoblastic leukemia: strength and weakness. Int J Lab Hematol. 2011;33(1):92-96 9. Stow P, Key L, Chen X, et al. Clinical significance of low levels of minimal residual disease at the end of remission induction therapy in childhood acute lymphoblastic leukemia. Blood. 2010;115(23):4657-4663 10. Wood BL. Principals of minimal residual disease detection for hematopoietic neoplasms by flow cytometry. Cytometry B Clin Cytom. 2016;90(1):47-53

BLBLF
609451

B-Cell Lymphoblastic Leukemia/Lymphoma, FISH, Tissue

Clinical Information: In the United States, the incidence of B-lymphoblastic leukemia/lymphoma (B-ALL/LBL) is roughly 6000 new cases per year, or approximately 1 in 50,000. B-ALL/LBL accounts for approximately 70% of all childhood leukemia cases (ages 0 to 19 years), making it the most common type of childhood cancer. It has a peak incidence at 2 to 5 years of age. This incidence decreases with age before increasing again at around 50 years of age. Per National Comprehensive Cancer Network guidelines, a combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients with B-ALL/lymphoblastic lymphoma (LBL). Additional cytogenetic techniques, such as chromosomal microarray (CMAH / Chromosomal Microarray, Hematologic Disorders, Varies), may be helpful in resolving either questions related to ploidy (hyperdiploid clone vs doubled hypodiploid clone) or certain clonal structural rearrangements, such as the presence or absence of intra-chromosomal amplification of chromosome 21 (iAMP21). A summary of the characteristic chromosome abnormalities identified in B-ALL is listed in the following table. Table. Common Chromosome Abnormalities in B-cell Acute Lymphoblastic Leukemia Leukemia type Cytogenetic change Typical demographic Risk category B-acute lymphoblastic leukemia t(12;21)(p13;q22), ETV6::RUNX1 Pediatric Favorable Hyperdiploidy Pediatric Favorable t(1;19)(q23;p13.3), PBX1::TCF3 Pediatric Intermediate to favorable t(9;22)(q34;q11.2), BCR::ABL1 All ages Unfavorable iAMP21, RUNX1 Pediatric Unfavorable del(9p), CDKN2A All ages Unknown t(11q23;var), MLL rearrangement All ages Unfavorable t(4;11)(q21;q23), AFF1::MLL All ages Unfavorable t(6;11)(q27;q23), MLLT4(AFDN)::MLL All ages Unfavorable t(9;11)(p22;q23), MLLT3::MLL All ages Unfavorable t(10;11)(p12;q23), MLLT10::MLL All ages Unfavorable t(11;19)(q23;p13.1), MLL::ELL All ages Unfavorable t(11;19)(q23;p13.3), MLL::MLLT1 All ages Unfavorable t(14q32;var), IGH rearrangement All ages Variable t(X;14)(p22;q32)/t(Y;14)(p11;q32), CRLF2::IGH Adolescent/ young adult Unfavorable t(Xp22.33;var) or t(Yp11.32;var), CRLF2 rearrangement All ages Unfavorable t(Xp22.33;var) or t(Yp11.32;var), P2RY8 rearrangement All ages Unfavorable -17/17p-, TP53 All ages Unfavorable t(8q24.2;var), MYC rearrangement *representing Burkitt or other mature B-cell lymphoma Pediatric/ adolescent/ young adult Complex karyotype (> or =4 abnormalities) Adult Unfavorable Low hypodiploidy/near triploidy Adult Unfavorable Near-haploid/hypodiploid All ages Unfavorable del(7p) IKZF1 All ages Unfavorable in absence of ERG deletion Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) t(1q25;var), ABL2 Pediatric/ adolescent/ young adult Unfavorable t(5q32;var), PDGFRB t(9p24.1;var), JAK2 t(9q34;var), ABL1 t(Xp22.33;var) or t(Yp11.32;var), CRLF2 t(Xp22.33;var) or t(Yp11.32;var), P2RY8

Useful For: Detecting, at diagnosis, recurrent common chromosome abnormalities associated with B-cell acute lymphoblastic leukemia/lymphoma (B-ALL/LBL) and Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) in paraffin-embedded specimens

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. A positive result is not diagnostic for B-cell lymphoblastic lymphoma but may provide relevant prognostic information. The absence of an abnormal clone does not rule out the presence of an acute B-cell lymphoblastic leukemia/lymphoma or another neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Moorman AV, Harrison CJ, Buck GA, et al.: Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood. 2007. Apr 15;109(8):3189-3197 2. Moorman AV.: The clinical relevance of chromosomal and genetic abnormalities in B-cell precursor acute lymphoblastic leukemia. Blood Rev. 2012 May;26(3):123-135 3. Roberts KG, Li Y, Payne-Turner D, et al.: Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med. 2014 Sept

11;371(11):1005-1015 4. Mullighan CG.: The genomic landscape of acute lymphoblastic leukemia in children and young adults. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):174-180 5. Arber DA, Orazi A, Hasserjian R, et al.: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-2405 6. Swerdlow SH, Campo E, Harris NL, et al, eds.: WHO Classification of Tumours. Vol 2.WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours. Vol 2.

BLYM
65878

B-Cell Lymphoma, FISH, Tissue

Clinical Information:

Useful For: Detecting recurrent common chromosome abnormalities associated with various B-cell lymphomas in paraffin-embedded tissue specimens at diagnosis

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. Detection of an abnormal clone is supportive of a diagnosis of a B-cell lymphoma. The specific abnormality detected may help determine a B-cell lymphoma subtype and/or contribute to the prognosis. The absence of an abnormal clone, or Negative result, does not rule out the presence of a neoplastic disorder or change the pathologic diagnosis.

Reference Values:
An interpretive report will be provided.

Clinical References: Swerdlow SH, Campo E, Harris NL, eds, et al: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC; 2017. WHO Classification of Tumours. Vol 2

JLYMF
614564

B-Cell Lymphoma, FISH, Tissue

Clinical Information:

Useful For: Providing essential information for an integrated pathologic diagnosis, an individualized treatment plan, and predicting patient response to treatment

Interpretation: The frequency of each gene rearrangement in a particular subtype of B-cell lymphoma varies from 100% to less than 10%; therefore, a negative result of a particular fluorescence in situ hybridization (FISH) test will not change the pathologic diagnosis. MYC rearrangement is mainly caused by t(8;14)(q24.1;q32) translocation and less commonly by t(2;8)(p12;q24.1) and t(8;22)(q24.1;q11.2). The tri-color dual fusion probe detects MYC-IGH fusion caused by t(8;14). The dual color-MYC break apart probe used in this test detects the MYC rearrangement caused by all 3 different translocations. Similarly, the rearrangement of BCL2 and BCL6 have involved multiple partner genes, and these can be detected by BCL2 and BCL6 break apart probes. The diffuse large B-cell lymphoma is associated with BCL2, BCL6, and MYC rearrangements. A double-hit (rarely triple-hit) high-grade B-cell lymphoma is identified when a tumor shows BCL2 or BCL6 rearrangement along with IGH-MYC fusion or other types of MYC rearrangement. The FISH results will be correlated with clinical, pathological, and immunologic features by a pathologist for final interpretation.

Reference Values:
An interpretive report will be provided.

Clinical References: Campo E, Harris NL, Jaffe ES, eds. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. IARC; 2017

BLPMF
614227

B-Cell Lymphoma, Specified FISH, Varies

Clinical Information: Mature B-cell lymphoma can be low grade, intermediate grade, or high grade, and the prognosis and clinical course are highly variable. Genetic abnormalities can assist diagnosis and have served as important prognostic markers in B-cell lymphomas. Fluorescence in situ hybridization (FISH) permits the detection of recurrent gene rearrangements associated with various chromosomal abnormalities in specific B-cell lymphoma subtypes (see Table). Table. Common Chromosome Abnormalities in B-cell Lymphomas Lymphoma type Chromosome abnormality FISH probe Burkitt (pediatric, < or =18 years old) 8q24.1 rearrangement 5'/3' MYC t(2;8)(p12;q24.1) IGK/MYC t(8;14)(q24.1;q32) MYC/IGH t(8;22)(q24.1;q11.2) MYC/IGL 3q27 rearrangement 3'/5' BCL6 18q21 rearrangement 3'/5' BCL2 Diffuse large B-cell, "double-hit" 8q24.1 rearrangement 5'/3' MYC t(8;14)(q24.1;q32) MYC/IGH ----Reflex: t(8;22)(q24.1;q11.2) MYC/IGL ----Reflex: t(2;8)(p12;q24.1) IGK/MYC ----Reflex: 3q27 rearrangement 3'/5' BCL6 ----Reflex: 18q21 rearrangement 3'/5' BCL2 Follicular 18q21 rearrangement 3'/5' BCL2 3q27 rearrangement 3'/5' BCL6 Mantle cell t(11;14)(q13;q32) CCND1/IGH ----Reflex: 11q13 rearrangement 5'/3' CCND1 Blastoid subtype only: deletion of 17p TP53/D17Z1 Blastoid subtype only: 8q24.1 rearrangement 5'/3' MYC Splenic marginal zone Deletion of 7q D7Z1/7q32 Deletion of 17p TP53/D17Z1

Useful For: Detecting, at diagnosis, common chromosome abnormalities associated with specific B-cell lymphoma subtypes using client specified FISH probes

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. Detection of an abnormal clone supports a diagnosis of B-cell lymphoma. The specific abnormality detected may help to determine a specific B-cell lymphoma subtype. The absence of an abnormal clone does not rule out the presence of lymphoma or another neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours. Vol 2 2. King RL, McPhail ED, Meyer RG, et al. False-negative rates for MYC fluorescence in situ hybridization probes in B-cell neoplasms. Haematologica. 2019;104(6):e248-e251 3. Pophali PA, Marinelli LM, Ketterling RP, et al. High level MYC amplification in B-cell lymphomas: is it a marker of aggressive disease?. Blood Cancer J. 2020;10(1):5

IABCS
88800

B-Cell Phenotyping Profile for Immunodeficiency and Immune Competence Assessment, Blood

Clinical Information: Normal immunity requires a balance between the activities of various lymphocyte subpopulations with different effector and regulatory functions. Different immune cells can be characterized by unique surface membrane antigens described by a cluster of differentiation nomenclature (eg, CD3 is an antigen found on the surface of T lymphocytes). Abnormalities in the number and percent of T (CD3, CD4, CD8), B (CD19), and natural killer (CD16+CD56) lymphocytes have been described in a number of different diseases. In patients infected with HIV, the CD4 count is measured for AIDS diagnosis and initiation of antiviral therapy. The progressive loss of CD4 T

lymphocytes in patients infected with HIV is associated with increased infections and complications. The United States Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T lymphocytes. The adaptive immune response includes both cell-mediated (mediated by T cells and natural killer [NK] cells) and humoral immunity (mediated by B cells). After antigen recognition and maturation in secondary lymphoid organs, some antigen-specific B cells terminally differentiate into antibody-secreting plasma cells or become memory B cells. Memory B cells are 3 subsets: marginal zone B cells (MZ or non-switched memory), class-switched memory B cells, and IgM-only memory B cells. Decreased B-cell numbers, B-cell function, or both result in immune deficiency states and increased susceptibility to infections. These decreases may be either primary (genetic) or secondary. Secondary causes include medications, malignancies, infections, and autoimmune disorders. Common variable immunodeficiency (CVID), a disorder of B-cell function, is the most prevalent primary immunodeficiency with a prevalence of 1 to 25,000 to 1 to 50,000.(1) CVID has a bimodal presentation with a subset of patients presenting in early childhood and a second set presenting between 15 and 40 years or, occasionally, even later. Many different genetic defects have been associated with CVID, including variants in the ICOS, CD19, BAFF-R, and TACI genes. TACI variants account for 8% to 15% of CVID cases. Common variable immunodeficiency is characterized by hypogammaglobulinemia, usually involving most or all of the immunoglobulin classes (IgG, IgA, IgM, and IgE), impaired functional antibody responses, and recurrent sinopulmonary infections.(1,2) B-cell numbers may be normal or decreased. A minority of patients with CVID (5%-10%) have very low B-cell counts (<1% of peripheral blood leukocytes), while another subset (5%-10%) exhibit noncaseating, sarcoid-like granulomas in different organs and also tend to develop a progressive T-cell deficiency.(1) Of all patients with CVID, 25% to 30% have increased numbers of CD8 T cells and a reduced CD4 to CD8 ratio (<1). Studies have shown the clinical relevance of classifying patients with CVID by assessing B-cell subsets since changes in different B-cell subsets are associated with specific clinical phenotypes or presentations.(3,4) The B-cell phenotyping assay can be used in the diagnosis of hyper-IgM syndromes, which are characterized by increased or normal levels of IgM with low IgG and/or IgA.(5) Patients with hyper-IgM syndromes can have 1 of 5 known genetic defects- in the CD40L, CD40, AID (activation-induced cytidine deaminase), UNG (uracil DNA glycosylase), and NEMO (NF-kappa B essential modulator) genes.(5) Variants in CD40L and NEMO are inherited in an X-linked fashion, while variants in the other 3 genes are inherited in an autosomal recessive fashion. Patients with hyper-IgM syndromes have a defect in isotype class-switching, which leads to a decrease in class-switched memory B cells, with or without an increase in non-switched memory B cells and IgM-only memory B cells. In addition to its utility in the diagnosis of the above-described primary immunodeficiencies, B-cell phenotyping may be used to assess reconstitution of B-cell subsets after hematopoietic stem cell or bone marrow transplant. This test is also used to monitor B-cell-depicting therapies, such as Rituxan (rituximab) and Zevalin (ibritumomab tiuxetan). The etiology of CVID is heterogeneous. Variants of the gene that encodes TACI, TNFRSF13B (tumor necrosis factor receptor superfamily, member 13B), probably account for about 10% to 15% of all CVID cases.(6-8) Patients with variants in the TACI gene are particularly prone to developing autoimmune diseases, including cytopenias and lymphoproliferative disease. The other variants each have been reported in only a handful of patients. The etiopathogenesis is still undefined in 65% to 75% of patients with CVID. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day.(9) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(10-12) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(10) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening(13) and during summer compared to winter.(14) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Screening for common variable immunodeficiency and hyper-IgM syndromes Assessing B-

cell subset reconstitution after stem cell or bone marrow transplant Assessing response to B-cell-depleting immunotherapy This test is not indicated for the evaluation of lymphoproliferative disorders (eg, leukemia, lymphoma, multiple myeloma).

Interpretation: Quantitative Lymphocyte Subsets: T, B, and natural killer: When the CD4 count falls below 500 cells/mcL, patients who are HIV-positive can be diagnosed with AIDS and can receive antiretroviral therapy. When the CD4 count falls below 200 cells/mcL, prophylaxis against Pneumocystis jiroveci pneumonia is recommended. Immune Assessment B Cell Subsets: The assay provides quantitative information on the various B-cell subsets (percentage and absolute counts in cells/microliter). Each specimen is evaluated for B-cell subsets with respect to the total number of CD19+ B cells present in the peripheral blood mononuclear cell population, compared to the reference range. In order to verify that there are no CD19-related defects, CD20 is used as an additional pan-B-cell marker (expressed as percentage of CD45+ lymphocytes). The B-cell panel assesses the following B-cell subsets: CD19+=B cells expressing CD19 as a percent of total lymphocytes CD19+ CD27+=total memory B cells CD19+ CD27+ IgD+ IgM+=marginal zone or non-switched memory B cells CD19+ CD27+ IgD- IgM+=IgM-only memory B cells CD19+ CD27+ IgD- IgM-=class-switched memory B cells CD19+ IgM+=IgM B cells CD19+ CD38+ IgM+=transitional B cells CD19+ CD38+ IgM-=plasmablasts CD19+ CD21-=CD21 low ("immature") B cells CD19+ CD21+=mature B cells CD19+ CD20+=B cells coexpressing both CD19 and CD20 as a percent of total lymphocytes

Reference Values:

The appropriate age-related reference values will be provided on the report.

Clinical References: 1. Warnatz K, Denz A, Drager R, et al. Severe deficiency of switched memory B cells (CD27+ IgM- IgD-) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. Blood. 2002;99(5):1544-1551 2. Brouet JC, Chedeville A, Fermand JP, Royer B. Study of the B cell memory compartment in common variable immunodeficiency. Eur J Immunol. 2000;30(9):2516-2520 3. Wehr C, Kivioja T, Schmitt C, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood. 2008;111(1):77-85 4. Alachkar H, Taubenheim N, Haeney MR, et al. Memory switched B-cell percentage and not serum immunoglobulin concentration is associated with clinical complications in children and adults with specific antibody deficiency and common variable immunodeficiency. Clin Immunol. 2006;120(3):310-318 5. Lee WI, Torgerson TR, Schumacher MJ, et al. Molecular analysis of a large cohort of patients with hyper immunoglobulin M (hyper IgM) syndrome. Blood. 2005;105(5):1881-1890 6. Ramirez NJ, Posadas-Cantera S, Caballero-Oteyza A, Camacho-Ordonez N, Grimbacher B. There is no gene for CVID - novel monogenetic causes for primary antibody deficiency. Curr Opin Immunol. 2021;72:176-185. doi:10.1016/j.coi.2021.05.010 7. Salzer U, Chapel HM, Webster ADB, et al. Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. Nat Genet. 2005;37(8):820-828 8. Salzer U, Grimbacher B. TACI deficiency - a complex system out of balance.Curr Opin Immunol. 2021;71:81-88. doi:10.1016/j.coi.2021.06.004 9. Carmichael KF, Abayomi A. Analysis of diurnal variation of lymphocyte subsets in healthy subjects in the Caribbean, and its implication in HIV monitoring and treatment. Afr J Med Med Sci. 2006;35(1):53-57 10. Dimitrov S, Benedict C, Heutling D, et al. Cortisol and epinephrine control opposing circadian rhythms in T-cell subsets. Blood. 2009;113(21);5134-5143 11. Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating antigen presenting cells regulated by sleep. Sleep 2007;30(4):401-411 12. Kronfol Z, Nair M, Zhang Q, et al. Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Pyschosom Med. 1997;59(1):42-50 13. Malone JL, Simms TE, Gray GC, et al. Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J AIDS. 1990;3(2):144-151 14. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994;34(6):512-516 15. U.S. Department of Health and Human Services: Recommendations for prophylaxis against Pneumocystis carinii pneumonia for adults and adolescents infected with human immunodeficiency virus. MMWR Morb Mortal Wkly Rep. 1994;43(RR-3):1-21 16. Thompson MA,

Horberg MA, Agwu AL, et al. Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2021;73(11):e3572-e3605. Erratum in: Clin Infect Dis. 2021 Dec 08 17. Kumanovics A, Sadighi Akha AA. Flow cytometry for B-cell subset analysis in immunodeficiencies. J Immunol Methods. 2022;509:113327. doi:10.1016/j.jim.2022.113327 18. Sadighi Akha AA, Csomos K, Ujhazi B, Walter JE, Kumanovics A. Evolving approach to clinical cytometry for immunodeficiencies and other immune disorders. Clin Lab Med. 2023;43(3):467-483. doi:10.1016/j.cll.2023.05.002

BNP
83873

B-Type Natriuretic Peptide, Plasma

Clinical Information: B-type natriuretic peptide (BNP, formerly brain natriuretic peptide) is a 32-amino acid-ringed peptide secreted by the heart to regulate blood pressure, and fluid balance.(1) BNP is stored in, and secreted predominantly from, membrane granules in the heart ventricles and is continuously released from the heart in response to both ventricle volume expansion and pressure overload.(2) The natriuretic peptide system and the renin-angiotensin system counteract each other in arterial pressure regulation. When arterial pressure decreases, the kidneys release renin, which activates angiotensinogen resulting in increased peripheral resistance of the arterioles, thus increasing arterial pressure. The natriuretic peptides counteract the effects of renin secretion, causing a reduction of blood pressure and extracellular fluid volume.(3) Both BNP and atrial natriuretic peptide are activated by atrial and ventricular distension due to increased intracardiac pressure. These peptides have both natriuretic and diuretic properties: they raise sodium and water excretion by increasing the glomerular filtration rate and inhibiting sodium reabsorption by the kidney. The New York Heart Association (NYHA) developed a functional classification system for congestive heart failure (CHF) consisting of 4 stages based on the severity of the symptoms. Various studies have demonstrated that circulating BNP concentrations increase with the severity of CHF based on the NYHA classification.(4-6)

Useful For: Aiding in the diagnosis of congestive heart failure (CHF) The role of B-type natriuretic peptide in monitoring CHF therapy is under investigation.

Interpretation: >Normal to <200 pg/mL: likely compensated congestive heart failure (CHF) > or =200 to < or =400 pg/mL: likely moderate CHF >400 pg/mL: likely moderate-to-severe CHF B-type natriuretic peptide (BNP) levels are loosely correlated with New York Heart Association (NYHA) functional class (see Table). Interpretive Levels for CHF Functional Class 5th to 95th Percentile Median I 15 to 499 pg/mL 95 pg/mL II 10 to 1080 pg/mL 222 pg/mL III 38 to >1300 pg/mL 459 pg/mL IV 147 to >1300 pg/mL 1,006 pg/mL All CHF 22 to >1300 pg/mL 360 pg/mL Elevation in BNP can occur due to right heart failure with cor pulmonale (200-500 pg/mL), pulmonary hypertension (300-500 pg/mL), and acute pulmonary embolism (150-500 pg/mL). Elevations also occur in patients with acute coronary syndromes.

Reference Values:

Males
< or =45 years: < or =35 pg/mL
46 years: < or =36 pg/mL
47 years: < or =37 pg/mL
48 years: < or =38 pg/mL
49 years: < or =39 pg/mL
50 years: < or =40 pg/mL
51 years: < or =41 pg/mL
52 years: < or =42 pg/mL
53 years: < or =43 pg/mL
54 years: < or =45 pg/mL
55 years: < or =46 pg/mL
56 years: < or =47 pg/mL

57 years: < or =48 pg/mL
58 years: < or =49 pg/mL
59 years: < or =51 pg/mL
60 years: < or =52 pg/mL
61 years: < or =53 pg/mL
62 years: < or =55 pg/mL
63 years: < or =56 pg/mL
64 years: < or =57 pg/mL
65 years: < or =59 pg/mL
66 years: < or =60 pg/mL
67 years: < or =62 pg/mL
68 years: < or =64 pg/mL
69 years: < or =65 pg/mL
70 years: < or =67 pg/mL
71 years: < or =69 pg/mL
72 years: < or =70 pg/mL
73 years: < or =72 pg/mL
74 years: < or =74 pg/mL
75 years: < or =76 pg/mL
76 years: < or =78 pg/mL
77 years: < or =80 pg/mL
78 years: < or =82 pg/mL
79 years: < or =84 pg/mL
80 years: < or =86 pg/mL
81 years: < or =88 pg/mL
82 years: < or =91 pg/mL
> or =83 years: < or =93 pg/mL

Females
< or =45 years: < or =64 pg/mL
46 years: < or =66 pg/mL
47 years: < or =67 pg/mL
48 years: < or =69 pg/mL
49 years: < or =71 pg/mL
50 years: < or =73 pg/mL
51 years: < or =74 pg/mL
52 years: < or =76 pg/mL
53 years: < or =78 pg/mL
54 years: < or =80 pg/mL
55 years: < or =82 pg/mL
56 years: < or =84 pg/mL
57 years: < or =87 pg/mL
58 years: < or =89 pg/mL
59 years: < or =91 pg/mL
60 years: < or =93 pg/mL
61 years: < or =96 pg/mL
62 years: < or =98 pg/mL
63 years: < or =101 pg/mL
64 years: < or =103 pg/mL
65 years: < or =106 pg/mL
66 years: < or =109 pg/mL
67 years: < or =112 pg/mL
68 years: < or =114 pg/mL
69 years: < or =117 pg/mL

70 years: < or =120 pg/mL
71 years: < or =123 pg/mL
72 years: < or =127 pg/mL
73 years: < or =130 pg/mL
74 years: < or =133 pg/mL
75 years: < or =137 pg/mL
76 years: < or =140 pg/mL
77 years: < or =144 pg/mL
78 years: < or =147 pg/mL
79 years: < or =151 pg/mL
80 years: < or =155 pg/mL
81 years: < or =159 pg/mL
82 years: < or =163 pg/mL
> or =83 years: < or =167 pg/mL

Clinical References: 1. Krishnaswamy P, Lubien E, Clopton P, et al. Utility of B-natriuretic peptide as a rapid, point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. Am J Med. 2001;111(4):274-279 2. McNairy M, Gardetto N, Clopton P, et al. Stability of B-type natriuretic peptide levels during exercise in patients with congestive heart failure: implications for outpatient monitoring with B-type natriuretic peptide. Am Heart J. 2002;143(3):406-411 3. Apple FS, Goetze JP, Jaffe AS: Cardiac function. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1201-1255 4. Dietzen DJ: Amino acids, peptides, and proteins. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:373-403

BABG
81128

Babesia microti IgG Antibodies, Serum

Clinical Information: Babesiosis is a zoonotic infection caused by the protozoan parasite Babesia microti. The infection is acquired by contact with Ixodes ticks carrying the parasite. The deer mouse is the animal reservoir, and overall, the epidemiology of this infection is much like that of Lyme disease. Babesiosis is most prevalent in the Northeast, upper Midwest, and Pacific Coast of the United States. Infectious forms (sporozoites) are injected during tick bites, and the organism enters the vascular system where it infects red blood cells (RBC). During this intraerythrocytic stage, it becomes disseminated throughout the reticuloendothelial system. Asexual reproduction occurs in RBC, and daughter cells (merozoites) are formed that are liberated on rupture (hemolysis) of the RBC. Most cases of babesiosis are subclinical or mild, but the infection can be severe and life-threatening, especially in older or asplenic patients. Fever, fatigue, malaise, headache, and other flu-like symptoms occur most commonly. In the most severe cases, hemolysis, acute respiratory distress syndrome, and shock may develop. Patients may have hepatomegaly and splenomegaly. A serologic test can be used as an adjunct in the diagnosis and follow-up of babesiosis, when infection is chronic or persistent, or in seroepidemiologic surveys of the prevalence of the infection in certain populations. Babesiosis is usually diagnosed by observing the organisms in infected RBC on Giemsa-stained thin blood films of smeared peripheral blood. Serology may also be useful if the parasitemia is too low to detect or if the infection has cleared naturally or following treatment.

Useful For: An adjunct in the diagnosis of babesiosis Follow-up of documented babesiosis

Interpretation: A positive result of an indirect fluorescent antibody test (titer > or =1:64) suggests current or previous infection with Babesia microti. In general, the higher the titer, the more likely it is that the patient has an active infection. Patients with documented infections have usually had titers ranging from 1:320 to 1:2560.

Reference Values:
<1:64
Reference values apply to all ages.

Clinical References:

BABPB
618303

Babesia species, Molecular Detection, PCR, Blood

Clinical Information: Babesiosis is a tick-transmitted zoonosis caused by intraerythrocytic protozoa in the genus Babesia. Babesia microti is responsible for the vast majority of human cases in the United States, with most cases occurring along the Northeast Coast and the upper Midwestern states. A small number of cases of Babesia duncani human infection have also been reported along Pacific Coast states from Washington to northern California, and Babesia divergens/B divergens-like strains have been detected in humans in Missouri (MO-1 strain), Kentucky, and Washington. In Europe, B divergens and Babesia venatorum are the primary causes of human babesiosis. Humans most commonly acquire infection through the bite of an infected tick. The most common tick vectors in the United States are Ixodes scapularis and Ixodes pacificus, while Ixodes ricinus and other ticks transmit the parasite in Europe and Asia. Less commonly, babesiosis may be acquired through blood transfusion and across the placenta from the mother to the fetus. Most patients with babesiosis are asymptomatic or have only a self-limited, mild, flu-like illness, but some develop a severe illness that may result in death. Patient symptoms may include fever, chills, extreme fatigue, and severe anemia. The most severe cases occur in asplenic individuals and those over 50 years of age. Rare cases of chronic parasitemia, usually in immunocompromised patients, have been described. Babesiosis is conventionally diagnosed through microscopic examination of Giemsa-stained thick and thin peripheral blood films looking for characteristic intraerythrocytic Babesia parasites. This method is relatively rapid, widely available, and capable of detecting (but not differentiating) human-infective Babesia species. It is also necessary for calculating the percentage of parasitemia, which is used to predict prognosis, guide patient management, and monitor response to treatment. However, microscopic examination requires skilled microscopists and may be challenging in the setting of low parasitemia or prior drug therapy. Also, Babesia species may closely resemble those of Plasmodium falciparum. The Mayo Clinic real-time polymerase chain reaction assay provides a rapid and more sensitive alternative to blood film examination for detection and differentiation of B microti, B duncani, and B divergens/B divergens-like parasites. It does not cross-react with malaria parasites.

Useful For: Initial screening or confirmatory testing for suspected babesiosis during the acute febrile stage of infection in patients from endemic areas, especially when Giemsa-stained peripheral blood smears do not reveal any organisms, or the organism morphology is inconclusive

Interpretation: A positive result indicates the presence of Babesia species DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with blood smear microscopy, serological results, and clinical findings. A negative result indicates absence of detectable DNA from Babesia species in the specimen but does not always rule out ongoing babesiosis in a seropositive person since the parasitemia may be present at a very low level or may be sporadic. Other tests to consider in the evaluation of a patient presenting with an acute febrile illness following tick exposure include serologic tests for Lyme disease (Borrelia burgdorferi) and molecular detection (polymerase chain reaction: PCR) for ehrlichiosis/anaplasmosis. For patients who are past the acute stage of infection, serologic tests for these organisms should be ordered prior to PCR testing.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Krause PJ, Auwaerter PG, Bannuru RR, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA): 2020 Guideline on Diagnosis and Management of Babesiosis. Clin Infect Dis. 2021;72(2):185-189 2. Kumar A, O'Bryan J, Krause PJ. The Global Emergence of Human Babesiosis. Pathogens 2021;10(11):1447 3. Mareedu N, Schotthoefer AM, Tompkins J, Hall MC, Fritsche TR, Frost HM. Risk factors for severe infection, hospitalization, and prolonged antimicrobial therapy in patients with babesiosis. Am J Trop Med Hyg. 2017;97(4):1218-1225 4. Vannier E, Krause PJ. Human babesiosis. N Engl J Med. 2012;366(25):2397-2407

FBACS
75397

Baclofen, Serum

Interpretation: Serum concentrations required for therapeutic effects reportedly range from 0.08 - 0.40 mcg/mL.

Reference Values:
Reporting limit determined each analysis.
None Detected mcg/mL

MSCSF
620941

Bacteria, Virus, Fungus, and Parasite Metagenomic Sequencing, Spinal Fluid

Clinical Information: The target population is patients with suspected, but undiagnosed, central nervous system infection. Infection of the central nervous system is a potentially life-threating condition that requires rapid diagnosis and clinical treatment. Infections of the central nervous system have broad pathogen etiology, including bacteria, fungi, viruses, and parasites. The breadth of causative agents challenges diagnostic test ordering and pathogen identification. Current clinical diagnostic methods, such as culture and specific-polymerase chain reaction assays, have limitations in the ability to detect non-viable organisms, or nucleic acids that are not targeted by specific assays, respectively. An unbiased metagenomic sequencing approach overcomes diagnostic test limitations by interrogating microbiota without bias towards any specific microorganisms. Bioinformatic analysis of the resultant large sequencing dataset enables identification of a diversity of pathogens in this assay. The test can identify multiple pathogens in a single specimen if present.

Useful For: Detecting and identifying pathogenic organisms including bacteria, fungi, DNA viruses, RNA viruses, and parasites in cerebrospinal fluid This test is not recommended as a test of cure because nucleic acids may persist after successful treatment.

Interpretation: A positive result indicates that nucleic acid of one or more potentially pathogenic microorganisms was detected. A negative result indicates absence of detectable nucleic acids from potentially pathogenic bacteria, fungi, viruses, or parasites. A negative result does not rule the presence of a pathogen due lack of a reference sequence in the database used, the presence of microbial nucleic acids in quantities lower than the limit of detection of the assay, or inhibition from high levels of competing human nucleic acid. If testing indicates inhibition, testing will be repeated. If inhibition is again detected, the result will be reported with a comment indicating that inhibition was present.

Reference Values:
Negative.
No pathogenic DNA virus detected.
No pathogenic RNA virus detected.
No pathogenic parasite detected.
No pathogenic bacterium detected.

No pathogenic fungus detected.

Clinical References: Rodino KG, Toledano M, Norgan AP, et al. Retrospective review of clinical utility of shotgun metagenomic sequencing testing of cerebrospinal fluid from a U.S. tertiary care medical center. J Clin Microbiol. 2020;58(12):e01729-20. doi:10.1128/JCM.01729-20

ANAES 60519 Bacterial Culture, Anaerobic with Antimicrobial Susceptibilities, Varies

Clinical Information: Anaerobic bacteria are the greatest component of the human body's normal bacterial flora. Anaerobes colonize the skin, oral cavity, and genitourinary and lower gastrointestinal tracts, and generally do not cause infection. Their presence is important for vitamin and other nutrient absorption and in preventing infection with pathogenic bacteria. When usual skin and mucosal barriers are compromised, in an anaerobic environment, these bacteria can behave as pathogens. Typical anaerobic infections include periodontitis, abdominal or pelvic abscesses, endometritis, pelvic inflammatory disease, aspiration pneumonia, empyema and lung abscesses, sinusitis, brain abscesses, gas gangrene, and other soft tissue infections. Anaerobes grow aggressively in the body under anaerobic conditions and may possess a variety of virulence factors including capsules and extracellular enzymes. They also can develop resistance to antimicrobials by producing beta-lactamase and other modifying enzymes, and by alterations in membrane permeability and structure of penicillin-binding proteins. Susceptibility testing results are useful to clinicians because anaerobic bacteria are a significant cause of human infection, and they are often resistant to commonly used antimicrobials. Bacteroides and Parabacteroides species produce beta-lactamases. Ertapenem, metronidazole, and clindamycin are generally effective agents although resistance to clindamycin, and occasionally ertapenem, is increasing. The minimal inhibitory concentration (MIC) obtained during antimicrobial susceptibility testing is helpful in indicating the concentration of antimicrobial agent required at the site of infection necessary to inhibit the infecting organism. For each organism-antimicrobial agent combination, the Clinical and Laboratory Standards Institute and/or the European Committee on Antimicrobial Susceptibility Testing provides interpretive criteria for determining whether the MIC should be interpreted as susceptible, susceptible dose dependent, intermediate, nonsusceptible, resistant, or epidemiological cutoff value.

Useful For: Diagnosing anaerobic bacterial infections Directing antimicrobial therapy for anaerobic infections

Interpretation: Isolation of anaerobes in significant numbers from specimens collected under sterile conditions including blood, other normally sterile body fluids, or closed collections of purulent fluid indicates infection with those organisms. A susceptible category result and a low minimum inhibitory concentration value indicate in vitro susceptibility of the organism to the antimicrobial tested. For interpretation of various antimicrobial susceptibility interpretive categories (ie, susceptible, intermediate, resistant, or epidemiological cutoff value), see Reference Values.

Reference Values:
No growth

Identification of probable pathogens

Susceptibility results are reported as minimal inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as clinical breakpoints) are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, or nonsusceptible according to breakpoint setting organizations, either the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST), as applicable.

In some instances, an interpretive category cannot be provided based on available data; therefore, the following comment will be included on the report: There are no established interpretive guidelines for agents reported without interpretations.

For information regarding CLSI and EUCAST susceptibility interpretations, see Susceptibility Interpretative Category Definitions.

Clinical References: 1. Rosenblatt JE, Brook I. Clinical relevance of susceptibility testing of anaerobic bacteria. Clin Infect Dis. 1993;16(Suppl 4):S446-S448 2. Summanen P, Baron EJ, Citron DM, et al. Wadsworth Anaerobic Bacteriology Manual. 6th ed. Star Publishing Co; 2002 3. Schuetz AN, Carpenter DE. Susceptibility test methods: anaerobic bacteria. In: Carroll KC, Pfaller MA, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:1377-1397 4. Hall GS. Anaerobic Bacteriology. In: Leber AL, ed. Clinical Microbiology Procedures Handbook. Vol 1. 4th ed. ASM Press; 2016:section 4 5. Jenkins SG, Schuetz AN. Current concepts in laboratory testing to guide antimicrobial therapy. Mayo Clin Proc. 2012;87(3):290-308

ANAE
84292

Bacterial Culture, Anaerobic, Varies

Clinical Information: Anaerobic bacteria are the greatest component of the human body's normal bacterial flora colonizing the skin, oral cavity, and genitourinary and lower gastrointestinal tracts and generally do not cause infection. Their presence is important for vitamin and other nutrient absorption and in preventing infection with pathogenic bacteria. When usual skin and mucosal barriers are penetrated as well as in an anaerobic environment, these bacteria can behave as pathogens. Typical anaerobic infections include periodontitis, abdominal or pelvic abscesses, endometritis, pelvic inflammatory disease, aspiration pneumonia, empyema and lung abscesses, sinusitis, brain abscesses, gas gangrene, and other soft tissue infections. Anaerobes grow aggressively in the body under anaerobic conditions and may possess a variety of virulence factors including capsules and extracellular enzymes. They also can develop resistance to antimicrobials by producing beta-lactamase and other modifying enzymes as well as by alterations in membrane permeability and structure of penicillin-binding proteins. Because anaerobic bacteria are a significant cause of human infection and are often resistant to commonly used antimicrobials, susceptibility testing results are useful to clinicians. Bacteroides and Parabacteroides species produce beta-lactamases. Ertapenem, metronidazole, and clindamycin are generally effective agents although resistance to clindamycin, and occasionally ertapenem, is increasing.

Useful For: Diagnosing anaerobic bacterial infections

Interpretation: Isolation of anaerobes in significant numbers from well-collected specimens including blood, other normally sterile body fluids, or closed collections of purulent fluid, indicates infection with the identified organisms.

Reference Values:
No growth
Identification of probable pathogens

Clinical References: 1. Summanen P, Baron EJ, Citron DM, et al: Wadsworth Anaerobic Bacteriology Manual. 6th ed. Star Publishing Co; 2002 2. Schuetz AN, Carpenter DE: Susceptibility test methods: anaerobic bacteria. In: Carroll KC, Pfaller MA, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:1377-1397 3. Hall GS: Anaerobic bacteriology. In: Leber AL, ed. Clinical Microbiology Procedures Handbook. Vol 1. 4th ed. ASM Press; 2016: chap 44

CFRCS
60563

Bacterial Culture, Cystic Fibrosis with Antimicrobial Susceptibilities, Varies

Clinical Information: Life expectancy of patients with cystic fibrosis (CF) has increased steadily over the past 50 years, in large part due to improvements in the management of lung disease in this patient population. Still, chronic lung infection is responsible for 75% to 85% of deaths in patients with CF. Appropriate treatment for the causative organism can reduce morbidity and mortality. The number of microbial species associated with CF lung disease is relatively limited. These include Pseudomonas aeruginosa (mucoid and nonmucoid), Staphylococcus aureus, Burkholderia cepacia complex, Stenotrophomonas maltophilia, other non-fermenting gram-negative rods, Haemophilus influenzae, and Streptococcus pneumoniae. Nontuberculous mycobacteria and Aspergillus species may also play a role in CF lung disease, in addition to common respiratory viruses. This culture is specifically designed and utilizes conventional and additional selective media (compared to non-CF respiratory cultures) to isolate bacteria commonly associated with pulmonary disease in patients with CF. In selected centers, lung transplantation is performed on patients with CF. This test is appropriate for lung transplant patients with underlying CF because they can continue to harbor the same types of organisms as they did pretransplantation. Patients with CF may be colonized or chronically infected by these organisms over a long period of time. Antimicrobial susceptibility testing determines the minimal inhibitory concentration (MIC) value of selected antimicrobial agents against isolated potentially pathogenic bacteria. The MIC is the lowest antimicrobial concentration (of a series of increasing concentrations) that inhibits growth of the bacterium. Agar dilution MIC testing is performed by testing for growth of bacteria on agar plates containing varying concentrations of antimicrobial agents. For each organism-antimicrobial agent combination, the Clinical and Laboratory Standards Institute and/or the European Committee on Antimicrobial Susceptibility Testing provide interpretive criteria for determining whether the MIC should be interpreted as susceptible, susceptible-dose dependent, intermediate, nonsusceptible, resistant, or epidemiological cutoff value.

Useful For: Detecting disease-causing aerobic bacteria in specimens from patients with cystic fibrosis Determining the in vitro antimicrobial susceptibility of potentially pathogenic aerobic bacteria, if appropriate

Interpretation: A negative test result is no growth of bacteria or growth of only usual microbiota. A negative result does not rule out all causes of infectious lung disease. For more information, see Cautions. Organisms associated with lower respiratory tract infections are reported. For positive test results, disease-causing bacteria are identified. Patients with cystic fibrosis may be colonized or chronically infected by some organisms over a long period of time, therefore, positive results must be interpreted in conjunction with previous findings and the clinical picture to appropriately evaluate results. A susceptible category result and a low minimum inhibitory concentration value indicate in vitro susceptibility of the organism to the antimicrobial tested. For interpretation of various antimicrobial susceptibility interpretive categories (ie, susceptible, susceptible-dose dependent, intermediate, nonsusceptible, resistant, or epidemiological cutoff value), see Reference Values.

Reference Values:
No growth or usual microbiota

Susceptibility results are reported as minimal inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as clinical breakpoints) are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, or nonsusceptible according to breakpoint setting organizations, either the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST), as applicable.

In some instances, an interpretive category cannot be provided based on available data; therefore, the following comment will be included on the report: There are no established interpretive guidelines for

agents reported without interpretations.

For information regarding CLSI and EUCAST susceptibility interpretations, see Susceptibility Interpretative Category Definitions.

Clinical References: 1. Miller JM, Binnicker MJ, Campbell S, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiology. Clin Infect Dis. 2018;67(6):e1-e94. doi:10.1093/cid/ciy381 2. York MK, Gilligan P, Alby K: Lower respiratory tract cultures. In: Leber AL, ed. Clinical Microbiology Procedures Handbook, Vol 1, 4th ed. ASM Press; 2016:section 3.11.2 3. LiPuma JJ, Currie BJ, Peacock SJ, VanDamme PAR: Burkholderia, Stenotrophomonas, Ralstonia, Cupriavidus, Pandoraea, Brevundimonas, Comamonas, Delftia, and Acidovorax. In: Carroll KC, Pfaller MC, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:807-828

CFRC
89653

Bacterial Culture, Cystic Fibrosis, Respiratory

Clinical Information: Life expectancy of patients with cystic fibrosis (CF) has increased steadily over the past 50 years, in large part due to improvements in the management of lung disease in this patient population. Still, chronic lung infection is responsible for 75% to 85% of deaths in patients with CF. Appropriate treatment for the causative organism can reduce morbidity and mortality. The number of microbial species associated with CF lung disease is relatively limited. These include Pseudomonas aeruginosa (mucoid and nonmucoid), Staphylococcus aureus, Burkholderia cepacia complex, Stenotrophomonas maltophilia, other non-fermenting gram-negative rods, Haemophilus influenzae, and Streptococcus pneumoniae. Nontuberculous mycobacteria and Aspergillus species may also play a role in CF lung disease, in addition to common respiratory viruses. This culture is specifically designed and utilizes conventional and additional selective media (compared to non-CF respiratory cultures) to isolate bacteria commonly associated with pulmonary disease in patients with CF. In selected centers, lung transplantation is performed on patients with CF. This test is appropriate for lung transplant patients with underlying CF because they can continue to harbor the same types of organisms as they did pretransplantation. Patients with CF may be colonized or chronically infected by these organisms over a long period of time.

Useful For: Detecting disease-causing aerobic bacteria in specimens from patients with cystic fibrosis

Interpretation: A negative test result is no growth of bacteria or growth of only usual microbiota. A negative result does not rule out all causes of infectious lung disease. For more information, see Cautions. Organisms associated with lower respiratory tract infections are reported. For positive test results, disease-causing bacteria are identified. Patients with cystic fibrosis may be colonized or chronically infected by some organisms over a long period of time, therefore, positive results must be interpreted in conjunction with previous findings and the clinical picture to appropriately evaluate results.

Reference Values:
No growth or usual microbiota
Identification of probable pathogens

Clinical References: 1. Miller JM, Binnicker MJ, Campbell S, et al: A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiology. Clin Infect Dis. 2018 Aug 31;67(6):e1-e94. doi: 10.1093/cid/ciy381 2. York MK, Gilligan P, Alby K: Lower respiratory tract cultures. In: Leber AL, ed. Clinical Microbiology Procedures Handbook. Vol 1. 4th ed. ASM Press; 2016:section 3.11.2 3. LiPuma JJ, Currie BJ, Peacock SJ, VanDamme PAR: Burkholderia, Stenotrophomonas, Ralstonia, Cupriavidus, Pandoraea, Brevundimonas, Comamonas, Delftia, and

Acidovorax. In: Jorgensen JH, Carroll KC, Pfaller MC, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:807-828

BTWGS
65162

Bacterial Typing, Whole Genome Sequencing, Varies

Clinical Information: Bacterial strain typing may be useful for determining strain relatedness in the setting of possible nosocomial transmission or community outbreaks. Serial isolates obtained from the same patient may be typed to assess similarity. Typing may allow discrimination of 2 or more isolates of the same species, which can inform recognition of an outbreak, nosocomial transmission, or identify a potential source of infection in an individual patient. Pulse-field gel electrophoresis (PFGE) has traditionally been used for strain typing but does not always discriminate between different bacterial strains (eg, 2 genetically dissimilar strains may have indistinguishable PFGE patterns). Whole genome sequencing offers a higher level of resolution of genetic relatedness of strains than PFGE does.

Useful For: Aiding in the investigation of a potential outbreak by a single bacterial species May assist in identification of recurrent infection in an individual patient

Interpretation: The genomic sequence of individual isolates will be determined and compared to the genomic sequences of the other co-submitted isolates. The report will indicate the degree of relatedness between the isolates. A link to the interpretive report will be sent to the registered email address provided by the client.

Reference Values:
Reported as isolates are "related," "possibly related," or "unrelated."

Clinical References: 1. Cunningham SA, Chia N, Jeraldo PR, et al. Comparison of whole-genome sequencing methods for analysis of three methicillin-resistant Staphylococcus aureus outbreaks. J Clin Microbiol. 2017;55(6):1946-1953. doi;10.1128/JCM.00029-17 2. Park KH, Greenwood-Quaintance KE, Uhl JR, et al. Molecular epidemiology of Staphylococcus aureus bacteremia in a single large Minnesota medical center in 2015 as assessed using MLST, core genome MLST and spa typing. PLoS ONE. 2017;12(6):e0179003. doi:10.1371/journal.pone.0179003 3. Madigan T, Cunningham SA, Patel R, et al. Whole-genome sequencing for methicillin-resistant Staphylococcus aureus (MRSA) outbreak investigation in a neonatal intensive care unit. Infect Control Hosp Epidemiol. 2018; 39(12):1412-1418. doi:10.1017/ice.2018.239 4. Trees E, Fei Fan Ng T, MacCannell D, et al. Molecular epidemiology. In: Carroll K, Pfaller M, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:167-196

BVRNA
621435

Bacterial Vaginosis, Nucleic Acid Amplification, Vaginal

Clinical Information: The Aptima BV (bacterial vaginosis) assay is intended to aid in the diagnosis of BV in individuals with clinical presentation consistent with vaginitis and/or vaginosis. Vaginitis is characterized by a spectrum of signs and symptoms, including vaginal/vulvar irritation, odor, discharge, and pruritus. Vaginitis may develop as a result of mechanical or chemical irritants (eg, feminine hygiene products, contraceptive materials) or due to a dysbiosis of the microbiota in the vaginal tract. Up to 90% of vaginitis cases are infectious, due to BV, vulvovaginal candidiasis (Candida vaginitis: CV) and/or trichomoniasis (Trichomonas vaginalis: TV). BV, CV, and TV individually account for 22% to 50%, 17% to 39%, and 4% to 35% of vaginitis cases, respectively. BV has been associated with pelvic inflammatory disease, cervicitis, elevated risk of acquisition of sexually transmitted infections (such as chlamydia, gonorrhea, herpes simplex virus, and HIV), spontaneous abortion, and preterm birth. Bacterial vaginosis is characterized by a change in the vaginal microbiota dominated by Lactobacillus species to a polymicrobial anaerobe-dominated microbiota that includes Gardnerella vaginalis, Atopobium vaginae, Prevotella, Bacteroides, Peptostreptococcus, Mobiluncus, Sneathia (Leptotrichia),

Mycoplasma, and BV-associated bacteria. A change in the normal vaginal microbiota is associated with the development of multiple signs and symptoms (eg, discharge, vaginal discomfort, and discharge). Diagnosis of BV can alternatively be established based on clinical criteria alone, referred to as Amsel's criteria, which include measuring vaginal pH, assessment for the presence of clue cells (eg, epithelial cells layered with bacterial cells), discharge, and malodor.

Useful For: Aid for diagnosis of bacterial vaginosis This test is not intended for use in medico-legal applications.

Interpretation: Positive: Results should be interpreted alongside clinical presentation. Up to 40% of asymptomatic patients may test positive by this assay. Assay result is based on relative amounts of Lactobacillus (Lactobacillus gasseri, Lactobacillus crispatus, Lactobacillus jensenii), Gardnerella vaginalis, and Atopobium vaginae. Individual organisms are not reported. Negative: A negative result does not exclude infection. Assay result is based on relative amounts of Lactobacillus (L gasseri, L crispatus, L jensenii), G vaginalis, and A vaginae. Inconclusive: Repeat testing on a new sample is recommended if clinically indicated.

Reference Values:
Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187 2. Muzny CA, Cerca N, Elnaggar JH, Taylor CM, Sobel JD, Van Der Pol B. State of the art for diagnosis of bacterial vaginosis. J Clin Microbiol. 2023;61(8):e0083722. doi:10.1128/jcm.00837-22

BAHG
82711

Bahia Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Bahia grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BYST
82759

Baker's Yeast, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to baker's yeast Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BCYP
82722

Bald Cypress, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to bald cypress Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BAMB
82879

Bamboo Shoot, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to bamboo shoots Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FBANG
57635

Banana IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

BANA
82746

Banana, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to bananas Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not

useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BAP1
71481

BAP1 Immunostain, Technical Component Only

Clinical Information: BRCA1-asssociated protein 1 (BAP1) is a deubiquitinating enzyme that is a member of the polycomb group proteins of transcriptional repressors and exhibits tumor suppressive activity. BAP1 is located on chromosome 3p21 where loss of one copy of the gene and inactivating mutations are associated with the increased risk and development of various tumors, such as malignant mesotheliomas, uveal melanomas, clear cell renal cell carcinoma, and esophageal squamous carcinomas. In some of these cases, loss of nuclear staining for BAP1 has been reported.

Useful For: As part of a panel of immunostains where loss of staining can be used as a marker of various neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Carbone M, Ferris LK, Baumann F, et al. BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBAITS. J Transl Med 2012;10:179 2.

Koopmans AE, Verdijk RM, Brouwer RWW, et al. Clinical significance of immunohistochemistry for detection of BAP1 mutations in uveal melanoma. Mod Path 2014;27:1321-1330 3. Joseph RW, Kapur P, Serie DJ, et al. Clear cell renal cell carcinoma subtypes identified by BAP1 and PBRM1 Expression. Jl of Urology 2016;195:180-187 4. Klebe S, Driml J, Nasu M, et al. BAP1 hereditary cancer predisposition syndrome: a case report and review of literature. Biomark Res 2015;3:14 5. Mori T, Sumii M, Fujishima F, et al. Somatic alteration and depleted nuclear expression of BAP1 in human esophageal squamous cell carcinoma. Cancer Sci 2015;106:1118-1129 6. Churg A, Sheffield BS, Galateau-Salle F: New markers for separating benign from malignant mesothelials: Are we there yet? Arch Pathol Lab Med 2016;140(4):318-321 7. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

BAP1Z
614581

BAP1-Tumor Predisposition Syndrome, BAP1 Full Gene Analysis, Varies

Clinical Information: Germline variants in the BAP1 gene are associated with BAP1-tumor predisposition syndrome (BAP1-TPDS), a rare autosomal dominant hereditary cancer syndrome.(1) BAP1-TPDS is characterized by increased risk to develop a variety of tumors, including BAP1-inactivated melanocytic tumor (also known as atypical Spitz tumor, or "BAPoma"), uveal and cutaneous melanoma, malignant mesothelioma, and renal cell carcinoma.(1) Many other tumor types, including basal cell carcinoma, hepatocellular carcinoma, cholangiocarcinoma, and meningioma, have also been associated with this syndrome.(1-6) While the true penetrance of BAP1-TDPS is unknown due to both its rarity and ascertainment bias in the existing data, studies have shown up to 88% of individuals with an identified variant had a cancer diagnosis.(1,2) Management and surveillance guidelines have been proposed by several multi-disciplinary expert groups.(1,5)

Useful For: Evaluating patients with a personal or family history suggestive of BAP1-tumor predisposition syndrome (BAP1-TPDS) Establishing a diagnosis of BAP1-TPDS allowing for targeted cancer surveillance based on associated risks Identifying genetic variants associated with increased risk for BAP1-TPDS, allowing for predictive testing and appropriate screening of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Pilarski R, Carlo M, Cebulla C, Abdel-Rahman M. BAP1 tumor predisposition syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2016. Updated March 24, 2022. Accessed September 10, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK390611/ 2. Walpole S, Pritchard AL, Cebulla CM, et al. Comprehensive study of the clinical phenotype of germline BAP1 variant-carrying families worldwide. J Natl Cancer Inst. 2018; 110(12):1328-1341. doi:10.1093/jnci/djy171 3. Star P, Goodwin A, Kapoor R, et al. Germline BAP1-positive patients: the dilemmas of cancer surveillance and a proposed interdisciplinary consensus monitoring strategy. Eur J Cancer. 2018;92:48-53. doi:10.1016/j.ejca.2017.12.022 4. Carbone M, Ferris LK, Baumann F, et al. BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBAITs. J Transl Med. 2012;10:179. doi:10.1186/1479-5876-10-179 5. Battaglia A. The importance of multidisciplinary approach in early detection of BAP1 tumor predisposition syndrome: Clinical management and risk assessment. Clin Med Insights Oncol. 2014;8:37-47. doi:10.4137/CMO.S15239 6. Rai K, Pilarski R, Cebulla CM, Abdel-Rahman MH. Comprehensive review

of BAP1 tumor predisposition syndrome with report of two new cases. Clin Genet. 2016;89(3):285-294. doi:10.1111/cge.12630 7. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30

BARBX 62713 Barbiturates Confirmation, Chain of Custody, Random, Urine

Clinical Information: Barbiturates represent a class of drugs that were originally introduced as sleep inducers. Butalbital is also used to control severe headaches. Mephobarbital and phenobarbital are frequently used to control major motor (grand mal) seizures. These drugs are commonly abused as "downers" to induce sleep after an amphetamine- or cocaine-induced "high." Chain of custody is a record of the disposition of a specimen to document the personnel who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting drug abuse involving barbiturates such as amobarbital, butalbital, pentobarbital, phenobarbital, and secobarbital Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of a barbiturate in urine indicates use of one of these drugs. Most of the barbiturates are fast acting; their presence indicates use within the past 3 days. Phenobarbital, commonly used to control epilepsy, has a very long half-life. The presence of phenobarbital in urine indicates that the patient has used the drug sometime within the past 30 days.

Reference Values:

Negative
Positive results are reported with a quantitative result.

Cutoff concentrations:
Immunoassay screen: 200 ng/mL

Gas chromatography mass spectrometry:
Butalbital: 100 ng/mL
Amobarbital: 100 ng/mL
Pentobarbital: 100 ng/mL
Secobarbital: 100 ng/mL
Phenobarbital: 100 ng/mL

Clinical References: 1. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 10th ed. Biomedical Publications; 2014 2. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

BARBU 80372 Barbiturates Confirmation, Random, Urine

Clinical Information: Barbiturates represent a class of drugs that were originally introduced as sleep inducers. Butalbital is also used to control severe headaches. Mephobarbital and phenobarbital are frequently used to control major motor (grand mal) seizures. These drugs are commonly abused as

"downers" to induce sleep after an amphetamine- or cocaine-induced "high."

Useful For: Detecting drug abuse involving barbiturates such as amobarbital, butalbital, pentobarbital, phenobarbital, and secobarbital

Interpretation: The presence of a barbiturate in urine indicates use of one of these drugs. Most of the barbiturates are fast acting; their presence indicates use within the past 3 days. Phenobarbital, commonly used to control epilepsy, has a very long half-life. The presence of phenobarbital in urine indicates that the patient has used the drug sometime within the past 30 days.

Reference Values:
Negative (Positive results are reported with a quantitative result)

Cutoff concentrations by gas chromatography mass spectrometry:
Butalbital: 100 ng/mL

Amobarbital: 100 ng/mL

Pentobarbital: 100 ng/mL

Secobarbital: 100 ng/mL

Phenobarbital: 100 ng/mL

Clinical References: 1. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 10th ed. Biomedical Publications; 2014 2. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

FBCFS
75839

Barbiturates Confirmation, Serum

Reference Values:

Reporting limit determined each analysis. Test	Result	Units
Butabarbital	None Detected	mcg/mL
Plasma concentrations of 2-3 mcg/mL produce sedation and plasma concentrations of 25 mcg/mL produce sleep in most patients. Plasma concentrations of greater than 30 mcg/mL may produce coma and plasma concentrations in excess of 50 mcg/mL are potentially lethal. Butalbital	None Detected	mcg/mL
A single oral 100 mcg dose resulted in a mean	None Detected	mcg/mL

peak blood concentration of 2.1 mcg/mL (range, 1.7-2.6 mcg/mL) at 2 hours, with a decline to 1.5 mcg/mL (range, 1.3-1.7 mcg/mL) by 24 hours. Potentially toxic at plasma concentrations greater than 10 mcg/mL. Pentobarbital

Peak serum concentrations of 1.2-3.1 mcg/mL were produced 0.5-2.0 hours after a 100 mg oral dose and peak serum concentration of 3 mcg/mL were produced 6 min. following a 100 mg IV dose. Potentially toxic at blood concentrations greater than 10 mcg/mL. Secobarbital	None Detected	mcg/mL
A 3.3 mg/kg oral dose (approx. 230 mg/70 kg) produced a mean peak blood concentration of 2.0 mcg/mL (range, 1.8-2.2 mcg/mL) at 3 hours, diminishing to 1.3 mcg/mL by 20 hours and 0.8 mcg/mL by 40 hours. Potentially toxic at blood concentrations greater than 8 mcg/mL. Phenobarbital	None Detected	mcg/mL

FCDUB
75786

Barbiturates, Umbilical Cord Tissue

Reference Values:
Reporting limit determined each analysis.

Units: ng/g

Only orderable as part of a profile-see FCDSU.

FBARS
57742

Barium, Serum

Reference Values:
Units: ng/mL

Reference range has not been established.

BGRS
82785

Barley Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an

allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Barley grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FBARG
57578

Barley IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet eliminations and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of this test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

BRLY
82687

Barley, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to barley Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FBART
91439

Bartonella Antibody Panel, IFA CSF

Reference Values:
REFERENCE RANGE: <1:1

INTERPRETIVE CRITERIA:
<1:1 Antibody Not Detected
> or = 1:1 Antibody Detected

Infection with Bartonella henselae has been associated with cat scratch disease, bacillary angiomatosis, peliosis hepatis and febrile bacteremia syndrome. Infection with Bartonella quintana has been associated with trench fever and bacillary angiomatosis in both HIV positive and negative individuals.

IgG crossreactivity between B. henselae and B. Quintana may occur at any titer; however, the infecting species will typically have the higher IgG titer. Crossreactivity of IgM between the two species is limited and typically is not seen.

Diagnosis of infections of the central nervous system can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. However, interpreting results is complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps.

BART
81575

Bartonella Antibody Panel, IgG and IgM, Serum

Clinical Information: Bartonella henselae and Bartonella quintana are small, rod-shaped, pleomorphic, gram-negative bacteria. The human body louse (Pediculus humanis) is the proposed vector for B quintana. No animal reservoir has been determined for B quintana. The domestic cat is believed to be both a reservoir and vector for B henselae. Cats may infect humans directly through scratches, bites, or licks, or indirectly through an arthropod vector. Humans remain the only host in which Bartonella infection leads to significant disease. The sight of entry for Bartonella is through openings in the skin. Microscopically, Bartonella lesions appear as rounded aggregates that proliferate rapidly. These aggregates are masses of Bartonella bacteria. Warthin-Starry staining has shown that Bartonella organisms can be present within the vacuoles of endothelial cells, in macrophages, and between cells in areas of necrosis. Occasionally organisms are seen in the lumens of vessels. While cutaneous lesions are common, disseminated tissue infection by Bartonella has been seen in the blood, lymph nodes, spleen, liver, bone marrow, and heart. B henselae has been associated with cat scratch disease (CSD), peliosis hepatitis (PH), bacillary angiomatosis (BA), and endocarditis. B quintana has been associated with trench fever, BA, and endocarditis. BA is a vascular proliferative disease usually involving the skin and regional lymph nodes. CSD begins as a cutaneous papule or pustule that usually develops within a week after animal contact. Regional lymphadenopathy follows and is the predominant clinical feature of CSD. Trench fever was a significant problem during World War I and World War II and is characterized by a relapsing fever and severe pain in the shins. PH and febrile bacteremia syndrome are both syndromes that have afflicted patients with AIDS and patients who are immunocompromised. While trench fever and CSD are usually self-limiting illnesses, the other Bartonella-associated diseases can be life-threatening. Interest in B quintana and B henselae has recently increased since its increased prevalence in patients with AIDS, a transplanted organ, or suppressed immunity.

Useful For: Diagnosis of Bartonella infection, especially in the context of a cat scratch

Interpretation: A positive immunofluorescence assay (IFA) IgM (titer >1:20) suggests a current infection with either Bartonella henselae or Bartonella quintana. A positive IgG (titer >1:128) suggests a current or previous infection. Increases in IgG titers in serial specimens suggest active infection. Normal serum specimens usually have an IgG titer of less than 1:128. However, 5% to 10% of healthy controls exhibit a B henselae and B quintana titer of 1:128. Sera from healthy volunteers rarely show titers of 1:256 or greater. IgM titers in normal serum are typically less than 1:20. IgM titers at 1:20 or greater have not been seen in the normal population. Molecular testing of tissue for Bartonella species nucleic acid is recommended in cases of suspected endocarditis.

Reference Values:
BARTONELLA HENSELAE
IgG: <1:128
IgM: <1:20

BARTONELLA QUINTANA
IgG: <1:128
IgM: <1:20

Clinical References: 1. Rodino KG, Stone E, Saleh OA, Theel ES. The Brief case: Bartonella henselae endocarditis-a case of delayed diagnosis. J Clin Microbiol. 2019;57(9). e00114-19. doi:10.1128/JCM.00114-19 2. Wolf LA, Cherry NA, Maggi RG, Breitschwerdt EB. In pursuit of a stealth pathogen: Laboratory diagnosis of bartonellosis. Clin Micro News. 2014;36(5):33-39

BARTB 89983 Bartonella, Molecular Detection, PCR, Blood

Clinical Information: Bartonella henselae and Bartonella quintana are small, pleomorphic, gram-negative bacilli that are difficult to isolate by culture due to their fastidious growth requirements. B henselae has been associated with cat scratch disease, bacillary angiomatosis, peliosis hepatitis, and endocarditis. B quintana has been associated with trench fever, bacillary angiomatosis, and endocarditis. The diagnosis of Bartonella infection has traditionally been made by Warthin-Starry staining of infected tissue and serology. However, these methods may be nonspecific or falsely negative, especially in the early stages of disease. Evaluation of infected tissue or blood using polymerase chain reaction (PCR) has been shown to be an effective tool for diagnosing Bartonella infection. Mayo Clinic Laboratories has developed a real-time PCR test that permits rapid identification of Bartonella species. The assay targets a unique sequence of the citrate synthase (gltA) gene present in Bartonella species.

Useful For: Aiding in the diagnosis of Bartonella infection when Bartonella DNA would be expected to be present in blood, especially endocarditis

Interpretation: A positive result indicates the presence of Bartonella species DNA. A negative result indicates the absence of detectable Bartonella DNA but does not negate the presence of the organism and may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of Bartonella DNA in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. Liesman RM, Pritt BS, Maleszewski JJ, Patel R: Laboratory diagnosis of infective endocarditis. J Clin Microbiol. 2017 Sep;55(9):2599-2608. doi: 10.1128/jcm.00635-17 2. Dumler JS, Carroll KC, Patel R: Bartonella. In: Carroll KC, Pfaller M, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:chap 50

BARRP 84440 Bartonella, Molecular Detection, PCR, Varies

Clinical Information: Bartonella henselae and Bartonella quintana are small, pleomorphic Gram stain-negative bacilli that are difficult to isolate by culture due to their fastidious growth requirements. B henselae has been associated with cat scratch disease, bacillary angiomatosis, peliosis hepatitis, and endocarditis. B quintana has been associated with trench fever, bacillary angiomatosis, and endocarditis. The diagnosis of Bartonella infection has traditionally been made by Warthin-Starry staining of infected tissue or serology. However, these methods may be falsely negative or nonspecific, respectively.

Culture is insensitive. Evaluation of infected tissue using polymerase chain reaction (PCR) has been shown to be an effective tool for diagnosing Bartonella infection. Mayo Clinic Laboratories has developed a real-time PCR test that permits rapid identification of Bartonella species. The assay targets a unique sequence of the citrate synthase gene present in Bartonella species.

Useful For: Aiding in the diagnosis of Bartonella infection

Interpretation: A positive result indicates the presence of Bartonella species DNA. A negative result indicates the absence of detectable Bartonella DNA but does not negate the presence of the organism and may occur due to inhibition of the polymerase chain reaction, sequence variability underlying primers or probes, or the presence of Bartonella DNA in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. Liesman RM, Pritt BS, Maleszewski JJ, Patel R: Laboratory diagnosis of infective endocarditis. J Clin Microbiol. 2017 Sep;55(9):2599-2608. doi: 10.1128/jcm.00635-17 2. Dumler JS, Carroll KC, Patel R: Bartonella. In: Carroll K, Pfaller M, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:chap 50

RBART
618100

Bartter Syndrome Gene Panel, Varies

Clinical Information: Bartter syndrome (BS) is a rare, hereditary tubulopathy of highly variable severity that can cause renal salt-wasting in infants and young children due to impaired sodium/chloride reabsorption in the thick ascending limb of the nephron.(1) Characteristic clinical features are hypokalemic, hypochloremic metabolic alkalosis and normal blood pressure despite hyperreninemia and hyperaldosteronism.(1) Children with BS have hypercalciuria and normal serum magnesium levels and may present with symptoms in early childhood or before birth. These symptoms distinguish BS from a more common and milder renal salt-wasting disorder called Gitelman syndrome, which features hypocalciuria and low serum magnesium levels and typically presents after 6 years of age. Autosomal dominant hypocalcemia may resemble Bartter syndrome in patients with a markedly activating gain-of-function variant but is distinguishable from BS by mode of inheritance and the presence of hypocalcemia and hypomagnesemia. Age of onset and disease severity is highly variable in Bartter syndrome. The most severe form, antenatal Bartter syndrome (also known as hyperprostaglandin E syndrome or neonatal Bartter syndrome), typically results in polyhydramnios, leading to premature birth. Infants often demonstrate failure to thrive and have significant polyuria resulting in risk for life-threatening salt and water loss. There are four subtypes of Bartter syndrome that typically present antenatally. BS type 1, caused by biallelic alterations in SLC12A1, may also feature fever, vomiting, and nephrocalcinosis in infancy. BS type 2, caused by biallelic variants in KCNJ1, causes symptoms like BS type 1, but patients may demonstrate transient hyperkalemia and acidosis. BS type 4a, caused by biallelic alterations in BSND, and BS type 4b, caused by alterations in CLCNKA and CLCNKB, may be accompanied by sensorineural deafness in addition to renal salt-wasting and related symptoms. Type 4b is also inherited in an autosomal recessive (or biallelic) pattern or can result from digenic inheritance. Classic Bartter syndrome, also known as type 3, is the second major form of BS and is caused by alterations in CLCNKB. All BS type 3 patients have marked hypochloremia. Age of onset varies in BS type 3 and may correlate with genotype, with individuals with truncating variants presenting earlier in life. Individuals with BS type 3 may present antenatally with polyhydramnios, during infancy with failure to thrive and lethargy, or in adolescence or adulthood with symptoms of chronic hypokalemia, such as constipation, muscle cramps, salt-craving, nocturia, and vomiting. Nephrocalcinosis is uncommon in BS type 3, and patients are usually normocalciuric but may still have severe electrolyte imbalances. A third from of BS called transient neonatal Bartter syndrome (BS type 5), is associated with severe polyhydramnios and extreme salt wasting at birth that spontaneously resolves in the first few months of life in surviving

patients. BS type 5 is caused by variants in MAGED2 inherited in an X-linked recessive pattern. Although there is some phenotypic overlap between Bartter syndrome, Gitelman syndrome, and autosomal dominant hypocalcemia, they have different genetic causes. This panel does not include the genes associated with Gitelman syndrome (SLC12A3) or autosomal dominant hypocalcemia (CASR). If simultaneous genetic testing for Bartter syndrome, Gitelman syndrome and/or autosomal dominant hypocalcemic hypercalciuria is desired, order RSCGP / Nephrocalcinosis, Nephrolithiasis, and Renal Electrolyte Imbalance Gene Panel, Varies.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of Bartter syndrome Establishing a diagnosis of Bartter syndrome

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(2) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Fulchiero R, Seo-Mayer P. Bartter Syndrome and Gitelman Syndrome. Pediatr Clin North Am. 2019 Feb;66(1):121-134. 2. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424.

BMAMA
113630

Basic Metabolic Panel, Serum

Clinical Information: The basic metabolic panel measures 8 analytes and calculates an anion gap. It is used to assess kidney status, electrolyte, and acid/base balance, and blood glucose.

Useful For: Routine health monitoring or patient monitoring while hospitalized for information regarding metabolism, including the current kidney status, electrolyte, and acid/base balance, and blood glucose

Interpretation: Basic metabolic panel results are usually evaluated in conjunction with each other for patterns of results. A single abnormal test result could be indicative of something different than if more than 1 of the test results are abnormal. Many conditions will cause abnormal results including kidney failure, breathing problems, and diabetes-related complications.

Reference Values:
SODIUM
<1 year: Not established
> or =1 year: 135-145 mmol/L

POTASSIUM
<1 year: Not established
> or =1 year: 3.6-5.2 mmol/L

CHLORIDE
<1 year: Not established
1-17 years: 102-112 mmol/L
> or =18 years: 98-107 mmol/L

BICARBONATE
Males:
<1 year: Not established
1-2 years: 17-25 mmol/L
3 years: 18-26 mmol/L
4-5 years: 19-27 mmol/L
6-7 years: 20-28 mmol/L
8-17 years: 21-29 mmol/L
> or =18 years: 22-29 mmol/L

Females:
<1 year: Not established
1-3 years: 18-25 mmol/L
4-5 years: 19-26 mmol/L
6-7 years: 20-27 mmol/L
8-9 years: 21-28 mmol/L
> or =10 years: 22-29 mmol/L

ANION GAP
<7 years: Not established
> or =7 years: 7-15

BLOOD UREA NITROGEN
Males:
<12 months: Not established
1-17 years: 7-20 mg/dL
> or =18 years: 8-24 mg/dL

Females:
<12 months: Not established
1-17 years: 7-20 mg/dL
> or =18 years: 6-21 mg/dL

CREATININE
Males:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL

Females:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL

ESTIMATED GLOMERULAR FILTRATION RATE (eGFR)
>= 18 years old: > or =60 mL/min/BSA (body surface area)
Estimated GFR calculated using the 2021 CKD-EPI creatinine equation
Note: eGFR results will not be calculated for patients younger than 18 years old.

CALCIUM
<1 year: 8.7-11.0 mg/dL
1-17 years: 9.3-10.6 mg/dL
18-59 years: 8.6-10.0 mg/dL
60-90 years: 8.8-10.2 mg/dL
>90 years: 8.2-9.6 mg/dL

GLUCOSE
0-11 months: Not established
> or =1 year: 70-140 mg/dL

Clinical References: 1. Oh MS: Evaluation of renal function, water, electrolytes, and acid-base balance. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 22nd ed. Elsevier Saunders; 2011:chap 14 2. Basic Metabolic Panel (BMP). Testing.com; Updated November 9, 2021. Accessed July 13, 2022. Available at www.testing.com/tests/basic-metabolic-panel-bmp/

FBSLG
57660

Basil IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

BASL
82489

Basil, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to basil Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FBBLE
57546

Bass Black (Sea Bass) (Centropristis striata) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

FBSQU
75774

Bath Salts Panel (Qualitative), Urine

Clinical Information: Alpha-Pyrrolidinohexiophenone (PHP)/Alpha-Pyrrolidinoisohexanophenone (PiHP): Novel psychoactive stimulants 4-Chloro Alpha-Pyrrolidinovalerophenone: 4-Chloro alpha-PVP (4-chloro-alpha-pyrrolidinovalerophenone) is a psychoactive stimulant of the pyrrolidinophenone series that is structurally related to alpha-PVP. This analyte has been sold as a novel psychoactive substance (NPS) for its stimulating and empathogenic effects and is used as an alternative to amphetamine, MDMA (3,4-methylenedioxymethamphetamine), and/or cocaine. Eutylone: Eutylone is classified as a synthetic stimulant and belongs to the beta-keto-methylenedioxyamphetamine subclass, which includes synthetic stimulants methylone, butylone, ethylone and N-ethylpentylone. Benzylone: Benzylone is classified as a synthetic stimulant and belongs to the beta-keto-methylenedioxyamphetamine subclass, which includes synthetic stimulants methylone, butylone, ethylone and N-ethylpentylone. N-Butyl Pentylone: N-Butyl pentylone is classified as a synthetic stimulant and belongs to the beta-ketomethylenedioxyamphetamine subclass, which includes synthetic stimulants methylone, butylone, ethylone and N-ethylpentylone.

Reference Values:
Reporting limit determined each analysis.

alpha-PHP/alpha-PiHP: None detected

4-chloro alpha-PVP: None detected

Eutylone: None detected

Benzylone: None detected

N-butyl Pentylone: None detected

BAYL
82601

Bay Leaf, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to bay leaf Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive

5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FBWME
57583

Bayberry/Wax Myrtle (Myrica spp) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 5 6 17.50 - 49.99 50.00 - 99.99 >99.99 Very High Positive Very High Positive Very High Positive

Reference Values:
<0.35 kU/L

BCL2
70362

BCL-2 Immunostain, Technical Component Only

Clinical Information: BCL-2 is in a family of regulators of apoptosis, which together control the balance between pro- and antiapoptotic signals. BCL-2 protein acts as an inhibitor of apoptosis. It is normally expressed in mantle zone B cells and T cells, with an intense perinuclear cytoplasmic pattern, but it is not expressed in reactive germinal center B cells. In most cases of follicular lymphoma, the BCL2 gene is involved in a translocation with IgH, t(14;18)(q32;q21), leading to overexpression of the BCL-2 protein. Thus, BCL-2 expression in germinal center B cells supports a diagnosis of follicular lymphoma.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Choi WWL, Weisenburger DD, Greiner TC, et al. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. Clin Cancer Res 2009; 15:5594-5502 2. Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: A report from The International DLBCL Rituximab-CHOP Consortium Program. Blood 2013; 121(20):4021-4031 3. Iqbal J, Neppalli VT, Wright G, et al. BCL2 expression is a prognostic marker for the activated B-cell-like type of diffuse large B-cell lymphoma. Journal of Clinical Oncology 2006; 24(6)961-968 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

BCL6
70363

BCL-6 Immunostain, Technical Component Only

Clinical Information: BCL-6 protein is a transcription factor expressed by follicle center B cells and other cells of the follicle center. It is useful in the classification of lymphomas.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Choi WW, Weisenburger DD, Greiner TC, et al. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. Clin Cancer Res. 2009;15:5594-5502 2. Dogan A, Bagdi E, Munson P, Isaacson PG. CD10 and BCL-6 expression in paraffin sections of normal lymphoid tissue and B-cell lymphomas. Am J Surg Pathol. 2000;24(6):846-852 3. Gualco G, Weiss LM, Harrington WJ Jr, Bacchi CE. BCL6, MUM1, and CD10 expression in mantle cell lymphoma. Appl Immunohistochem Mol Morphol. 2010;18(2):103-108 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

BCOR
605260

BCOR Immunostain, Technical Component Only

Clinical Information: Round cell sarcomas are a heterogeneous group of tumors that have diverse genetic abnormalities, clinical presentations, and outcomes despite similar cytomorphology. The diagnosis of these emerging entities has relied on molecular tests until recent immunohistochemical screening markers. BCOR (BCL-6 interacting corepressor) is involved in suppressing gene expression by either interacting with BCL-6 or binding to PCGF1 (poly-comb-group RING finger homologue1) and inducing gene silencing by histone modification. BCOR immunohistochemistry is a highly sensitive marker in identifying round cell sarcomas with BCOR abnormalities.

Useful For: Aiding in the distinction of a subset of primitive round cell sarcomas with BCOR rearrangements from other Ewing/Ewing-like sarcomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Machado I, Yoshida A, Lopez-Guerrero JA, et al. Immunohistochemical analysis of NKX2.2, ETV4, and BCOR in a large series of genetically confirmed Ewing sarcoma family of tumors. Pathol Res Pract 2017; 213:1048-1053 2. Chiang S, Lee CH, Stewart CJR, et al. BCOR is a robust diagnostic immunohistochemical marker of genetically diverse high-grade endometrial stromal sarcoma, including tumors exhibiting variant morphology. Mod Pathol 2017; 30:1251-1261 3. Kao YC, Sung YS, Zhang L, et al. BCOR overexpression is a highly sensitive marker in round cell sarcomas with BCOR genetic abnormalities. Am J Surg Pathol 2016;40(12):1670-1678 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

BCRFX
65248

BCR/ABL1 Qualitative Diagnostic Assay with Reflex to BCR/ABL1 p190 Quantitative Assay or BCR/ABL1 p210 Quantitative Assay, Varies

Clinical Information: The t(9;22)/BCR::ABL1 abnormality is associated with chronic myelogenous leukemia (CML) and "Philadelphia-positive" acute lymphoblastic leukemia of B-cell lineage (Ph+ ALL). Very rarely, this abnormality has also been identified in cases of acute myeloid leukemia and T-cell lymphoblastic leukemia/lymphoma. The fusion gene on the derivative chromosome 22q11 produces a chimeric BCR::ABL1 messenger RNA (mRNA) transcript and corresponding translated oncoprotein. Despite substantial breakpoint heterogeneity at the DNA level, a consistent set of BCR::ABL1 mRNA transcripts are produced that can be readily and sensitively detected by reverse transcription polymerase chain reaction (RT-PCR) technique. In CML, breakpoints in BCR result in either exons 13 or 14 (e13, e14) joined to exon 2 of ABL1 (a2). The corresponding e13-a2 or e14-a2 BCR::ABL1 mRNAs produce a 210 kDa protein (p210). Rare cases of CML are characterized by an e19-a2 type mRNA with a corresponding p230 protein. In Ph+ ALL, the majority of cases harbor an e1-a2 BCR::ABL1 mRNA transcript, producing a p190 protein. However, chimeric mRNA type is not invariably associated with disease type, as noted by the presence of p210-positive Ph ALL and very rare cases of p190-positive CML. Therefore, positive results from a screening (diagnostic) assay for BCR::ABL1 mRNA need to be correlated with clinical and pathologic findings. In addition to the main transcript variants described above, rare occurrences of both CML and Ph+ ALL can have alternative break-fusion events resulting in unusual BCR::ABL1 transcript types. Examples include e6-a2 and BCR exon fusions to ABL1 exon a3 (eg, e13-a3, e14-a3, or e1-a3). In addition to detecting common BCR::ABL1 mRNA transcripts, this assay also can identify these rarer BCR::ABL1 transcript variants and is therefore a comprehensive screen for both usual and uncommon BCR::ABL1 gene fusions in hematopoietic malignancies. Given the nature of genetic events in tumors however, this assay will not identify extremely rare and unexpected BCR::ABL1 events involving other exons (eg, case report level) and is therefore not absolutely specific but is predicted to detect greater than 99.5% of BCR::ABL1 events. Therefore, it is recommended that for diagnosis, RT-PCR plus a second method (eg, BCR::ABL1 fluorescence in situ hybridization or cytogenetics) should be used. However, this RT-PCR assay is invaluable at diagnosis for identifying the precise BCR::ABL1 mRNA type (eg, for future quantitative assay disease monitoring), which complementary methods cannot. This assay is intended as a qualitative method, providing information on the presence (and specific mRNA type) or absence of the BCR::ABL1 mRNA. Results from this test can be used to determine the correct subsequent assay for monitoring of transcript levels following therapy (eg, BCRAB / BCR/ABL1, p210, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Chronic Myeloid Leukemia (CML), Varies; BA190 / BCR/ABL1, p190, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Assay, Varies). Because the assay is analytically sensitive, it compensates for situations such as partially degraded RNA quality or low cell number, but it is not intended for quantitative or monitoring purposes.

Useful For: Diagnostic workup of patients with high probability of BCR::ABL1-positive hematopoietic neoplasms, predominantly chronic myeloid/myelogenous leukemia and acute lymphoblastic leukemia

Interpretation: An interpretive report will be provided. When positive, the test identifies which specific messenger RNA fusion variant is present to guide selection of an appropriate monitoring assay. If common p210 or p190 fusion variant detected, quantitative reflex will be performed. -Common fusion variants detected: e13-a2 or e14-a2 (p210), e1-a2 (p190), and e6-a2 (p205*) -Rare fusion variants detected: e13-a3 (p210), e14-a3 (p210), e1-a3 (p190), e19-a2 (p230) -Potential rare fusions detected: e12-a3, e19-a3 *This is formerly observed as the e6-a2 (p185) fusion form

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Burmeister T, Reinhardt R. A multiplex PCR for improved detection of typical and atypical BCR-ABL fusion transcripts. Leuk Res. 2008;32(4):579-585 2. Melo JV. The diversity of BCR-ABL fusion proteins and their relationship to leukemia phenotype. Blood. 1996;88(7):2375-2384 3. Melo JV. BCR-ABL gene variants. Baillieres Clin Haematol. 1997;10(2):203-222 4. Baccarini M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-884 5. Cross NC, White HE, Muller MC, et al. Standardized definitions of molecular response in chronic myeloid leukemia. Leukemia. 2012;26(10):2172-2175 6. Deininger MW, Shah NP, Altman JK, et al. Chronic Myeloid Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020;18(10):1385-1415. doi:10.6004/jnccn.2020.0047

BA190
83336

BCR/ABL1, p190, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Assay, Varies

Clinical Information: Messenger RNA (mRNA) transcribed from BCR/ABL1 (fusion of the breakpoint cluster region gene [BCR] at chromosome 22q11 to the Abelson gene [ABL1] at chromosome 9q34) is detected in all patients with chronic myeloid leukemia (CML) and a subset of patients with both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Although breakpoints in the BCR and ABL1 genes may occur in a variety of locations, splicing of the primary RNA transcripts result in only 8 fusion site variants (e1/a2, e6/a2, e13/a2, e14/a2, e19/a2, and e1/a3, e13/a3, e14/a3), which incorporate the entire sequence of the exons on both sides of the fusion site. The e1/a2 and e1/a3 fusion forms produce a 190-kDa protein designated p190. This BCR/ABL1 protein form is found in approximately 75% of patients with childhood ALL and approximately 50% of patients with adult ALL, with the majority arising from e1/a2 mRNA. The p190 is also the predominant fusion form in a small subset of patients with CML, although the vast majority of CML cases contain the p210 protein, typically from e13/a2 or e14/a2 mRNA fusions. Other fusion forms are very rare. Quantitative reverse-transcription polymerase chain reaction (qRT-PCR) is the most sensitive method for monitoring BCR/ABL1 levels during treatment. This test detects mRNA coding for the most common p190 fusion form (e1/a2).

Useful For: Monitoring response to therapy in patients with known e1/a2 BCR/ABL1 (p190) fusion forms

Interpretation: An interpretive report will be provided.

Reference Values:
The presence or absence of the BCR/ABL1 messenger RNA fusion form producing the p190 fusion protein is reported. If positive, the level is reported as the ratio of BCR/ABL1 (p190) transcript to ABL1 transcript in the form of a percentage.

Clinical References: 1. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med. 2003;349(15):1423-1432 2. Radich JP, Gooley T, Bryant E, et al. The significance of BCR-ABL molecular detection in chronic myeloid leukemia patients "late," 18 months or more after transplantation. Blood. 2001;98(6):1701-1707 3. Olavarria E, Kanfer E, Szydlo R, et al. Early detection of BCR-ABL transcripts by quantitative reverse transcriptase-polymerase chain reaction predicts outcome after allogeneic stem cell transplantation for chronic myeloid leukemia. Blood. 2001;97(6):1560-1565 4. Tefferi A. The classic myeloproliferative neoplasms: Chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia, and primary myelofibrosis. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019, Accessed December 27, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225078035&bookid=2709

B190R
48391

BCR/ABL1, p190, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Reflex, Varies

Clinical Information: The t(9;22)/BCR-ABL1 abnormality is associated with chronic myeloid leukemia (CML) and "Philadelphia positive" acute lymphoblastic leukemia of B-cell lineage (Ph+ ALL). Very rarely, this abnormality has also been identified in cases of acute myeloid leukemia and T-lymphoblastic leukemia/lymphoma. The fusion gene on the derivative chromosome 22q11 produces a chimeric BCR-ABL1 messenger RNA (mRNA) transcript and corresponding translated oncoprotein. Despite substantial breakpoint heterogeneity at the DNA level, a consistent set of BCR-ABL1 mRNA transcripts are produced that can be readily and sensitively detected by reverse transcription polymerase chain reaction (RT-PCR) technique. In CML, breakpoints in BCR nearly always result in either exons 13 or 14 (e13, e14) joined to exon 2 of ABL1 (a2). The corresponding e13-a2 or e14-a2 BCR-ABL1 mRNAs produce a 210 kDa protein (p210). Rare cases of CML are characterized by an e19-a2 type mRNA with a corresponding p230 protein. In Ph+ ALL, the majority of cases harbor an e1-a2 BCR-ABL1 mRNA transcript, producing a p190 protein, although some ALL patients may alternatively present with the e13/e14-a2 (p210) type fusion. This assay provides information at the time of diagnosis regarding the presence (and specific mRNA type) or absence of the BCR-ABL1 mRNA. If positive, the reflex test will follow to provide an initial quantitative level of the specific BCR-ABL1 transcript. For example, when positive for the e1-a2 (p190) type mRNA, the reflex test provides a corresponding p190 quantitative value. Results from this test are also useful to determine the correct quantitative assay for subsequent monitoring of transcript levels (ie, p190 or p210) during tyrosine kinase inhibitor therapy.

Useful For: Diagnostic workup of patients with a high probability of BCR-ABL1-positive hematopoietic neoplasms, particularly acute lymphoblastic leukemia (B-lymphoblastic leukemia), to provide a pretreatment quantitative level of BCR-ABL1 mRNA transcript if the initial diagnostic reverse transcription polymerase chain reaction screen is positive When positive, the reflex test provides a quantitative value for the corresponding e1-a2 (p190) BCR-ABL1 mRNA fusion variant.

Interpretation: An interpretive report will be provided.

Reference Values:
Only orderable as a reflex. For more information see BCRFX / BCR/ABL1 Qualitative Diagnostic Assay with Reflex to BCR/ABL1 p190 Quantitative Assay or BCR/ABL1 p210 Quantitative Assay, Varies.

Clinical References: 1. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med. 2003;349(15):1423-1432 2. Radich JP, Gooley T, Bryant E, et al. The significance of BCR-ABL molecular detection in chronic myeloid leukemia patients "late," 18 months or more after transplantation. Blood. 2001;98(6):1701-1707. doi:10.1182/blood.v98.6.1701 3. Olavarria E, Kanfer E, Szydlo R, et al. Early detection of BCR-ABL transcripts by quantitative reverse transcriptase-polymerase chain reaction predicts outcome after allogeneic stem cell transplant for chronic myeloid leukemia. Blood. 2001;97(6):1560-1565 4. Tefferi A. The classic myeloproliferative neoplasms: Chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia, and primary myelofibrosis. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019, Accessed December 27, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225078035&bookid=2709

BCRAM
113538

BCR/ABL1, p210, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Chronic Myeloid Leukemia (CML), Bone Marrow

Clinical Information: Chronic myeloid leukemia (CML) is a hematopoietic stem cell neoplasm included in the broader diagnostic category of myeloproliferative neoplasms. CML is consistently associated with fusion of the breakpoint cluster region gene (BCR) at chromosome 22q11 to the Abelson gene (ABL1) at chromosome 9q23. This fusion is designated BCR/ABL1 and may be seen on routine karyotype as the Philadelphia chromosome. Although various breakpoints within the BCR and ABL1 genes have been described, more than 95% of CML cases contain a consistent messenger RNA transcript in which either the BCR exon 13 (e13) or BCR exon 14 (e14) is fused to the ABL1 exon 2 (a2), yielding fusion forms e13/a2 and e14/a2, respectively. The e13/a2 and e14/a2 fusion forms produce a 210-kDa protein (p210). The p210 fusion protein is an abnormal tyrosine kinase known to be critical for the clinical and pathologic features of CML, and agents that block the tyrosine kinase activity (ie, tyrosine kinase inhibitors or TKI, such as imatinib mesylate) have been used successfully for treatment. Monitoring the level of BCR/ABL1 mRNA in CML patients during treatment is helpful for both prognosis and management of therapy.(1-3) Rising BCR/ABL1 mRNA levels following attainment of critical therapeutic milestones can be indicative of acquired resistance variants involving the ABL1 portion of the BCR/ABL1 fusion gene. Quantitative reverse-transcription PCR is the most sensitive method for monitoring BCR-ABL1 levels during treatment. This test detects the BCR/ABL1 mRNA fusion forms found in CML (e13/a2 and e14/a2).

Useful For: Monitoring response to therapy in patients with chronic myeloid leukemia who are known to have the e13/a2 or e14/a2 BCR/ABL1 fusion transcript forms

Interpretation: An interpretive report will be provided. When BCR/ABL1 mRNA is present, quantitative results are reported on the international scale (IS), established from data originally reported in the IRIS (International Randomized Study of Interferon versus STI571) trial involving newly diagnosed chronic myeloid leukemia patients. Using the IS, a result of less than 0.1% BCR/ABL1 (p210):ABL1 is equivalent to a major molecular remission. This value is also designated on a log scale (molecular response [MR]) as MR3. For additional discussion of the international scale, see Clinical References.

Reference Values:
The presence or absence of BCR/ABL1 messenger RNA fusion form e13/e14-a2 producing the p210 fusion protein is identified. If positive, the quantitative level is reported as the normalized ratio of BCR/ABL1 (p210) to endogenous ABL1 mRNA with conversion to a percentage referenced to the international scale , on which 0.1% BCR/ABL1:ABL1 (also represented on a log scale as molecular response 3 [MR3]) is designated as a major molecular response threshold.

Clinical References: 1. Hughes TP, Kaeda J, Branford S, et al: Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med. 2003;349(15):1423-1432 2. Baccarini M, Deininger MW, Rosti G, et al: European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-884. doi:10.1182/blood-2013-05-501569 3. Press RD, Kamel-Reid S, Ang D: BCR-ABL1 RT-qPCR for monitoring the molecular response to tyrosine kinase inhibitors in chronic myeloid leukemia. J Mol Diagn. 2013;15(5):565-576. doi:10.1016/j.jmoldx.2013.04.007 4. Cross NC, White HE, Muller MC, Saglio G, Hochhaus A: Standardized definitions of molecular response in chronic myeloid leukemia. Leukemia. 2012;26(10):2172-2175. doi:10.1038/leu.2012.104 5. National Comprehensive Cancer Network Practice Guidelines in Oncology: Chronic Myeloid Leukemia 2015. Available at https://www.nccn.org

BCRAB
89007

BCR/ABL1, p210, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Chronic Myeloid Leukemia (CML), Varies

Clinical Information: Chronic myeloid leukemia (CML) is a hematopoietic stem cell neoplasm included in the broader diagnostic category of myeloproliferative neoplasms. CML is consistently associated with fusion of the breakpoint cluster region gene (BCR) at chromosome 22q11 to the Abelson gene (ABL1) at chromosome 9q23. This fusion is designated BCR/ABL1 and may be seen on routine karyotype as the Philadelphia chromosome. Although various breakpoints within the BCR and ABL1 genes have been described, more than 95% of CMLs contain a consistent mRNA transcript in which either the BCR exon 13 (e13) or BCR exon 14 (e14) is fused to the ABL1 exon 2 (a2), yielding fusion forms e13/a2 and e14/a2, respectively. The e13/a2 and e14/a2 fusion forms produce a 210-kDa protein (p210). The p210 fusion protein is an abnormal tyrosine kinase known to be critical for the clinical and pathologic features of CML, and agents that block the tyrosine kinase activity (ie, tyrosine kinase inhibitors or TKI, such as imatinib mesylate) have been used successfully for treatment. Monitoring the level of BCR/ABL1 mRNA in CML patients during treatment is helpful for both prognosis and management of therapy.(1-3) Rising BCR/ABL1 mRNA levels following attainment of critical therapeutic milestones (see Clinical References) can be indicative of acquired resistance mutations involving the ABL1 portion of the BCR/ABL1 fusion gene. Quantitative reverse-transcription polymerase chain reaction is the most sensitive method for monitoring BCR-ABL1 levels during treatment. This test detects the BCR/ABL1 mRNA fusion forms found in CML (e13/a2 and e14/a2).

Useful For: Monitoring response to therapy in patients with chronic myeloid leukemia who are known to have the e13/a2 or e14/a2 BCR/ABL1 fusion transcript forms

Interpretation: An interpretive report will be provided. When BCR/ABL1 mRNA is present, quantitative results are reported on the international scale (IS), established from data originally reported in the IRIS (International Randomized Study of Interferon versus STI571) trial involving newly diagnosed chronic myeloid leukemia patients. Using the IS, a result of less than 0.1% BCR/ABL1 (p210):ABL1 is equivalent to a major molecular remission. This value is also designated on a log scale (Molecular Response, MR) as MR3. For further discussion of the international scale, see Clinical References.

Reference Values:
The presence or absence of BCR/ABL1 mRNA fusion form e13/e14-a2 producing the p210 fusion protein is identified. If positive, the quantitative level is reported as the normalized ratio of BCR/ABL1 (p210) to endogenous ABL1 mRNA with conversion to a percentage referenced to the international scale (IS), on which 0.1% BCR/ABL1:ABL1 (also represented on a log scale as Molecular Response 3, or MR3) is designated as a major molecular response (MMR) threshold.

Clinical References: 1. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med. 2003;349(15):1423-1432 2. Baccarini M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-884 3. Press RD, Kamel-Reid S, Ang D. BCR-ABL1 RT-qPCR for monitoring the molecular response to tyrosine kinase inhibitors in chronic myeloid leukemia. J Mol Diagn. 2013;15(5):565-576 4. Cross NC, White HE, Muller MC, Saglio G, Hochhaus A. Standardized definitions of molecular response in chronic myeloid leukemia. Leukemia. 2012;26(10):2172-2175 5. National Comprehensive Cancer Network Practice Guidelines in Oncology: Chronic Myeloid Leukemia 2015. Accessed December 27, 2023. Available at www.nccn.org

B210R 48390 BCR/ABL1, p210, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Reflex, Varies

Clinical Information: The t(9;22)/BCR-ABL1 abnormality is associated with chronic myeloid leukemia (CML) and "Philadelphia positive" acute lymphoblastic leukemia of B-cell lineage (Ph ALL). Very rarely, this abnormality has also been identified in cases of acute myeloid leukemia and T-

lymphoblastic leukemia/lymphoma. The fusion gene on the derivative chromosome 22q11 produces a chimeric BCR-ABL1 messenger RNA (mRNA) transcript and corresponding translated oncoprotein. Despite substantial breakpoint heterogeneity at the DNA level, a consistent set of BCR-ABL1 mRNA transcripts are produced that can be readily and sensitively detected by reverse transcription polymerase chain reaction (RT-PCR) technique. In CML, breakpoints in BCR nearly always result in either exons 13 or 14 (e13, e14) joined to exon 2 of ABL1 (a2). The corresponding e13-a2 or e14-a2 BCR-ABL1 mRNAs produce a 210 kDa protein (p210). Rare cases of CML are characterized by an e19-a2 type mRNA with a corresponding p230 protein. In Ph ALL, the majority of cases harbor an e1-a2 BCR-ABL1 mRNA transcript, producing a p190 protein, although some ALL patients may alternatively present with the e13/e14-a2 or p210 type fusion. This assay provides information at the time of diagnosis regarding the presence (and specific mRNA type) or absence of the BCR-ABL1 mRNA. If positive, the reflex test will follow to provide an initial quantitative level of the specific BCR-ABL1 transcript. For example, when positive for the e13/e14-a2 (p210) type mRNA, the reflex test provides a corresponding p210 quantitative value. Results from this test are also useful to determine the correct quantitative assay for subsequent monitoring of transcript levels (ie, p190 or p210) during tyrosine kinase inhibitor therapy.

Useful For: Diagnostic workup of patients with a high probability of BCR-ABL1-positive hematopoietic neoplasms, particularly chronic myeloid leukemia and Ph+ acute lymphoblastic leukemia (B-lymphoblastic leukemia), to provide a pretreatment quantitative level of BCR-ABL1 mRNA transcript if the initial diagnostic reverse transcription polymerase chain reaction screen is positive When positive, the reflex test provides a quantitative value for the corresponding e13-a2 or e14-a2 (p210) BCR-ABL1 mRNA fusion variant

Interpretation: An interpretive report will be provided.

Reference Values:
Only orderable as a reflex. For more information see BCRFX / BCR/ABL1 Qualitative Diagnostic Assay with Reflex to BCR/ABL1 p190 Quantitative Assay or BCR/ABL1 p210 Quantitative Assay, Varies.

Clinical References: 1. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med. 2003;349(15):1423-1432 2. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-884 3. Press RD, Kamel-Reid S, Ang D. BCR-ABL1 RT-qPCR for monitoring the molecular response to tyrosine kinase inhibitors in chronic myeloid leukemia. J Mol Diagn. 2013;15(5):565-576 4. Cross NC, White HE, Muller MC, Saglio G, Hochhaus A. Standardized definitions of molecular response in chronic myeloid leukemia. Leukemia. 2012;26(10):2172-2175 5. National Comprehensive Cancer Network Practice Guidelines in Oncology: Chronic Myeloid Leukemia 2015. Accessed December 27, 2023. Available at www.nccn.org

BADX
89006

BCR/ABL1, Qualitative, Diagnostic Assay, Varies

Clinical Information: The t(9;22)/BCR::ABL1 abnormality is associated with chronic myeloid leukemia (CML) and "Philadelphia-positive" acute lymphoblastic leukemia of B-cell lineage (Ph+ ALL). Very rarely, this abnormality has also been identified in cases of acute myeloid leukemia and T-cell lymphoblastic leukemia/lymphoma. The fusion gene on the derivative chromosome 22q11 produces a chimeric BCR::ABL1 messenger RNA (mRNA) transcript and corresponding translated oncoprotein. Despite substantial breakpoint heterogeneity at the DNA level, a consistent set of BCR::ABL1 mRNA transcripts are produced that can be readily and sensitively detected by reverse transcription polymerase chain reaction (RT-PCR) technique. In CML, breakpoints in BCR result in either exons 13 or 14 (e13,

e14) joined to exon 2 of ABL1 (a2). The corresponding e13-a2 or e14-a2 BCR::ABL1 mRNAs produce a 210 kDa protein (p210). Rare cases of CML are characterized by an e19-a2 type mRNA with a corresponding p230 protein. In Ph+ ALL, the majority of cases harbor an e1-a2 BCR::ABL1 mRNA transcript, producing a p190 protein. However, chimeric mRNA type is not invariably associated with disease type, as noted by the presence of p210-positive Ph ALL and very rare cases of p190-positive CML. Therefore, positive results from a screening (diagnostic) assay for BCR-ABL1 mRNA need to be correlated with clinical and pathologic findings. In addition to the main transcript variants described above, rare occurrences of both CML and Ph+ ALL can have alternative break-fusion events resulting in unusual BCR-ABL1 transcript types. Examples include e6-a2 and BCR exon fusions to ABL1 exon a3 (eg, e13-a3, e14-a3, or e1-a3). In addition to detecting common BCR::ABL1 mRNA transcripts, this assay also can identify these rarer BCR::ABL1 transcript variants and is, therefore, a comprehensive screen for both usual and uncommon BCR::ABL1 gene fusions in hematopoietic malignancies. Given the nature of genetic events in tumors, however, this assay will not identify extremely rare and unexpected BCR::ABL1 events involving other exons (eg, case report level) and is, therefore, not absolutely specific but is predicted to detect more than 99.5% of BCR::ABL1 events. Therefore, it is recommended that for diagnosis, RT-PCR plus a second method (eg, BCR::ABL1 fluorescence in situ hybridization or cytogenetics) should be used. However, this RT-PCR assay is invaluable at diagnosis for identifying the precise BCR::ABL1 mRNA type (eg, for future quantitative assay disease monitoring), which cannot be done by complementary methods. This assay is intended as a qualitative method, providing information on the presence (and specific mRNA type) or absence of the BCR::ABL1 mRNA. Results from this test can be used to determine the correct subsequent assay for monitoring of transcript levels following therapy (eg, BCRAB / BCR/ABL1, p210, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Chronic Myeloid Leukemia (CML), Varies; BA190 / BCR/ABL1, p190, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Assay, Varies). Because the assay is analytically sensitive, it compensates for situations such as partially degraded RNA quality or low cell number, but it is not intended for quantitative or monitoring purposes.

Useful For: Diagnostic workup of patients with a high probability of BCR::ABL1-positive hematopoietic neoplasms, predominantly chronic myeloid leukemia and acute lymphoblastic leukemia

Interpretation: An interpretive report will be provided. When positive, the test identifies the specific messenger RNA fusion variant present to guide selection of an appropriate monitoring assay. Monitoring is available for common p210 or p190 fusion variant detected. -Common fusion variants detected: e13-a2 or e14-a2 (p210), e1-a2 (p190), and e6-a2 (p205*) -Rare fusion variants detected: e13-a3 (p210), e14-a3 (p210), e1-a3 (p190), e19-a2 (p230) -Potential rare fusions detected: e12-a3, e19-a3 *This is formerly observed as the e6-a2 (p185) fusion form.

Reference Values:
A qualitative result is provided that indicates the presence or absence of BCR::ABL1 messenger RNA. When positive, the fusion variant is also reported.

Clinical References: 1. Burmeister T, Reinhardt R. A multiplex PCR for improved detection of typical and atypical BCR-ABL fusion transcripts. Leuk Res 2008;32(4):579-585 2. Melo JV. The diversity of BCR-ABL fusion proteins and their relationship to leukemia phenotype. Blood. 1996;88(7):2375-2384 3. Melo JV. BCR-ABL gene variants. Baillieres Clin Haematol. 1997;10(2):203-222 4. Tefferi A. The classic myeloproliferative neoplasms: Chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia, and primary myelofibrosis. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019, Accessed January 5, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225078035&bookid=2709

BAKDM 89609 BCR/ABL1, Tyrosine Kinase Inhibitor Resistance, Kinase

Domain Mutation Screen, Sanger Sequencing, Varies

Clinical Information: Chronic myeloid leukemia (CML) is characterized by the presence of the t(9:22) BCR::ABL1 abnormality, resulting in formation of a fusion BCR::ABL1 messenger RNA (mRNA) and protein. The ABL1 component of this oncoprotein contains tyrosine kinase activity and is thought to play a central role in the proliferative phenotype of this leukemia. Recent advances have resulted in a number of therapeutic drugs that inhibit the ABL1 tyrosine kinase, as well as other protein tyrosine kinases. Imatinib mesylate (Gleevec, Novartis) is the prototype of these tyrosine kinase inhibitors (TKI), which can induce durable hematologic and (in most patients) cytogenetic remissions. Unfortunately, a significant subset of patients can develop functional resistance to TKI, due in a large number of cases (approximately 50%) to the acquisition of point mutations in the kinase domain (KD) of the chimeric ABL1 gene. To date, over 50 distinct mutations have been described, although a smaller subset of these (<20) account for the majority of patients with clinical resistance to TKI or have well documented in vitro data in the published literature. Recognition of TKI resistance is important in CML, as the effect of some mutations can be overcome by increasing imatinib dosage, whereas others require switching to either a different (second-generation) TKI, or alternative therapy. The common T315I KD mutation is particularly important, given that this alteration confers pan-resistance to all currently employed TKI except ponatinib. Typically, TKI resistance is suspected in a CML patient who shows loss of initial therapeutic response (eg, cytogenetic relapse), or a significant and sustained increase in molecular BCR::ABL1 quantitative levels. Similar considerations are also present in patients with Philadelphia chromosome positive B-cell acute lymphoblastic leukemia, who can also be treated using TKI therapy. Point mutations in the oncogenic BCR::ABL1 are typically detected by direct sequencing of polymerase chain reaction (PCR) products, following reverse transcription PCR (RT-PCR) amplification of the BCR::ABL mRNA transcript from a peripheral blood specimen. This approach ensures comprehensive screening of the clinically relevant KD region. Because this technique requires inclusion of a longer region of ABL1 in the BCR::ABL1 RT-PCR product, low levels of the BCR::ABL1 mRNA transcript (below 0.01% normalized BCR::ABL1 on the international scale) may not be efficiently amplified (in contrast to similar amplicons generated by quantitative RT-PCR for diagnosis or monitoring).

Useful For: Evaluating patients with chronic myelogenous leukemia and Philadelphia chromosome positive B-cell acute lymphoblastic leukemia receiving tyrosine kinase inhibitor (TKI) therapy, who are apparently failing treatment Preferred initial test to identify the presence of acquired BCR::ABL1 mutations associated with TKI-resistance

Interpretation: The presence of one or more point mutations in the translocated portion of the ABL1 region of the BCR::ABL1 fusion messenger RNA is considered a positive result, indicating tyrosine kinase inhibitor (TKI) resistance. The specific type of mutation may influence the sensitivity to a specific TKI and could be useful in guiding therapeutic options for an individual patient.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Hughes T, Deininger M, Hochhaus A, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood. 2006;108(1):28-37. doi:10.1182/blood-2006-01-0092 2. Press RD, Kamel-Reid S, Ang D. BCR-ABL1 RT-qPCR for Monitoring the Molecular Response to Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia. J Mol Diagn. 2013;15(5):565-576. doi:10.1016/j.jmoldx.2013.04.007 3. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-884. doi:10.1182/blood-2013-05-501569 4. Jones D, Kamel-Reid S, Bahler D, et al. Laboratory practice guidelines for detecting and reporting BCR-ABL drug resistance mutations in

chronic myelogenous leukemia and acute lymphoblastic leukemia: a report of the Association for Molecular Pathology. J Mol Diagn. 2009;11(1):4-11. doi: 10.2353/jmoldx.2009.080095 5. Iezza M, Cortesi S, Ottaviani E, et al. Prognosis in chronic myeloid leukemia: Baseline factors, dynamic risk assessment and novel insights. Cells. 2023;12(13):1703. doi:10.3390/cells12131703

P190M
618879

BCR::ABL1, p190, mRNA Detection, Reverse Transcription PCR, Quantitative, Monitoring Assay, Bone Marrow

Clinical Information: Messenger RNA (mRNA) transcribed from BCR::ABL1 (fusion of the breakpoint cluster region gene [BCR] at chromosome 22q11 to the Abelson gene [ABL1] at chromosome 9q34) is detected in all patients with chronic myeloid leukemia (CML) and a subset of patients with both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia. Although breakpoints in the BCR and ABL1 genes may occur in a variety of locations, splicing of the primary RNA transcripts result in only 8 fusion site variants (e1/a2, e6/a2, e13/a2, e14/a2, e19/a2, and e1/a3, e13/a3, e14/a3), which incorporate the entire sequence of the exons on both sides of the fusion site. The e1/a2 and e1/a3 fusion forms produce a 190-kDa protein designated p190. This BCR::ABL1 protein form is found in approximately 75% of patients with childhood ALL and approximately 50% of patients with adult ALL, with the majority arising from e1/a2 mRNA. The p190 is also the predominant fusion form in a small subset of patients with CML, although the vast majority of CML cases contain the p210 protein, typically from e13/a2 or e14/a2 mRNA fusions. Other fusion forms are very rare. Quantitative reverse-transcription polymerase chain reaction is the most sensitive method for monitoring BCR::ABL1 levels during treatment. This test detects mRNA coding for the most common p190 fusion form (e1/a2).

Useful For: Detection of e1/a2 BCR::ABL1 (p190) fusion at diagnosis of acute myeloid leukemia (ALL) and BCR::ABL1 (p210) negative chronic myeloid leukemia (CML) using bone marrow specimens Monitoring response to therapy in patients with known e1/a2 BCR::ABL1 (p190) fusion forms in childhood ALL, adult ALL, and rare CML cases

Interpretation: The interpretive report includes an overview of the findings.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med. 2003;349(15):1423-1432 2. Radich JP, Gooley T, Bryant E, et al. The significance of BCR/ABL molecular detection in chronic myeloid leukemia patients "late," 18 months or more after transplantation. Blood. 2001;98(6):1701-1707 3. Olavarria E, Kanfer E, Szydlo R, et al. Early detection of BCR-ABL transcripts by quantitative reverse transcriptase-polymerase chain reaction predicts outcome after allogeneic stem cell transplant for chronic myeloid leukemia. Blood. 2001;97(6):1560-1565 4. Tefferi A. The classic myeloproliferative neoplasms: Chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia, and primary myelofibrosis. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed November 27, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225078035&bookid=2709

FBEBE
57521

Bean Black (Phaseolus spp) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >=49.99 Very Strong

Positive

Reference Values:
<0.35 kU/L

FBGSG
57522

Bean Green/String IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

FBKG
57662

Bean Kidney IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

FBLME
57523

Bean Lima (Phaseolus limensis) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 5 6 17.50 - 49.99 50.00 - 99.99 > 99.99 Very High Positive Very High Positive Very High Positive

Reference Values:
<0.35 kU/L

FNBE
57937

Bean Navy/White (Phaseolus vulgaris) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal/Borderline 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 49.99 Very High Positive 5 50.00 – 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

FBNWG
57655

Bean Navy/White IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

BWRS
35376

Beckwith-Wiedemann Syndrome/Russell-Silver Syndrome, Molecular Analysis, Varies

Clinical Information: Beckwith-Wiedemann syndrome (BWS) is a disorder characterized by prenatal and/or postnatal overgrowth, neonatal hypoglycemia, congenital malformations, and an increased risk for embryonal tumors. Physical findings are variable and can include abdominal wall defects, macroglossia, and hemihyperplasia. The predisposition for tumor development is associated with specific tumor types such as adrenal carcinoma, nephroblastoma (Wilms tumor), hepatoblastoma, and rhabdomyosarcoma. In infancy, BWS has a mortality rate of approximately 20%. Current data suggest that the etiology of BWS is due to dysregulation of imprinted genes in the 11p15 region of chromosome 11, including H19 (maternally expressed), LIT1 (official symbol KCNQ1OT1; paternally expressed), IGF2 (paternally expressed), and CDKN1C (aliases p57 and KIP2; maternally expressed). Expression of these genes is controlled by 2 imprinting centers (IC). Approximately 85% of BWS cases appear to be sporadic, while 15% of cases are associated with an autosomal dominant inheritance pattern. When a family history is present, the etiology is often due to inherited point alterations in CDKN1C or an unknown cause. The etiology of sporadic cases includes: -Hypomethylation of imprinting center 2 (IC2) (LIT1): approximately 50% to 60% -Paternal uniparental disomy of chromosome 11: approximately 10% to 20% -Hypermethylation of imprinting center 1 (IC1) (H19): approximately 2% to 7% -Unknown: approximately 10% to 20% -Point alteration in CDKN1C: approximately 5% to 10% -Cytogenetic abnormality: approximately 1% to 2% -Differentially methylated region 1 (DMR1) or DMR2 microdeletion: rare The clinical presentation of BWS is dependent on which gene in the 11p15 region is involved. The risk for cancer has been shown to be significantly higher in patients with abnormal methylation of IC1 (H19) versus IC2 (LIT1). In patients with abnormal methylation of IC2 (LIT1), abdominal wall defects and overgrowth are seen at a higher frequency. Russell-Silver syndrome (RSS) is a rare genetic condition with an incidence of approximately 1 in 100,000. RSS is characterized by pre- and postnatal growth retardation with normal head circumference, characteristic facies, fifth finger clinodactyly, and asymmetry of the face, body, and/or limbs. Less commonly observed clinical features include cafe au lait spots, genitourinary anomalies, motor, speech, cognitive delays, and hypoglycemia. Although clinical diagnostic criteria have been developed, it has been demonstrated that many patients with molecularly confirmed RSS do not meet strict clinical diagnostic criteria for RSS. Therefore, most groups recommend a relatively low threshold for considering molecular testing in suspected cases of RSS. Russell-Silver syndrome is a genetically heterogeneous condition that is associated with genetic and epigenetic alterations at chromosome 7 and the chromosome 11p15.5 region. The majority of cases of RSS are sporadic, although familial cases have been reported. The etiology of sporadic cases of RSS includes: -Hypomethylation of IC1 (H19): approximately 30% to 50% -Maternal uniparental disomy (UPD) of chromosome 7: approximately 5% to 10% -11p15.5 duplications: rare -Chromosome 7 duplications: rare *Note that this test does not detect chromosome 7 UPD. However, testing is available; order UNIPD / Uniparental Disomy, Varies. The clinical phenotype of RSS has been associated with the specific underlying molecular etiology. Patients with hypomethylation of IC1 (H19) are more likely to exhibit "classic" RSS phenotype (ie, severe intrauterine growth retardation, postnatal growth retardation,

and asymmetry), while patients with maternal UPD7 often show a milder clinical phenotype. Despite these general genotype-phenotype correlations, many exceptions have been reported. Methylation abnormalities of IC1 (H19) and IC2 (LIT1) can be detected by methylation-sensitive multiple ligation-dependent probe amplification. While testing can determine methylation status, it does not identify the mechanism responsible for the methylation defect (such as paternal uniparental disomy or cytogenetic abnormalities). Hypomethylation of IC2 (LIT1) is hypothesized to silence the expression of a number of maternally expressed genes, including CDKN1C. Hypermethylation of IC1 is hypothesized to silence the expression of H19, while also resulting in overexpression of IGF2. Absence of CDKN1C and H19 expression, in addition to overexpression of IGF2, is postulated to contribute to the clinical phenotype of BWS. Hypomethylation of IC1 is hypothesized to result in overexpression of H19 and underexpression of the IGF2, which is thought to contribute to the clinical phenotype of RSS.

Useful For: Confirming a clinical diagnosis of Beckwith-Wiedemann syndrome (BWS) or Russell-Silver syndrome (RSS) Prenatal diagnosis if there is a high suspicion of BWS/RSS based on ultrasound findings or in families at risk for BWS/RSS This assay does not detect maternal uniparental disomy of chromosome 7 or cytogenetic abnormalities such as translocations or inversions.

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. DeBaun MR, Niemitz EL, McNeil DE, Brandenburg SA, Lee MP, Feinberg AP. Epigenetic alterations of H19 and LIT1 distinguish patients with Beckwith-Wiedemann Syndrome with cancer and birth defects. Am J Hum Genet. 2002;70(3):604-611 2. Choufani S, Shuman C, Weksberg R. Beckwith-Wiedemann Syndrome. Am J Med Genet C Semin Med Genet. 2010;154C(3):343-354 3. Wakeling EL. Silver-Russell syndrome. Arch Dis Child. 2011;96(12):1156-1161 4. Eggermann T, Begemann M, Binder G, Spengler S. Silver-Russell syndrome: genetic basis and molecular genetic testing. Orphanet J Rare Dis. 2010;5:19 5. Priolo M, Sparago A, Mammi C, Cerrato F, Lagana C, Riccio A. MS-MLPA is a specific and sensitive technique for detecting all chromosome 11p15.5 imprinting defects of BWS and SRS in a single-tube experiment. Eur J Hum Genet. 2008;16(5):565-571 6. Brioude F, Kalish JM, Mussa A, et al. Expert consensus document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. Nat Rev Endocrinol. 2018;14(4):229-249. doi:10.1038/nrendo.2017.166 7. Wakeling EL, Brioude F, Lokulo-Sodipe O, et al. Diagnosis and management of Silver-Russell syndrome: first international consensus statement. Nat Rev Endocrinol. 2017;13(2):105-124. doi:10.1038/nrendo.2016.138

BECH
82669

Beech, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to beech Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FBEFG
57626

Beef IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

BEEF
82697

Beef, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are

caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to beef Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FBTRG
57689

Beet Root IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by

the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

BEETS
82618

Beets (Beetroot), IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to beets Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FPHEN 91136 Benzene as Phenol, Occupational Exposure, Urine

Reference Values:

Creatinine: >50 mg/dL

Phenol: mg/L
Phenol: mg/G creat

Normal (unexposed population):
less than 10 mg/L

Exposed:
Biological Exposure Index (BEI): 50 mg/g creatinine (End of Shift)

Toxic:
Not Established

FBEN 90294 Benzene, Occupational Exposure, Blood

Reference Values:

Units: mg/L

Normal (unexposed population):
None detected
Exposed (end-of-shift):
Blood benzene concentrations of greater than 0.1 mg/L correlate with exposure to greater than 10 ppm benzene in air.
Toxic:
Blood benzene concentrations greater than 0.90 mg/L have been observed in fatal cases of benzene exposure.

FBCQ 75822 Benzodiazepine Confirmation, Urine

Reference Values:

Only orderable as a reflex. For further information see FSHPU/Sedative Hypnotic Panel, Urine Diazepam:	**ng/mL**
Desmethyldiazepam:	ng/mL
Oxazepam:	ng/mL
Temazepam:	ng/mL

Alprazolam:	ng/mL
Alpha-Hydroxyalprazolam:	ng/mL
Lorazepam:	ng/mL
Alpha-Hydroxytriazolam:	ng/mL
7-Aminoclonazepam:	ng/mL
Alpha-Hydroxymidazolam:	ng/mL
Hydroxyethylflurazepam:	ng/mL

BNZX
608279

Benzodiazepines Confirmation, Chain of Custody, Random, Urine

Clinical Information: Benzodiazepines are any of a group of compounds having a common molecular structure and acting similarly as depressants of the central nervous system. As a class of drugs, benzodiazepines are among the most prescribed drugs in the western hemisphere because of their efficacy, safety, low addiction potential, minimal side effects, and high public demand for sedative and anxiolytic agents. Chain of custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting drug use involving benzodiazepines such as alprazolam, chlordiazepoxide, clonazepam, diazepam, midazolam, oxazepam, temazepam, clobazam, flunitrazepam, flurazepam, lorazepam, prazepam, triazolam, and zolpidem, in urine specimens handled through the chain-of-custody process Providing chain of custody for when the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: Benzodiazepines are extensively metabolized, and the parent compounds are not detected in urine. This test screens for (and confirms) the presence of: -Alprazolam -Alpha-hydroxyalprazolam (metabolite of alprazolam) -Chlordiazepoxide -Clonazepam -7-Aminoclonazepam (metabolite of clonazepam) -Diazepam (separate prescribable drug and metabolite of medzazepam) -Nordiazepam (metabolite of clorazepate, halazepam, prazepam, diazepam and medazepam) -Midazolam -Alpha-hydroxy midazolam (metabolite of midazolam) -Oxazepam (separate prescribable drug and metabolite of clorazepate, halazepam, prazepam, medazepam, temazepam, and diazepam) -Temazepam (separate prescribable drug and metabolite of medazepam and diazepam) -Clobazam -N-Desmethylclobazam (metabolite of clobazam) -Flunitrazepam -7-Aminoflunitrazepam (metabolite of flunitrazepam) -Flurazepam -2-Hydroxy ethyl flurazepam (metabolite of flurazepam) -Lorazepam -Prazepam -Triazolam -Alpha-hydroxy triazolam (metabolite of triazolam) -Zolpidem -Zolpidem phenyl-4-carboxylic acid (metabolite of zolpidem) The clearance half-life of long-acting benzodiazepines is more than 24 hours. It takes 5 to 7 half-lives to clear 98% of a drug dose. Therefore, the presence of a long-acting benzodiazepine greater than the limit of quantification indicates exposure within a 5 to 20-day interval preceding specimen collection. Following a dose of diazepam, the drug and its metabolites appear in the urine within 30 minutes. Peak urine output is reached between 1 and 8 hours. For additional

information including metabolism, clearance (half-life), and approximate detection times, see Optimize Urine Drug Monitoring for CNS Depressants.

Reference Values:

Negative
Positive results are reported with a quantitative result.

Cutoff concentrations:

Immunoassay screen:
100 ng/mL

Liquid chromatography tandem mass spectrometry:
Alprazolam: 10 ng/mL
Alpha-hydroxyalprazolam: 10 ng/mL
Chlordiazepoxide: 10 ng/mL
Clonazepam: 10 ng/mL
7-Aminoclonazepam: 10 ng/mL
Diazepam: 10 ng/mL
Nordiazepam: 10 ng/mL
Midazolam: 10 ng/mL
Alpha-hydroxy midazolam: 10 ng/mL
Oxazepam: 10 ng/mL
Temazepam: 10 ng/mL
Clobazam: 10 ng/mL
N-Desmethylclobazam by LC-MS/MS: 10 ng/mL
Flunitrazepam: 10 ng/mL
7-Aminoflunitrazepam: 10 ng/mL
Flurazepam: 10 ng/mL
2-Hydroxy ethyl flurazepam: 10 ng/mL
Lorazepam: 10 ng/mL
Prazepam: 10 ng/mL
Triazolam: 10 ng/mL
Alpha-hydroxy triazolam: 10 ng/mL
Zolpidem: 10 ng/mL
Zolpidem phenyl-4-carboxylic acid: 10 ng/mL

Clinical References: 1. Gudin JA, Mogali S, Jones JD, Comer SD. Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. Postgrad Med. 2013;125(4):115-130. doi:10.3810/pgm.2013.07.2684 2. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain - United States, 2022. MMWR Recomm Rep. 2022;71(3):1-95 3. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020 4. Langman LJ, Bechtel LK, Holstege C. Clinical toxicology. In: Rifai N, Chiu RWK, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

BNZU
608255

Benzodiazepines Confirmation, Random, Urine

Clinical Information: Benzodiazepines are any of a group of compounds having a common molecular structure and acting similarly as depressants of the central nervous system. As a class of drugs, benzodiazepines are among the drugs most frequently prescribed in the western hemisphere because of their efficacy, safety, low addiction potential, minimal side effects, and high public demand for sedative and anxiolytic agents.

Useful For: Detecting drug use involving benzodiazepines such as alprazolam, chlordiazepoxide, clonazepam, diazepam, midazolam, oxazepam, temazepam, clobazam, flunitrazepam, flurazepam, lorazepam, prazepam, triazolam, and zolpidem

Interpretation: Benzodiazepines are extensively metabolized, and the parent compounds are not detected in urine. This test screens for (and confirms) the presence of: -Alprazolam -Alpha-hydroxyalprazolam (metabolite of alprazolam) -Chlordiazepoxide -Clonazepam -7-Aminoclonazepam (metabolite of clonazepam) -Diazepam (separate prescribable drug and metabolite of medzazepam) -Nordiazepam (metabolite of clorazepate, halazepam, prazepam, diazepam and medazepam) -Midazolam -Alpha-hydroxy midazolam (metabolite of midazolam) -Oxazepam (separate prescribable drug and metabolite of clorazepate, halazepam, prazepam, medazepam, temazepam, and diazepam) -Temazepam (separate prescribable drug and metabolite of medazepam and diazepam) -Clobazam -N-Desmethylclobazam (metabolite of clobazam) -Flunitrazepam -7-Aminoflunitrazepam (metabolite of flunitrazepam) -Flurazepam -2-Hydroxy ethyl flurazepam (metabolite of flurazepam) -Lorazepam -Prazepam -Triazolam -Alpha-hydroxy triazolam (metabolite of triazolam) -Zolpidem -Zolpidem phenyl-4-carboxylic acid (metabolite of zolpidem) The clearance half-life of long-acting benzodiazepines is more than 24 hours. It takes 5 to 7 half-lives to clear 98% of a drug dose. Therefore, the presence of a long-acting benzodiazepine greater than the limit of quantification indicates exposure within a 5 to 20-day interval preceding specimen collection. Following a dose of diazepam, the drug and its metabolites appear in the urine within 30 minutes. Peak urine output is reached between 1 and 8 hours. For additional information, including metabolism, clearance (half-life), and approximate detection times, see Optimize Urine Drug Monitoring for CNS Depressants.

Reference Values:
Negative (Positive results are reported with a quantitative result.)

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Alprazolam: 10 ng/mL
Alpha-hydroxyalprazolam: 10 ng/mL
Chlordiazepoxide: 10 ng/mL
Clonazepam: 10 ng/mL
7-Aminoclonazepam: 10 ng/mL
Diazepam: 10 ng/mL
Nordiazepam: 10 ng/mL
Midazolam: 10 ng/mL
Alpha-hydroxy midazolam: 10 ng/mL
Oxazepam: 10 ng/mL
Temazepam: 10 ng/mL
Clobazam: 10 ng/mL
N-Desmethylclobazam: 10 ng/mL
Flunitrazepam: 10 ng/mL
7-Aminoflunitrazepam: 10 ng/mL
Flurazepam: 10 ng/mL
2-Hydroxy ethyl flurazepam: 10 ng/mL
Lorazepam: 10 ng/mL
Prazepam: 10 ng/mL
Triazolam: 10 ng/mL
Alpha-hydroxy triazolam: 10 ng/mL
Zolpidem: 10 ng/mL
Zolpidem phenyl-4-carboxylic acid: 10 ng/mL

Clinical References: 1. Gudin JA, Mogali S, Jones JD, Comer SD. Risks, management, and monitoring of combination of opioid, benzodiazepines, and/or alcohol use. Postgrad Med. 2013;125(4):115-130. doi:10.3810/pgm.2013.07.2684 2. Dowell D, Ragan KR, Jones CM, Baldwin GT,

Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain-United States. MMWR Recomm Rep. 2022;71(No. RR-3):1-95 3. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

FCDU2 Benzodiazepines, Umbilical Cord Tissue

75777

Reference Values:
Reporting limit determined each analysis.

Units: ng/g

Only orderable as part of a profile-see FCDSU.

FBENZ Benztropine (Cogentin), Serum

90092

Reference Values:
Reference Range: 5.0 - 25.0 ng/mL

BBEET Berlin Beetle, IgE, Serum

82838

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Berlin beetle Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BERG
82892

Bermuda Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Bermuda grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FBERY
91092

Beryllium, Blood

Reference Values:
Reference Range: <1.0 ng/mL

BETV2
609436

BET v2 (Profilin), IgE, Serum

Clinical Information: Immunoglobulin E antibodies to the Bet v 2a profilin protein have been reported in 10% to 38% of birch pollen-allergic patients. Birch pollen is highly allergenic and is a significant cause of immediate hypersensitivity, affecting as much as 5% to 50% of the population of Western Europe. The presence of antibodies to Bet v 2, may also indicate sensitivity to other profilin containing pollens including ragweed pollen, mugwort pollen, and timothy grass pollen. The profilin Bet v2 is related to, and cross-reactive with, antibodies to the potential peanut allergen profilin Ara h5. As profilin proteins are present in many other foods, sensitivity to profilin Bet v2 may be associated in broad allergen cross-reactivity among foods, including mango, peach, apple, hazelnut, celery, carrot, paprika, anise, fennel, coriander, cumin, tomato, and potato. The most common manifestation of allergy to food in profilin related allergic individuals is oral allergy syndrome. Profilins are generally not resistant to heat and digestion. Individuals with birch pollen allergy and oral allergy syndrome are more frequently allergic to apples and peaches than to other foods. In cases of allergic reaction associated with oral allergy syndrome, rhinitis, itching, tingling, and other mild reactions on the oropharyngeal mucosa were reported to be the most common complaints.

Useful For: Evaluation of patients suspected birch pollen allergy Evaluation of patients with suspected peanut allergy Evaluation of patients with oral allergy syndrome to other pollens or plant-based foods Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Profilins are potentially cross-reactive allergenic proteins found in many plant pollens and tissues. IgE antibodies to the profilin Bet v2, while associated with birch pollen sensitivity,

also represent a minor peanut allergen marker as it is cross-reactive with the peanut profilin Ara h5. The presence of antibodies to profilin Bet v2 is typically associated with milder allergic reactions and oral allergy syndrome.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/Equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Anhoej C, Backer V, Nolte H: Diagnostic evaluation of grass- and birch-allergic patients with oral allergy syndrome. Allergy. 2001 Jun;56(6):548-552. doi: 10.1034/j.1398-9995.2001.056006548.x 2. Sekerkova A, Polackova M: Detection of Bet v1, Bet v2 and Bet v4 specific IgE antibodies in the sera of children and adult patients allergic to birch pollen: evaluation of different IgE reactivity profiles depending on age and local sensitization. Int Arch Allergy Immunol. 2011;154(4):278-85. doi: 10.1159/000321819 3. D'Amato G, Cecchi L, Bonini S, et al: Allergenic pollen and pollen allergy in Europe. Allergy. 2007 Sep;62(9):976-990. doi: 10.1111/j.1398-9995.2007.01393.x 4. Cabanos C, Tandang-Silvas MR, Odijk V, et al: Expression, purification, cross-reactivity and homology modeling of peanut profilin. Protein Expr Purif. 2010 Sep;73(1):36-45. doi: 10.1016/j.pep.2010.03.005 5. Bublin M, Breiteneder H: Cross-reactivity of peanut allergens. Curr Allergy Asthma Rep. 2014 Apr;14(4):426. doi: 10.1007/s11882-014-0426-8 6. Chan ES, Greenhawt MJ, Fleischer DM, Caubet JC: Managing cross-reactivity in those with peanut allergy. J Allergy Clin Immunol Pract. 2019 Feb;7(2):381-386. doi: 10.1016/j.jaip.2018.11.012 7. Simberloff T, Parambi R, Bartnikas LM, et al: Implementation of a standardized clinical assessment and management plan (SCAMP) for food challenges. J Allergy Clin Immunol Pract. 2017 Mar-Apr;5(2):335-344.e3. doi:10.1016/j.jaip.2016.05.021

WBSEQ
62128

Beta-Globin Gene Sequencing, Varies

Clinical Information: Beta-globin gene sequencing is useful in the evaluation of beta-globin chain variants and beta thalassemia. It detects almost all beta-globin variants and the most common beta thalassemia sequence variants, although prevalence is ethnicity dependent. Because these conditions are often complex, this test should always be interpreted in the context of protein studies, such as hemoglobin electrophoresis and red blood cell indices. The majority of beta-globin chain variants are clinically and hematologically benign; however, some have important clinical consequences, such as erythrocytosis, cyanosis/hypoxia, chronic hemolysis, or unexplained microcytosis. Most of the common clinically significant hemoglobin (Hb) variants (ie, HbS, HbC, HbE, and others) are easily distinguished by hemoglobin electrophoresis and do not require molecular analysis. In addition, they are frequently found in complex hemoglobin disorders due to multiple genetic variants, and accurate classification requires sequencing data within the context of protein data. In some instances, beta-globin sequencing is necessary to identify or confirm the identity of rare variants, especially those associated with erythrocytosis and chronic hemolytic anemia. Rare hyper-unstable variants (also termed dominant beta thalassemia mutations) result in hemolytic anemia and do not create protein stable enough to be detectable by protein methods, including stability studies. They are not always associated with elevated HbA2 or microcytosis

and, therefore, can be electrophoretically silent. These require a high degree of clinical suspicion as all electrophoretic testing as well as stability studies cannot exclude this condition. Beta thalassemia is an autosomal recessive condition characterized by decreased or absent synthesis of beta-globin chains due to sequence variants in the beta-globin gene (HBB). No abnormal protein is present and diagnosis by electrophoresis relies on hemoglobin fraction percentage alterations (ie, HbA2 or HbF elevations). Beta thalassemia can be split into 3 broad classes (categorized by clinical features): 1. Beta thalassemia trait (also called beta thalassemia minor and beta thalassemia carrier) (B[A]B[+] or B[A]B[0]) 2. Beta thalassemia intermedia (B[+]B[+] or B[+]B[0]) 3. Beta thalassemia major (B[+]B[0] or B[0]B[0]) Beta thalassemia trait is typically a harmless condition with varying degrees of microcytosis and hypochromia and sometimes mild anemia. Transfusions are not required. Beta thalassemia intermedia is a clinical distinction and is characterized by a more severe degree of anemia than beta thalassemia trait with few or intermittent transfusions required. Later in life, these individuals are at risk for iron overload even in the absence of chronic transfusion due to increased intestinal absorption of iron. Beta thalassemia major typically comes to medical attention early in life due to severe anemia, hepatosplenomegaly, and failure to thrive. Skeletal changes are also common due to expansion of the bone marrow. Without appropriate treatment these patients have a shortened lifespan. The majority of beta thalassemia variations (>90%) are point alterations, small deletions, or insertions, which are detected by beta-globin gene sequencing. The remaining beta thalassemia sequence variants are either due to large genomic deletions of HBB or, very rarely, trans-acting beta thalassemia variations located outside of the beta-globin gene cluster. Some rare beta-chain variants can be clinically or electrophoretically indistinguishable from beta thalassemia and cannot be confirmed without molecular analysis.

Useful For: Diagnosis of beta thalassemia intermedia or major Identification of a specific beta thalassemia sequence variant (ie, unusually severe beta thalassemia trait) Evaluation of an abnormal hemoglobin electrophoresis identifying a rare beta-globin variant Evaluation of chronic hemolytic anemia of unknown etiology Evaluation of hereditary erythrocytosis with left-shifted p50 oxygen dissociation results Preconception screening when there is a concern for a beta-hemoglobin disorder based on family history

Interpretation: The alteration will be provided with the classification, if known. Further interpretation requires correlation with protein studies and red blood cell indices.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Hoyer JD, Hoffman DR. The thalassemia and hemoglobinopathy syndromes. In: McClatchey KD, ed. Clinical Laboratory Medicine. 2nd ed. Lippincott Williams and Wilkins; 2002:866-895 2. Thein SL. The molecular basis of beta-thalassemia. Cold Spring Harb Perspect Med. 2013;3(5):a011700 3. Hoyer JD, Kroft, SH. Color Atlas of Hemoglobin Disorders: A Compendium Based on Proficiency Testing. CAP; 2003 4. Merchant S, Oliveira JL, Hoyer JD, Viswanatha DS. Molecular diagnosis in hematopathology. In: Hsi E, Volume ed. Goldblum J, ed. Hematopathology: A Volume in Foundations in Diagnostic Pathology Series. 2nd ed. Churchill Livingstone; 2012

FBLGG
57667

Beta Lactoglobulin IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the

limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

AB2GP
86180

Beta-2 Glycoprotein 1 Antibodies, IgA, Serum

Clinical Information: Antiphospholipid syndrome (APS) has traditionally been described as a systemic autoimmune disease characterized by thrombosis or specific pregnancy-related morbidities associated with persistent documentation of "criterial" antiphospholipid antibody (aPL) tests.(1-2) Based on the 2006 revised Sapporo consensus classification, the "criterial" aPL antibody tests include lupus anticoagulant (LAC), and IgG/IgM antibodies to the cardiolipin (aCL) and beta-2-glyocoprotein I (anti-B2GPI) with all tests carrying equal diagnostic significance for disease.(1) In 2023, the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) published new classification criteria for APS, which includes an entry criterion of at least one positive aPL antibody test within 3 years of identification of an aPL-associated clinical criterion, followed by additive weighted criteria (score range 1-7 points each) clustered into 6 clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and 2 laboratory domains (LAC functional coagulation assays and solid-phase enzyme-linked immunosorbent assays [ELISA] for IgG/IgM aCL and/or IgG/IgM anti-B2GPI).(3) Of note, aPL antibodies also occur in patients with autoimmune diseases with significant prevalence in systemic lupus erythematosus (SLE) as well as other clinical manifestations (eg, heart valve disease, livedo reticularis, thrombocytopenia, nephropathy and neurological) often associated with APS.(1-3) Thus, in addition to the 2023 APS classification criteria, the 2012 derivation and validation of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE recommends testing for the criteria aPL antibody tests as well as aCL IgA and anti-B2GPI IgA.(4) B2GPI is a 326-amino acid protein that is synthesized by hepatocytes, endothelial cells, and trophoblast cells.(5) It contains 5 repetitive structures or "sushi domains," termed domain 1 through 5, for a combined molecular weight of 54 kDa.(5-7) Autoantibodies to B2GPI may be detected by solid-phase immunoassays (SPA) and functional coagulation assays. Unlike the LAC, the SPA provides quantitative measurements and antibody isotype class determinations that are important for risk assessment. Immunoassays for the detection and quantification of anti-B2GPI antibodies can be performed using either a composite substrate comprised of B2GPI plus anionic phospholipid (ie, cardiolipin-dependent B2GPI) or B2GPI alone. Antibodies detected using B2GPI substrate without another phospholipid (direct assays) are referred to simply as "anti-B2GPI 1 antibodies." Some anti-B2GPI antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low concentrations of phospholipid cofactors.(6) Antibodies detected by functional coagulation assays are commonly referred to as LAC. Anti-B2GPI antibodies associated with thromboembolic events target domain 1 of the molecule and are responsible for LAC (functional, phospholipid-dependent prolongation of the clotting time) and aCL-dependent B2GPI antibody positivity.(2) For the detection of anti-B2GPI IgG and IgM antibodies, the APS guidance advocates for the use of values above the 99th percentile of the laboratory's population in the establishment of reference intervals for tests. While this recommendation may be used for anti-B2GPI IgA immunoassays, there is no consensus for their determination.(6) aPL antibodies were traditionally determined using the classic ELISA, with more diverse methods recently developed and adapted for clinical testing. Recognizing the analytical and diagnostic challenges associated with aPL antibody testing, initiatives to support assay harmonization and utilization, including the development of calibrators, test development, and validation efforts as well as preanalytical, analytical, and postanalytical measures have been published.(7) The interpretation and relevance of aPL antibody tests are dependent on factors such as the type of aPL (LAC, aCL or anti-B2GPI), the source of cardiolipin and/or B2GPI, aPL antibody class (IgG, IgM or IgA) and level, as well as whether antibody positivity is single, double or triple.(1-3,7,8) The 2023 ACR/EULAR classification criteria for APS are meant for clinical studies and may not be appropriate for routine patient evaluation and management. Therefore, in clinical practice, if suspicion for disease is high but criteria aPL antibody tests are inconclusive or negative, deviation from the APS classification criteria may be

justified. This may include testing for non-criteria aPL antibody tests, such the aCL IgA and anti-B2GPI IgA recommended in 2012 SLICC guidance for SLE or evaluation of other non-criteria aPL antibody tests.(4,9,10) However, there is no formal guidance for the measurement and interpretation of aCL and anti-B2GPI IgA antibodies in patients with APS or SLE. Some clinical relevance between APS-related clinical symptoms and the presence of aCL/anti-B2GPI IgA have been reported; however, the added value is minimal.(10,11) Isolated aPL IgA is rare, and these antibodies are usually found in association with IgG or IgM.

Useful For: Evaluating patients with suspected antiphospholipid syndrome by identification of beta-2 glycoprotein 1 IgA antibodies Evaluating patients at-risk for antiphospholipid syndrome (APS) who are negative for criteria APS tests Estimating the risk of thrombosis and/or pregnancy-related morbidity in patients with systemic lupus erythematosus

Interpretation: The presence of anti-beta-2 glycoprotein 1 (anti-B2GPI) IgA antibodies may be associated with a diagnosis of antiphospholipid syndrome (APS) or systemic lupus erythematosus (SLE). In the absence of "criteria" aPL antibodies for APS and diagnostic tests for SLE, isolated anti-B2GPI IgA must be interpreted with a high degree of caution. Documentation of persistence for anti-B2GPI IgA, as is the case for criteria B2GPI IgG and IgM antibodies, would be consistent with best clinical practice. Detection of B2GPI antibodies is not affected by anticoagulant treatment.

Reference Values:

<15.0 SAU (negative)
15.0-39.9 SAU (weakly positive)
40.0-79.9 SAU (positive)
> or =80.0 SAU (strongly positive)
Results are reported in standard IgA anti-beta 2 glycoprotein 1 units (SAU).

Reference values apply to all ages.

Clinical References:

B2GMG
62926

Beta-2 Glycoprotein 1 Antibodies, IgG and IgM, Serum

Clinical Information:

Useful For: Evaluating patients with suspected antiphospholipid syndrome by identification of beta-2 glycoprotein 1 IgM and IgG antibodies First-line test when antiphospholipid syndrome is strongly suspected in conjunction with cardiolipin antibodies (IgG and IgM) and lupus anticoagulant testing Estimating the risk of thrombosis and/or pregnancy-related morbidity in patients with systemic lupus erythematosus

Interpretation: Positive results for beta-2 glycoprotein 1 (B2GPI) IgG and IgM antibodies, in association with specific clinical manifestations, may be diagnostic for antiphospholipid syndrome (APS). Low levels of B2GPIIgG or IgM antibodies, especially in the absence of other criterial phospholipid antibodies should be interpreted with a high degree of suspicion. Compared to B2GPI IgG, low and isolated levels of B2GP1 IgM antibodies have been reported to demonstrate a low risk for APS. Documentation of persistent anti-B2GPI antibodies is a requirement for the diagnosis of definite APS. Antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of B2GPI antibodies using the enzyme-linked immunoassay method or other solid-phase immunoassays is not affected by anticoagulant treatment.

Reference Values:

BETA 2 GLYCOPROTEIN 1 (GP1) ANTIBODIES IgG:
<15.0 SGU (negative)
15.0-39.9 SGU (weakly positive)
40.0-79.9 SGU (positive)
> or = 80.0 SGU (strongly positive)
Results are reported in standard IgG anti-beta 2 GP1 units (SGU).

Reference values apply to all ages.

BETA 2 GLYCOPROTEIN 1 ANTIBODIES IgM:
<15.0 SMU (negative)
15.0-39.9 SMU (weakly positive)
40.0-79.9 SMU (positive)
> or = 80.0 SMU (strongly positive)
Results are reported in standard IgM anti-beta 2 GP1 units (SMU).

Reference values apply to all ages.

Clinical References:

GB2GP
86182

Beta-2 Glycoprotein 1 Antibodies, IgG, Serum

Clinical Information: Antiphospholipid syndrome (APS) has traditionally been described as a systemic autoimmune disease characterized by thrombosis or specific pregnancy-related morbidities associated with persistent documentation of "criterial" antiphospholipid antibody (aPL) tests.(1,2) Based on the 2006 revised Sapporo consensus classification, the "criterial" aPL antibody tests include lupus anticoagulant (LAC), and IgG/IgM antibodies to the cardiolipin (aCL) and beta-2-glyocoprotein I (anti-B2GPI) with all tests carrying equal diagnostic significance for disease.(1) In 2023, the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) published new classification criteria for APS, which includes an entry criterion of at least one positive aPL antibody test within 3 years of identification of an aPL-associated clinical criterion, followed by additive weighted criteria (score range 1-7 points each) clustered into 6 clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and 2 laboratory domains (LAC functional coagulation assays and solid-phase enzyme-linked immunosorbent assays [ELISA] for IgG/IgM aCL and/or IgG/IgM anti-B2GPI).(3) Of note, aPL antibodies also occur in patients with autoimmune diseases with significant prevalence in systemic lupus erythematosus (SLE) as well as other clinical manifestations (eg, heart valve disease, livedo reticularis, thrombocytopenia, nephropathy and neurological) often associated with APS.(1-3) B2GPI is a 326-amino acid protein that is synthesized by hepatocytes, endothelial cells, and trophoblast cells.(4) It contains 5 repetitive structures or "sushi domains," termed domain 1 through 5, for a combined molecular weight of 54 kDa.(5-7) Autoantibodies to B2GPI may detected by solid-phase immunoassays (SPA) and functional coagulation assays. Unlike the LAC, the SPA provides quantitative measurements and antibody isotype class determinations that are important for risk assessment. Immunoassays for the detection and quantification of anti-B2GPI antibodies can be performed using either a composite substrate comprised of B2GPI plus anionic phospholipid (ie, cardiolipin-dependent B2GPI) or B2GPI alone. Antibodies detected using B2GPI substrate without another phospholipid (direct assays) are referred to simply as "anti-B2GPI 1 antibodies." Some anti-B2GPI antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low concentrations of phospholipid cofactors.(5) Antibodies detected by functional coagulation assays are commonly referred to as LAC. Anti-B2GPI antibodies associated with thromboembolic events target domain 1 of the molecule and are responsible for LAC (functional, phospholipid-dependent prolongation of the clotting time) and aCL-dependent B2GPI antibody positivity.(2) For the detection of anti-B2GPI IgG and IgM antibodies, the APS guidance advocates for the use of values above the 99th percentile of the laboratory's population in the establishment of reference

intervals for tests. While this recommendation may be used for anti-B2GPI IgA immunoassays, there is no consensus for their determination.(6) Thrombosis and obstetric complications are common clinical events in the general population and are not unique to APS; therefore, the presence of aPL antibodies is an absolute requirement for the diagnosis of definite APS.(1,5,7) Furthermore, aPL antibodies are heterogeneous with overlapping tendencies; the lack of aPL test harmonization or standardization requires the use of all 3 tests for optimal APS diagnosis.(1,3,6,7) aPL antibodies were traditionally determined using the classic ELISA, with more diverse methods recently developed and adapted for clinical testing. Recognizing the analytical and diagnostic challenges associated with aPL antibody testing, initiatives to support assay harmonization and utilization, including the development of calibrators, test development, and validation efforts, as well as preanalytical, analytical, and postanalytical measures, have been published.(6-8) Overall, the interpretation and relevance of aPL antibody tests are dependent on factors such as the type of aPL (LAC, aCL or anti-B2GPI), the source of cardiolipin and/or B2GPI , aPL antibody class (IgG, IgM or IgA) and level, as well as whether antibody positivity is single, double or triple.(1-3,6-8) The 2023 ACR/EULAR classification criteria for APS are meant for clinical studies and may not be appropriate for routine patient evaluation and management. Therefore, in clinical practice, if suspicion for disease is high but criteria aPL antibody tests are inconclusive or negative, deviation from the APS diagnostic criteria may be justified. This may include testing for noncriteria aPL antibody tests, such the aCL IgA, anti-B2GPI IgA and anti-phosphatidylserine/prothrombin complex IgG and IgM antibodies.(2,6,9,10) However, there is no formal guidance for the measurement and interpretation of these non-criterial aPL antibodies in patients with APS or SLE.

Useful For: Evaluating patients with suspected antiphospholipid syndrome by identification of beta-2 glycoprotein 1 IgG antibodies First-line test when antiphospholipid syndrome is strongly suspected, in conjunction with cardiolipin antibodies (IgG and IgM) and lupus anticoagulant testing Estimating the risk of thrombosis and/or pregnancy-related morbidity in patients with systemic lupus erythematosus

Interpretation: Positive results for beta-2 glycoprotein 1 (B2GPI) IgG antibodies, in association with specific clinical manifestations, may be diagnostic for antiphospholipid syndrome (APS). Low levels of B2GPIIgG antibodies, especially in the absence of other criteria phospholipid antibodies, should be interpreted with a high degree of suspicion. Documentation of persistent anti- B2GPIIgG antibodies is a requirement for the diagnosis of definite APS. Antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of B2GPIantibodies using the enzyme-linked immunosorbent assay method or other solid-phase immunoassays is not affected by anticoagulant treatment.

Reference Values:

<15.0 SGU (negative)
15.0-39.9 SGU (weakly positive)
40.0-79.9 SGU (positive)
> or =80.0 SGU (strongly positive)
Results are reported in standard IgG anti-beta 2 glycoprotein 1 units (SGU).

Reference values apply to all ages.

Clinical References:

MB2GP
86181

Beta-2 Glycoprotein 1 Antibodies, IgM, Serum

Clinical Information: Antiphospholipid syndrome (APS) has traditionally been described as a systemic autoimmune disease characterized by thrombosis or specific pregnancy-related morbidities associated with persistent documentation of "criterial" antiphospholipid antibody (aPL) tests.(1,2) Based

on the 2006 revised Sapporo consensus classification, the "criterial" aPL antibody tests include lupus anticoagulant (LAC), and IgG/IgM antibodies to the cardiolipin (aCL) and beta-2-glyocoprotein I (anti-B2GPI) with all tests carrying equal diagnostic significance for disease.(1) In 2023, the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) published new classification criteria for APS, which includes an entry criterion of at least one positive aPL antibody test within 3 years of identification of an aPL-associated clinical criterion, followed by additive weighted criteria (score range 1-7 points each) clustered into 6 clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and 2 laboratory domains (LAC functional coagulation assays and solid-phase enzyme-linked immunosorbent assays [ELISA] for IgG/IgM aCL and/or IgG/IgM anti-B2GPI).(3) Of note, aPL antibodies also occur in patients with autoimmune diseases with significant prevalence in systemic lupus erythematosus (SLE) as well as other clinical manifestations (eg, heart valve disease, livedo reticularis, thrombocytopenia, nephropathy and neurological) often associated with APS.(1-3) B2GPI is a 326-amino acid protein that is synthesized by hepatocytes, endothelial cells, and trophoblast cells.(4) It contains 5 repetitive structures or "sushi domains," termed domain 1 through 5, for a combined molecular weight of 54 kDa.(5-7) Autoantibodies to B2GPI may detected by solid-phase immunoassays (SPA) and functional coagulation assays. Unlike the LAC, the SPA provides quantitative measurements and antibody isotype class determinations that are important for risk assessment. Immunoassays for the detection and quantification of anti-B2GPI antibodies can be performed using either a composite substrate comprised of B2GPI plus anionic phospholipid (ie, cardiolipin-dependent B2GPI) or B2GPI alone. Antibodies detected using B2GPI substrate without another phospholipid (direct assays) are referred to simply as "anti-B2GPI 1 antibodies." Some anti-B2GPI antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low concentrations of phospholipid cofactors.(5) Antibodies detected by functional coagulation assays are commonly referred to as LAC. Anti-B2GPI antibodies associated with thromboembolic events target domain 1 of the molecule and are responsible for LAC (functional, phospholipid-dependent prolongation of the clotting time) and aCL-dependent B2GPI antibody positivity.(2) For the detection of anti-B2GPI IgG and IgM antibodies, the APS guidance advocates for the use of values above the 99th percentile of the laboratory's population in the establishment of reference intervals for tests. While this recommendation may be used for anti-B2GPI IgA immunoassays, there is no consensus for their determination.(6) Thrombosis and obstetric complications are common clinical events in the general population and are not unique to APS; therefore, the presence of aPL antibodies is an absolute requirement for the diagnosis of definite APS.(1,5,7) Furthermore, aPL antibodies are heterogeneous with overlapping tendencies; the lack of aPL test harmonization or standardization requires the use of all 3 tests for optimal APS diagnosis.(1,3,6,7) aPL antibodies were traditionally determined using the classic ELISA, with more diverse methods recently developed and adapted for clinical testing. Recognizing the analytical and diagnostic challenges associated with aPL antibody testing, initiatives to support assay harmonization and utilization, including the development of calibrators, test development, and validation efforts, as well as preanalytical, analytical, and postanalytical measures, have been published.(6-8) Overall, the interpretation and relevance of aPL antibody tests are dependent on factors such as the type of aPL (LAC, aCL or anti-B2GPI), the source of cardiolipin and/or B2GPI , aPL antibody class (IgG, IgM or IgA) and level, as well as whether antibody positivity is single, double or triple.(1-3,6-8) The 2023 ACR/EULAR classification criteria for APS are meant for clinical studies and may not be appropriate for routine patient evaluation and management. Therefore, in clinical practice, if suspicion for disease is high but criteria aPL antibody tests are inconclusive or negative, deviation from the APS diagnostic criteria may be justified. This may include testing for noncriteria aPL antibody tests, such the aCL IgA, anti-B2GPI IgA and anti-phosphatidylserine/prothrombin complex IgG and IgM antibodies.(2,6,9,10) However, there is no formal guidance for the measurement and interpretation of these non-criterial aPL antibodies in patients with APS or SLE.

Useful For: Evaluating patients with suspected antiphospholipid syndrome by identification of beta-2 glycoprotein 1 IgM antibodies First-line test when antiphospholipid syndrome is strongly suspected in conjunction with cardiolipin antibodies (IgG and IgM) and lupus anticoagulant testing Estimating the risk of thrombosis and/or pregnancy-related morbidity in patients with systemic lupus erythematosus

Interpretation: Positive results for beta-2 glycoprotein 1 (B2GPI) IgM antibodies in association with specific clinical manifestations may be diagnostic for antiphospholipid syndrome (APS). Compared to IgG antibodies B2GPI, the presence of isolated and low levels of B2GPI IgM antibodies have been reported to demonstrate a low risk for APS. Documentation of persistent anti- B2GPI IgM antibodies is a requirement for the diagnosis of definite APS. Antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of B2GPI antibodies using the enzyme-linked immunosorbent assay method or other solid-phase immunoassays is not affected by anticoagulant treatment.

Reference Values:
<15.0 SMU (negative)
15.0-39.9 SMU (weakly positive)
40.0-79.9 SMU (positive)
> or =80.0 SMU (strongly positive)
Results are reported in standard IgM anti-beta 2 glycoprotein 1 units (SMU).

Reference values apply to all ages.

Clinical References:

B2MU
602026

Beta-2 Microglobulin, Random, Urine

Clinical Information: Beta-2 microglobulin is a low-molecular-weight protein that forms the light chain component of class I histocompatibility (HLA: human leukocyte antigen) antigens. Because of its low molecular weight (11,800 daltons), 95% of free beta-2 microglobulin is rapidly eliminated by glomerular filtration. Proximal tubular cells then take up 99.9% of this filtered amount by endocytosis, after which degradation to amino acids occurs. Normal urinary excretion of beta-2 microglobulin is less than 370 micrograms per 24 hours; higher rates are interpreted as evidence of tubular dysfunction. Increased urine levels are seen in proximal tubular renal damage due to a variety of causes including Wilson disease, Fanconi syndrome, untreated congenital galactosemia, nephrocalcinosis, cystinosis, chronic potassium depletion, interstitial nephritis, connective-tissue diseases such as rheumatoid arthritis and Sjogren syndrome. Occupational exposure to heavy metals such as cadmium and mercury could also lead to increase levels of beta-2 microglobulin in urine.

Useful For: Evaluation of renal tubular damage Monitoring exposure to cadmium and mercury

Interpretation: Increased excretion is consistent with renal tubular damage. Beta-2 microglobulin excretion is increased 100 to 1000 times the upper limit of the reference interval in cadmium-exposed workers.

Reference Values:
< or =300 mcg/L

Clinical References: 1. Ikeda M, Ezaki T, Tsukahara T, et al. Threshold levels of urinary cadmium in relation to increases in urinary beta2-microglobulin among general Japanese populations. Toxicol Lett. 2003;137(3):135-141 2. Moriguchi J, Ezaki T, Tsukahara T, et al. Comparative evaluation of four urinary tubular dysfunction markers, with special references to the effects of aging and correction for creatinine concentration. Toxicol Lett. 2003;143(3):279-290 3. Stefanovic V, Cukuranovic R, Mitic-Zlatkovic M, Hall PW. Increased urinary albumin excretion in children from families with Balkan nephropathy. Pediatr Nephrol. 2002;17(11):913-916 4. Assounga AG. Beta 2 microglobulin in kidney failure: A review and an algorithm for renal replacement therapy. Saudi J Kidney Dis Transpl. 2021;32(5):1214-1220. doi:10.4103/1319-2442.344740 5. Khanijou V, Zafari N,

Coughlan MT, MacIsaac RJ, Ekinci EI. Review of potential biomarkers of inflammation and kidney injury in diabetic kidney disease. Diabetes Metab Res Rev. 2022;38(6):e3556. doi:10.1002/dmrr.3556

BETA2
80351

Beta-2 Transferrin: Detection of Spinal Fluid in Other Body Fluid

Clinical Information: The diagnosis of cerebrospinal fluid (CSF) rhinorrhea or otorrhea (leakage of CSF into the nose or ear canal, usually as a result of head trauma, tumor, congenital malformation, or surgery) is often difficult to confirm. Traditional chemical analyses (eg, glucose, protein, specific gravity) are unreliable. Radiographic studies, especially those involving the injection of dyes or radiographic compounds, are costly and may introduce additional risks to the patient. Transferrin that migrates in the beta-1 electrophoretic fraction (beta-1 transferrin) is found in most body fluids. Beta-2 transferrin is a CSF-specific variant of transferrin and is used as an endogenous marker of CSF leakage. Beta-2 transferrin is formed by loss of sialic acid due to the presence of neuraminidase in the central nervous system. Beta-2 transferrin has also been called CSF-specific transferrin and tau protein. Prompt diagnosis and localization facilitates appropriate decisions and decreases the risk of meningitis.

Useful For: Detection of spinal fluid in body fluids, such as ear or nasal fluid

Interpretation: The cerebrospinal fluid (CSF) variant of transferrin is identified by its unique electrophoretic migration. If beta-1 and beta-2 transferrin are detected in drainage fluids, the specimen is presumed to be contaminated with CSF. The presence of beta-2 transferrin band is detectable with as little as 2.5% spinal fluid contamination of body fluid.

Reference Values:
Negative, no beta-2 transferrin (spinal fluid) detected

Clinical References: 1. Oberascher G. Cerebrospinal fluid otorrhea-new trends in diagnosis. Am J Otol. 1988;9(2):102-108 2. Normansell DE, Stacy EK, Booker CF, et al. Detection of beta-2 transferrin in otorrhea and rhinorrhea in a routine clinical laboratory setting. Clin Diag Lab Immunol. 1994;1(1):68-70. doi:10.1128/cdli.1.1.68-70.1994 3. Sanders EL, Clark RJ, Katzmann JA. Cerebrospinal fluid leakage: agarose gel electrophoresis detection of beta(2)-transferrin and nephelometric quantification of beta-trace protein. Clin Chem. 2004;50(12):2401-2403. doi:10.1373/clinchem.2004.040246 4. McCudden CR, Senior BA, Hainsworth S, et al. Evaluation of high resolution gel beta (2)-transferrin for detection of cerebrospinal fluid leak. Clin Chem Lab Med. 2013;51(2):311-315. doi:10.1515/cclm-2012-0408 5. O'Cearbhaill RM, Kavanagh EC. Beta-2 Transferrin and IR. J Vasc Interv Radiol. 2018;29(3):439. doi:10.1016/j.jvir.2017.10.002 6. Zervos TM, Macki M, Cook B, Schultz LR, Rock JP, Craig JR. Beta-2 transferrin is detectable for 14 days whether refrigerated or stored at room temperature. Int Forum Allergy Rhinol. 2018;8(9):1052-1055. doi:10.1002/alr.22136

B2MC
60546

Beta-2-Microglobulin (Beta-2-M), Spinal Fluid

Clinical Information: Beta-2-microglobulin (beta-2-M) is a small membrane protein (11,800 Da) associated with the heavy chains of class I major histocompatibility complex proteins and is, therefore, on the surface of all nucleated cells. The small size allows beta-2-M to pass through the glomerular membrane, but it is almost completely reabsorbed in the proximal tubules. Increased beta-2-M levels in the cerebrospinal fluid (CSF) have been shown to be of diagnostic use in non-Hodgkin lymphoma with central nervous system involvement. Elevated CSF:serum ratios seen in patients with aseptic meningoencephalitis suggest the possibility of neurologic processes including those associated with HIV infection and acute lymphoblastic leukemia. Beta-2-M measurement in multiple sclerosis seems to be of

indeterminate usefulness.

Useful For: Evaluation of central nervous system inflammation and B-cell proliferative diseases

Interpretation: Elevations of cerebrospinal fluid beta-2-microgobulin levels may be seen in a number of diseases including malignancies, autoimmune disease, and neurological disorders.

Reference Values:
0.70-1.80 mcg/mL

Clinical References: 1. Koch TR, Lichtenfeld KM, Wiernik PH. Detection of central nervous system metastasis with cerebrospinal fluid beta-2-microglobulin. Cancer. 1983;52(1):101-104 2. Mavligit GM, Stuckey SE, Cabanillas FF, et al. Diagnosis of leukemia or lymphoma in the central nervous system by beta-2-microglobulin determination. N Engl J Med. 1980;303(13):718-722 3. Jeffery GM, Frampton CM, Legge HM, Hart DN. Cerebrospinal fluid beta 2-microglobulin levels in meningeal involvement by malignancy. Pathology. 1990;22(1):20-23 4. Us O, Lolli F, Baig S, Link H. Intrathecal synthesis of beta-2-microglobulin in multiple sclerosis and aseptic meningo-encephalitis. Acta Neurol Scand. 1989;80(6):598-602 5. Elovaara I, Livanainen M, Poutianen E, et al. CSF and serum beta-2-microglobulin in HIV infection related to neurological dysfunction. Acta Neurol Scand. 1989;79(2):81-87 6. Dolan MJ, Lucey DR, Hendrix CW, Melcher GP, Spencer GA, Boswell RN. Early markers of HIV infection and subclinical disease progression. Vaccine. 1993;11(5):548-551 7. Brew BJ, Bhalla RB, Fleisher M, et al. Cerebrospinal fluid beta 2 microglobulin in patients infected with human immunodeficiency virus. Neurology. 1989;39(6):830-834 8. Musto P, Tomasi P, Cascavilla N, et al. Significance and limits of cerebrospinal fluid beta-2-microglobulin measurement in course of acute lymphoblastic leukemia. Am J Hematol. 1988;28(4):213-218 9. Lucey DR, McGuire SA, Clerici M, et al. Comparison of spinal fluid beta 2-microglobulin levels with CD4+ T cell count, in vitro T helper cell function, and spinal fluid IgG parameters in 163 neurologically normal adults infected with the human immunodeficiency virus type l. J Infect Dis. 1991;163(5):971-975 10. Bjerrum OW, Bach FW, Zeeberg I. Increased level of cerebrospinal fluid beta 2-microglobulin is related to neurologic impairment in multiple sclerosis. Acta Neurol Scand. 1988;78(1):72-75 11. Dietzen DJ, Willrich MAV. Amino acids, peptides, and proteins. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 31

B2M
9234

Beta-2-Microglobulin, Serum

Clinical Information: Beta-2-microglobulin (beta-2-M) is a small membrane protein (11,800 Da) associated with the heavy chains of class I major histocompatibility complex proteins and is, therefore, on the surface of all nucleated cells. The small size allows beta-2-M to pass through the glomerular membrane, but it is almost completely reabsorbed in the proximal tubules. Serum beta-2-M levels are elevated in diseases associated with increased cell turnover. Levels are also elevated in several benign conditions such as chronic inflammation, liver disease, kidney dysfunction, some acute viral infections, and a number of malignancies, especially hematologic malignancies associated with the B-lymphocyte lineage. In multiple myeloma, beta-2-M is a powerful prognostic factor, and values less than 4 mcg/mL are considered a good prognostic factor. In renal tubular disease, serum levels are low and urine levels are high. Although urine beta-2-M has been used to assess tubular dysfunction, it is not stable in urine below pH 5.5.

Useful For: Prognosis assessment of multiple myeloma Evaluation of renal tubular disorders

Interpretation: A serum beta-2-microglobulin (beta-2-M) value of less than 4 mcg/mL is a good prognostic factor in patients with multiple myeloma. In a study of pretreatment serum beta-2-M levels in 100 patients with myeloma, it was reported that the median survival of patients with values greater

than 4 mcg/mL was 12 months, whereas median survival for patients with values less than 4 mcg/mL was 43 months.

Reference Values:
1.21-2.70 mcg/mL

Clinical References: 1. Bataille R, Magub M, Grenier J, Donnadio D, Sany J. Serum beta-2-microglobulin in multiple myeloma: Relation to presenting features and clinical status. Eur J Cancer Clin Oncol. 1982;18(1):59-66 2. Garewal H, Durie BG, Kyle RA, Finley P, Bower B, Serokman R. Serum beta-2-microglobulin in the initial staging and subsequent monitoring of monoclonal plasma cell disorders. J Clin Oncol. 1984;2(1):51-57 3. Norfolk D, Child JA, Cooper EH, Kerruish S, Ward AM. Serum beta-2-microglobulin in myelomatosis: potential value in stratification and monitoring. Br J Cancer. 1980;42(4):510-550 4. Dolan MJ, Lucey DR, Hendrix CW, Melcher GP, Spencer GA, Boswell RN. Early markers of HIV infection and subclinical disease progression. Vaccine. 1993;11(5):548-551 5. Karlsson FA, Wibell L, Evrin PE. Beta-2-microglobulin in clinical medicine. Scand J Clin Lab Invest. 1986;154:27-37 6. Greipp PR, Katzmann JA, O'Fallon WM, Kyle RA. Value of beta-2-microglobulin level and plasma cell labeling indices as prognostic factors in patients with newly diagnosed myeloma. Blood. 1988;72(1):219-223 7. Dietzen DJ, Willrich MAV. Amino acids, peptides, and proteins. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 31

BAMY
70634

Beta-Amyloid Immunostain, Technical Component Only

Clinical Information: Beta amyloid is a component of senile and diffuse plaques and neurofibrillary tangles, a characteristic of Alzheimer disease. Beta amyloid is also a component of vascular amyloid in the brain of dementia patients.

Useful For: Identification of senile plaques in neurodegenerative disease

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Hubin E, van Nuland NA, Broersen K, Pauwels K. Transient dynamics of A (Beta) contribute to toxicity in Alzheimer's disease. Cell Mol Life Sci. 2014;71(18):3507-3521 2. Bloom GS: Amyloid-(Beta) and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurol. 2014;71(4):505-508 3. Skaper SD. Alzheimer's disease and amyloid: culprit or coincidence? Int Rev Neurobiol. 2012;102:277-316 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

AMYR
615903

Beta-Amyloid Ratio (1-42/1-40), Spinal Fluid

Clinical Information: One of the neuropathologic features found in the brain of patients with Alzheimer disease (AD) is the presence of plaques composed of beta-amyloid. The two beta-amyloid peptides evaluated by this assay are 1-40 and 1-42. Beta-amyloid 1-40 typically exists at a higher physiological concentration than beta-amyloid 1-42. In AD, beta-amyloid 1-42 accumulation, either by overproduction or decreased clearance, leads to aggregation into plaques and neurotoxicity. Beta-amyloid 1-40 is much less prone to aggregation, with levels remaining unchanged when comparing patients with

AD to healthy individuals. In cerebrospinal fluid (CSF), approximately a 50% reduction in beta-amyloid 1-42 concentrations has been observed in AD patients compared to the concentrations found in cognitively normal individuals. This is believed to be as consequence of the decrease in soluble beta-amyloid 1-42 in the brain interstitial fluid as the peptide becomes increasingly insoluble and form deposits in the form of large numbers of diffuse and neuritic plaques. Unlike beta-amyloid 1-42, the values for beta-amyloid 1-40 in CSF remain relatively stable in individuals regardless of the presence of amyloid-pathology. Various studies have demonstrated that the use of the beta-amyloid ratio (1-42/1-40) increases diagnostic accuracy for AD versus use of beta-amyloid 1-42 alone. The beta-amyloid ratio (1-42/1-40) demonstrates high concordance with amyloid positron emission tomography (PET) when distinguishing amyloid deposition due to AD from alternative causes of mild cognitive impairment or dementia. In addition, the use of the CSF beta-amyloid ratio (1-42/1-40) could partially mitigate the effect of some preanalytical confounders that have been described to alter the results of beta-amyloid 1-42 in CSF.

Useful For: Assisting in the evaluation of adult patients, aged 55 years and older, presenting with cognitive impairment and are being assessed for Alzheimer disease and other causes of cognitive decline This test is not intended as a screening or stand-alone diagnostic assay.

Interpretation: A normal beta-amyloid ratio (1-42/1-40) of 0.073 and above is consistent with a negative (normal) amyloid positron emission tomography (PET) scan result. This result indicates a reduced likelihood that a patient's cognitive impairment is due to Alzheimer disease (AD). A beta-amyloid ratio (1-42/1-40) between 0.059 and 0.072 (likely positive) is more likely consistent with a positive amyloid PET scan result. A likely positive result does not establish a diagnosis of AD or other cognitive disorder and has increased uncertainty in regard to amyloid PET positivity. An abnormal beta-amyloid ratio (1-42/1-40) of 0.058 and below is consistent with a positive (abnormal) amyloid PET scan result. This result does not establish a diagnosis of AD or other cognitive disorder. The performance of the beta-amyloid ratio (1-42/1-40) compared to amyloid PET is shown below and described as amyloid PET-positive predictive value (indicated as Predictive Value: PV): Table. Beta-amyloid ratio (1-42/1-40) Amyloid PET Positive (n=199) Negative (n=93) Total (n=293) Amyloid PET-positive PV, % 95% CI, % Positive (abnormal) (ratio < or =0.058) 171 6 177 96.6 92.8-98.4 Likely positive (ratio 0.059 to 0.072) 13 9 22 59.1 38.7-66.7 Negative (ratio > or =0.073) 15 78 93 16.1 10.0-24.9

Reference Values:
Beta-Amyloid Ratio (1-42/1-40): > or =0.073

Clinical References: 1. Wiltfang J, Esselmann H, Bibl M, et al. Amyloid beta peptide ratio 42/40 but not A beta 42 correlates with phospho-Tau in patients with low- and high-CSF A beta 40 load. J Neurochem. 2007;101(4):1053-1059. doi:10.1111/j.1471-4159.2006.04404.x 2. Dumurgier J, Schraen S, Gabelle A, et al. Cerebrospinal fluid amyloid-beta 42/40 ratio in clinical setting of memory centers: a multicentric study. Alzheimers Res Ther. 2015 ;7(1):30. doi:10.1186/s13195-015-0114-5 3. Gervaise-Henry C, Watfa G, Albuisson E, et al. Cerebrospinal fluid ABeta42/ABeta40 as a means to limiting tube- and storage-dependent pre-analytical variability in clinical setting. J Alzheimers Dis. 2017;57(2):437-445. doi:10.3233/JAD-160865 4. Toombs J, Foiani MS, Wellington H, et al. Amyloid Beta peptides are differentially vulnerable to preanalytical surface exposure, an effect incompletely mitigated by the use of ratios. Alzheimers Dement (Amst). 2018;10:311-321. doi:10.1016/j.dadm.2018.02.005 5. Delaby C, Munoz L, Torres S, et al. Impact of CSF storage volume on the analysis of Alzheimer's disease biomarkers on an automated platform. Clin Chim Acta. 2019;490:98-101. doi:10.1016/j.cca.2018.12.021

BCATN
70361

Beta-Catenin Immunostain, Technical Component Only

Clinical Information: Beta-catenin is involved in cellular cohesion through binding to the

cytoplasmic tail of epithelial cadherin and in intracellular signaling as a component of the Wnt pathway. In normal cells, beta-catenin levels are regulated by the adenomatous polyposis coli (APC) protein, which promotes normal degradation of the protein. Alterations in either beta-catenin or APC can result in accumulation of the protein and abnormal localization in the nucleus. In the nucleus, beta-catenin acts as a cofactor in the upregulation of oncogenes including cyclin D1 and cmyc. In normal tissues, staining for beta-catenin is limited to the membrane. Aberrant nuclear staining can be used diagnostically in selected tumors of the soft tissue (fibromatoses, endometrial stromal sarcoma), pancreas, liver, and lung.

Useful For: Identification of aberrant nuclear staining pattern observed in some tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Klymkowsky MW. Beta-catenin and its regulatory network. Hum Pathol. 2005;36(3):225-227 2. Bell DA. Origins and molecular pathology of ovarian cancer. Mod Pathol. 2005;18(Suppl 2):S19-32 3. Smith ME, Pignatelli M. The molecular histology of neoplasia: the role of the cadherin/catenin complex. Histopathology. 1997;31(2):107-111 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CTX
83175

Beta-CrossLaps, Serum

Clinical Information: Human bone is continuously remodeled through a process of bone formation and resorption. Approximately 90% of the organic matrix of bone is type I collagen, a helical protein that is crosslinked at the N- and C-terminal ends of the molecule. During bone resorption, osteoclasts secrete a mixture of acid and neutral proteases that degrade the collagen fibrils into molecular fragments, including C-terminal telopeptide (CTx). As bone ages, the alpha form of aspartic acid present in CTx converts to the beta form. Beta-CTx is released into the bloodstream during bone resorption and serves as a specific marker for the degradation of mature type I collagen. Elevated serum concentrations of beta-CTx have been reported in patients with increased bone resorption. Bone turnover markers are physiologically elevated during childhood, growth, and fracture healing. The elevations in bone resorption markers and bone formation markers are typically balanced in these circumstances and are of no diagnostic value. By contrast, bone turnover markers may be useful when the bone remodeling process is unbalanced. Abnormalities in the process of bone remodeling can result in changes in skeletal mass and shape. Many diseases, in particular hyperthyroidism, all forms of hyperparathyroidism, most forms of osteomalacia and rickets (even if not associated with hyperparathyroidism), hypercalcemia of malignancy, Paget disease, multiple myeloma, and bone metastases, as well as various congenital diseases of bone formation and remodeling, can result in accelerated and unbalanced bone turnover. Unbalanced bone turnover is also found in age-related and postmenopausal osteopenia and osteoporosis. Disease-associated bone turnover abnormalities should normalize in response to effective therapeutic interventions, which can be monitored by measurement of serum and urine bone resorption markers.

Useful For: Monitoring antiresorptive therapies (eg, bisphosphonates and hormone replacement therapy) in postmenopausal women treated for osteoporosis and individuals diagnosed with osteopenia An adjunct in the diagnosis of medical conditions associated with increased bone turnover

Interpretation: Elevated levels of beta-C-terminal telopeptide (CTx) indicate increased bone resorption. Increased levels are associated with osteoporosis, osteopenia, Paget disease, hyperthyroidism, and hyperparathyroidism. In patients taking antiresorptive agents (bisphosphonates or hormone

replacement therapy), a decrease of 25% or more from baseline beta-CTx levels (ie, prior to the start of therapy) 3 to 6 months after initiation of therapy indicates an adequate therapeutic response.

Reference Values:

Males
<5 years: 242-1292 pg/mL
5-9 years: 351-1532 pg/mL
10-15 years: 447-2457 pg/mL
16-17 years: 478-1666 pg/mL
18-29 years: 238-1019 pg/mL
30-39 years: 225-936 pg/mL
40-49 years: 182-801 pg/mL
50-59 years: 161-737 pg/mL
60-69 years: 132-752 pg/mL
> or =70 years: 118-776 pg/mL

Females
<5 years: 347-1508 pg/mL
5-9 years: 383-1556 pg/mL
10-15 years: 311-1776 pg/mL
16-17 years: 146-1266 pg/mL
18-29 years: 148-967 pg/mL
30-39 years: 150-635 pg/mL
40-49 years: 131-670 pg/mL
50-59 years: 183-1060 pg/mL
60-69 years: 171-970 pg/mL
> or =70 years: 152-858 pg/mL
Premenopausal: 136-689 pg/mL
Postmenopausal: 177-1015 pg/mL

Clinical References: 1. Christgau S, Bitsch-Jensen O, Hanover Bjarnason N, et al. Serum CrossLaps for monitoring the response in individuals undergoing antiresorptive therapy. Bone. 2000;26(5):505-511 2. Garnero P, Borel O, Delmas PD. Evaluation of a fully automated serum assay for C-terminal cross-linking telopeptide of type I collagen in osteoporosis. Clin Chem. 2001;47(4):694-702 3. Fraser W: Bone and mineral metabolism. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1422-1491 4. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J; Committee of Scientific Advisors of the International Osteoporosis Foundation]. The use of biochemical markers of bone turnover in osteoporosis. Committee of Scientific Advisors of the International Osteoporosis Foundation. Osteoporos Int. 2000;11 Suppl 6:S2-S17. doi:10.1007/s001980070002 5. Saint Paul LP, Debruyne D, Bernard D, Mock DM, and Defer GL. Pharmacokinetics and pharmacodynamics of MD1003 (high-dose biotin) in the treatment of progressive multiple sclerosis. Expert Opin Drug Metab Toxicol. 2016;12:3,327-344 6. Grimsey P, Frey N, Bendig G,et al: Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. J Pharmacokinet Pharmacodyn. 2017;2(4),247-256

BGA
8486

Beta-Galactosidase, Leukocytes

Clinical Information: Beta-galactosidase is a lysosomal enzyme responsible for catalyzing the hydrolysis of gangliosides. Isolated deficiency of this enzyme can be expressed clinically as 2 different diseases, GM1 gangliosidosis (GM1) and Morquio syndrome B (MPS IVB: mucopolysaccharidosis IVB), or in some patients as a disease that combines the skeletal features of MPS IVB and neurologic features of GM1. Galactosialidosis is also associated with a deficiency of beta-galactosidase but in

conjunction with neuraminidase secondary to a defect in protective protein cathepsin A (CTSA). Enzymatic testing is not reliable for carrier detection of these conditions. GM1 gangliosidosis is autosomal recessive and absent or reduced beta-galactosidase enzyme activity leads to the accumulation of GM1 gangliosides, oligosaccharides, and keratan sulfate. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. Type 1, or infantile onset, typically presents between birth and 6 months with a very rapid progression of hypotonia, dysostosis multiplex, hepatosplenomegaly, central nervous system degeneration, and death usually by 1 to 2 years. Type 2 is generally classified as late infantile or juvenile with onset between 7 months and 3 years, presenting with developmental delays or regression and a slower clinical course. Type 3 is an adult or chronic variant with onset between 3 and 30 years and is typically characterized by slowly progressive dementia with parkinsonian features and dystonia. In MPS IVB, reduced or absent beta-galactosidase activity leads to the accumulation of glycosaminoglycans (GAG), specifically keratan sulfate, in cells, tissues, and organs interfering with their normal function. MPS IVB typically manifests as a systemic skeletal disorder with variable severity ranging from early severe disease to a later onset attenuated form. Virtually all patients have dysostosis multiplex and short stature along with other symptoms that may include coarse facies, hepatosplenomegaly, hoarse voice, stiff joints, and cardiac disease but no neurological involvement. Galactosialidosis (GS) is an autosomal recessive lysosomal storage disease caused by variants in CTSA resulting in a combined deficiency of the enzymes beta-galactosidase and neuraminidase. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. Typical clinical presentation includes coarse facial features, cherry-red spots, and skeletal dysplasia. The early infantile form is associated with fetal hydrops, visceromegaly, skeletal dysplasia, and early death. The late infantile form typically presents with short stature, dysostosis multiplex, coarse facial features, hepatosplenomegaly, and/or heart valve problems. The majority of individuals with the juvenile/adult form of GS are of Japanese ancestry and develop symptoms after 4 years of age, which include neurologic degeneration, ataxia, and angiokeratomas. Patients with mucolipidosis II/III (I-cell disease) may also demonstrate deficiency of beta-galactosidase in leukocytes, in addition to deficiency of other hydrolases. I-cell disease is an autosomal recessive lysosomal storage disorder resulting in impaired transport and phosphorylation of newly synthesized lysosomal proteins to the lysosome due to deficiency of N-acetylglucosamine 1-phosphotransferase (GlcNAc). Characteristic clinical features include short stature, skeletal and cardiac abnormalities, and developmental delay. Measurement of beta-galactosidase activity is not the preferred diagnostic test for I-cell disease but may be included in the testing strategy. A diagnostic workup in an individual with GM1 gangliosidosis, MPS IVB, or GS typically demonstrates decreased beta-galactosidase enzyme activity in leukocytes or fibroblasts; however, additional testing and consideration of the patient's clinical findings are necessary to differentiate between these conditions. Follow-up testing may include LSDS / Lysosomal Storage Disorders Screen, Random, Urine, which analyzes mucopolysaccharides, oligosaccharides, ceramide trihexosides, and sulfatides to help differentiate between the 3 conditions and guide physicians in choosing the best confirmatory molecular testing option, which may include LSDGP / Lysosomal Storage Disease Gene Panel, Varies.

Interpretation: Very-low enzyme activity levels are consistent with GM1 gangliosidosis and Morquio B disease. Clinical findings must be used to differentiate between those 2 diseases. The deficiency of beta-galactosidase combined with neuraminidase deficiency is characteristic of galactosialidosis.

Reference Values:

> or =1.56 nmol/min/mg

Clinical References: 1. Suzuki Y, Nanba E, Matsuda J, Higaki K, Oshima A. Beta-galactosidase deficiency (beta-galactosidosis): GM1 gangliosidosis and Morquio B disease. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed June 9, 2025. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225547263 2. d'Azzo A, Andria G, Bonten E, Annunziata I. Galactosialidosis. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, et al, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed June 9, 2025. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225547663 3. Caciotti A,

Garman SC, Rivera-Colon Y, et al. GM1 gangliosidosis and Morquio B disease: an update on genetic alterations and clinical findings. Biochim Biophys Acta. 2011;1812(7):782-790. doi:10.1016/j.bbadis.2011.03.018 4. Kingma SDK, Ceulemans B, Kenis S, Jonckheere AI. Are GMI gangliosidosis and Morquio type B two different disorders or part of one phenotypic spectrum?. JIMD Rep. 2021;59(1):90-103. doi:10.1002/jmd2.12204

WBGDR620975 Beta-Globin Gene Cluster Deletion/Duplication, Blood

Clinical Information: Large deletions involving the beta-globin cluster locus on chromosome 11 manifest with widely variable clinical phenotypes. Up to 10% of beta thalassemia cases (dependent on ethnicity) are caused by large deletions in the beta-globin cluster. Other thalassemias, including delta-beta thalassemia, gamma-delta-beta thalassemia, epsilon gamma thalassemia, and epsilon-gamma-delta-beta thalassemia, also result from functional loss of genes or the locus control region that controls globin gene expression. In addition, hereditary persistence of fetal hemoglobin (HPFH) is caused by deletions of variable size along the beta-globin cluster locus. Most, but not all, of the large deletion beta-globin cluster disorders are associated with variably elevated hemoglobin (Hb) F percentages that persist after 2 years of age. In addition, many manifest in microcytosis. A notable exception is HPFH, which can have normal to minimal decreased mean corpuscular volume values. The correct classification of these deletions is important as they confer variable predicted protective phenotypes, and some are more protective than others when found in combination with a second beta-globin variant, such as Hb S or beta-thalassemia. In addition, identification of these deletions can explain lifelong microcytosis in the setting of normal iron studies and negative alpha thalassemia molecular results.

Useful For: Determining the etiology of hereditary persistence of fetal hemoglobin (HPFH), delta-beta thalassemia, or other large deletions involving the beta-globin gene cluster Diagnosing less common causes of beta-thalassemia; these large deletional beta-thalassemia alterations result in elevated hemoglobin (Hb) A2 and can have slightly elevated Hb F levels Distinguishing homozygous Hb S disease from a compound heterozygous Hb S/large beta-globin cluster deletion disorder (ie, Hb S/beta zero thalassemia, Hb S/delta beta zero thalassemia, Hb S/HPFH, Hb S/gamma-delta-beta-thalassemia) Diagnosing complex thalassemias where the beta-globin gene and 1 or more of the other genes in the beta-globin cluster have been deleted Evaluating and classifying unexplained increased Hb F percentages Evaluating microcytic neonatal anemia Evaluating unexplained long standing microcytosis in the setting of normal iron studies and negative alpha thalassemia testing/normal Hb A2 percentages Confirming gene fusion hemoglobin variants such as Hb Lepore and Hb P-Nilotic Confirming homozygosity versus hemizygosity of alterations in the beta-like genes (HBB, HBD, HBG1, HBG2) Investigating newborns with Hb A levels greater than Hb F on newborn screen in the absence of transfusion. This test is not useful for diagnosis or confirmation of alpha thalassemia, the most common beta thalassemias, or hemoglobin variants. It also does not detect non-deletional HPFH.

Interpretation: The alterations will be provided with the classification that fits the probe pattern, if known. Further interpretation requires correlation with protein studies and red blood cell indices.

Reference Values:

Only orderable as a reflex. For more information see:
-HAEV1 / Hemolytic Anemia Evaluation, Blood
-HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood
-MEV1 / Methemoglobinemia Evaluation, Blood
-REVE2 / Erythrocytosis Evaluation, Blood
-THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum

An interpretive report will be provided.

Clinical References: 1. Hein MS, Oliveira JL, Swanson KC, et al. Large deletions involving the beta globin gene complex: genotype-phenotype correlation of 119 cases. Blood. 2015;126(23):3374 2. Kipp BR, Roellinger SE, Lundquist PA, Highsmith WE, Dawson DB. Development and clinical implementation of a combination deletion PCR and multiplex ligation-dependent probe amplification assay for detecting deletions involving the human alpha-globin gene cluster. J Mol Diagn. 2011;13(5):549-557. doi:10.1016/j.jmoldx.2011.04.001 3. Rund D, Rachmilewitz E. Beta-thalassemia. N Engl J Med. 2005;353(11):1135-1146 4. Nussbaum R, McInnes R, Willard H. Principles of molecular disease: Lessons from the hemoglobinopathies. In: Thompson and Thompson Genetics in Medicine. 7th ed. Saunders Elsevier; 2007:323-342 5. Wood WG. Hereditary persistence of fetal hemoglobin and delta beta thalassemia. In: Steinberg MH, Forget BG, Higgs DR, Nagel RL, eds. Disorders of Hemoglobin: Genetics, Pathophysiology, and Clinical Management. Cambridge University Press, 2001;356-388 6. Oliveira JL, Thompson CH, Saravanaperumal SA, et al. eg-Thalassemia, a new hemoglobinopathy category. Clin Chem. 2023;69(7):711-717. doi:10.1093/clinchem/hvad038

WBGDD
620979

Beta-Globin Gene Cluster, Deletion/Duplication, Varies

Clinical Information: Large deletions involving the beta-globin cluster locus on chromosome 11 manifest with widely variable clinical phenotypes. Up to 10% of beta-thalassemia cases (dependent on ethnicity) are caused by large deletions in the beta-globin cluster. Other thalassemias including delta-beta thalassemia, gamma-delta-beta-thalassemia, epsilon gamma thalassemia, and epsilon-gamma-delta-beta-thalassemia, also result from functional loss of genes or the locus control region that controls globin gene expression. In addition, hereditary persistence of fetal hemoglobin (HPFH) is caused by deletions of variable size along the beta-globin cluster locus. Most, but not all, of the large deletion beta-globin cluster disorders are associated with variably elevated hemoglobin F percentages that persist after 2 years of age. In addition, many manifest in microcytosis. A notable exception is HPFH, which can have normal to minimal decreased mean corpuscular volume values. The correct classification of these deletions is important as they confer variable predicted protective phenotypes, and some are more protective than others when found in combination with a second beta-globin variant, such as HbS or beta thalassemia. In addition, identification of these deletions can explain lifelong microcytosis in the setting of normal iron studies and negative alpha thalassemia molecular results.

Useful For: Determining the etiology of hereditary persistence of fetal hemoglobin (HPFH), delta-beta thalassemia, or other large deletions involving the beta-globin gene cluster Diagnosing less common causes of beta thalassemia; these large deletional beta-thalassemia variants result in elevated hemoglobin (Hb) A2 and can have elevated HbF levels Distinguishing homozygous HbS disease from a compound heterozygous HbS/large beta-globin cluster deletion disorder (ie, HbS/beta zero thalassemia, HbS/delta-beta zero thalassemia, HbS/HPFH, HbS/gamma-delta-beta thalassemia) Diagnosing complex thalassemias where the beta-globin gene and one or more of the other genes in the beta-globin cluster have been deleted Evaluating and classifying unexplained increased HbF percentages Evaluating microcytic neonatal anemia Evaluating unexplained long standing microcytosis in the setting of normal iron studies and negative alpha-thalassemia testing/normal Hb A2 percentages Confirming gene fusion hemoglobin variants such as Hb Lepore and HbP-Nilotic Confirming homozygosity vs hemizygosity of variants in the beta-like genes (HBB, HBD, HBG1, HBG2) Investigating newborns with HbA levels greater than HbF on newborn screen in the absence of transfusion This test is not useful for diagnosis or confirmation of alpha thalassemia, the most common beta thalassemias, or hemoglobin variants. It also does not detect non-deletional HPFH.

Interpretation: The alterations will be provided with the classification that fits the probe pattern, if known. Further interpretation requires correlation with protein studies and red blood cell indices.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Hein MS, Oliveira JL, Swanson KC, et al. Large deletions involving the beta globin gene complex: genotype-phenotype correlation of 119 cases. Blood. 2015;126(23):3374 2. Kipp BR, Roellinger SE, Lundquist PA, Highsmith WE, Dawson DB. Development and clinical implementation of a combination deletion PCR and multiplex ligation-dependent probe amplification assay for detecting deletions involving the human alpha-globin gene cluster. J Mol Diagn. 2011;13(5):549-557. doi:10.1016/j.jmoldx.2011.04.001 3. Rund D, Rachmilewitz E. Beta-thalassemia. N Engl J Med. 2005;353(11):1135-1146 4. Nussbaum R, McInnes R, Willard H. Principles of molecular disease: Lessons from the hemoglobinopathies. In: Thompson and Thompson Genetics in Medicine. 7th ed. Saunders Elsevier; 2007:323-342 5. Wood WG. Hereditary persistence of fetal hemoglobin and delta beta thalassemia. In: Steinberg MH, Forget BG, Higgs DR, Nagel RL, eds. Disorders of Hemoglobin: Genetics, Pathophysiology, and Clinical Management. Cambridge University Press, 2001;356-388 6. Oliveira JL, Thompson CH, Saravanaperumal SA, et al. eg-Thalassemia, a new hemoglobinopathy category. Clin Chem. 2023;69(7):711-717. doi:10.1093/clinchem/hvad038

WBSQR 47959 Beta-Globin Gene Sequencing, Blood

Clinical Information: Beta-globin gene sequencing is useful in the evaluation of beta-globin chain variants and beta thalassemia. It detects almost all beta-globin variants and the most common beta-thalassemia sequence variants, although prevalence is ethnicity dependent. Because these conditions are often complex, this test should always be interpreted in the context of protein studies, such as hemoglobin electrophoresis and red blood cell indices. The majority of beta-globin chain variants are clinically and hematologically benign; however, some have important clinical consequences, such as erythrocytosis, cyanosis/hypoxia, chronic hemolysis, or unexplained microcytosis. Most of the common clinically significant hemoglobin (Hb) variants (ie, HbS, HbC, HbE, and others) are easily distinguished by hemoglobin electrophoresis and do not require molecular analysis. In addition, they are frequently found in complex hemoglobin disorders due to multiple genetic variants, and accurate classification requires sequencing data within the context of protein data. In some instances, beta-globin sequencing is necessary to identify or confirm the identity of rare variants, especially those associated with erythrocytosis and chronic hemolytic anemia. Rare hyper-unstable variants (also termed dominant beta thalassemia mutations) result in hemolytic anemia and do not create protein stable enough to be detectable by protein methods, including stability studies. They are not always associated with elevated HbA2 or microcytosis and, therefore, can be electrophoretically silent. These require a high degree of clinical suspicion as all electrophoretic testing as well as stability studies cannot exclude this condition. Beta thalassemia is an autosomal recessive condition characterized by decreased or absent synthesis of beta-globin chains due to alterations in the beta-globin gene (HBB). No abnormal protein is present and diagnosis by electrophoresis relies on hemoglobin fraction percentage alterations (ie, HbA2 or HbF elevations). Beta-thalassemia can be split into 3 broad classes (categorized by clinical features): 1. Beta thalassemia trait (also called beta thalassemia minor and beta thalassemia carrier) (B[A]B[+] or B[A]B[0]). 2. Beta thalassemia intermedia (B[+]B[+] or B[+]B[0]) 3. Beta thalassemia major (B[+]B[0] or B[0]B[0]) Beta thalassemia trait is typically a harmless condition with varying degrees of microcytosis and hypochromia and sometimes mild anemia. Transfusions are not required. Beta thalassemia intermedia is a clinical distinction and is characterized by a more severe degree of anemia than beta thalassemia trait with few or intermittent transfusions required. Later in life, these individuals are at risk for iron overload even in the absence of chronic transfusion due to increased intestinal absorption of iron. Beta thalassemia major typically comes to medical attention early in life due to severe anemia, hepatosplenomegaly, and failure to thrive. Skeletal changes are also common due to expansion of the bone marrow. Without appropriate treatment these patients have a shortened lifespan. The majority of beta-thalassemia variations (>90%) are point alterations, small deletions, or insertions, which are detected by beta-globin gene sequencing. The remaining beta-thalassemia sequence variants are either due to large genomic deletions of HBB or, very rarely, trans-acting beta thalassemia variations located outside of the beta-globin gene cluster. Some rare beta-chain variants can be clinically or electrophoretically indistinguishable from beta thalassemia and cannot be confirmed without molecular analysis.

Useful For: Evaluating for the following in an algorithmic process for the HAEV1 / Hemolytic Anemia Evaluation, Blood; HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood; MEV1 / Methemoglobinemia Evaluation, Blood; REVE2 / Erythrocytosis Evaluation, Blood; THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum: -Diagnosing of beta thalassemia intermedia or major -Identifying a specific beta thalassemia sequence variant (ie, unusually severe beta thalassemia trait) -Evaluating an abnormal hemoglobin electrophoresis identifying a rare beta-globin variant -Evaluating chronic hemolytic anemia of unknown etiology -Evaluating hereditary erythrocytosis with left-shifted p50 oxygen dissociation results -Preconception screening when there is a concern for a beta-hemoglobin disorder based on family history

Interpretation: The alteration will be provided with the classification, if known. Further interpretation requires correlation with protein studies and red blood cell indices.

Reference Values:
Only orderable as a reflex. For more information see:
-HAEV1 / Hemolytic Anemia Evaluation, Blood
-HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood
-MEV1 / Methemoglobinemia Evaluation, Blood
-REVE2 / Erythrocytosis Evaluation, Blood
-THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum

An interpretive report will be provided.

Clinical References: 1. Hoyer JD, Hoffman DR: The thalassemia and hemoglobinopathy syndromes. In: McClatchey KD, ed. Clinical Laboratory Medicine. 2nd ed. Lippincott Williams and Wilkins; 2002;866-895 2. Thein SL: The molecular basis of beta-thalassemia. Cold Spring Harb Perspect Med. 2013 May 1;1;3(5):a011700 3. Hoyer JD, Kroft, SH: Color Atlas of Hemoglobin Disorders: A Compendium Based on Proficiency Testing. CAP; 2003 4. Merchant S, Oliveira JL, Hoyer JD, Viswanatha DS: Molecular diagnosis in hematopathology. In: Goldblum J, His E, eds. Hematopathology: A Volume in Foundations in Diagnostic Pathology Series. 2nd ed. Churchill Livingstone; 2012

GBAW
606273

Beta-Glucosidase, Leukocytes

Clinical Information: Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by reduced or absent acid beta-glucosidase (glucocerebrosidase) enzyme activity resulting in accumulation of glucosylceramide (glucocerebroside) and glucopsychosine (glucosylsphingosine) in the lysosomes. This interferes with the normal functioning of cells and leads to clinical abnormalities characteristic of the disease. While clinical features and severity of symptoms are widely variable within Gaucher disease, common features include abnormal blood parameters such as decreased red blood cells (anemia) and/or platelets (thrombocytopenia), bone disease, and hepatosplenomegaly. Three clinical subtypes have been identified based on the presence and progression of central nervous system (CNS) involvement. Type 1 is the most common type, representing 95% of all cases, and is generally characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, coagulation abnormalities, lung disease, and no CNS involvement. Type 2 or acute neuronopathic (GD2), typically has a very severe progression with onset in the first 2 years of life including neurologic disease, hepatosplenomegaly, and lung disease, with death usually between 2 and 4 years due to lung failure. Individuals with type 3 or chronic neuronopathic (GD3) may have onset prior to 2 years of age, but the progression is not as severe, and they may survive into the third and fourth decade. Finally, within the spectrum, there is a perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, and corneal opacities. Treatment is available in the form of enzyme replacement therapy (ERT), substrate reduction therapy, and chaperone therapy for types 1 and 3. Individuals with type 3 may

benefit from bone marrow transplantation. Currently, only supportive therapy is available for type 2. Emerging therapies currently listed at Clinicaltrials.gov include gene therapy and in utero ERT. The incidence of type 1 ranges from 1 in 20,000 to 200,000 in the general population, but it is much more frequent among Ashkenazi Jewish population with an incidence between 1 in 400 and 900. Types 2 and 3 both have an incidence of approximately 1 in 100,000 in the general population. A diagnostic workup for Gaucher disease may demonstrate the characteristic finding of "Gaucher cells" on bone marrow examination. Significantly reduced or absent enzyme activity of acid beta-glucosidase along with elevation of the biomarker, glucopsychosine (GPSY / Glucopsychosine, Blood Spot; GPSYP / Glucopsychosine, Plasma; GPSYW / Glucopsychosine, Blood) is diagnostic. Molecular analysis of the GBA gene allows for detection of disease-causing variants in affected patients (GBAZ / Gaucher Disease, Full Gene Analysis, Varies or CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies [specify GBA Gene List ID IEMCP-M4F13T]).

Useful For: Diagnosis of Gaucher disease This test is not intended for carrier detection.

Interpretation: Individuals affected with Gaucher disease will have enzyme levels less than 3.53 nmol/h/mg protein. In our experience some carriers will also have less than 3.53 nmol/h/mg protein activity.

Reference Values:

> or =3.53 nmol/hour/mg protein
An interpretative report will be provided.
Note: Results from this assay do not reflect carrier status because of individual variation of beta-glucosidase enzyme levels.

Clinical References: 1. Newborn Screening ACT Sheet [Decreased beta-glucocerebrosidase] Gaucher Disease. American College of Medical Genetics and Genomics; 2022. Revised March 2022. Accessed June 10, 2024. Available at www.acmg.net/PDFLibrary/Gaucher.pdf 2. Martins AM, Valadares ER, Porta G, et al: Recommendations on diagnosis, treatment, and monitoring for Gaucher disease. J Pediatr. 2009 Oct;155(4 Suppl):S10-S18 3. Daykin EC, Ryan E, Sidransky E: Diagnosing neuronopathic Gaucher disease: New considerations and challenges in assigning Gaucher phenotypes. Mol Genet Metab. 2021 Feb;132(2):49-58. doi: 10.1016/j.ymgme.2021.01.002 4. Pastores GM, Hughes DA: Gaucher disease. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated June 21, 2018. Accessed March 1, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1269/ 5. Weinreb NJ, Andersson HC, Banikazemi M, et al: Prevalence of type 1 Gaucher disease in the United States. Arch Intern Med. 2008 Feb;168:326-328 6. Elliott S, Buroker N, Cournoyer JJ, et al: Pilot study of newborn screening for six lysosomal storage diseases using tandem mass spectrometry. Mol Genet Metab. 2016 Aug;118(4):304-309

GUSBB
618288

Beta-Glucuronidase, Blood Spot

Clinical Information: Mucopolysaccharidosis VII (MPS VII, Sly syndrome) is an autosomal recessive lysosomal storage disorder caused by the deficiency of beta-glucuronidase. Clinical features and severity of symptoms of MPS VII are widely variable ranging from severe lethal hydrops fetalis to more mild forms which generally present with later onset and a milder clinical presentation. In general, symptoms may include skeletal anomalies, coarse facies, hepatomegaly, neurological issues, and intellectual disability. Sly syndrome is 1 of the least common mucopolysaccharidoses with an incidence of 1 in 250,000 live births. A diagnostic workup for MPS includes glycosaminoglycan (GAG) determination in urine (MPSQU / Mucopolysaccharides Quantitative, Random, Urine) or blood (MPSBS / Mucopolysaccharidosis, Blood Spot, or MPSER / Mucopolysaccharides Quantitative, Serum) and molecular genetic analysis of the relevant gene. For MPS VII, molecular analysis of the GUSB gene (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID:

IEMCP-L613TF) allows for detection of disease-causing variants in affected patients and subsequent carrier detection in relatives.

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidosis VII (MPS VII, Sly syndrome) This test is not useful for determining carrier status for MPS VII.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular genetic analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
>2.60 nmol/mL/hour

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed May 24, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ, Ballabio A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed May 24, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546905

GUSBW
618289

Beta-Glucuronidase, Leukocytes

Clinical Information: Mucopolysaccharidosis VII (MPS VII, Sly syndrome) is an autosomal recessive lysosomal storage disorder caused by the deficiency of beta-glucuronidase. Clinical features and severity of symptoms of MPS VII are widely variable ranging from severe lethal hydrops fetalis to more mild forms which generally present with later onset and a milder clinical presentation. In general, symptoms may include skeletal anomalies, coarse facies, hepatomegaly, neurological issues, and intellectual disability. Sly syndrome is one of the least common mucopolysaccharidoses with an incidence of 1 in 250,000 live births. A diagnostic workup for MPS includes glycosaminoglycan (GAG) determination in urine (MPSQU / Mucopolysaccharides Quantitative, Random, Urine) or blood (MPSBS / Mucopolysaccharidosis, Blood Spot, or MPSER / Mucopolysaccharides Quantitative, Serum) and molecular genetic analysis of the relevant gene. For MPS VII, molecular analysis of the GUSB gene (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-L613TF) allows for detection of disease-causing variants in affected patients and subsequent carrier detection in relatives.

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidosis type VII (MPS VII, Sly syndrome) in whole blood This test is not useful for carrier detection.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory

studies (enzyme assay, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
>3.50 nmol/hour/mg protein

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed May 25, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ, Ballabio A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed May 25, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546905

BHCG
61718

Beta-Human Chorionic Gonadotropin, Quantitative, Serum

Clinical Information: Human chorionic gonadotropin (hCG) is a glycoprotein hormone (molecular weight: MW approximately 36,000 Da) consisting of 2 noncovalently bound subunits. The alpha subunit (92-amino acids; "naked" protein MW 10,205 Da) is essentially identical to that of luteinizing hormone (LH), follicle-stimulating hormone, and thyrotropin (previously known as thyroid-stimulating hormone: TSH). The alpha subunit is essential for receptor transactivation. The different beta subunits of the above hormones are transcribed from separate genes, show less homology, and convey the receptor-specificity of the dimeric hormones. The chorionic gonadotropin, beta gene (coding for a 145-amino acid, "naked" protein MW 15,531 Da, glycosylated subunit MW approximately 22,500 Da) is highly homologous to the beta subunit of LH and acts through the same receptor. However, while LH is a classical tropic pituitary hormone, hCG does not usually circulate in significant concentrations. In pregnant primates (including humans) it is synthesized in the placenta and maintains the corpus luteum and, hence, progesterone production, during the first trimester. Thereafter, the placenta produces steroid hormones, diminishing the role of hCG. hCG concentrations fall, leveling off around week 20, significantly above prepregnancy levels. After delivery, miscarriage, or pregnancy termination, hCG falls with a half-life of 24 to 36 hours, until prepregnancy levels are reached. Outside of pregnancy, hCG may be secreted by abnormal germ cell, placental, or embryonal tissues, in particular seminomatous and nonseminomatous testicular tumors; ovarian germ cell tumors; gestational trophoblastic disease (hydatidiform mole and choriocarcinoma); and benign or malignant nontesticular teratomas. Rarely, other tumors including hepatic, neuroendocrine, breast, ovarian, pancreatic, cervical, and gastric cancers may secrete hCG, usually in relatively modest quantities. During pathological hCG production, the highly coordinated secretion of alpha and beta subunits of hCG may be disturbed. In addition to secreting intact hCG, tumors may produce disproportionate quantities of free alpha-subunits or, more commonly, free beta-subunits. Assays that detect both intact hCG and free beta-hCG, including this assay, tend to be more sensitive in detecting hCG-producing tumors. With successful treatment of hCG-producing tumors, hCG levels should fall with a half-life of 24 to 36 hours, and eventually return to the reference range.

Useful For: Monitoring patients for retained products of conception Aiding in the diagnosis of gestational trophoblastic disease (GTD), testicular tumors, ovarian germ cell tumors, teratomas, and, rarely, other human chorionic gonadotropin (hCG)-secreting tumors Serial measurement of hCG following treatment for: -Monitoring therapeutic response in GTD or in hCG-secreting tumors -Detecting persistent or recurrent GTD or hCG-secreting tumors This test is not intended to detect or monitor pregnancy.

Interpretation: After delivery, miscarriage, or pregnancy termination, human chorionic gonadotropin (hCG) falls with a half-life of 24 to 36 hours, until prepregnancy levels are reached. An absent or significantly slower decline is seen in patients with retained products of conception. Gestational trophoblastic disease (GTD) is associated with very considerable elevations of hCG, usually above 2 multiples of the medians for gestational age persisting or even rising beyond the first trimester. Serum hCG levels are elevated in approximately 40% to 50% of patients with nonseminomatous testicular cancer and 20% to 40% of patients with seminoma. Markedly elevated levels of hCG (>5000 IU/L) are uncommon in patients with pure seminoma and indicate the presence of a mixed testicular cancer. Ovarian germ cell tumors (approximately 10% of ovarian tumors) display elevated hCG levels in 20% to 50% of cases. Teratomas in children may overproduce hCG, even when benign, resulting in precocious pseudopuberty. Levels may be elevated to similar levels as seen in testicular cancer. Among nonreproductive tumors, hepatobiliary tumors (hepatoblastomas, hepatocellular carcinomas, and cholangiocarcinomas) and neuroendocrine tumors (eg, islet cell tumors and carcinoids) are those most commonly associated with hCG production. Many hCG-producing tumors also produce other embryonic proteins or antigens, in particular alpha fetoprotein (AFP). AFP should, therefore, also be measured in the diagnostic workup of such neoplasms. Complete therapeutic response in hCG-secreting tumors is characterized by a decline in hCG levels with an apparent half-life of 24 to 36 hours and eventual return to concentrations within the reference range. GTD and some tumors may produce hyperglycosylated hCG with a longer half-life, but an apparent half-life of more than 3 days suggests the presence of residual hCG-producing tumor tissue. A rise in hCG levels above the reference range in patients with hCG-producing tumors that had previously been treated successfully, suggests possible local or distant metastatic recurrence.

Reference Values:

Clinical References: 1. Cole LA, Khanlian SA, Muller CY. Detection of perimenopause or postmenopause human chorionic gonadotropin: an unnecessary source of alarm. Am J Obstet Gynecol. 2008;198:275.e1-275.e7 2. Schneider DT, Calaminus G, Gobel U. Diagnostic value of alpha 1-fetoprotein and beta-human chorionic gonadotropin in infancy and childhood. Pediatr Hematol Oncol. 2001;18(1):11-26 3. Cole LA, Butler S. Detection of hCG in trophoblastic disease. The USA hCG reference service experience. J Reprod Med. 2002;40(6):433-444 4. von Eyben FE. Laboratory markers and germ cell tumors. Crit Rev Clin Lab Sci. 2003;40(4):377-427 5. Sturgeon CM, Duffy MJ, Stenman UH, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. Clin Chem. 2008;54(12):e11-e79 6. Franks CE, Li J, Martinez M, et al. Utility of commercially available quantitative hCG immunoassays as tumor markers in trophoblastic and non-trophoblastic disease. Clin Chem. Published online May 19, 2023. doi:10.1093/clinchem/hvad045

BHSP
92371

Beta-Hydroxybutyrate, Serum

~~Human Chorionic Gonadotropin, Quantitative, Spinal Fluid~~

Clinical Information: Beta-hydroxybutyrate (BHB) is 1 of 3 sources of ketone bodies. Its relative proportion in the blood (78%) is greater than the other 2 ketone bodies, acetoacetate (20%) and acetone (2%). During carbohydrate deprivation (starvation, digestive disturbances, frequent vomiting), decreased carbohydrate utilization (diabetes mellitus), glycogen storage diseases, and alkalosis, acetoacetate production increases. The increase may exceed the metabolic capacity of the peripheral tissues. As acetoacetate accumulates in the blood, a small amount is converted to acetone by spontaneous decarboxylation. The remaining and greater portion of acetoacetate is converted to BHB.

Useful For: Monitoring therapy for diabetic ketoacidosis Investigating the differential diagnosis of any patient presenting to the emergency room with hypoglycemia, acidosis, suspected alcohol ingestion, or an unexplained increase in the anion gap In pediatric patients, the presence or absence of ketonemia/uria is an essential component in the differential diagnosis of inborn errors of metabolism Serum beta-

hydroxybutyrate is a key parameter monitored during controlled 24-hour fasts

Interpretation: The beta-hydroxybutyrate (BHB)/acetoacetate ratio is typically between 3:1 and 7:1 in severe ketotic states. Serum BHB increases in response to fasting, but should not exceed 0.4 mmol/L following an overnight fast (up to 12 hours). In pediatric patients, a hypo- or hyper-ketotic state (with or without hypoglycemia) may suggest specific groups of metabolic disorders.

Reference Values:
<0.4 mmol/L

Clinical References: 1. Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. Philadelphia, WB Saunders Co. 1999 2. Vassault A, Bonnefont JP, Specola N, et al: Lactate, pyruvate, and ketone bodies. In Techniques in Diagnostic Human Biochemical Genetics - A Laboratory Manual. Edited by F Hommes. New York, Wiley-Liss, 1991 3. Bonnefont JP, Specola NB, Vassault A, et al: The fasting test in paediatrics: application to the diagnosis of pathological hypo- and hyperketotic states. Eur J Pediatr 1990;150:80-85

BLAC
82896

Beta-Lactoglobulin, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to beta-lactoglobulin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

HCO3
876

Bicarbonate, Serum

Clinical Information: Bicarbonate is the second largest fraction of the anions in plasma. Included in this fraction are the bicarbonate (HCO3[-]) and carbonate (CO3[-2]) ions, carbon dioxide in physical solution, as well as the carbamino compounds. At the physiological pH of blood, the concentration of carbonate is 1/1000 that of bicarbonate. The carbamino compounds are also present in such low quantities that they are generally not mentioned specifically. The bicarbonate content of serum or plasma is a significant indicator of electrolyte dispersion and anion deficit. Together with pH determination, bicarbonate measurements are used in the diagnosis and treatment of numerous potentially serious disorders associated with acid-base imbalance in the respiratory and metabolic systems. Some of these conditions are diarrhea, renal tubular acidosis, carbonic anhydrase inhibitors, hyperkalemic acidosis, renal failure, and ketoacidosis.

Useful For: Diagnosis and treatment of acid-base imbalance in respiratory and metabolic systems

Interpretation: Alterations of bicarbonate (HCO3) and carbon dioxide (CO2) dissolved in plasma are characteristic of acid-base imbalance. The nature of the imbalance cannot, however, be inferred from the bicarbonate value itself, and the determination of bicarbonate is rarely ordered alone. Its value has significance in the context of other electrolytes determined with it and in screening for electrolyte imbalance.

Reference Values:
Males
12-24 months: 17-25 mmol/L
3 years: 18-26 mmol/L
4-5 years: 19-27 mmol/L
6-7 years: 20-28 mmol/L
8-17 years: 21-29 mmol/L
> or =18 years: 22-29 mmol/L
Females
1-3 years: 18-25 mmol/L
4-5 years: 19-26 mmol/L

6-7 years: 20-27 mmol/L
8-9 years: 21-28 mmol/L
> or =10 years: 22-29 mmol/L

Reference values have not been established for patients that are <12 months of age.

Clinical References: Tietz Textbook of Clinical Chemistry, Edited by Burtis and Ashwood. Philadelphia, PA, WB Saunders Company, 1994.

FBIUR
75383

Bicarbonate, Urine

Reference Values:
Reporting limit determined each analysis.

Normally: None Detected

BAPS
62538

Bile Acid Profile, Serum

Clinical Information: Bile acids are formed in the liver from cholesterol, conjugated primarily to glycine and taurine, stored and concentrated in the gallbladder, and secreted into the intestine after the ingestion of a meal. In the intestinal lumen, the bile acids serve to emulsify ingested fats to promote digestion. During the absorptive phase of digestion, approximately 90% of the bile acids are reabsorbed. The efficiency of the hepatic clearance of bile acids from portal blood maintains serum concentrations at low levels in normal persons. An elevated fasting level of bile acids due to impaired hepatic clearance is a sensitive indicator of liver disease. Following meals, serum bile acid levels have been shown to increase only slightly in normal persons, but they are markedly elevated in patients with various liver diseases, including cirrhosis, hepatitis, cholestasis, portal-vein thrombosis, Budd-Chiari syndrome, cholangitis, Wilson disease, and hemochromatosis. No increase in bile acids will be noted in patients with intestinal malabsorption. Metabolic hepatic disorders involving organic anions (eg, Gilbert disease, Crigler-Najjar syndrome, and Dubin-Johnson syndrome) do not cause abnormal serum bile acid concentrations. The concentration of bile acids in serum is influenced by many different liver diseases due to the inability of the liver to efficiently extract circulating bile acids from portal blood. In addition, bile acid levels are altered in several biochemical genetic conditions, such as peroxisomal biogenesis disorders (eg, Zellweger spectrum disorder) and disorders of bile acid synthesis (eg, D-bifunctional protein deficiency and alpha methyl-CoA racemase deficiency), due to the loss of specific enzymes important for bile acid metabolism. This analysis includes a quantitative characterization of primary and secondary bile acids as well as 2 bile acid precursor species for the assessment of bile acid metabolism.

Useful For: Evaluating the enterohepatic cycle consisting of the biliary system, intestine, portal circulation, and hepatocytes Supporting researchers in need of free and conjugated values of all 20 bile acid species as well as total bile acid

Interpretation: Total bile acids are metabolized in the liver and can serve as a marker for normal liver function. Increases in serum C27 bile acids are seen in patients with peroxisomal biogenesis disorders (eg, as Zellweger spectrum disorder) or single enzyme defects of bile acid synthesis (eg, D-bifunctional protein deficiency and alpha methyl CoA racemases). Totals of the free and conjugated bile acid species for all 20 bile acids in addition to total bile acids will be reported. No interpretive report will be provided.

Reference Values:
Chenodeoxycholic acid: < or =2.26 nmol/mL

Cholic acid: < or =2.74 nmol/mL
Deoxycholic acid: < or =2.84 nmol/mL
Dihydroxycholestanoic acid: < or =0.07 nmol/mL
Glycochenodeoxycholic acid: < or =5.14 nmol/mL
Glycocholic acid: < or =2.17 nmol/mL
Glycodeoxycholic acid: < or =3.88 nmol/mL
Glycohyodeoxycholic acid: < or =0.01 nmol/mL
Glycolithocholic acid: < or =0.11 nmol/mL
Glycoursodeoxycholic acid: < or =1.00 nmol/mL
Hyodeoxycholic acid: < or =0.12 nmol/mL
Lithocholic acid: < or =0.09 nmol/mL
Taurochenodeoxycholic acid: < or =0.80 nmol/mL
Taurocholic acid: < or =0.31 nmol/mL
Taurodeoxycholic acid: < or =0.78 nmol/mL
Taurohyodeoxycholic acid: < or =0.02 nmol/mL
Taurolithocholic acid: < or =0.04 nmol/mL
Tauroursodeoxycholic acid: < or =0.05 nmol/mL
Trihydroxycholestanoic acid: < or =1.73 nmol/mL
Ursodeoxycholic acid: < or =0.64 nmol/mL
Total bile acids: < or =19.00 nmol/mL

Clinical References: 1. Sundaram SS, Bove KE, Lovell MA, Sokol RJ. Mechanisms of disease: inborn errors of bile acid synthesis. Nat Clin Pract Gastroenterol Hepatol. 2008;5(8):456-468 2. Wanders RJA, Rizzo WB. Inborn errors of peroxisome biogenesis and function. In: Sarafoglou K, Hoffmann GF, Roth KS, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. McGraw-Hill Medical Division. 2nd ed. 2017:427-446 3. Ducroq DH, Morton MS, Shadi N, et al. Analysis of serum bile acids by isotope dilution-mass spectrometry to assess the performance of routine total bile acid methods. Ann Clin Biochem. 2010;47(Pt 6):535-540 4. Fischler B, Eggertsen G, Bjorkhem I. Genetic Defects in Synthesis and Transport of Bile Acids. In: Sarafoglou K, Hoffmann GF, Roth KS. eds. Pediatric Endocrinology and Inborn Errors of Metabolism, 2e. McGraw-Hill Education; 2017. Accessed April 1, 2025. Available at https://accesspediatrics.mhmedical.com/content.aspx?bookid=2042&sectionid=154112839

BAIPD
41445

Bile Acids for Peroxisomal Disorders, Serum

Clinical Information: Bile acids are formed in the liver from cholesterol, conjugated primarily to glycine and taurine, stored and concentrated in the gallbladder, and secreted into the intestine after the ingestion of a meal. In the intestinal lumen, the bile acids serve to emulsify ingested fats to promote digestion. During the absorptive phase of digestion, approximately 90% of the bile acids are reabsorbed. The efficiency of the hepatic clearance of bile acids from portal blood maintains serum concentrations at low levels in normal persons. An elevated fasting level of bile acids due to impaired hepatic clearance is a sensitive indicator of liver disease. Following meals, serum bile acid levels have been shown to increase only slightly in normal persons, but they are markedly elevated in patients with various liver diseases, including cirrhosis, hepatitis, cholestasis, portal-vein thrombosis, Budd-Chiari syndrome, cholangitis, Wilson disease, and hemochromatosis. No increase in bile acids will be noted in patients with intestinal malabsorption. Metabolic hepatic disorders involving organic anions (eg, Gilbert disease, Crigler-Najjar syndrome, and Dubin-Johnson syndrome) do not cause abnormal serum bile acid concentrations. This bile acid test for peroxisomal disorders measures concentrations of C27 bile acids, which are diagnostic markers for peroxisomal biogenesis disorders, such as Zellweger spectrum disorder and single enzyme defects of bile acid synthesis, such as D-bifunctional protein deficiency and alpha methyl-CoA racemase deficiency. Elevated levels of C27 bile acids may enable diagnosis of peroxisomal biogenesis disorders and bile acid synthesis defects in children with liver cholestasis. Treatment for peroxisomal biogenesis disorders and bile acid synthesis defects with cholic acid is available. Measurement of C27 bile acids before and during treatment with bile acid therapy, such as cholic acid can assist with monitoring of

treatment efficacy.

Useful For: Biomarker for peroxisomal biogenesis disorders, such as Zellweger spectrum disorder and single enzyme defects of bile acid synthesis, including D-bifunctional protein deficiency and alpha methyl CoA racemases Monitoring patients receiving bile acid therapy, such as cholic acid, for liver disease due to peroxisomal biogenesis disorders or single enzyme defects in bile acid synthesis

Interpretation: Increases in serum C27 bile acids are seen in patients with peroxisomal biogenesis disorders (eg, Zellweger spectrum disorder) or single enzyme defects of bile acid synthesis (eg, D-bifunctional protein deficiency and alpha methyl CoA racemaces). Total bile acids are metabolized in the liver and can serve as a marker for normal liver function. The values of 2 bile acid precursors, dihydroxycholestanoic acid and trihydroxycholestanoic acid, will be reported, along with total cholic acid, total chenodeoxycholic acid, total ursodeoxycholic acid, and total bile acids. No interpretive report will be provided.

Reference Values:

Dihydroxycholestanoic acid: < or =0.10 nmol/mL
Trihydroxycholestanoic acid: < or =1.30 nmol/mL
Total cholic acid: < or =5.00 nmol/mL
Total chenodeoxycholic acid: < or =6.00 nmol/mL
Total ursodeoxycholic acid: < or =2.00 nmol/mL
Total bile acids: < or =19.00 nmol/mL

Clinical References: 1. Johnson DW, ten Brink HJ, Schuit RC, Jakobs C. Rapid and quantitative analysis of unconjugated C(27) bile acids in plasma and blood samples by tandem mass spectrometry. J Lipid Res. 2001;42(1):9-16 2. Bootsma AH, Overmars H, van Rooij A, et al. Rapid analysis of conjugated bile acids in plasma using electrospray tandem mass spectrometry: application for selective screening of peroxisomal disorders. J Inherit Metab Dis. 1999;22(3):307-310 3. Ferdinandusse S, Jimenez-Sanchez G, Koster J, et al. A novel bile acid biosynthesis defect due to a deficiency of peroxisomal ABCD3. Hum Mol Genet. 2015;24(2):361-370 4. Heubi JE, Setchell KDR, Bove KE. Inborn errors of bile acid metabolism. Clin Liver Dis. 2018;22(4):671-687. doi:10.1016/j.cld.2018.06.006 5. Sundaram SS, Bove KE, Lovell MA, Sokol RJ. Mechanisms of disease: inborn errors of bile acid synthesis. Nat Clin Pract Gastroenterol Hepatol. 2008;5(8):456-468 6. Wanders RJA, Rizzo WB. Inborn errors of peroxisome biogenesis and function. In: Sarafoglou K, Hoffmann GF, Roth KS, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. 2nd ed. McGraw-Hill Medical Division; 2017:427-446 7. Fischler B, Eggertsen G, Bjorkhem I. Genetic Defects in Synthesis and Transport of Bile Acids. In: Sarafoglou K, Hoffmann GF, Roth KS. eds. Pediatric Endocrinology and Inborn Errors of Metabolism, 2e. McGraw-Hill Education; 2017. Accessed April 1, 2025. Available at https://accesspediatrics.mhmedical.com/content.aspx?bookid=2042&sectionid=154112839 8. Society for Maternal-Fetal Medicine (SMFM). Lee RH, Mara Greenberg, Metz TD, Pettker CM. Society for Maternal-Fetal Medicine Consult Series #53: Intrahepatic cholestasis of pregnancy: replaces consult #13, April 2011. Am J Obstet Gynecol. 2021;224(2):B2-B9. doi:10.1016/j.ajog.2020.11.002

BAMRP
619919

Bile Acids Malabsorption Panel, Serum and Feces

Clinical Information: Bile acids are synthesized from cholesterol in the liver and released into the digestive tract where they function to emulsify dietary fats and facilitate lipid absorption in the small intestine. The majority of bile acids are reabsorbed in the ileum of the healthy individual, with only 5% excreted in feces.(1) The synthesis of bile acids in the liver is regulated by a negative feedback mechanism from the bile acids reabsorbed from the intestine. 7Alpha-hydroxy-4-cholesten-3-one (7aC4) is an intermediate in the biosynthesis pathway of cholesterol to bile acids. Primary bile acids

cholic acid (CA) and chenodeoxycholic acid (CDCA) are deconjugated and dehydroxylated via intestinal bacteria into secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA), respectively.(2) The sum of CA, CDCA, DCA, LCA, and ursodeoxycholic acid composes the majority of bile acids in the feces. The concentration of 7aC4 in serum is a surrogate for the amount of bile acid synthesis in the liver. There is some diurnal variation in 7aC4 serum concentrations, so measurement should be performed on a fasting morning sample. Patients with increased bile acid in their stool suffer from chronic diarrhea, termed bile acid diarrhea (BAD). Approximately 10% to 33% of patients with irritable bowel syndrome with diarrhea (IBS-D) have BAD. Additionally, BAD has been identified as a contributor of diarrhea in other conditions such as irritable bowel disease, Celiac disease, microscopic colitis, and neuroendocrine tumors.(3) Identifying patients with BAD can be done by measuring total and fractionated bile acids in stool. The increased bile acids in feces can be caused by an inability to reabsorb bile acids in the terminal ileum. The loss of intestinal reabsorption leads to increase synthesis of bile acids in the liver. Recent studies have shown that serum concentrations of 7aC4 are elevated in patients with BAD. Several intestinal diseases or functional abnormalities can lead to BAD. Identification of these patients can influence treatment decisions that could include the use of bile acid sequestrants. Conversely, patients with IBS with constipation (IBS-C) may have lower circulating 7aC4 as compared to healthy individuals. The definitive test in the United States for BAD is the 48-hour stool bile acids test (BA48F / Bile Acids, Bowel Dysfunction, 48 Hour, Feces). However, given the challenge of a 48-hour specimen collection, a random stool collection can be used in combination with the results from serum 7aC4 testing. From a random stool collection, only the percentage of primary bile acids can be reported. Internal studies have shown that a combination of serum 7aC4 result above 52.5 ng/mL and primary fecal bile acid result above 10% is 66% sensitive and 95% specific for bile acid malabsorption.(4) Quantitation of fecal bile acids aids in screening for BAD and identifying patients with chronic diarrhea who may benefit from bile acid sequestrant therapy.

Useful For: Aiding in the evaluation of patients suspected of having chronic diarrhea symptoms due to bile acid malabsorption

Interpretation: When serum 7alpha-hydroxy-4-cholesten-3-one results are above 52.5 ng/mL and primary fecal bile acid results are above 10%, this test is 66% sensitive and 95% specific for bile acid malabsorption. Pharmacological treatment with bile acid sequestrants has been shown to improve symptoms in some patients.

Reference Values:

BILE ACID MALABSORPTION, FECAL:
> or =18 years:
Sum of cholic acid and chenodeoxycholic acid: < or =10.0%

7AC4, BILE ACID SYNTHESIS, SERUM:
2.5-63.2 ng/mL

Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Vijayvargiya P, Camilleri M, Chedid V, et al. Analysis of fecal primary bile acids detects increased stool weight and colonic transit in patients with chronic functional diarrhea. Clin Gastroenterol Hepatol. 2019;17(5):922-929.e2 2. Vijayvargiya P, Camilleri M: Current practice in the diagnosis of bile acid diarrhea. Gastroenterology. 2019;156:(5):1233-1238 3. Vijayvargiya P, Gonzalez Izundegui D, Calderon G, et al. Increased fecal bile acid excretion in a significant subset of patients with other inflammatory diarrheal diseases. Dig Dis Sci. 2022;67(6):2413-2419. doi:10.1007/s10620-021-06993-5 4. Vijayvargiya P, Camilleri M, Taylor A, Busciglio I, Loftus EV Jr, Donato LJ: Combined fasting serum C4 and primary bile acids from a single stool sample to diagnose bile acid diarrhea. Gastroenterology. 2020;159(5):1952-1954.e2 5. Duboc H, Rainteau D, Rajca S, et al. Increase in fecal primary bile acids and dysbiosis in patients with diarrhea-predominant irritable bowel syndrome. Neurogastroenterol Motil. 2012;24(6):513-520, e246-7 6. Vijayvargiya P, Camilleri M, Shin

A, Saenger A. Methods for diagnosis of bile acid malabsorption in clinical practice. Clin Gastroenterol Hepatol. 2013;11(10):1232-1239 7. Vijayvargiya P, Camilleri M, Carlson P, et al. Performance characteristics of serum C4 and FGF19 measurements to exclude the diagnosis of bile acid diarrhoea in IBS-diarrhoea and functional diarrhoea. Aliment Pharmacol Ther. 2017;46(6):581-588. doi:10.1111/apt.14214 8. Camilleri M, Nadeau A, Tremaine WJ, et al. Measurement of serum 7 alpha-hydroxy-4-cholesten-3-one (or 7AC4), a surrogate test for bile acid malabsorption in health, ileal disease and irritable bowel syndrome using liquid chromatography-tandem mass spectrometry. Neurogastroenterol Motil. 2009;21(7):734-743 9. Wong BS, Camilleri M, Carlson P, et al. Increased bile acid biosynthesis is associated with irritable bowel syndrome with diarrhea. Clin Gastroenterol Hepatol. 2012;10(9):1009-1015.e3

BA48F
607368

Bile Acids, Bowel Dysfunction, 48 Hour, Feces

Clinical Information: Bile acids are natural products of cholesterol synthesis that aid in the emulsification and absorption of dietary fats in the small intestine. The majority of bile acids are reabsorbed in the ileum of the healthy individual, with only 5% excreted in feces.(1) Primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA) are deconjugated and dehydroxylated via intestinal bacteria into secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA), respectively.(2) The sum of CA, CDCA, DCA, LCA, and ursodeoxycholic acid (UDCA) compose the majority of bile acids in the feces. Impaired absorption of bile acids in the terminal ileum leads to excess bile acids in the colon that can cause diarrhea from chloride and water secretion; a condition called bile acid malabsorption (BAM). Irritable bowel syndrome (IBS) is a nonspecific multifactorial disorder involving the large intestine. IBS is characterized by cramping, bloating, diarrhea, and constipation and classified as either IBS-D (diarrhea) or IBS-C (constipation) by the Rome III criteria.(3) Up to 50% of IBS-D patients have accelerated colonic transit time; the mechanism of IBS-D pathophysiology is varied with more than 25% having BAM.(1,4) Several methods have been developed for detection of BAM, but are not widely available in clinical practice.(5) Therefore, patients are often placed on trials of bile acids sequestrants to determine if symptoms improve. Quantitation of fecal bile acids aids in screening for IBS-D and identification of patients with chronic diarrhea who may benefit from bile acid sequestrant therapy.

Useful For: Aids in evaluation of patients suspected of having irritable bowel syndrome-diarrhea symptoms due to bile acid malabsorption

Interpretation: Elevated total fecal bile acid or percent cholic acid plus chenodeoxycholic acid is consistent with the diagnosis of bile acid malabsorption. Pharmacological treatment with bile acid sequestrants has been shown to improve symptoms in some patients.

Reference Values:
> or = to 18 years:
Sum of cholic acid and chenodeoxycholic acid < or =9.7%
Total bile acids < or =2619 mcmoles/48 h

Reference values have not been established for patients who are younger than 18 years of age

Clinical References:

BAFS
62234

Bile Acids, Fractionated and Total, Serum

Clinical Information: Bile acids are formed in the liver from cholesterol, conjugated primarily to glycine and taurine, stored and concentrated in the gallbladder, and secreted into the intestine after the

ingestion of a meal. In the intestinal lumen, the bile acids serve to emulsify ingested fats to promote digestion. During the absorptive phase of digestion, approximately 90% of the bile acids are reabsorbed. The efficiency of the hepatic clearance of bile acids from portal blood maintains serum concentrations at low levels in normal persons. An elevated fasting level of bile acids due to impaired hepatic clearance is a sensitive indicator of liver disease. Following meals, serum bile acid levels have been shown to increase only slightly in normal persons, but they are markedly elevated in patients with various liver diseases, including cirrhosis, hepatitis, cholestasis, portal-vein thrombosis, Budd-Chiari syndrome, cholangitis, Wilson disease, and hemochromatosis. No increase in bile acids will be noted in patients with intestinal malabsorption. Metabolic hepatic disorders involving organic anions (eg, Gilbert disease, Crigler-Najjar syndrome, and Dubin-Johnson syndrome) do not cause abnormal serum bile acid concentrations.

Useful For: Measuring tauro- and glycol-conjugated and unconjugated bile acid constituents in serum specimens Monitoring patients receiving bile acid therapy, such as cholic acid, deoxycholic acid, or ursodeoxycholic acid Aiding in the evaluation of liver function; evaluation of liver function changes before the formation of more advanced clinical signs of illness such as icterus Determining hepatic dysfunction as a result of chemical and environmental injury Indicating hepatic histological improvement in chronic hepatitis C patients responding to interferon treatment Indicating intrahepatic cholestasis of pregnancy This assay is not useful for the diagnosis of peroxisomal biogenesis disorders or inborn errors of bile acid metabolism.

Interpretation: Total bile acids are metabolized in the liver and can serve as a marker for normal liver function. Increases in serum bile acids are seen in patients with acute hepatitis, chronic hepatitis, liver sclerosis, liver cancer, and intrahepatic cholestasis of pregnancy.

Reference Values:

Total cholic acid: < or =5.00 nmol/mL
Total chenodeoxycholic acid: < or =6.00 nmol/mL
Total deoxycholic acid: < or =6.00 nmol/mL
Total ursodeoxycholic acid: < or =2.00 nmol/mL
Total bile acids: < or =19.00 nmol/mL

Clinical References: 1. Marschall HU. Management of intrahepatic cholestasis of pregnancy. Expert Rev Gastroenterol Hepatol. 2015;9(10):1273-1279 2. Ducroq DH, Morton MS, Shadi N, et al. Analysis of serum bile acids by isotope dilution-mass spectrometry to assess the performance of routine total bile acid methods. Ann Clin Biochem. 2010;47(Pt 6):535-540 3. Piechota J, Jelski W. Intrahepatic cholestasis in pregnancy: Review of the literature. J Clin Med. 2020;9(5):1361. doi:10.3390/jcm9051361 4. Society for Maternal-Fetal Medicine (SMFM). Lee RH, Mara Greenberg, Metz TD, Pettker CM. Society for Maternal-Fetal Medicine Consult Series #53: Intrahepatic cholestasis of pregnancy: replaces consult #13, April 2011. Am J Obstet Gynecol. 2021;224(2):B2-B9. doi:10.1016/j.ajog.2020.11.002

BILEA
84689

Bile Acids, Total, Serum

Clinical Information: Bile acids are formed in the liver from cholesterol, conjugated primarily to glycine and taurine, stored and concentrated in the gallbladder, and secreted into the intestine after the ingestion of a meal. In the intestinal lumen, the bile acids serve to emulsify ingested fats and thereby promote digestion. During the absorptive phase of digestion, approximately 90% of the bile acids are reabsorbed. The efficiency of the hepatic clearance of bile acids from portal blood maintains serum concentrations at low levels in normal persons. An elevated fasting level, due to impaired hepatic clearance, is a sensitive indicator of liver disease. Following meals, serum bile acid levels have been shown to increase only slightly in normal persons but markedly in patients with various liver diseases, including cirrhosis, hepatitis, cholestasis, portal-vein thrombosis, Budd-Chiari syndrome, cholangitis, Wilson disease, and hemochromatosis. No increase in bile acids will be noted in patients with intestinal

malabsorption. Metabolic hepatic disorders involving organic anions (eg, Gilbert disease, Crigler-Najjar syndrome, and Dubin-Johnson syndrome) do not cause abnormal serum bile acid concentrations. Significant increases in total bile acids in nonfasting pregnant females can aid in the diagnosis of cholestasis. Other factors, such as complete medical history, physical exam, and liver function tests should also be considered.

Useful For: An aid in the evaluation of liver function Evaluation of liver function changes before the formation of more advanced clinical signs of illness such as icterus An aid in the determination of hepatic dysfunction as a result of chemical and environmental injury An indicator of hepatic histological improvement in chronic hepatitis C patients responding to interferon treatment An indicator for intrahepatic cholestasis of pregnancy

Interpretation: Total bile acids are metabolized in the liver and can serve as a marker for normal liver function. Increases in serum bile acids are seen in patients with acute hepatitis, chronic hepatitis, liver sclerosis, and liver cancer.

Reference Values:
< or =10 mcmol/L

Reference interval applies to fasting total bile acid concentrations.

Clinical References: 1. Sawkat Anwer M, Meyer DJ: Bile Acids in the diagnosis, pathology, and therapy of hepatobiliary diseases. Vet Clin North Am Small Anim Pract. 1995 March;25(2):503-517 2. Javitt NB: Diagnostic value of serum bile acids. Clin Gastroenterol. 1977;6:219-226 3. Osuga T, Mitamura K, Mashige F, et al: Evaluation of fluorimetrically estimated serum bile acid in liver disease. Clin Chim Acta. 1977;75:81-90 4. Shima T, Tada H, Morimoto M, et al: Serum total bile acid level as a sensitive indicator of hepatic histological improvement in chronic hepatitis C patients responding to interferon treatment. J Gastroenterol Hepatol. 2000 March;15(30):294-299 5. Lebovics E, Seif F, Kim D, et al: Pruritus in chronic hepatitis C: Association with high serum bile acids, advanced pathology, and bile duct abnormalities. Dig Dis Sci. 1997 May;42(5):1094-1099 6. Korman MG, Hofmann AF, Summerskill WHJ: Assessment of activity in chronic active liver disease. Serum bile acids compared with conventional tests and histology. NEJM 1974 June 20;290:1399-1402 7. Manzotti C, Casazza G, Stimac T, Nikolova D, Gluud C. Total serum bile acids or serum bile acid profile, or both, for the diagnosis of intrahepatic cholestasis of pregnancy. Cochrane Database Syst Rev. 2019 Jul 5;7(7):CD012546. doi: 10.1002/14651858.CD012546.pub2

FBAC
75012

Bile Acids, Urine

Clinical Information: Diagnostic testing in pediatric and adult patients presenting with conditions of cholestatic liver disease, neurological disease, or fat-soluble vitamin malabsorption of unknown etiology. Urine FAB-MS analysis provides a rapid and cost-effective means of diagnosing the most common of the genetic defects in the metabolism of cholesterol to the primary bile acids. Mass spectrometry testing may be used to monitor the biochemical response to primary bile acid therapy and to help in decisions on dose adjustments, where compliance should lead to a reduction in levels of atypical bile acids.

BILAO
71917

Biliary Tract Malignancy, FISH, Varies

Clinical Information: Endoscopic retrograde cholangiopancreatography (ERCP) is used to examine patients with biliary tract obstruction or stricture for possible malignancy. Biopsies and cytologic specimens are obtained at the time of ERCP. Cytologic analysis complements biopsy by

sometimes detecting malignancy in patients with a negative biopsy. Nonetheless, a number of studies suggest that the overall sensitivity of bile duct brushing and bile aspirate cytology is quite low. Fluorescence in situ hybridization (FISH) is a technique that utilizes fluorescently-labeled DNA probes to examine cells for chromosomal alterations. FISH can be used to detect cells with chromosomal changes (eg, aneuploidy) that are indicative of malignancy. Studies in our laboratory indicate that the sensitivity of FISH to detect malignant cells in biliary brush specimens is superior to that of conventional cytology.

Useful For: Assessing bile duct brushing or hepatobiliary brushing specimens for biliary tract malignancy

Interpretation: An interpretive report will be provided.

Reference Values:
No abnormality detected by fluorescence in situ hybridization

Clinical References: 1. Barr Fritcher EG, Voss JS, Brankley SM, et al. An optimized set of fluorescence in situ hybridization probes for detection of pancreatobiliary tract cancer in cytology brush samples. Gastroenterology. 2015;149(7):1813-1824. doi:10.1053/j.gastro.2015.08.046 2. Barr Fritcher EG, Kipp BR, Voss JS, et al. ST27: The development of a tailored pancreatobiliary fluorescence in situ hybridization (FISH) assay to improve detection of malignancy in pancreatobiliary brushings. J Mol Diagn. 2013;15(6):909 3. Barr Fritcher EG, Kipp BR, Halling KC, et al. A multivariable model using advanced cytologic methods for the evaluation of indeterminate pancreatobiliary strictures. Gastroenterology. 2009;136(7):2180-2186. doi:10.1053/j.gastro.2009.02.040

FBILM
70587

Biliary Tract Malignancy-Cytology, FISH, Varies

Clinical Information: Endoscopic retrograde cholangiopancreatography (ERCP) is used to examine patients with biliary tract obstruction or stricture for possible malignancy. Biopsies and cytologic specimens are obtained at the time of ERCP. Cytologic analysis complements biopsy by sometimes detecting malignancy in patients with a negative biopsy. Nonetheless, a number of studies suggest that the overall sensitivity of bile duct brushing and bile aspirate cytology is quite low. Fluorescence in situ hybridization (FISH) is a technique that utilizes fluorescently labeled DNA probes to examine cells for chromosomal alterations. FISH can be used to detect cells with chromosomal changes (eg, aneuploidy) that are indicative of malignancy. Studies in our laboratory indicate that the sensitivity of FISH to detect malignant cells in biliary brush specimens is superior to that of conventional cytology.

Useful For: Assessing bile duct brushing or hepatobiliary brushing specimens for bile tract malignancy

BILID
81787

Bilirubin Direct, Serum

Clinical Information: Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin while the remaining 15% is produced from the RBC precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce mono- and diglucuronide, which are excreted in the bile. Direct bilirubin is a measurement of conjugated bilirubin. Jaundice can occur as a result of problems at any step in the metabolic pathway. Disorders may be classified as those due to increased bilirubin production (eg, hemolysis and ineffective erythropoiesis), decreased bilirubin excretion (eg, obstruction and hepatitis), and abnormal bilirubin metabolism (eg, hereditary and neonatal jaundice). Inherited disorders in which direct bilirubinemia occurs include Dubin-Johnson syndrome and Rotor syndrome. Jaundice of the newborn where direct bilirubin is elevated includes idiopathic neonatal hepatitis and biliary atresia. The most commonly occurring form of jaundice of the newborn, physiological jaundice, results in unconjugated (indirect) hyperbilirubinemia. Elevated unconjugated bilirubin in the neonatal period may result in brain damage (kernicterus). Treatment options are phototherapy and, if severe, exchange transfusion. The increased production of bilirubin that

accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis results in hyperbilirubinemia in the absence of any liver abnormality. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin is retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubin are increased in hepatocellular diseases such as hepatitis and space-occupying lesions of the liver, and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

Useful For: Evaluation of jaundice and liver functions

Interpretation: Direct bilirubin levels must be assessed in conjunction with total and indirect levels and the clinical setting.

Reference Values:
> or =12 months: 0.0-0.3 mg/dL
Reference values have not been established for patients <12 months.

Clinical References: 1. Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 2. Roche/Hitachi Modular Analytics Reference Guide, Vol 7

BFBL
606895

Bilirubin, Body Fluid

Clinical Information: Peritoneal fluid: Bilirubin is typically measured in peritoneal fluid of patients with suspected bile duct leak or gallbladder perforation as a screening test prior to imaging or cholescintigraphy. If the value is higher than that of serum and is greater than 6 mg/dL, and the ascitic fluid amylase is not elevated (indicating upper intestinal perforation), it can be assumed that the gallbladder has perforated into the peritoneum (choleperitoneum) or either bowel or biliary perforation has occurred.(1) Furthermore, biliary leakage after laparoscopic cholecystectomy is the most common post-operative complication.(2) While endoscopy is a beneficial first-line treatment for the management of bile leaks there often are logistical issues which hinder the procedure from being performed rapidly. Post-cholecystectomy patients generally have a drain in place (particularly a Jackson Pratt [JP] drain) and may undergo bilirubin testing on the drain fluid as an objective assessment of a bile leak. A body fluid/serum bilirubin ratio of greater than 5 in a JP drain fluid is highly sensitive and specific for bile leak.(3) Pleural fluid: Measurement of bilirubin in pleural fluid has been investigated to aid in the differentiation of transudative and exudative effusions in pursuit of more specific biomarkers than traditional light criteria measuring total protein and lactate dehydrogenase. Bilirubin values tend to be higher in exudates than in transudates, although there is some overlap between groups which limits the usefulness of its measure.(4) Other fluids: Determination of body fluid bilirubin concentration can aid in the distinction between a transudative and an exudative fluid or identify the presence of bile in other fluid compartments.

Useful For: Evaluating peritoneal fluid or abdominal drain fluid as a screening test for bile leakage
May aid in the distinction between a transudative and an exudative pleural effusion

Interpretation: Bilirubin may be measured in other fluids although the decision limits are not well defined in fluids other than pleural fluid. Fluid to serum bilirubin ratios are expected to be less than or equal to 1.0 and should be interpreted in conjunction with other clinical findings.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Runyon BA. Ascitic fluid bilirubin concentration as a key to choleperitoneum. J Clin Gastroenterol. 1987;9(5):543-545 2. Koch M, Garden OJ, Padbury R, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery 2011;149(5):680-688. doi:10.1016/j.surg.2010.12.002 3. Darwin P, Goldberg E, Uradomo L. Jackson Pratt drain fluid-to-serum bilirubin concentration ratio for the diagnosis of bile leaks. Gastrointest Endosc. 2010;71(1):99-104. doi:10.1016/j.gie.2009.08.015 4. Metintas M, Alatas O, Alatas F, Colak O, Ozdemir N, Erginel S. Comparative analysis of biochemical parameters for differentiation of pleural exudates from transudates Light's criteria, cholesterol, bilirubin, albumin gradient, alkaline phosphatase, creatine kinase, and uric acid. Clin Chim Acta. 1997;264(2):149-162. doi:10.1016/s0009-8981(97)00091-0 5. Block DR, Lasho MA, Donato, LJ, Meeusen JW. Establishing hemolysis, icterus, and lipemia interference limits for body fluid chemistry analytes measured on the Roche cobas instrument. AM J Clin Pathol. 2024:aqae040. doi: 10.1093/ajcp/aqae040

BILI3
8452

Bilirubin, Serum

Clinical Information: Bilirubin is one of the most frequently used tests to assess liver function. Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin, while the remaining 15% is produced from red blood cell precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce bilirubin mono- and diglucuronide, which are then excreted in the bile. A number of inherited and acquired diseases affect 1 or more of the steps involved in the production, uptake, storage, metabolism, and excretion of bilirubin. Bilirubinemia is frequently a direct result of these disturbances. The most commonly occurring form of unconjugated hyperbilirubinemia is that seen in newborns and referred to as physiological jaundice. The increased production of bilirubin, that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis, results in hyperbilirubinemia in the absence of any liver abnormality. The rare genetic disorders, Crigler-Najjar syndromes type I and type II, are caused by a low or absent activity of bilirubin uridine 5'-diphospho--glucuronosyltransferase. In type I, the enzyme activity is totally absent, the excretion rate of bilirubin is greatly reduced, and the serum concentration of unconjugated bilirubin is greatly increased. Patients with this disease may die in infancy owing to the development of kernicterus. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin are retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubins are increased in hepatitis, space-occupying lesions of the liver, and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

Useful For: Assessing liver function Evaluating a wide range of diseases affecting the production, uptake, storage, metabolism, or excretion of bilirubin Monitoring the efficacy of neonatal phototherapy

Interpretation: The level of bilirubinemia that results in kernicterus in a given infant is unknown. In preterm infants, the risk of a handicap increases by 30% for each 2.9 mg/dL increase of maximal total bilirubin concentration. While central nervous system damage is rare when total serum bilirubin (TSB) is less than 20 mg/dL, premature infants may be affected at lower levels. The decision to institute therapy is based on a number of factors, including TSB, age, clinical history, physical examination, and coexisting conditions. Phototherapy is typically discontinued when TSB level reaches 14 to 15 mg/dL. Physiologic jaundice should resolve in 5 to 10 days in full-term infants and by 14 days in preterm infants. When any portion of the biliary tree becomes blocked, bilirubin levels will increase.

Reference Values:
Direct Bilirubin
> or =12 months: 0.0-0.3 mg/dL

Reference values have not been established for patients who are younger than 12 months of age.

Total Bilirubin
0-6 days: Refer to www.bilitool.org for information on age-specific (postnatal hour of life) serum bilirubin values.
7-14 days: 0.0-14.9 mg/dL
15 days to 17 years: 0.0-1.0 mg/dL
> or =18 years 0.0-1.2 mg/dL

Clinical References: 1. Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 2. Scharschmidt BF, Blanckaert N, Farina FA, Kabra PM, Stafford BE, Weisiger RA. Measurement of serum bilirubin and its mono- and diconjugates: Applications to patients with hepatobiliary disease. Gut. 1982;23(8):643-649 3. Practice parameter: management of hyperbilirubinemia in the healthy term newborn. American Academy of Pediatrics. Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia [published correction appears in Pediatrics 1995 Mar;95(3):458-61]. Pediatrics. 1994;94(4 Pt 1):558-565.

BILIT
81785

Bilirubin, Total, Serum

Clinical Information: Bilirubin is one of the most frequently used tests to assess liver function. Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin, while the remaining 15% is produced from the red blood cell precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce mono- and diglucuronide, which are excreted in the bile. A number of inherited and acquired diseases affect 1 or more of the steps involved in the production, uptake, storage, metabolism, and excretion of bilirubin. Bilirubinemia is a frequent and direct result of these disturbances. Jaundice can occur as a result of problems at each step in the metabolic pathway. Disorders may be classified as those due to increased bilirubin production (eg, hemolysis and ineffective erythropoiesis), decreased bilirubin excretion (eg, obstruction and hepatitis), and abnormal bilirubin metabolism (eg, hereditary and neonatal jaundice). The most commonly occurring form of unconjugated hyperbilirubinemia is that seen in newborns and referred to as physiological jaundice. Elevated unconjugated bilirubin in the neonatal period may result in brain damage (kernicterus). Treatment options are phototherapy and, if severe, exchange transfusion. The rare genetic disorders, Crigler-Najjar syndromes type I and type II, are caused by a low or absent activity of bilirubin uridine 5'-diphospho-glucuronosyltransferase. In type I, the enzyme activity is totally absent, the excretion rate of bilirubin is greatly reduced, and the serum concentration of unconjugated bilirubin is greatly increased. Patients with this disease may die in infancy owing to the development of kernicterus. The increased production of bilirubin, that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis, results in hyperbilirubinemia in the absence of any liver abnormality. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin is retained, and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubin are increased in hepatitis, space-occupying lesions of the liver, and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

Useful For: Assessing liver function Evaluating a wide range of diseases affecting the production, uptake, storage, metabolism, or excretion of bilirubin Monitoring the efficacy of neonatal phototherapy

Interpretation: The level of bilirubinemia that results in kernicterus in a given infant is unknown. While central nervous system damage is rare when total serum bilirubin (TSB) is less than 20 mg/dL, premature infants may be affected at lower levels. The decision to institute therapy is based on a number

of factors including TSB, age, clinical history, physical examination and coexisting conditions. Phototherapy typically is discontinued when TSB level reaches 14 to 15 mg/dL. Physiologic jaundice should resolve in 5 to 10 days in full-term infants and by 14 days in preterm infants. In preterm infants, the risk of a handicap increases by 30% for each 2.9 mg/dL increase of maximal total bilirubin concentration. When any portion of the biliary tree becomes blocked, bilirubin levels will increase.

Reference Values:
0-6 days: Refer to www.bilitool.org for information on age-specific (postnatal hour of life) serum bilirubin values.
7-14 days: 0.0-14.9 mg/dL
15 days to 17 years: 0.0-1.0 mg/dL
> or =18 years: 0.0-1.2 mg/dL

Clinical References: 1. Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 2. Scharschmidt BF, Blanckaert N, Farina FA, Kabra PM, Stafford BE, Weisiger RA. Measurement of serum bilirubin and its mono- and diconjugates: Applications to patients with hepatobiliary disease. Gut. 1982;23(8):643-649 3. Practice parameter: management of hyperbilirubinemia in the healthy term newborn. American Academy of Pediatrics. Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia [published correction appears in Pediatrics 1995 Mar;95(3):458-61]. Pediatrics. 1994;94(4 Pt 1):558-565

BIOTN
606867

Biotin, Serum

Clinical Information: Biotin is a water soluble B complex vitamin (vitamin B7 or vitamin H) that is an essential cofactor for the synthesis of fatty acids, catabolism of branched chained amino acids, and for gluconeogenesis. It is usually found at relatively low endogenous concentrations in patients on a normal diet. However, biotin can be found in over-the-counter multi-vitamins, prenatal vitamins, and dietary supplements marketed for hair, skin, and nail growth. Additionally, treatment of certain progressive multiple sclerosis patients with high doses of biotin has been reported to be beneficial. Biotin supplementation from either over-the-counter or prescription sources can result in extremely elevated circulating biotin. Some immunoassays in the clinical laboratory use chemistry that utilizes the high affinity and avidity that biotin has for binding avidin (or streptavidin). As a result, high serum biotin concentrations can yield inaccurate laboratory results in laboratory assays that utilize this biotin-streptavidin chemistry. Specifically, specimens with high biotin can yield falsely decreased results when the testing methodology utilizes sandwich-based methods or falsely increased results when the methodology utilizes competitive binding methods. Each clinical laboratory method that utilizes biotin-streptavidin chemistry has a defined biotin concentration limit above which serum biotin can interfere with assay results. This test measures free biotin concentrations in serum and can be used to determine whether a patient has high biotin concentrations that are likely from biotin supplementation/treatment.

Useful For: Measurement of biotin in serum Assessment of biotin concentrations in individuals taking biotin supplements Investigation of unexpected results from immunoassays that utilize biotin-streptavidin detection methods This test is not useful as a screen for biotinidase deficiency.

Interpretation: Biotin results that are significantly higher than the reference interval indicate biotin supplementation.

Reference Values:
> or =18 years: < or =0.3 ng/mL
Reference values have not been established for patients who are <18 years of age.

Clinical References: 1. Elston MS, Sehgal S, Du Toit S, Yarndley T, Conaglen JV. Factitious

Graves' disease due to biotin immunoassay interference-a case and review of the literature. J Clin Endocrinol Metab. 2016;101(9):3251-3255 2. Grimsey P, Frey N, Bendig G, et al. Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. Int J Pharmacokinet. 2017;2:247-256 3. Katzman BM, Lueke AJ, Donato LJ, Jaffe AS, Baumann NA. Prevalence of biotin supplement usage in outpatients and plasma biotin concentrations in patients presenting to the emergency department. Clin Biochem. 2018;60:11-16

BTDZ
35375

Biotinidase Deficiency, BTD Full Gene Analysis, Varies

Clinical Information: Biotinidase deficiency is an inherited metabolic disease caused by reduced levels of biotinidase, an enzyme that recycles biotin by releasing it from its metabolic product, biocytin, or exogenous dietary proteins. Biotin is a vitamin that serves as a coenzyme for 4 carboxylases that are essential for amino acid catabolism, gluconeogenesis, and fatty acid synthesis. Depletion of free biotin reduces carboxylase activity, resulting in secondary carboxylase deficiency. Depending on the amount of residual biotinidase activity, individuals can have either profound or partial biotinidase deficiency. Age of onset and clinical phenotype vary among individuals. Profound biotinidase deficiency occurs in approximately 1 in 137,000 live births and partial biotinidase deficiency occurs in approximately 1 in 110,000 live births, resulting in a combined incidence of about 1 in 61,000. Untreated profound biotinidase deficiency (<10% of normal biotinidase activity) manifests within the first decade of life as seizures, hypotonia, neurosensory hearing loss, respiratory problems, and cutaneous symptoms including skin rash, alopecia, and recurrent viral or fungal infections. Among children and adolescents with profound biotinidase deficiency, clinical features include ataxia, sensorineural hearing loss, developmental delay, and eye problems such as optic neuropathy leading to blindness. Partial biotinidase deficiency (10%-30% of normal biotinidase activity) is associated with a milder clinical presentation, which may include cutaneous symptoms without neurologic involvement. Treatment with biotin has been successful in both preventing and reversing the clinical features associated with biotinidase deficiency. As a result, biotinidase deficiency is included in most newborn screening programs in order to prevent disease. Biotinidase deficiency exhibits a similar clinical presentation to carboxylase and holocarboxylase synthetase deficiency. Therefore, measurement of the biotinidase enzyme is required to differentiate between these diseases and ensure proper diagnosis. Newborn screening for biotinidase deficiency involves direct analysis of the biotinidase enzyme from blood spots obtained shortly after birth. This enables early identification of potentially affected individuals and quick follow-up with confirmatory biochemical and molecular testing. Biotinidase deficiency is inherited in an autosomal recessive manner, caused by mutations in the biotinidase gene (BTD). The carrier frequency for biotinidase deficiency in the general population is about 1:120. Several common mutations in the BTD gene have been identified, accounting for about 60% of affected individuals. Sequencing of the entire BTD gene detects other, less common, disease-causing mutations. While genotype-phenotype correlations are not well established, it appears that certain mutations are associated with profound biotinidase deficiency, while others are associated with partial deficiency. The recommended first-tier test to screen for biotinidase deficiency is a biochemical test that measures biotinidase enzyme activity, either newborn screening or BIOTS / Biotinidase, Serum. Molecular tests form the basis of confirmatory or carrier testing. Individuals with decreased enzyme activity are more likely to have 2 identifiable mutations in the BTD gene by molecular genetic testing.

Useful For: Second-tier test for confirming biotinidase deficiency (indicated by biochemical testing or newborn screening) Carrier testing of individuals with a family history of biotinidase deficiency, but disease-causing mutations have not been identified in an affected individual

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424 2. Kaye CI, Committee on Genetics, Accurso F, et al: Newborn screening fact sheets. Pediatrics 2006 Sep;118(3):e934-963 3. Moslinger D, Muhl A, Suormala T, et al: Molecular characterization and neuropsychological outcome of 21 patients with profound biotinidase deficiency detected by newborn screening and family studies. Eur J Pediatr 2003 Dec;162 Suppl 1:S46-49 Epub 2003 Nov 20 4. Nyhan WL, Barshop B, Ozand PT: Multiple carboxylase deficiency/biotinidase deficiency. In Altas of Metabolic Diseases. Second edition. New York, Oxford University Press, 2005 pp 42-48 5. Wolf B, Jensen KP, Barshop B, et al: Biotinidase deficiency: novel mutations and their biochemical and clinical correlates. Hum Mutat 2005 Apr;25(4):413

BIOTS
88205

Biotinidase, Serum

Clinical Information: Biotinidase deficiency is an autosomal recessive disorder caused by variants in the biotinidase gene (BTD). Age of onset and clinical phenotype vary among individuals depending on the amount of residual biotinidase activity. Profound biotinidase deficiency occurs in approximately 1 in 137,000 live births and partial biotinidase deficiency occurs in approximately 1 in 110,000 live births, resulting in a combined incidence of about 1 in 61,000. The carrier frequency for biotinidase deficiency within the general population is about 1 in 120. Untreated profound biotinidase deficiency typically manifests within the first decade of life as seizures, ataxia, developmental delay, hypotonia, sensorineural hearing loss, vision problems, skin rash, and alopecia. Partial biotinidase deficiency is associated with a milder clinical presentation and may include cutaneous symptoms without neurologic involvement. Certain organic acidurias, such as holocarboxylase synthase deficiency, isolated carboxylase synthase deficiency, and 3-methylcrotonylglycinuria, present similarly to biotinidase deficiency. Serum biotinidase levels can help rule out these disorders. Treatment with biotin is successful in preventing the clinical features associated with biotinidase deficiency. In symptomatic patients, treatment will reverse many of the clinical features except developmental delay, vision, and hearing complications. As a result, biotinidase deficiency is included in most newborn screening programs. This enables early identification and treatment of presymptomatic patients. Molecular tests are useful for confirmation of diagnosis or carrier testing. When biotinidase enzyme activity is deficient, sequencing of the entire BTD gene (BTDZ / Biotinidase Deficiency, BTD Full Gene Analysis, Varies) allows for detection of disease-causing variants in affected patients. Identification of familial variants allows for testing of at-risk family members (FMTT / Familial Variant, Targeted Testing, Varies). While genotype-phenotype correlations are not well established, it appears that certain genetic variants are associated with profound biotinidase deficiency, while others are associated with partial deficiency.

Useful For: Preferred test for the diagnosis of biotinidase deficiency Follow-up testing for certain organic acidurias

Interpretation: An interpretive report is provided. Values below 3.5 U/L are occasionally seen in specimens from unaffected patients.

Reference Values:
3.5-13.8 U/L

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Accessed January 19, 2024. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-

Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Zempleni J, Barshop BA, Cordonier EL, et al. Disorders of biotin metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Diseases. McGraw-Hill; Accessed January 19, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225548571 3. Wolf B. Biotinidase Deficiency. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. GeneReviews [Internet]. University of Washington, Seattle; 1993-2023. Updated May 25, 2023. Accessed January 19, 2024. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1322/

FBFPI
57925

Bird Fancier's Precipitin Panel I

Interpretation: The gel diffusion method was used to test this patient's serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and immunological sensitization. The clinical significance varies, depending on the history and symptoms.

Reference Values:
Negative

BHDZ
614584

Birt-Hogg-Dube Syndrome, FLCN, Full Gene Analysis, Varies

Clinical Information: Germline variants in the FLCN gene are associated with Birt-Hogg-Dube (BHD) syndrome. BHD syndrome is characterized by cutaneous manifestations (fibrofolliculomas, trichodiscomas/angiofibromas, perifollicular fibromas, and acrochordons), pulmonary cysts/history of pneumothorax, and various types of renal tumors. BHD syndrome is inherited in an autosomal dominant manner and the penetrance is considered to be very high.(1-6) While there is no consensus on clinical surveillance of BHD syndrome, many recommendations have been put forth for the individual manifestations of the condition by different groups, such as the National Cancer Institute.(4-6)

Useful For: Evaluating patients with a personal or family history suggestive of Birt-Hogg-Dube (BHD) syndrome Establishing a diagnosis of BHD syndrome allowing for targeted cancer surveillance based on associated risks Identifying variants within genes known to be associated with increased risk for BHD syndrome allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Sattler EC, Steinlein OK: Birt-Hogg-Dube syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews. [Internet]. University of Washington, Seattle; 2006. Updated January 30, 2020. Accessed April 26, 2024. Available at: www.ncbi.nlm.nih.gov/books/NBK1522/ 2. Houweling AC, Gijezen LM, Joneker MA, et al. Renal cancer and pneumothorax risk in Birt-Hogg-Dube syndrome; an analysis of 115 FLCN mutation carriers from 35 BHD families. Br J Cancer. 2011;105(12):1912-1919 3. Schmidt LS, Nickerson ML, Warren MB, et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dube Syndrome. Am J Hum Genet. 2005;76(6):1023-1033 4. Stamatakis L, Metwalli AR, Middelton LA, Linehan WM. Diagnosis and management of BHD-associated kidney cancer. Fam

Cancer. 2013;12(3):397-402 5. Farrant PBJ, Emerson R: Letter. hyfrecation and curettage as a treatment for fibrofolliculomas in Birt-Hogg-Dube syndrome. Dermatol Surg. 2007;33(10):1287-1288 6. Kim D, Wysong A, Teng JM, Rahman Z. Laser-assisted delivery of topical rapamycin: mTOR inhibition for Birt-Hogg-Dube syndrome. Dermatol Surg. 2019;45(12):1713-1715 7. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

BIWB
64274

Bismuth, Blood

Clinical Information: Bismuth is used in the production of alloys, pigments, and chemical additives. Various compounds have also been used as therapeutic agents, astringents, and antacids.(1) Bismuth subsalicylate (Pepto-Bismol) is one example commonly used for indigestion and diarrhea. In unexposed individuals, bismuth blood concentrations are typically less than 0.02 mcg/L compared to peptic ulcer patients taking bismuth medications where the concentrations ranged from 4 to 30 mcg/L.(2-4) Elimination from the body takes place primarily by the urinary and fecal routes, but the exact proportion contributed by each route is still unknown. Elimination from blood displays multicompartment pharmacokinetics with half-lives of 8 to 16 hours (early) and 5 to 11 days (late).(1) A number of toxic effects have been attributed to bismuth compounds in humans including nephropathy, encephalopathy, osteoarthropathy, gingivitis, stomatitis, and colitis. Common early symptoms include salivation, mucosal swelling, discoloration of the tongue, gums, abdominal pain, and nausea.(1,6)

Useful For: Determining bismuth toxicity

Interpretation: Normal blood concentrations for unexposed individuals are less than 1 ng/mL and the therapeutic range is 4 to 30 ng/mL.(2-5)

Reference Values:
<1 ng/mL (unexposed)
4-30 ng/mL (therapeutic)

Clinical References: 1. Baselt R. Disposition of Toxic Drugs and Chemicals In Man. 10th ed. Biomedical Publications; 2014 2. Heitland P, Koster HD. Biomonitoring of 37 trace elements in blood samples from inhabitants of northern Germany by ICP-MS. J Trace Elem Med Biol. 2006;20(4):253-262 3. Serfontein WJ, Mekel R, Bank S, Barbezat G, Novis B. Bismuth toxicity in man-I. Bismuth blood and urine levels in patients after administration of a bismuth protein complex (Bicitropeptide). Res Commun Chem Pathol Pharmacol. 1979;26(2):383-389 4. Serfontein WJ, Mekel R. Bismuth toxicity in man II. Review of bismuth blood and urine levels in patients after administration of therapeutic bismuth formulations in relation to the problem of bismuth toxicity in man. Res Commun Chem Pathol Pharmacol. 1979;26(2):391-411 5. Sodi R. Vitamins and trace elements. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:417-417 6. Keogan DM, Griffith DM. Current and potential applications of bismuth-based drugs. Molecules. 2014;19(9):15258-97. doi:10.3390/molecules190915258

BIVAL
614120

Bivalirudin, Ecarin, Plasma

Clinical Information: Bivalirudin, is a parenteral anticoagulant that directly inhibits thrombin (direct thrombin inhibitor), factor IIa. It is indicated for use in patients with unstable angina undergoing percutaneous coronary intervention (PCI), in those undergoing PCI with provisional use of glycoprotein IIb/IIIa inhibitor (GPI), or in those with, or at risk of, heparin- induced thrombocytopenia (HIT) or HIT and thrombosis syndrome (HITTS) undergoing PCI. In these indications, it is intended for use with

aspirin. Frequently, bivalirudin is used for prevention of treatment of thrombosis in patients with HIT with or without thrombosis and with kidney and/or hepatic dysfunction. Bivalirudin is administered via continuous intravenous infusion, is removed by a combination of proteolytic cleavage by thrombin and renal clearance mechanisms and can inhibit both soluble and clot-bound thrombin. Bivalirudin's effect is typically monitored using the activated partial thromboplastin time (aPTT) test with a target aPTT ratio of 1.5 to 2.5 times the patient's baseline value. However, in instances where patients have a prolonged baseline aPTT (eg, lupus anticoagulants and factor XII deficiency), aPTT monitoring of bivalirudin is not reliable, and direct measurement of the effect of bivalirudin on factor IIa may be more reliable. For HIT, monitoring every 2 to 4 hours until in range and then once daily; for PCI, monitoring is unnecessary unless kidney failure is present. Internal laboratory validation demonstrates that plasma concentrations of bivalirudin from 0.25 to 1.25 mcg/mL correspond to an aPTT ratio of 1.5 to 2.5 and plasma concentrations of bivalirudin from 0.25 to 2.00 mcg/mL correspond to an aPTT ratio of 1.5 to 3.0. Correlation of bivalirudin drug concentrations with aPTT ratios may vary with different aPTT reagents.

Useful For: Monitoring of bivalirudin therapy for patients with prolonged baseline activated partial thromboplastin time

Interpretation: Therapeutic reference ranges have not been established. See Clinical Information for activated partial thromboplastin time correlative information.

Reference Values:
<0.10 mcg/mL

Clinical References: 1. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e495S-e530s 2. Love JE, Ferrell C, Chandler WL. Monitoring direct thrombin inhibitors with a plasma diluted thrombin time. Thromb Haemost. 2007;98(1):234-242 3. Van Cott EM, Roberts AJ, Dager WE. Laboratory Monitoring of Parenteral Direct Thrombin Inhibitors. Semin Thromb Hemost. 2017;43(3):270-276 4. Gosselin RC, Douxfils J. Ecarin based coagulation testing. Am J Hematol. 2020;95(7):863-869. doi:10.1002/ajh.25852 5. Gosselin RC, King JH, Janatpour KA, Dager WE, Larkin EC, Owings JT: Comparing direct thrombin inhibitors using aPTT, ecarin clotting times, and thrombin inhibitor management testing. Ann Pharmacother. 2004 Sep;38(9):1383-1388. doi:10.1345/aph.1D565 6. Beyer JT, Lind SE, Fisher S, Trujillo TC, Wempe MF, Kiser TH: Evaluation of intravenous direct thrombin inhibitor monitoring tests: Correlation with plasma concentrations and clinical outcomes in hospitalized patients. J Thromb Thrombolysis. 2020 Feb;49(2):259-267. doi: 10.1007/s11239-019-01961-3

PBKQN
614567

BK Virus DNA Detection and Quantification, Plasma

Clinical Information: BK virus (BKV) is a circular, double-stranded DNA virus with an approximately 5 kilobase-size genome in the polyomavirus family, of which 13 members of the family are known, including the JC virus (JCV) and SV40. BKV shares about 75% of its DNA sequence with JCV. Nearly 80% of the adult population worldwide have antibodies to both viruses, indicating previous infection or exposure to these viruses. Initial infection with BKV is usually acquired in childhood, mostly asymptomatic or manifesting as a mild flu-like illness. After primary infection, BKV establishes latency in the kidney and bladder of the infected individual. In the setting of immunosuppression, the virus reactivates and begins to replicate, triggering renal tubular cell lysis and viruria. As the reactivation progresses, the virus multiplies and crosses into the bloodstream, causing viremia and invading the kidney graft. In patients with kidney transplants, reactivation of BKV typically reaches peak incidence at 3 months posttransplantation with BK viral replication in the kidney graft, causing

BKV-associated nephropathy (BKVAN), which manifests as kidney dysfunction that may result in eventual loss of the transplanted kidney. Reactivation of BKV in the bladder can lead to hemorrhagic cystitis. Currently, there are no US Food and Drug Administration-approved antiviral agents or treatments for BKVAN or BKV-associated hemorrhagic cystitis. The main treatment is to decrease the immunosuppression, with the risk of acute rejection of the kidney graft. After BK reactivation, the virus is first detectable in the urine, with viremia developing several weeks later. Quantitative BKV DNA in the plasma is the most widely used and preferred test for the laboratory diagnosis of BKVAN and BKV-associated hemorrhagic cystitis, as BKV viremia has higher positive predictive value (50%-60%) than BKV viruria for the diagnosis of BKVAN. Serial monitoring of BKV DNA level in plasma is recommended to guide optimal immunosuppressant dosing regimen. In those with BKVAN, clearance of BK viremia is a sign of resolution of the nephropathy.

Useful For: Detection and serial monitoring of BK virus-associated nephropathy in kidney transplant recipients using plasma specimens Detection and serial monitoring of BK virus-associated hemorrhagic cystitis in organ transplant recipients

Interpretation: The quantification range of this assay is 22 to 100,000,000 IU/mL (1.34 log to 8.00 log IU/mL), with a limit of detection (95% detection rate) at 22 IU/mL. An "Undetected" test result indicates the absence of BK virus (BKV) DNA in the plasma. A test result of "<22 IU/mL (<1.34 log IU/mL)" indicates that BKV DNA is detected in the plasma, but the assay cannot accurately quantify the BKV DNA present below this level. A quantitative value (reported in IU/mL and log IU/mL) indicates the level of BKV DNA (ie, viral load) present in the plasma. A test result of ">100,000,000 IU/mL (>8.00 log IU/mL)" indicates that BKV DNA level present in plasma is above 100,000,000 IU/mL (8.00 log IU/mL), and the assay cannot accurately quantify BKV DNA present above this level. An "Inconclusive" result indicates that the presence or absence of BKV DNA in the plasma specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to polymerase chain reaction inhibition or presence of interfering substance. Submission of a new specimen for testing is recommended if clinically indicated.

Reference Values:
Undetected

Clinical References: 1. Bechert CJ, Schnadig VJ, Payne DA, Dong J. Monitoring of BK viral load in renal allograft recipients by real time PCR assays. Am J Clin Pathol. 2010;133(2):242-250. doi:10.1309/AJCP63VDFCKCRUUL 2. Hirsch HH, Randhawa P; AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:179-188. doi:10.1111/ajt.12110 3. Hirsch HH, Randhawa PS; AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation-guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13528. doi:10.1111/ctr.13528 4. Muhsin SA, Wojciechowski D. BK virus in transplant recipients: current perspectives. Transplant Research and Risk Management. 2019:11:47-58. doi:10.2147/TRRM.S188021

UBKQN
614568

BK Virus DNA Detection and Quantification, Random, Urine

Clinical Information: BK virus (BKV) is a circular, double-stranded DNA virus with an approximately 5 kilobase-size genome in the polyomavirus family, of which 13 members of the family are known, including the JC virus (JCV) and SV40. BKV shares about 75% of its DNA sequence with JCV. Nearly 80% of the adult population worldwide have antibodies to both viruses, indicating previous infection or exposure to these viruses. Initial infection with BKV is usually acquired in childhood, mostly asymptomatic or manifesting as a mild flu-like illness. After primary infection, BKV establishes latency in the kidney and bladder of the infected individual. In the setting of immunosuppression, the virus reactivates and begins to replicate, triggering renal tubular cell lysis and viruria. As the reactivation

progresses, the virus multiplies and crosses into the bloodstream, causing viremia and invading the kidney graft. In patients with kidney transplants, reactivation of BKV typically reaches peak incidence at 3 months post-transplantation with BK viral replication in the kidney graft, causing BKV-associated nephropathy (BKVAN), which manifests as kidney dysfunction that may result in eventual loss of the transplanted kidney. Reactivation of BKV in the bladder can lead to hemorrhagic cystitis. Currently, there are no US Food and Drug Administration-approved antiviral agents or treatments for BKVAN or BKV-associated hemorrhagic cystitis. The main treatment is to decrease the immunosuppression with risk of acute rejection of the kidney graft. After BK reactivation, the virus is first detectable in the urine, with viremia developing several weeks later. Quantitative BKV DNA in the plasma is the most widely used and preferred test for the laboratory diagnosis of BKVAN and BKV-associated hemorrhagic cystitis, as BKV viremia has higher positive predictive value (50%-60%) than BKV viruria for the diagnosis of BKVAN. Serial monitoring of BKV DNA level in plasma is recommended to guide optimal immunosuppressant dosing regimen. In those with BKVAN, clearance of BK viremia is a sign of resolution of the nephropathy.

Useful For: Detection and serial monitoring of BK virus (BKV)-associated nephropathy in kidney transplant recipients using random urine specimens Detection and serial monitoring of BKV-associated hemorrhagic cystitis in organ transplant recipients

Interpretation: The quantification range of this assay is 200 to 100,000,000 IU/mL (2.30 log to 8.00 log IU/mL), with a limit of detection (95% detection rate) at 12 IU/mL. An "Undetected" test result indicates the absence of BK virus (BKV) DNA in the urine. A test result of "<200 IU/mL (<2.30 log IU/mL)" indicates that BKV DNA is detected in the urine, but the assay cannot accurately quantify the BKV DNA present below this level. A quantitative value (reported in IU/mL and log IU/mL) indicates the level of BKV DNA (ie, viral load) present in the urine. A test result of ">100,000,000 IU/mL (>8.00 log IU/mL)" indicates that BKV DNA level present in urine is above 100,000,000 IU/mL (8.00 log IU/mL), and the assay cannot accurately quantify BKV DNA present above this level. An "Inconclusive" result indicates that the presence or absence of BKV DNA in the urine specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to polymerase chain reaction inhibition or presence of interfering substance. Submission of a new specimen for testing is recommended if clinically indicated.

Clinical References: 1. Bechert CJ, Schnadig VJ, Payne DA, Dong J. Monitoring of BK viral load in renal allograft recipients by real-time PCR assays. Am J Clin Pathol. 2010;133(2):242-250. doi:10.1309/AJCP63VDFCKCRUUL 2. Hirsch HH, Randhawa P, AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):179-188. doi:10.1111/ajt.12110 3. Hirsch HH, Randhawa PS, AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13528. doi:10.1111/ctr.13528 4. Muhsin SA, Wojciechowski D. BK virus in transplant recipients: current perspectives. Transplant Research and Risk Management. 2019;11:47-58. doi:10.2147/TRRM.S188021

BLPEP 82814 Black/White Pepper, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in

infants and children younger 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to black or white pepper Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BLACK
82361

Blackberry, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to blackberry Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SBL
8237

Blastomyces Antibody Immunodiffusion, Serum

Clinical Information: The dimorphic fungus, Blastomyces dermatitidis, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease-cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon.

Useful For: Detection of antibodies in serum specimens from patients with blastomycosis

Interpretation: A positive result is suggestive of infection, but the results cannot distinguish between active disease and prior exposure. Routine culture of clinical specimens (eg, respiratory specimen) is recommended in cases of suspected, active blastomycosis.

Reference Values:
Negative

Clinical References: 1. Kaufman L, Kovacs JA, Reiss E. Clinical immunomycology. In: Rose NL, Conway-de Macario E, Folds JD, Lane HC, Nakamura RM, eds. Manual of Clinical Laboratory Immunology. ASM Press; 1997:588-589 2. Gauthier GM, Klein BS. Blastomycosis. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3177-3189

CBL
81541

Blastomyces Antibody Immunodiffusion, Spinal Fluid

Clinical Information: The dimorphic fungus, Blastomyces dermatitidis, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease-cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon. Central nervous system disease is uncommon.

Useful For: Detection of antibodies in spinal fluid specimens from patients with blastomycosis

Interpretation: A positive result is suggestive of infection, but the results cannot distinguish between active disease and prior exposure. Furthermore, detection of antibodies in cerebrospinal fluid (CSF) may reflect intrathecal antibody production or may occur due to passive transfer or introduction of antibodies from the blood during lumbar puncture. Routine fungal culture of clinical specimens (eg, CSF) is recommended in cases of suspected blastomycosis involving the central nervous system.

Reference Values:
Negative

Clinical References: 1. Kaufman L, Kovacs JA, Reiss E. Clinical immunomycology. In: Rose NL, Conway-de Macario E, Folds JD, Lane HC, Nakamura RM, eds. Manual of Clinical Laboratory Immunology. ASM Press; 1997:588-589 2. Gauthier GM, Klein BS. Blastomycosis. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3177-3189

BLAST
35793

Blastomyces Antibody, Enzyme Immunoassay, Serum

Clinical Information: Blastomyces dermatitidis, a dimorphic fungus, is endemic throughout the Midwestern, South-central, and Southeastern US, particularly in regions around the Ohio and Mississippi river valleys, the Great Lakes, and the Saint Lawrence River. It is also found in regions of Canada. Blastomyces is an environmental fungus, preferring moist soil and decomposing organic matter, which produces fungal spores that are released and inhaled by animals or humans. At body temperature, the spores mature into yeast, which can stay in the lungs or disseminate through the bloodstream to other parts of the body. Recently, through phylogenetic analysis, B dermatitidis has been separated into 2 distinct species; B dermatitidis and Blastomyces gilchristii, both able to cause blastomycosis in infected patients. Interestingly, B dermatitidis infections are associated more frequently with dissemination, particularly in older adults, individuals who smoke, and those who are immunocompromised, while B gilchristii has primarily been associated with pulmonary and constitutional symptoms. Approximately 50% of patients infected with Blastomyces will develop symptoms, which are frequently nonspecific and include fever, cough, night sweats, myalgia or arthralgia, weight loss, chest pain and fatigue. Typically, symptoms appear anywhere from 3 weeks to 3 months following infection. Diagnosis of blastomycosis relies on a combination of assays, including culture and molecular testing on appropriate specimens and serologic evaluation for both antibodies to and antigen released from Blastomyces. Although culture remains the gold standard method and is highly specific, the organism can take several days to weeks to grow, and sensitivity is diminished in cases of acute or localized disease. Similarly, molecular testing

offers high specificity and a rapid turnaround time, however, sensitivity is imperfect. Detection of an antibody response to Blastomyces offers high specificity, however, results may be falsely negative in acutely infected patients and in patients who are immunosuppressed.

Useful For: Aiding in the diagnosis of blastomycosis

Interpretation: A positive result indicates that IgG and/or IgM antibodies to Blastomyces were detected. The presence of antibodies is presumptive evidence that the patient was or is currently infected with (or was exposed to) Blastomyces. A negative result indicates that antibodies to Blastomyces were not detected. The absence of antibodies is presumptive evidence that the patient was not infected with Blastomyces. However, the specimen may have been obtained before antibodies were detectable or the patient may be immunosuppressed. If infection is suspected, another specimen should be collected 7 to 14 days later and submitted for testing. Specimens testing positive or equivocal will be submitted for further testing by another conventional serologic test (eg, SBL / Blastomyces Antibody by Immunodiffusion, Serum).

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Kaufman L, Kovacs JA, Reiss E. Clinical immunomycology. In: Rose NR, De Macario EC, Folds JD, et al, eds. Manual of Clinical and Laboratory Immunology. ASM Press; 1997:588-589 2. O'Dowd TR, Mc Hugh JW, Theel ES, et al. Diagnostic methods and risk factors for severe disease and mortality in Blastomycosis: A retrospective cohort study. J Fungi (Basel). 2021;7(11):888. doi:10.3390/jof7110888

ALBLD
603305

Bleeding Diathesis Profile, Limited, Plasma

Clinical Information: Bleeding problems may be associated with a wide variety of coagulation abnormalities or may be due to problems not associated with coagulation (eg, trauma and surgery). A partial listing of causes follows. -Deficiency or functional abnormality (congenital or acquired) of any of the following coagulation proteins: fibrinogen (factor I), factor II (prothrombin), factor V, factor VII, factor VIII (hemophilia A), factor IX (hemophilia B), factor X, factor XI (hemophilia C; bleeding severity not always proportionate to factor level), factor XIII (fibrin-stabilizing factor), von Willebrand factor (VWF antigen and activity), alpha-2 plasmin inhibitor, and plasminogen activator inhibitor (PAI-I; severe deficiency in rare cases). Neither alpha-2 plasmin inhibitor nor PAI-I are included as a routine bleeding diathesis assay component, but either can be performed if indicated or requested. -Deficiency (thrombocytopenia) or functional abnormality of platelets such as congenital (Glanzmann thrombasthenia, Bernard-Soulier syndrome, storage pool disorders, etc) and acquired (myeloproliferative disorders, uremia, drugs, etc) disorders. Platelet function abnormalities cannot be studied on mailed-in specimens. -Specific factor inhibitors (most frequently directed against factor VIII); factor inhibitors occur in 10% to15% of the hemophilia population and are more commonly associated with severe deficiencies of factor VIII or IX (antigen <1%). The inhibitor appears in response to transfusion therapy with factor concentrates with no correlation of occurrence and amount of therapy. Factor VIII inhibitors may occur spontaneously in the postpartum patient, with certain malignancies, in association with autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), in older adults, and for no apparent reason. -Other acquired causes of increased bleeding include paraproteinemia; other factor-specific inhibitors, including those against factor V, factor XI; or virtually any of the coagulation proteins. -Acute disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF), which is a fairly common cause of bleeding. Bleeding can also occur in patients with chronic ICF.

Useful For: Detection of the more common potential causes of abnormal bleeding (eg, factor deficiencies/hemophilia, von Willebrand disease, factor-specific inhibitors) and a simple screen to evaluate for an inhibitor or severe deficiency of factor XIII (rare) This test is not useful for assessing platelet function (eg, congenital or acquired disorders such as Glanzmann thrombasthenia, Bernard-Soulier syndrome, storage pool disease, myeloproliferative disease, associated platelet dysfunction), which requires fresh platelets.

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: Boender J, Kruip MJ, Leebeek FW. A diagnostic approach to mild bleeding disorders. J Thromb Haemost. 2016;14(8):1507-1516. doi:10.1111/jth.13368

GNBLC
619257

Bleeding Disorders, Comprehensive Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Congenital or acquired bleeding diatheses are caused by a wide variety of coagulation abnormalities. The clinical presentation of an underlying bleeding disorder may include epistaxis, easy bruising, ecchymoses, umbilical stump bleeding, subcutaneous and muscle hematomas, prolonged post-injury or post-operative bleeding, bleeding into joint spaces, mucosal tract bleeds, intracranial bleeding, or gastrointestinal bleeding. Affected women may have an increased risk for bleeding during menstrual periods, pregnancy, and after childbirth, as well as recurrent pregnancy loss. Determination of a hereditary bleeding disorder contributing to bleeding events in an individual or family can be useful for prognosis and risk assessment. Identification of an alteration that is known or suspected to cause disease can also be useful for determining the risk for bleeding for family members. This panel evaluates 25 genes associated with a variety of hereditary bleeding disorders or abnormal coagulation laboratory results such as prolonged clotting times, including prothrombin deficiency; factor V deficiency; factor VII deficiency; hemophilia A; hemophilia B; factor X deficiency; factor XI deficiency; factor XIII deficiency; fibrinogen deficiencies (afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia, and hypodysfibrinogenemia); vitamin K-dependent clotting factors deficiencies 1 and 2; platelet-type von Willebrand disease; fletcher factor (prekallikrein) deficiency; kininogen deficiency; combined factor V and VIII deficiency; familial hyperfibrinolysis; hemorrhagic diathesis due to antithrombin Pittsburgh; plasminogen activator inhibitor 1 deficiency; alpha 2 antiplasmin deficiency; bleeding due to high soluble thrombomodulin; and von Willebrand disease. The risk for developing bleeding associated with these syndromes varies. For example, intracranial bleeding was reported in 5% of cases with afibrinogenemia and hypofibrinogenemia, 7% of cases with prothrombin deficiency, 8% of cases with factor V deficiency, 21% of symptomatic cases with factor X deficiency, and is considered very uncommon in cases with factor XI deficiency or combined factor V and factor VIII deficiency.(1) Several of the genes on this panel have established bleeding risk or expert group guidelines.(1-7) Indications for testing include, but are not limited to: -Individuals with a suspected bleeding disorder for which there is no specific coagulation assay readily available -Individuals who are at risk for being a carrier of a bleeding disorder, especially those bleeding disorders where carrier status cannot be easily determined by available coagulation assays -Individuals whose personal or family history indicate coinheritance of multiple hereditary bleeding disorders

Useful For: Evaluating hereditary bleeding in patients with a personal or family history suggestive of a hereditary bleeding disorder Confirming a hereditary bleeding disorder diagnosis with the identification of a known or suspected disease-causing alteration in one or more of 25 genes associated with a variety of hereditary bleeding disorders Determining the disease-causing alterations within one or more of these 25 genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of a bleeding

disorder Identifying the causative alteration for genetic counseling purposes Prognosis and risk assessment based on the genotype-phenotype correlations Carrier testing for close family members of an individual with a hereditary bleeding disorder diagnosis

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

GNBLF
619243

Bleeding Disorders, Focused Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Congenital or acquired bleeding diatheses are caused by a wide variety of coagulation abnormalities. The clinical presentation of an underlying bleeding disorder may include epistaxis, easy bruising, ecchymoses, muscle hematomas, menorrhagia, post-operative bleeding, bleeding into joint spaces, mucosal tract bleeds, intracranial bleeding, or gastrointestinal bleeding. Determination of a hereditary bleeding disorder contributing to bleeding events in an individual or family can be useful for prognosis and risk assessment. Identification of an alteration that is known or suspected to cause disease can also be useful for determining the risk of bleeding for family members. This panel evaluates 6 genes associated with a variety of hereditary bleeding disorders, including factor VII deficiency, hemophilia A, hemophilia B, factor XI deficiency, platelet-type von Willebrand disease, and von Willebrand disease. The risk for developing bleeding associated with these syndromes varies. For example, in symptomatic individuals with factor VII deficiency, the most common symptoms have been reported as mucocutaneous, soft tissue, and joint and gastrointestinal bleeding; while those in individuals with factor X deficiency were bleeding after surgery and trauma; additionally, heavy menstrual bleeding was reported as common in both disorders.(1) Several of the genes on this panel have established bleeding risk or expert group guidelines.(1-7) Indications for testing include, but are not limited to: -Individuals with a suspected bleeding disorder for which there is no specific coagulation assay readily available -Individuals who are at risk for being a carrier of a bleeding disorder, especially those bleeding disorders where carrier status cannot be easily determined by available coagulation assays -Individuals whose personal or family histories indicate coinheritance of multiple hereditary bleeding disorders

Useful For: Evaluating hereditary bleeding in patients with a personal or family history suggestive of a hereditary bleeding disorder and initial laboratory testing results are suggestive for factors VII, VIII, IX, or XI deficiency, or a von Willebrand disease Confirming a hereditary bleeding disorder diagnosis with the identification of a known or suspected disease-causing alteration in one or more of 6 genes associated with a variety of hereditary bleeding disorders Determining the disease-causing alterations within one or more of these 6 genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of a bleeding disorder Identifying the causative alteration for genetic counseling purposes Prognosis and risk assessment based on the genotype-phenotype correlations Carrier testing for close family members of an individual with a hereditary bleeding disorder diagnosis

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

BTROP
82374

Blomia tropicalis, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Blomia tropicalis Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus

MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BUN
81793

Blood Urea Nitrogen (BUN), Serum

Clinical Information: Urea is the final degradation product of protein and amino acid metabolism. In protein catabolism, the proteins are broken down to amino acids and deaminated. The ammonia formed in this process is synthesized to urea in the liver. This is the most important catabolic pathway for eliminating excess nitrogen in the human body. Increased blood urea nitrogen (BUN) may be due to prerenal causes (cardiac decompensation, water depletion due to decreased intake and excessive loss, increased protein catabolism, and high protein diet), renal causes (acute glomerulonephritis, chronic nephritis, polycystic kidney disease, nephrosclerosis, and tubular necrosis), and postrenal causes (eg, all types of obstruction of the urinary tract, such as stones, enlarged prostate gland, tumors). The determination of serum BUN currently is the most widely used screening test for the evaluation of kidney function. The test is frequently requested along with the serum creatinine test since simultaneous determination of these 2 compounds appears to aid in the differential diagnosis of prerenal, renal and postrenal hyperuremia.

Useful For: Screening test for evaluation of kidney function

Reference Values:
Males
1-17 years: 7-20 mg/dL
> or =18 years: 8-24 mg/dL
Reference values have not been established for patients who are <12 months of age.

Females
1-17 years: 7-20 mg/dL
> or =18 years: 6-21 mg/dL
Reference values have not been established for patients who are <12 months of age.

Clinical References: Lamb EJ, Jones GRD: Kidney function tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:497-500

BWOR
82840

Blood Worm, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to blood worm Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or

anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MUSS
82548

Blue Mussel, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to blue mussel Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists

or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FBLUG
57658

Blueberry IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

BLUE
82359

Blueberry, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations.

In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to blueberry Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BOB1
70365

BOB-1 Immunostain, Technical Component Only

Clinical Information: BOB-1 is a transcriptional co-activator that interacts with the transcription factors OCT-1 or OCT-2 in regulating transcription of immunoglobulin genes. In normal tonsil tissue, germinal center B cells all express BOB-1, while only scattered cells in the mantle zone express this protein. Expression of BOB-1, OCT-2, and PU.1 transcription factors are often down-regulated in classic Hodgkin lymphomas, in contrast to many cases of diffuse large B-cell lymphoma.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Herbeck R, Teodorescu Brinzeu D, Giubelan M, Lazar E, Dema A, lonita H. B-cell transcription factors Pax-5, Oct-2, BOB.1, Bcl-6, and MUM1 are useful markers for the diagnosis of nodular lymphocyte predominant Hodgkin lymphoma. Rom J Morphol Embryol. 2011;52(1):69-74 2. Advani AS, Lim K, Gibson S, et al. OCT-2 expression and OCT-2/BOB.1 co-expression predict prognosis in patients with newly diagnosed acute myeloid leukemia. Leuk Lymphoma. 2010;51(4):606-612. doi:10.3109/10428191003592735 3. Hoeller S, Zihler D, Zlobec I, et al. BOB.1, CD79a and cyclin E are the most appropriate markers to discriminate classical Hodgkin's lymphoma from primary mediastinal large B-cell lymphoma. Histopathology. 2010;56(2):217-228. doi:10.1111/j.1365-2559.2009.03462.x 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

BAP
82985

Bone Alkaline Phosphatase, Serum

Clinical Information: Bone alkaline phosphatase (BAP) is the bone-specific isoform of alkaline phosphatase. A glycoprotein that is found on the surface of osteoblasts, BAP reflects the biosynthetic activity of these bone-forming cells. BAP has been shown to be a sensitive and reliable indicator of bone metabolism.(1) Normal bone is constantly undergoing remodeling in which bone degradation or resorption is balanced by bone formation. This process is necessary for maintaining bone health. If the process becomes uncoupled and the rate of resorption exceeds the rate of formation, the resulting bone loss can lead to osteoporosis and, consequently, a higher susceptibility to fractures. Osteoporosis is a metabolic bone disease characterized by low bone mass and abnormal bone microarchitecture. It can result from a number of clinical conditions including states of high bone turnover, endocrine disorders (primary and secondary hyperparathyroidism and thyrotoxicosis), osteomalacia, kidney failure, gastrointestinal diseases, long-term corticosteroid therapy, multiple myeloma, and cancer metastatic to the bones.(2) Paget disease is another common metabolic bone disease caused by excessive rates of bone remodeling resulting in local lesions of abnormal bone matrix. These lesions can result in fractures or neurological involvement. Antiresorptive therapies are used to restore the normal bone structure.

Useful For: Diagnosis and assessment of severity of metabolic bone disease including Paget disease, osteomalacia, and other states of high bone turnover Monitoring efficacy of antiresorptive therapies including postmenopausal osteoporosis treatment The assay is not intended as a screening test for osteoporosis. Measurements of bone turnover markers are not useful for the diagnosis of osteoporosis; diagnosis of osteoporosis should be made based on bone density.

Interpretation: Bone alkaline phosphatase (BAP) concentration is high in Paget disease and osteomalacia.(3) Antiresorptive therapies lower BAP from baseline measurements in Paget disease, osteomalacia, and osteoporosis. Several studies have shown that antiresorptive therapies for management of osteoporosis patients should result in at least a 25% decrease in BAP within 3 to 6 months of initiating therapy.(4,5) BAP also decreases following antiresorptive therapy in Paget disease.(6) When used as a marker for monitoring purposes, it is important to determine the critical difference (or least significant change). The critical difference is defined as the difference between 2 determinations that may be considered to have clinical significance. The critical difference for this method was calculated to be 25% with a 95% confidence level.(1)

Reference Values:

Males
<2 years: 25-221 mcg/L
2-9 years: 27-148 mcg/L
10-13 years: 35-169 mcg/L
14-17 years: 13-111 mcg/L
Adults: < or =20 mcg/L

Females
<2 years: 28-187 mcg/L
2-9 years: 31-152 mcg/L
10-13 years: 19-177 mcg/L
14-17 years: 7-41 mcg/L
Adults
Premenopausal: < or =14 mcg/L
Postmenopausal: < or =22 mcg/L

Clinical References:

BHISI
70314

Bone Histomorphometry, Consultant Interpretation, Slides Only

Clinical Information: Bone histomorphometry is a very sophisticated procedure utilizing full thickness bone biopsy. Techniques such as 2-time interval labeling with tetracycline permit the direct measurement of the rate of bone formation. The information derived is useful in the diagnosis of metabolic bone diseases including renal osteodystrophy, osteomalacia, and osteoporosis. Other obtainable information relates to disorders such as aluminum toxicity and iron abnormalities.

Useful For: Identifying undetermined metabolic bone disease in submitted slide specimens Diagnosing renal osteodystrophy Diagnosing osteomalacia Diagnosing osteoporosis Diagnosing Paget disease Assessing the effects of therapy Identifying disorders of the hematopoietic system Diagnosing aluminum toxicity Identifying the presence of iron in the bone

Interpretation: Clinical endocrinologists trained in histomorphometric techniques review and interpret the histological appearance. A pathologist interprets the bone marrow from a hematoxylin and eosin-stained slide. No histomorphometric values are given.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Recker RR: Bone Histomorphometry: Techniques and Interpretation. CRC Press; 1983 2. Dempster DW, Compston JE, Drezner MK, et al. Standardized nomenclature, symbols, and units for bone histomorphometry: a 2012 update of the report of the ASBMR Histomorphometry Nomenclature Committee. J Bone Miner Res. 2013;28(1):2-17. doi:10.1002/jbmr.1805 3. Chavassieux P, Chapurlat R. Interest of bone histomorphometry in bone pathophysiology investigation: Foundation, present, and future. Front Endocrinol (Lausanne). 2022;13:907914. Published 2022 Jul 28. doi:10.3389/fendo.2022.907914

BHISC
70312

Bone Histomorphometry, Gross Microscopic Exam

Clinical Information: Bone histomorphometry is a very sophisticated procedure utilizing full-thickness bone biopsy. Techniques such as 2-time interval labeling with tetracycline permit the direct measurement of the rate of bone formation. The information derived is useful in the diagnosis of

metabolic bone diseases, including renal osteodystrophy, osteomalacia, and osteoporosis, and other disorders, such as aluminum toxicity and iron abnormalities.

Useful For: Undetermined metabolic bone disease in wet tissue specimens Renal osteodystrophy Osteomalacia Osteoporosis Paget disease Assessing effects of therapy Identification of some disorders of the hematopoietic system Aluminum toxicity Presence of iron in the bone

Interpretation: Computer-generated histomorphometric values are given for adequate specimens. Normal histomorphometric values for iliac crest are provided. An interpretive report will be provided.

Reference Values:
A quantitative and interpretive report will be provided.

Clinical References: 1. Recker RR. Bone Histomorphometry: Techniques and Interpretation. CRC Press; 1983 2. Dempster DW, Compston JE, Drezner MK, et al. Standardized nomenclature, symbols, and units for bone histomorphometry: a 2012 update of the report of the ASBMR Histomorphometry Nomenclature Committee. J Bone Miner Res. 2013;28(1):2-17. doi:10.1002/jbmr.1805 3. Chavassieux P, Chapurlat R. Interest of bone histomorphometry in bone pathophysiology investigation: Foundation, present, and future. Front Endocrinol (Lausanne). 2022;13:907914. Published 2022 Jul 28. doi:10.3389/fendo.2022.907914

BMAPC
113350

Bone Marrow Aspirate (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

BMBPC
113351

Bone Marrow Biopsy (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

BMCPC
113352

Bone Marrow Clot (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

BPRPV
618299

Bordetella pertussis and Bordetella parapertussis, Molecular Detection, PCR, Varies

Clinical Information: Bordetella pertussis is the highly contagious etiological agent of pertussis or whooping cough. Bordetella parapertussis causes a similar, but generally less severe, illness. Despite vaccination efforts, B pertussis remains common in the United States, underscoring the need for effective diagnostic tests. In the United States, pertussis is most common in the late summer months. Pertussis vaccination does not prevent B parapertussis infection, which generally occurs in a younger

age group than disease caused by B pertussis. Diagnosis of pertussis is based on having a high clinical index of suspicion for the infection, along with confirmation by laboratory testing. Laboratory testing methods include nucleic acid amplification tests (eg, polymerase chain reaction [PCR]), serology, culture, and direct fluorescent antibody testing. Culture and direct fluorescent antibody testing are limited by low sensitivity, rendering nucleic acid amplification and serology the tests of choice. The Centers for Disease Control and Prevention recommends PCR testing for patients suspected of having acute pertussis. B pertussis PCR detects roughly twice as many cases as culture. After symptom onset B pertussis DNA can be detected up to 4 weeks or longer (up to 8 weeks in our experience).(1) However, over time, the amount of B pertussis and B parapertussis DNA will diminish, rendering the assay less sensitive. A serologic response to B pertussis is typically mounted within 2 weeks following infection, and therefore, detection of IgG-class antibodies to pertussis toxin, which is only produced by B pertussis, can be a useful adjunct for diagnosis at later stages of illness at a time when the amount of B pertussis may be below the limit of detection of the PCR assay.

Useful For: Preferred diagnostic test for the detection of Bordetella pertussis or Bordetella parapertussis This test is not recommended for screening asymptomatic individuals who may carry B pertussis or parapertussis. This test is not recommended for follow up of patients previously diagnosed with pertussis (ie, as a test of cure).

Interpretation: A positive result indicates the presence of DNA from Bordetella pertussis or Bordetella parapertussis. In some cases, a patient may test positive for both B pertussis and B parapertussis. Cross-reactivity with Bordetella holmesii and Bordetella bronchiseptica may occur with the B pertussis assay (see Cautions). A negative result indicates the absence of detectable B pertussis and B parapertussis DNA in the specimen but does not negate the presence of organism or active or recent disease (known inhibition rate of <1%) and may occur due to inhibition of polymerase chain reaction, sequence variability underlying primers and/or probes, or the presence of B pertussis or B parapertussis in quantities less than the limit of detection of the assay. Additionally, patients presenting late after symptom onset may test negative; in such cases, testing for B pertussis antibody, IgG, in serum (BORDG / Bordetella pertussis Antibody, IgG, Serum) may be considered.

Reference Values:
Not applicable

Clinical References: 1. Theofiles AG, Cunningham SA, Chia N, et al. Pertussis outbreak, southeastern Minnesota, 2012. Mayo Clin Proc. 2014;89(10):1378-1388 2. Guthrie JL, Robertson AV, Tang P, Drews SJ. Novel duplex real-time PCR assay detects Bordetella holmesii in specimens from patients with pertussis-like symptoms in Ontario, Canada. J Clin Microbiol. 2010 Apr;48(4):1435-1437 3. Sloan LM, Hopkins MK, Mitchell PS, et al. Multiplex LightCycler PCR assay for detection and differentiation of Bordetella pertussis and Bordetella parapertussis in nasopharyngeal specimens. J Clin Microbiol. 2002;40(1):96-100 4. Karalius VP, Rucinski SL, Mandrekar JN, Patel R. Bordetella parapertussis outbreak in Southeastern Minnesota and the United States, 2014. Medicine (Baltimore). 2017;96(20):e6730

BORDG
64780

Bordetella pertussis Antibody, IgG, Serum

Clinical Information: Bordetella pertussis, the causative agent of whooping cough, is highly contagious and remains endemic in the United States despite the high rate of vaccination. Acute B pertussis infections are typically diagnosed by culture or nucleic acid amplification testing (NAAT). However, symptomatic adults and adolescents often seek medical attention later in the course of infection, at which time the sensitivity of these 2 methods to detect the infectious agent decreases. A serologic response to B pertussis is typically mounted 2 weeks following infection, and therefore, detection of IgG-class antibodies to pertussis toxin (PT), which is only produced by B pertussis, can be a useful adjunct for

diagnosis at later stages of illness. Prior to testing, providers should review whether the patient was recently vaccinated using the Tdap (Tetanus-Diphtheria-acellular Pertussis) or DTap vaccines. The acellular pertussis vaccine contains 1 to 5 B pertussis antigens, including filamentous hemagglutinin, pertactin, 2 fimbrial agglutinogens, and significant levels of PT. Therefore, recent vaccination for B pertussis, specifically within the last 2 to 6 months, may lead to a positive result by the anti-PT IgG assay, and knowledge of the patient's vaccination history is important for accurate result interpretation.

Useful For: Diagnosis of recent infection with Bordetella pertussis in patients with symptoms consistent with whooping cough for 2 or more weeks This test should not be used in neonates, young infants or in children between the ages of 4 to 7 years as the routine childhood vaccine schedule may interfere with result interpretation. This test should not be used as a test of cure, to monitor response to treatment, or to determine vaccine status.

Interpretation: Negative (<40 IU/mL): No IgG antibodies to pertussis toxin (PT) detected. Results may be falsely negative in patients with less than 2 weeks of symptoms. Borderline (40-<100 IU/mL): Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive (> or =100 IU/mL): IgG antibodies to PT detected. Results suggest recent infection with or recent vaccination against Bordetella pertussis.

Reference Values:
> or =100 IU/mL (Positive)
40-<100 IU/mL (Borderline)
<40 IU/mL (Negative)
Reference values apply to all ages.

Clinical References: 1. Leber AL. Pertussis: relevant species and diagnostic update. Clin Lab Med. 2014;34(2):237-255 2. Guiso N, Berbers G, Fry NK, et al. What to do and what not to do in serological diagnosis of pertussis: recommendation from EU reference laboratories. Eur J Clin Microbiol Infect Dis. 2011;30(3):307-312 3. Andre P, Caro V, Njamkepo E, Wendelboe AM, Van Rie A, Guiso N. Comparison of serological and real-time PCR assays to diagnose Bordetella pertussis infection in 2007. J Clin Microbiol. 2008;46(5):1672-1677

BOAC
9723

Boron, Serum/Plasma

Interpretation: Specimens for elemental testing should be collected in certified metal-free containers. Elevated results for elemental testing may be caused by environmental contamination at the time of specimen collection and should be interpreted accordingly. It is recommended that unexpected elevated results be verified by testing another specimen.

Reference Values:
Reporting limit determined each analysis

Normally: Less than 100 mcg/L

BMIYC
64969

Borrelia miyamotoi Detection PCR, Spinal Fluid

Clinical Information: Borrelia miyamotoi is a spirochetal bacterium. It is closely related to the Borrelia species that cause tick-borne relapsing fever (TBRF) and is more distantly related to the Borrelia species that cause Lyme disease. This organism causes a febrile illness like TBRF, with body and join pain, fatigue, and, rarely, rash, and has been detected in Ixodes scapularis and Ixodes pacificus ticks. These ticks are also the vectors for Lyme disease, anaplasmosis, and babesiosis. The preferred

method for detecting B miyamotoi is real-time polymerase chain reaction. Less sensitive and specific methods for detecting B miyamotoi and agents of TBRF include identification of spirochetes in peripheral blood films, cerebrospinal fluid preparations, and serologic testing. This assay does not detect the Borrelia species that cause Lyme disease.

Useful For: Aids in the diagnosis of Borrelia miyamotoi infection in conjunction with clinical findings This test is not useful for detecting the Borrelia species that cause Lyme disease.

Interpretation: A positive result indicates the presence of Borrelia miyamotoi DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with symptoms and clinical findings of tick-borne relapsing fever.

Reference Values:
Negative

Clinical References: 1. Gugliotta JL, Goethert HK, Berardi VP, Telford SR III: Meningoencephalitis from Borrelia miyamotoi in an immunocompromised patient. N Engl J Med. 2013 Jan 17;368(3):240-245 2. Fomenko NV, Borgoiakov VL, Panov VV: Genetic features of Borrelia miyamotoi transmitted by Ixodes persulcatus. Mol Gen Mikrobiol Virusol. 2011;(2)12-17 3. Platonov AE, Karan LS, Kolyasnikova NM, et al: Humans infected with relapsing fever spirochete Borrelia miyamotoi, Russia. Emerg Infect Dis. 2011 Oct;17(10):1816-1823

BMIPB
618298

Borrelia miyamotoi Detection, PCR, Blood

Clinical Information: Borrelia miyamotoi is a spirochetal bacterium, closely related to the Borrelia species that causes tick-borne relapsing fever (TBRF), and it is more distantly related to the Borrelia species that cause Lyme disease. This organism causes a febrile illness like TBRF, with body and join pain, fatigue, and, rarely, rash. B miyamotoi has been detected in Ixodes scapularis and Ixodes pacificus ticks. These ticks are also the vectors for Lyme disease, anaplasmosis, and babesiosis. The preferred method for detecting B miyamotoi is real-time polymerase chain reaction. Less sensitive and specific methods for detecting B miyamotoi and agents of TBRF include serologic testing and identification of spirochetes in peripheral blood films or spinal fluid preparations. This assay does not detect the Borrelia species that cause Lyme disease.

Useful For: Aiding in the diagnosis of Borrelia miyamotoi infection in conjunction with clinical findings Preferred method for detection of B miyamotoi using blood specimens

Interpretation: A positive result indicates the presence of Borrelia miyamotoi DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with symptoms and clinical findings of tick-borne relapsing fever.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Hoornstra D, Azagi T, van Eck JA, et al. Prevalence and clinical manifestation of Borrelia miyamotoi in Ixodes ticks and humans in the northern hemisphere: a systematic review and meta-analysis. Lancet Microbe. 2022; 3:e772 2. McCormick DW, Brown CM, Bjork J, et al. Characteristics of hard tick relapsing fever caused by borrelia miyamotoi, United States, 2013-2019. Emerg Infect Dis. 2023; 29:1719-1729 3. Xu G, Luo CY, Ribbe F, et al. Borrelia miyamotoi in human-biting ticks, United States, 2013-2019. Emerg Infect Dis. 2021; 27:3193-3195 4. Kingry LC, Anacker M,

Pritt B, et al. Surveillance for and discovery of borrelia species in US patients suspected of tickborne illness. Clin Infect Dis. 2018; 66:1864-1871 5. Wormser GP, Shapiro ED, Fish D. Borrelia miyamotoi: an emerging tick-borne pathogen. Am J Med. 2019; 132(2):136-137 6. Telford SR, Goethert HK, Molloy PJ, Berardi V. Blood smears have poor sensitivity for confirming borrelia miyamotoi disease. J Clin Microbiol. 2019; 57(3):e01468-18. Published 2019 Feb 27. doi:10.1128/JCM.01468-18

BOT
82715

Botrytis cinerea, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Botrytis cinerea Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BOV
82135

Bovine Serum Albumin, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to bovine serum albumin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BXMPL
82876

Box Elder/Maple, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to box elder/maple Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BRACH
70366

Brachyury Immunostain, Technical Component Only

Clinical Information: Brachyury expression is required for the specification of mesodermal identity, representing one of the key genes regulating notochord formation. The brachyury gene, a T-box transcription factor, is uniquely expressed in chordomas.

Useful For: Aiding in the identification of chordomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Sangoi AR, Dulai MS, Beck AH, et al. Distinguishing chordoid meningiomas from their histologic mimics: an immunohistochemical evaluation. Am J Surg Pathol. 2009;33(5):669-681. doi:10.1097/PAS.0b013e318194c566 2. Sangoi AR, Karamchandani J, Lane B, et al. Specificity of brachyury in the distinction of chordoma from clear cell renal cell carcinoma and germ cell tumors: a study of 305 cases. Mod Pathol. 2011;24(3):425-429. doi:10.1038/modpathol.2010.196 3. Kikuchi Y, Yamaguchi T, Kishi H, et al. Pulmonary tumor with notochordal differentiation: report of 2 cases suggestive of benign notochordal cell tumor of extraosseous origin. Am J Surg Pathol. 2011;35(8):1158-1164. doi:10.1097/PAS.0b013e318220e085 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

BBRAF
35893

BRAF Analysis (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

BRFKT
616786

BRAF and KIT Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information: The signaling pathways stimulated by the KIT protein control many important cellular processes, such as cell growth and division (proliferation), survival, and movement (migration). KIT protein signaling is important for the development and function of certain cell types, including early blood cells (hematopoietic stem cells), mast cells, cells in the gastrointestinal tract, and melanocytes. BRAF is a member of the mitogen-activated protein/extracellular signal-regulated (MAP/ERK) kinase pathway, which plays a role in cell proliferation and differentiation. Dysregulation of this pathway is a key factor in tumor progression. Targeted therapies directed to pathways involving KIT and BRAF have demonstrated some success with increases both in progression-free and overall survival in patients with melanoma. Effectiveness of these therapies, however, depends in part on the mutation status of the pathway components.

Useful For: Identifying specific mutations within the BRAF and KIT genes that predict response to therapy

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:

An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al: Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. U.S. Food and Drug Administration (FDA): Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated February, 10, 2023, Accessed July 31, 2023. Available at www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling 4. Pham DDM, Guhan S, Tsao H. KIT and melanoma: Biological insights and clinical implications. Yonsei Med J. 2020;61(7):562-571. doi: 10.3349/ymj.2020.61.7.562 5. Carvajal RD, Antonescu CR, Wolchok JD, et al. KIT as a therapeutic target in metastatic melanoma. JAMA. 2011;305(22):2327-2334. doi: 10.1001/jama.2011.746 6. Guo W, Wang H, Chunying L. Signal pathways of melanoma and targeted therapy. Signal Transduct Target Ther. 2021 20;6(1):424

MBRAF
616925

BRAF V600 Somatic Mutation Analysis, Bone Marrow

Clinical Information: This test uses DNA extracted from the bone marrow to test for the presence of BRAF V600E/D and V600K/R/M alterations. BRAF mutations occur in many different types of human cancers. Testing for BRAF mutations in bone marrow specimens facilitates classification and possible targeted therapies of hematological neoplasms, such as hairy cell leukemia, Langerhans cell histiocytosis, and Erdheim-Chester disease. This is test is not designed for detection of BRAF mutations in liquid biopsy of tumors.

Useful For: Classification and/or possible targeted therapies of hematological neoplasms such as hairy cell leukemia, Langerhans cell histiocytosis, Erdheim-Chester disease

Interpretation: The interpretive report includes an overview of the findings. Results will be characterized as positive, negative, or indeterminate for a V600 somatic mutation.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Maitre E, Cornet E, Troussard X. Hairy cell leukemia: 2020 update on diagnosis, risk stratification, and treatment. Am J Hematol. 2019;94(12):1413-1422 2. Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. Blood. 2020;135(16):1319-1331 3. Haroche J, Cohen-Aubart F, Amoura Z. Erdheim-Chester disease. Blood. 2020;135(16):1311-1318

TBRAF
616940

BRAF V600 Somatic Mutation Analysis, Tumor, Tissue

Clinical Information: This test uses DNA extracted from tissue to test for the presence of BRAF V600E/D and V600K/R/M alterations. BRAF mutations occur in many different types of human cancers. Testing for BRAF mutation in a blood or bone marrow specimen facilitates classification and possible targeted therapies of hematological neoplasms, such as hairy cell leukemia, Langerhans cell histiocytosis, and Erdheim-Chester disease. This is test is not designed for detection of BRAF mutations in liquid biopsy for tumors.

Useful For: Classifying and, possibly, targeting therapies of hematological neoplasms, such as hairy cell leukemia, Langerhans cell histiocytosis, Erdheim-Chester disease

Interpretation: An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a V600 somatic mutation.

Reference Values:
An interpretive report will be provided.
Positive and negative for V600, a somatic mutation

Clinical References: 1. Maitre E, Cornet E Troussard X. Hairy cell leukemia: 2020 update on diagnosis, risk stratification, and treatment.Am J Hematol. 2019; 94(12):1413-1422 2. Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis Blood. 2020;135(16):1319-1331 3. Haroche J, Cohen-Aubart F, Amoura Z: Erdheim-Chester disease Blood. 2020;135(16):1311-1318

BRAFV
70367

BRAF V600E Immunostain, Technical Component Only

Clinical Information: BRAF is a serine/threonine protein kinase and a member of the Raf family. The BRAF V600E alteration leads to constitutive activation of the mitogen activated protein kinase pathway, which plays a role in cell proliferation and tumorigenesis. This genetic alteration has been detected in a variety of tumors such as melanoma, colorectal cancer, papillary thyroid carcinoma, hairy cell leukemia, Langerhans cell histiocytosis, and pleomorphic xanthoastrocytomas.

Useful For: Identification of BRAF V600E-mutated protein

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Ida C, Vrana JA, Rodriguez FJ, et al. Immunohistochemistry is highly sensitive and specific for detection of BRAF V600E mutation in pleomorphic xanthoastrocytoma. Acta Neuopath communications. 2013;1:20 2. Capper D, Berghoff AS, Magerle M, et al. Immunohistochemical testing of BRAF V600E status in 1,120 tumor tissue samples of patients with brain metastases. Acta Neuropathol. 2012;123(2):223-233 3. Andrulis M, Penzel R, Weichert W, von Deimling A, Capper D. Application of a BRAF V600E Mutation-specific Antibody for the Diagnosis of Hairy Cell Leukemia. Am J Surg Pathol. 2012;36(12):1796-1800 4. Koperek O, Kornauth C, Capper D, et al. Immunohistochemical detection of the BRAF V600E-mutated protein in papillary thyroid carcinoma. Am J Surg Pathol. 2012;36(6):844-850 5. Skorokhod A, Capper D, von Deimling A, Enk A, Helmbold P. Detection of BRAF V600E mutations in skin metastases of malignant melanoma by monoclonal antibody VE1. J Am Acad skin metastases of malignant melanoma by monoclonal antibody VE1. J Am Acad Dermatol. 2012;67(3):488-491 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

BRAFD
608305

BRAF V600E/V600K Somatic Mutation Analysis, Tumor

Clinical Information: This test assesses for somatic (tumor-specific) BRAF V600E and V600K mutation. The BRAF gene is a member of the mitogen-activated protein/extracellular signal-regulated (MAP/ERK) kinase pathway, which plays a role in cell proliferation and differentiation. Dysregulation of this pathway is a key factor in tumor progression and BRAF mutations occur frequently in many different tumor types. BRAF mutation analysis aids in the diagnosis of cancer types including anaplastic and

papillary thyroid carcinoma, hairy cell leukemia, and papillary craniopharyngioma. BRAF V600E and V600K mutations are associated with response or resistance to specific targeted therapies in cancer. Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. BRAF mutation analysis can provide helpful diagnostic information in the context of evaluation for Lynch syndrome. For more information see Lynch Syndrome Testing Algorithm.

Useful For: Therapy selection for patients with cancer (eg, melanomas that may respond to BRAF inhibitors, colon cancers that may not respond to EGFR inhibitors) Aiding in the diagnosis/prognosis of certain cancers (eg, hairy cell leukemia, papillary thyroid cancers, and association with aggressiveness) Aiding in determining risk for Lynch syndrome (eg, an adjunct to negative MLH1 germline testing in cases where colon tumor demonstrates MSI-H and loss of MLH1 protein expression) This test is not intended as a screening test to identify cancer.

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Chapman PB, Hauschild A, Robert C, et al. BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507-2516 2. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008;26(35):5705-5712 3. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med. 2015;373(8):726-736 4. Domingo E, Laiho P, Ollikainen M, et al. BRAF screening as a low-cost effective strategy for simplifying HNPCC genetic testing. J Med Genet. 2004;41(9):664-668

MSUSC
618716

Branched-Chain Amino Acids, Self-Collect, Blood Spot

Clinical Information: Maple syrup urine disease (MSUD) is an inborn error of metabolism caused by the deficiency of the branched-chain-ketoacid dehydrogenase (BCKDH) complex. The BCKDH complex is involved in the metabolism of the branched-chain amino acids (BCAA): isoleucine (Ile), leucine (Leu), and valine (Val). Classic MSUD presents in the neonate with feeding intolerance, failure to thrive, vomiting, lethargy, and maple-syrup odor to urine and cerumen. If untreated, it progresses to irreversible intellectual disability, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. Treatment of MSUD aims to normalize the concentration of BCAA by dietary restriction of these amino acids. BCAA are essential amino acids that require frequent adjustment of the dietary treatment. Dietary monitoring is accomplished by regular determination of BCAA and Allo-Ile concentrations.

Useful For: Monitoring patients with maple syrup urine disease using specimens collected at home

Interpretation: Quantitative results of allo-isoleucine, leucine, isoleucine, and valine with reference values are reported without added interpretation.

Reference Values:
Allo-isoleucine: <4 nmol/mL

Leucine: 52-269 nmol/mL
Isoleucine: 22-167 nmol/mL
Valine: 84-414 nmol/mL

Clinical References: 1. Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. Pediatrics. 2002;109(6):999-1008. doi:10.1542/peds.109.6.999 2. Strauss KA, Puffenberger EG, Carson VJ. Maple syrup urine disease. In: Adam MP, Ardinger HH, Pagon RA, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated April 23, 2020. Accessed June 21, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1319/

FBNC1
75583

Brazil Nut Component rBer e 1

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.10 kU/L

BRAZX
618852

Brazil Nut Component, IgE, Serum

Clinical Information: Allergies to tree nuts are relatively prevalent and can result in severe reactions. The main culprits in tree nut allergies include walnut, almond, pistachio, cashew, pecan, hazelnut, macadamia, Brazil nut, and pine nuts. Tree nut allergy often appears in young children and estimates of prevalence range from 0.1% to greater than 5% of the population, dependent on geographical region. In the case of nut-induced allergic reactions, as with many other foods, symptoms usually present within minutes of ingestion. Over 80% of reactions to tree nuts involve allergy related respiratory symptoms. Tree nut allergies are one of the most dangerous types of allergic reaction with 20% to 40% of cases of related anaphylaxis, and 70% to 90% of fatalities attributable to nut exposure (including peanut exposure). Allergy to Brazil nut has reported within the United States population. Among those suffering from tree-nut-allergic individuals, the prevalence of Brazil nut allergy is estimated to be 10% to 20%. Brazil nut allergy occurs primarily through oral ingestion. Following oral exposure, allergy may be associated with systemic reactions, including respiratory and urticaria, occasionally resulting in anaphylaxis. Ber e 1 is an abundant, heat and digestion resistant, storage protein component that is associated with systemic reactions to Brazil nuts. This major allergen component has been found to correlate with allergic symptoms. Exposure of the Ber e 1 at 100 degrees C for 20 minutes did not to reduce the potential allergenicity of the molecule. Immunological cross-reactivity has been reported between Brazil nut, hazelnut, cashew, pistachio, and almond, although cross reactivity with walnut, peanut, and coconut has also been reported. There is considerable homology between the 2S albumin of Brazil nut (Ber e 1) and other plant species, such as cottonseed, sunflower, rapeseed, castor bean, and sesame. Positive antibodies to total Brazil nuts may occur in cases of allergy to other Brazil nut storage proteins, profilins, or in the presence of cross-reacting carbohydrate determinants.

Useful For: Evaluation of patients with suspected Brazil nut allergy to component Ber e 1

Interpretation: When detectable total Brazil nut IgE antibody is present (> or =0.10 IgE kUa/L), additional specific component IgE antibody testing will be performed. If a potential specific allergenic Brazil nut component IgE is detectable (> or =0.10 IgE kUa/L), an interpretive report will be provided. When the sample is negative for total Brazil nut IgE antibody (<0.10 IgE kUa/L), further testing for specific Brazil nut component IgE antibodies will not be performed. A negative IgE result for total Brazil

nut antibody may indicate a lack of sensitization to the potential Brazil nut allergenic component.

Reference Values:

Only orderable as a reflex. For more information see BRAZR / Brazil Nut, IgE, with Reflex to Brazil Nut Component, IgE, Serum Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/Equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Salo PM, Arbes SJ Jr, Jaramillo R, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol. 2014;134(2):350-359. doi:10.1016/j.jaci.2013.12.1071 2. Waserman S, Watson W. Food allergy. Allergy Asthma Clin Immuno. 2011;7 Suppl 1(Suppl 1):S7 3. Abrams EM, Sicherer SH. Diagnosis and management of food allergy. CMAJ. 2016;188(15):1087-1093 4. Weinberger T, Sicherer S. Current perspectives on tree nut allergy: a review. J Asthma Allergy. 2018;11:41-51 5. Lomas JM, Jarvinen KM. Managing nut-induced anaphylaxis: challenges and solutions. J Asthma Allergy. 2015; 8:115-123 6. Maloney J, et al. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. J Allergy Clin Immunol. 2008;122(1):145-51 7. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. Pediatrics. 1998;102(1):e6 8. Crespo JF, James JM. Fernandez C, Rodriguez J. Food allergy: Nuts and tree nuts. Br J Nutr. 2006;96 Suppl 2:S95-102 9. Yang L, Clements S, Joks R. A retrospective study of peanut and tree nut allergy: Sensitization and correlations with clinical manifestations. [published online ahead of print, 2015 Feb 27]. Allergy Rhinol (Providence). 2015;doi:10.2500/ar.20105.6.0108 10. Masthoff L, Hoff R, Verhoeckx KC, et al. A systematic review of the effect of thermal processing on the allergenicity of tree nuts. Allergy. 2013;3;68(8):983-993 11. Borja JM, Bartolome B, Gomez E, Galindo PA, Feo F. Anaphylaxis from Brazil nut. Allergy. 1999;54(9):1007-1008 12. Mazokopakis EE, Liontiris MI. Commentary: Health concerns of Brazil nut consumption. J Altern Complement Med. 2018;24(1):3-6 13.McWilliam V, Koplin J, Lodge C, Tang M, Dharmage S, Allen K. The prevalence of tree nut allergy: A systematic review. Curr Allergy Asthma Rep. 2015;15(9):54. 14.Rayes H, Raza AA, Williams A, Matthews S, Arshad SH. Specific IgE to recombinant protein (Ber e 1) for the diagnosis of Brazil nut allergy. Clin Exp Allergy. 2016;46(4):654-656. 15.Pastorello EA, Farioli L, Pravettoni V, Ispano M, Conti A, Ansaloni R, et al. Sensitization to the major allergen of Brazil nut is correlated with the clinical expression of allergy. J Allergy Clin Immunol. 1998;102(6 Pt 1):1021-1027. 16. Moreno FJ, Clemente A. 2S Albumin storage proteins: What makes them food allergens? Open Biochem J. 2008;2:16-28

BRAZR
618851

Brazil Nut, IgE with Reflex to Brazil Nut Component, IgE, Serum

Clinical Information: Allergies to tree nuts are relatively prevalent and can result in severe reactions. The main culprits in tree nut allergies include walnut, almond, pistachio, cashew, pecan, hazelnut, macadamia, Brazil nut, and pine nuts. Tree nut allergy often appears in young children and estimates of prevalence range from 0.1% to greater than 5% of the population, dependent on geographical region. In the case of nut-induced allergic reactions, as with many other foods, symptoms usually present within minutes of ingestion. Over 80% of reactions to tree nuts involve allergy related respiratory symptoms. Tree nut allergies are one of the most dangerous types of allergic reaction with 20% to 40% of cases of related anaphylaxis, and 70% to 90% of fatalities attributable to nut exposure (including peanut exposure). Allergy to Brazil nut has reported within the United States population. Among those suffering from tree-nut-allergic individuals, the prevalence of Brazil nut allergy is estimated to be 10% to 20%. Brazil nut allergy occurs primarily through oral ingestion. Following oral exposure, allergy may be associated with systemic reactions, including respiratory and urticaria, occasionally resulting in anaphylaxis. Ber e 1 is an abundant, heat and digestion resistant, storage protein component that is associated with systemic reactions to Brazil nuts. This major allergen component has been found to correlate with allergic symptoms. Exposure of the Ber e 1 at 100 degrees C for 20 minutes did not to reduce the potential allergenicity of the molecule. Immunological cross-reactivity has been reported between Brazil nut, hazelnut, cashew, pistachio, and almond, although cross reactivity with walnut, peanut, and coconut has also been reported. There is considerable homology between the 2S albumin of Brazil nut (Ber e 1) and other plant species, such as cottonseed, sunflower, rapeseed, castor bean, and sesame. Positive antibodies to total Brazil nuts may occur in cases of allergy to other Brazil nut storage proteins, profilins, or in the presence of cross-reacting carbohydrate determinants.

Useful For: Evaluation of patients with suspected Brazil nut allergy

Interpretation: When detectable total Brazil nut IgE antibody is present (> or =0.10 IgE kUa/L), additional specific component IgE antibody testing will be performed. If a potential specific allergenic Brazil nut component IgE is detectable (> or =0.10 IgE kUa/L), an interpretive report will be provided. When the sample is negative for total Brazil nut IgE antibody (<0.10 IgE kUa/L), further testing for specific Brazil nut component IgE antibodies will not be performed. A negative IgE result for total Brazil nut antibody may indicate a lack of sensitization to the potential Brazil nut allergenic component.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/Equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Salo PM, Arbes SJ Jr, Jaramillo R, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES)

2005-2006. J Allergy Clin Immunol. 2014;134(2):350-359. doi:10.1016/j.jaci.2013.12.1071 2. Waserman S, Watson W. Food allergy. Allergy Asthma Clin Immuno. 2011;7 Suppl 1(Suppl 1):S7 3. Abrams EM, Sicherer SH. Diagnosis and management of food allergy. CMAJ. 2016;188(15):1087-1093 4. Weinberger T, Sicherer S. Current perspectives on tree nut allergy: a review. J Asthma Allergy. 2018;11:41-51 5. Lomas JM, Jarvinen KM. Managing nut-induced anaphylaxis: challenges and solutions. J Asthma Allergy. 2015; 8:115-123 6. Maloney J, et al. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. J Allergy Clin Immunol. 2008;122(1):145-51 7. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. Pediatrics. 1998;102(1):e6 8. Crespo JF, James JM. Fernandez C, Rodriguez J. Food allergy: Nuts and tree nuts. Br J Nutr. 2006;96 Suppl 2:S95-102 9. Yang L, Clements S, Joks R. A retrospective study of peanut and tree nut allergy: Sensitization and correlations with clinical manifestations. [published online ahead of print, 2015 Feb 27]. Allergy Rhinol (Providence). 2015;doi:10.2500/ar.20105.6.0108 10. Masthoff L, Hoff R, Verhoeckx KC, et al. A systematic review of the effect of thermal processing on the allergenicity of tree nuts. Allergy. 2013;3;68(8):983-993 11. Borja JM, Bartolome B, Gomez E, Galindo PA, Feo F. Anaphylaxis from Brazil nut. Allergy. 1999;54(9):1007-1008 12. Mazokopakis EE, Liontiris MI. Commentary: Health concerns of Brazil nut consumption. J Altern Complement Med. 2018;24(1):3-6 13.McWilliam V, Koplin J, Lodge C, Tang M, Dharmage S, Allen K. The prevalence of tree nut allergy: A systematic review. Curr Allergy Asthma Rep. 2015;15(9):54. 14.Rayes H, Raza AA, Williams A, Matthews S, Arshad SH. Specific IgE to recombinant protein (Ber e 1) for the diagnosis of Brazil nut allergy. Clin Exp Allergy. 2016;46(4):654-656. 15.Pastorello EA, Farioli L, Pravettoni V, Ispano M, Conti A, Ansaloni R, et al. Sensitization to the major allergen of Brazil nut is correlated with the clinical expression of allergy. J Allergy Clin Immunol. 1998;102(6 Pt 1):1021-1027. 16. Moreno FJ, Clemente A. 2S Albumin storage proteins: What makes them food allergens? Open Biochem J. 2008;2:16-28

BRAZ
82899

Brazil Nut, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Brazil nut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BRCAT
616495

BRCA1/2 Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information: Studies have shown that somatic mutations in the BRCA1 and BRCA2 genes are clinically relevant in the selection of therapy for patients diagnosed with cancer. Patients with ovarian, breast, prostate, and pancreatic tumors that harbor a somatic BRCA mutation may respond to treatment with PARP (poly [ADP-ribose] polymerase) inhibitors and be sensitive to platinum-based therapy.

Useful For: Identifying specific mutations within the BRCA1 and BRCA2 genes known to be associated with response to PARP inhibitors and sensitivity to platinum-based therapy This test is not intended for the evaluation of patients suspected of having inherited or germline BRCA1 or BRCA2 mutations.

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. US Food and Drug Administration (FDA): Table of Pharmacogenomic Biomarkers in Drug Labeling. Updated Febuary 10, 2023, Accessed July 31, 2023. Available at www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling 4. Petrucelli N, Daly MB, Pal T: BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated May 26, 2022. Accessed July 31, 2023. Available at

www.ncbi.nlm.nih.gov/books/NBK1247/ 5. Tung, NM, Garber, JE. BRCA1/2 testing: therapeutic implications for breast cancer management. Br J Cancer. 2018l;119(2):141-152. doi: 10.1038/s41416-018-0127-5

HBOCZ
614570

BRCA1/BRCA2 Genes, Full Gene Analysis, Varies

Clinical Information: Hereditary breast and ovarian cancer (HBOC) syndrome is an autosomal dominant hereditary cancer syndrome associated with germline variants in the BRCA1 or BRCA2 genes. Variants within BRCA1 and BRCA2 account for the majority of hereditary breast and ovarian cancer families.(1,2) However, additional genes are known to be associated with hereditary breast and ovarian cancer syndromes; see BRGYP / Hereditary Breast/Gynecologic Cancer Panel, Varies. HBOC syndrome is predominantly characterized by early-onset breast and ovarian cancer. Individuals with breast and ovarian cancer are also at increased risks for prostate, pancreatic, and male breast cancers. Some individuals develop multiple primary or bilateral cancers.(1,2) Individuals with biallelic disease-causing variants in BRCA1 and BRCA2 are at risk for Fanconi anemia, an autosomal recessive bone marrow failure syndrome. Of note, there are several other genes known to cause Fanconi anemia.(1) The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with HBOC syndrome.(2-4)

Useful For: Evaluating patients with a personal or family history suggestive of hereditary breast and ovarian cancer (HBOC) syndrome Establishing a diagnosis of HBOC syndrome allowing for targeted cancer surveillance based on associated risks Identifying variants within genes known to be associated with increased risk for HBOC syndrome allowing for predictive testing of at-risk family members Therapeutic eligibility including poly adenosine diphosphate-ribose polymerase inhibitors in select cancer types

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Petrucelli N, Daley MB, Pal T. BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. In: Adams MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated September 21, 2023. Accessed September 11, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1247/ 2. Daly MB, Pal T, Berry M, et al. NCCN Guidelines Insights: Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 2.2021. J Natl Compr Canc Netw. 2021;19(1):77-102 3. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007;57(2):75-89 4. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2019;69(3):184-210 5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

C2729
606583

Breast Carcinoma-Associated Antigen, Serum

Clinical Information: Carcinoma of the breast is the most prevalent form of cancer in women.

These tumors often produce mucinous antigens, which are large-molecular-weight glycoproteins with O-linked oligosaccharide chains. Monoclonal antibodies directed against these antigens have been developed, and several immunoassays are available to quantitate the levels of tumor-associated mucinous antigens in serum. The antibodies recognize epitopes of a breast cancer-associated antigen encoded by the human mucin 1 (MUC-1) gene, which is known by several names including MAM6, milk mucin antigen, cancer antigen (CA) 27.29, and CA 15-3. While CA 27.29 is expressed at the apical surface of normal epithelial cells, it is present throughout malignant epithelial cells of the breast, lung, ovary, pancreas, and other sites. The cancer-associated form of the antigen is less extensively glycosylated than the normal form and more specific for tumor cells.

Useful For: Aiding in the management of breast cancer in patients with metastatic disease by monitoring the progression or regression of disease in response to treatment Serial testing in women with prior stage II or III breast cancer who are clinically free of disease May be useful for predicting early recurrence of disease in women with treated carcinoma of the breast This test is not useful for screening women for or diagnosis of carcinoma of the breast.

Interpretation: Increased levels of cancer-associated antigen (CA 27.29) (>38 U/mL) may indicate recurrent disease in a woman with treated breast carcinoma and may be useful as an indication that additional tests or procedures should be performed to confirm recurrence.

Reference Values:

Males

> or =18 years: < or =38.0 U/mL (use not defined)

Females

> or =18 years: < or =38.0 U/mL

Reference values have not been established for patients who are younger than 18 years of age.

Serum markers are not specific for malignancy, and values may vary by method.

Clinical References: 1. Bon GG, von Mensdorff-Pouilly S, Kenemans P, van Kamp GJ, Verstraeten RA, Hilgers J. Clinical and technical evaluation of ACS BR serum assay of MUC1 gene-derived glycoprotein in breast cancer, and comparison with CA 15-3 assays. Clin Chem. 1997;43(4):585-593 2. Chan DW, Beveridge RA, Muss H. Use of Truquant BR radioimmunoassay for early detection of breast cancer recurrence in patients with stage II and stage III disease. J Clin Oncol. 1997;15(6):2322-2328 3. Lin DC, Genzen JR. Concordance analysis of paired cancer antigen (CA) 15-3 and 27.29 testing. Breast Cancer Res Treat. 2018;167(1):269-276

BRG1
71537

BRG1 (SMARCA4) Immunostain, Technical Component Only

Clinical Information: BRG1 (SMARCA4) is a member of the switch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex. Biallelic mutations in BRG1 (SMARCA4) have been reported in ovarian small cell carcinoma of hypercalcemic type (SCCOHT), amongst other tumors. Tumors with these mutations demonstrate a loss of BRG1 protein expression in the nucleus. SCCOHT is difficult to diagnose and loss of BRG1 expression can help in differentiating SSCOHT from its mimics including other primary or metastatic tumors of the ovaries.

Useful For: Diagnosing ovarian small cell carcinoma of hypercalcemic type (SCCOHT)

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Clarke BA, Witkowski L, Ton Nu TN, et al. Loss of SMARCA4 (BRG1) protein expression as determinded by immunohistochemistry in small cell carcinoma of the ovary, hypercalcemic type distinguishes these tumors from their mimics. Histopathology 2016;69(5):727-7382. Conlon N, Silva A, Guerra E, et al. Loss of SMARCA4 expression is both sensitive and specific for the diagnosis of small cell carcinoma of ovary, hypercalcemic type. Am J Pathol. 2016;40:395-403 3. Karanian-Philippe M, Velasco V, Longy M, et al. SMARCA4 (BRG1) loss of expression is a useful marker for the diagnosis of ovarian small cell carcinoma of the hypercalcemic type (ovarian rhabdoid tumor). Am J Surg Pathol 2015;39(9):1197-1205 4. Ramos P, Karnezis AN, Craig DW, et al. Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in SMARCA4. Nat Genet. 2014;46(5):427-430 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

BRIVA
620767

Brivaracetam, Plasma

Clinical Information: Brivaracetam is a newer antiepileptic drug, an analogue of levetiracetam, that is used as therapy for partial onset seizures in patients one month or older. It is available in both an oral and intravenous solution and oral tablet. When taken orally, it is rapidly and completely absorbed. It is primarily excreted through the renal system and has an elimination half-life of approximately nine hours. While the exact mechanism for brivaracetam's anticonvulsive effects is unknown, it has a high and selective binding affinity for synaptic vesicle protein 2A in the brain. The drug has a narrow therapeutic range and a wide interindividual variability in rate of elimination. Adults and children 16 years and older typically take 25 mg twice daily up to 100 mg twice daily. Trough therapeutic reference ranges in plasma have been reported between 0.5 to 0.9 mcg/mL (mg/L) with toxicity more common above 1.8 mcg/mL. The most common adverse effects include somnolence/sedation, dizziness, fatigue, and nausea/vomiting. Vertigo, balance disorder, fatigue, nausea, diplopia, anxiety, and bradycardia have also been reported following brivaracetam overdose.

Useful For: Assessing compliance and toxicity for brivaracetam

Interpretation: The report is intended for use by a physician to determine if the patient is receiving a dose sufficient to achieve a therapeutic effect or to assess whether the patient is compliant with prescribed dose. The reference range represents the concentrations observed to be associated with greatest drug efficacy without side effects or toxicity. Most individuals display optimal response to brivaracetam with plasma levels 0.2 to 2.0 mcg/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Toxic levels have not been well established. Therapeutic ranges are based on specimens collected at trough (ie, immediately before the next dose).

Reference Values:
0.2-2.0 mcg/mL

Clinical References: 1. Patsalos PN, Spencer EP, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs in epilepsy: A 2018 Update. Ther Drug Monit. 2018;40(5):526-548 2. Aalapati KK., Amit S, Patnaik, RS. Method development and validation of a novel UHPLC coupled with MS/MS system for the estimation of brivaracetam in human (K2EDTA) plasma samples and its application to pharmacokinetic study. Curr Pharm Anal. 2022;18.5:504-512 3. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017 [published correction appears in Pharmacopsychiatry. 2018 Jan;51(1-02):e1]. Pharmacopsychiatry. 2018;51(1-02):9-62 4. Khaleghi F, Nemec EC 2nd. Brivaracetam (Briviact): A novel adjunctive therapy for partial-onset seizures. P T. 2017;42(2):92-96 5. Mohamed S, Riva R, Contin M. Development and validation of an UHPLC-MS/MS assay for the therapeutic monitoring of

brivaracetam plasma concentrations in patients with epilepsy. Ther Drug Monit. 2020;42(3):445-451

BRBPS
65058

Broad Range Bacterial PCR and Sequencing, Varies

Clinical Information: Cultures from patients with suspected bacterial infection involving normally sterile sites may fail to provide bacterial (including mycobacterial) growth for identification due to the presence of fastidious or slow-growing bacteria or because of antecedent antimicrobial chemotherapy. Polymerase chain reaction amplification of a portion of the 16S ribosomal RNA (rRNA) gene followed by sequencing of the amplified product can be used to detect bacterial (including mycobacterial) nucleic acids in such situations, enabling a diagnosis. Sterile sources accepted for testing may have more than one bacterial species present or the presence of copy variants of the 16S rRNA gene within a single bacterial species, confounding Sanger sequencing analysis. Next-generation sequencing can be useful in such cases. Ideal specimens are those in which bacteria (includes mycobacteria) are visualized by microscopy. Heart valves from patients with endocarditis with positive Gram stains are, for example, especially suitable.

Useful For: Detecting and identifying bacteria (including mycobacteria) from normally sterile sources, including synovial fluid; body fluids such as pleural, peritoneal, and pericardial fluids, cerebrospinal fluid; and both fresh and formalin-fixed paraffin-embedded tissues This test is not recommended as a test of cure because nucleic acids may persist for long periods of time after successful treatment.

Interpretation: A positive broad-range polymerase chain reaction (PCR)/sequencing result indicates that bacterial nucleic acid of the specified organism was detected, which may be due to bacterial infection or environmental or contaminating nucleic acids in the specimen. A negative broad-range PCR/sequencing result indicates the absence of detectable bacterial (including mycobacterial) nucleic acids in the specimen but does not rule out false-negative results that may occur due to sampling error, sequence variability underlying the primers, the presence of bacterial nucleic acids in quantities below the limit of detection of the assay, or inhibition of PCR. If PCR testing appears to be negative but there is evidence of PCR inhibition, testing will be repeated. If inhibition is again detected, the result will be reported as "PCR inhibition present."

Reference Values:
No bacterial DNA detected

Clinical References: 1. Virk A, Pritt B, Patel R, et al. Mycobacterium lepromatosis lepromatous leprosy in US citizen who traveled to disease-endemic areas. Emerg Infect Dis. 2017;23(11):1864-1866. doi:10.3201/eid2311.171104 2. Liesman RM, Pritt BS, Maleszewski JJ, Patel R. Laboratory diagnosis of infective endocarditis. J Clin Microbiol. 2017;55(9):2599-2608. doi:10.1128/JCM.00635-17 3. Ramakrishna JM, Libertin CR, Yang JN, Diaz MA, Nengue AL, Patel R. 16S rRNA gene PCR/sequencing of cerebrospinal fluid in the diagnosis of post-operative meningitis. Access Microbiology. 2020;2(2):acmii.0.000100 4. Alvarez Otero J, Mandrekar J, Wolf MJ, et al. Pleural space infection microbiology as assessed using a clinically targeted sequencing-based assay: Fusobacterium nucleatum group, Streptococcus intermedius, and oral normal microbiota are the most common bacteria identified in community-acquired pleural space infections. J Clin Microbiol. 2024;62(12):00694-24-s0001 5. Azad MA, Wolf MJ, Strasburg AP, et al. Comparison of the BioFire Joint Infection Panel to 16S ribosomal RNA gene-based targeted metagenomic sequencing for testing synovial fluid from patients with knee arthroplasty failure. J Clin Microbiol. 2022;60(12):e0112622. doi:10.1128/jcm.01126-22 6. Fowler VG, Durack DT, Selton-Suty C, et al. The 2023 Duke-International Society for Cardiovascular Infectious Diseases criteria for infective endocarditis: Updating the modified Duke criteria [published correction appears in Clin Infect Dis. 2023 Oct 13;77(8):1222. doi: 10.1093/cid/ciad510]. Clin Infect Dis. 2023;77(4):518-526. doi:10.1093/cid/ciad271 7. Flurin L, Wolf MJ, Mutchler MM, Daniels ML, Wengenack NL, Patel R. Targeted metagenomic sequencing-based approach applied to 2146 tissue and

body fluid samples in routine clinical practice. Clin Infect Dis. 2022;75(10):1800-1808. doi:10.1093/cid/ciac247 8. Hong HL, Flurin L, Greenwood-Quaintance KE, et al. 16S rRNA gene PCR/sequencing of heart valves for diagnosis of infective endocarditis in routine clinical practice. J Clin Microbiol. 2023;61(8):e0034123. doi:10.1128/jcm.00341-23

FBRCG
57642

Broccoli IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

BROC
82817

Broccoli, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to broccoli Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BROM
82919

Brome Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to brome grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FBROM 75695 Bromine - Total, Blood

Reference Values:

Reporting limit determined each analysis.

Units: mg/L

The population reference interval derived from NMS Labs data (n=136) is usually between 1.4 and 8.8 mg/L (2.5th - 97.5th percentiles). Background concentrations are diet dependent. Workers exposed to methyl bromide with blood bromide concentrations greater than 12 mg/L have shown 3.5 times higher risk of electroencephalogram disturbances than compared to those with normal levels.

BRCMG 607346 Brucella Antibody Screen, IgM and IgG, ELISA, Serum

Clinical Information: Brucellosis is a major disease in humans and domesticated animals and is a systemic bacterial infection caused by gram-negative coccobacilli of the genus Brucella. Brucellosis is a zoonotic disease, and a variety of domestic animals serve as reservoir species: Brucella infects goats (Brucella melitensis), cattle (Brucella abortus), swine (Brucella suis), and dogs (Brucella canis). Transmission to humans results from direct contact with infected animals, exposure to infectious aerosols, or ingestion of unpasteurized dairy products; human-to-human transmission does not occur. While few cases are reported in the US, the majority of cases occur in the Mediterranean region, Western Asia, and parts of Latin America and Africa. Three species of Brucella commonly cause disease in humans: B melitensis, B suis, and B abortus. Clinical manifestations of brucellosis consist of fever, sweats, malaise, weight loss, headache, and weakness. The onset may be insidious or acute, generally beginning within 2 to 4 weeks after exposure. Any organ or system of the body may be involved, although death is uncommon. Presumptive diagnosis of brucellosis can be made by detection of high or rising titers of specific antibodies, typically to smooth lipopolysaccharide (S-LPS), a major antigenic virulence determinant. Serologic tests using S-LPS can detect antibody to the three major Brucella species due to this shared epitope. IgM antibodies appear during the first week of infection followed by a switch to IgG synthesis during the second week. A variety of serologic tests have been used for diagnosis of Brucella infection. Detection of anti-Brucella antibodies using enzyme-linked

immunosorbent assay (ELISA) has been demonstrated to be a sensitive diagnostic approach. However, all specimens testing positive by ELISA should be confirmed by an agglutination method to increase assay specificity.

Useful For: Evaluating patients with suspected brucellosis

Interpretation: In the acute stage of the disease, there is an initial production of IgM antibodies followed closely by production of IgG antibodies. IgG-class antibodies may decline after treatment; however, high levels of circulating IgG-class antibodies may be found without any active disease. Rising levels of specific antibody in paired sera can be regarded as serological evidence of recent infection. The presence of specific IgM in a single specimen may also indicate a recent infection, although IgM-class antibodies may persist for months following acute disease. The Centers for Disease Control and Prevention (CDC) recommends that specimens testing positive for IgG or IgM by enzyme-linked immunosorbent assay (ELISA) be confirmed by a Brucella-specific agglutination method.(1) The CDC/Council of State and Territorial Epidemiologists case definition for human brucellosis states that the laboratory criteria for diagnosis includes the following: 1. Isolation of Brucella species from a clinical specimen 2. Four-fold or greater rise in Brucella agglutination titer between acute- and convalescent-phase serum specimens obtained more than 2 weeks apart and studied at the same laboratory 3. Demonstration by immunofluorescence of Brucella species in a clinical specimen Positive results by ELISA that are not confirmed by Brucella-specific agglutination may represent false-positive screening results. If clinically indicated, a new specimen should be tested after 14 to 21 days. If results of ELISA are negative and a recent infection is suspected, a new specimen should be tested after 14 to 21 days.

Reference Values:

IgG SCREEN
Negative
Reference values apply to all ages.

IgM SCREEN
Negative
Reference values apply to all ages.

Clinical References: 1. Centers for Disease Control and Prevention (CDC): Public health consequences of a false-positive laboratory test result for Brucella--Florida, Georgia, and Michigan, 2005, MMWR Morb Mortal Wkly Rep. 2008 Jun 6:57(22);603-605 2. Gunes H, Dogan M: False-positivity in diagnosis of brucellosis associated with Rev-1 vaccine. Libyan J Med. 2013;8:20417 3. Yagupsky P, Morata P, Colmenero JD. Laboratory diagnosis of human brucellosis. Clin Microbiol Rev. 2019;33(1):e00073-19. Published 2019 Nov 13. doi:10.1128/CMR.00073-19 4. Stoddard RA. Detection of Brucella spp. antibodies. In: Leber AL, Burnham CAD, eds. Clinical Microbiology Procedures Handbook. 5th ed. ASM Press; 2023:chap 13.3

BRUTA
8112

Brucella Total Antibody Confirmation, Agglutination, Serum

Clinical Information: Brucella species are facultative intracellular, gram-negative bacilli that cause brucellosis in humans. Human disease is likely acquired by contact with animals infected with the organism (Brucella abortus, Brucella suis, Brucella melitensis, and occasionally Brucella canis) either by direct contact or by ingestion of meat or milk. The signs and symptoms associated with brucellosis may include fever, night sweats, chills, weakness, malaise, headache, and anorexia. The physical examination may reveal lymphadenopathy and hepatosplenomegaly. A definitive diagnosis of brucellosis is made by recovering the organism from bone marrow, blood, fluid (including urine), or tissue specimens. In cases of suspected brucellosis, serology may assist in the diagnosis and play a supplementary role in routine culture. Antibodies to Brucella species may not become detectable until 1 to 2 weeks following the onset

of symptoms, so serum specimens collected during acute disease may be negative by serology in patients with brucellosis. If serology is performed, the Centers for Disease Control and Prevention currently recommends that specimens testing positive or equivocal for IgG or IgM by a screening enzyme immunoassay be confirmed by a Brucella-specific agglutination method.

Useful For: Diagnosis of brucellosis

Interpretation: The Centers for Disease Control and Prevention recommends that specimens testing positive or equivocal for IgG or IgM by a screening enzyme immunoassay (EIA) be confirmed by a Brucella-specific agglutination method. Titers below 1:80 are seen in normal, healthy populations. Titers of 1:80 or greater are often considered clinically significant (1); however, a 4-fold or greater increase in titers between acute and convalescent phase sera is required to diagnose acute infection. Positive results by a screening EIA that are not confirmed by Brucella-specific agglutination may represent false-positive screening results. If clinically indicated, a new specimen should be tested after 7 to 14 days.

Reference Values:
<1:80

Clinical References: 1. Welch RJ, Litwin CM. A comparison of Brucella IgG and IgM ELISA assays with agglutination methodology. J Clin Lab Anal. 2010;24(3):160-162 2. Gunes H, Dogan M False-positivity in diagnosis of brucellosis associated with Rev-1 vaccine. Libyan J Med. 2013:8:10.3402/ljm.v8i0.20417 3. Stoddard RA. Detection of Brucella spp antibodies. In: Leber AL, Burnham CD, eds. Clinical Microbiology Procedures Handbook. 5th ed. AMS Press; 2023:section13.3.3

SCN5A
617449

Brugada Syndrome, SCN5A Full Gene Analysis, Varies

Clinical Information: Brugada syndrome (BrS) is a genetic cardiac disorder characterized by ST segment elevation in leads V1-V2 on electrocardiography (ECG) occurring spontaneously or after administration of sodium-channel blockers.(1) BrS leads to a high risk for ventricular arrhythmias, which can result in sudden cardiac arrest and sudden cardiac death including sudden unexpected nocturnal death syndrome and sudden infant death syndrome.(2) The diagnosis of BrS is established based on the characteristic ECG abnormality along with personal and family health history and requires exclusion of other causes including cardiac structural abnormalities, medications, and electrolyte imbalances.(2) Brugada syndrome has an estimated prevalence of 1:2000 to 1:5000.(1) Currently, BrS is definitively associated with gain-of-function variants in the SCN5A gene(3) and the condition follows an autosomal dominant pattern of inheritance. Approximately 20% of individuals meeting clinical diagnostic criteria for BrS are found to carry a causative variant in the SCN5A gene.(3) While variants in other genes have been reported in association with BrS, current evidence is not sufficient to define the role of these genes in BrS.(3)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of Brugada syndrome Establishing a diagnosis of Brugada syndrome

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(4) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present status of Brugada syndrome: JACC state-of-the-art review. J Am Coll Cardiol. 2018;72(9):1046-1059. doi:10.1016/j.jacc.2018.06.037 2. Brugada R, Campuzano O, Sarquella-Brugada G, Brugada P, Brugada J, Hong K. Brugada syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2005. Updated August 25, 2022. Accessed October 10, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1517/ 3. Schwartz PJ, Ackerman MJ, Antzelevitch C, et al. Inherited cardiac arrhythmias. Nat Rev Dis Primers. 2020;6(1):58. doi:10.1038/s41572-020-0188-7 4. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30

BSPR
82480

Brussels Sprouts, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to Brussels sprouts Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive

6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BTKSG
619760

Bruton Tyrosine Kinase, BTK Full Gene Analysis, Varies

Clinical Information: X-linked agammaglobulinemia (XLA) is a humoral primary immunodeficiency affecting male patients in approximately 1 in 200,000 live births. XLA is caused by variants in the Bruton tyrosine kinase gene (BTK), which results in a profound block in B-cell development within the bone marrow and a significant reduction, or complete absence, of mature B cells in peripheral blood.(1,2) Approximately 85% of male patients with defects in early B-cell development have XLA. Due to the lack of mature B cells, XLA patients have markedly reduced levels of all major classes of immunoglobulins in the serum and are, therefore, susceptible to severe and recurrent bacterial infections.(2) Pneumonia, otitis media, enteritis, and recurrent sinopulmonary infections are among the key diagnostic clinical characteristics of the disease. The spectrum of infectious complications also includes enteroviral meningitis, septic arthritis, cellulitis, and empyema, among others. XLA typically manifests in male infants.(2) However, other patients present with milder phenotypes, resulting in diagnosis later in childhood or in adulthood. Delayed diagnoses can be partly explained by the variable severity of XLA, even within families in which the same variant is present. X-inactivation of this gene is not typical, and XLA in female patients has rarely been reported.(3) Therefore, female patients with clinical features that are identical to XLA should be first evaluated for autosomal recessive agammaglobulinemia and for XLA if their biological father is affected with the disease. A diagnosis of XLA should be suspected in male patients with early-onset bacterial infections, marked reduction in all classes of serum immunoglobulins, and absent B cells (CD19+ cells). The decrease in numbers of peripheral B cells is a key feature, although this can also be seen in a small subset of patients with common variable immunodeficiency. Conversely, some BTK variants can preserve small numbers of circulating B cells and, therefore, all 3 of the criteria mentioned above need to be evaluated.(2) The preferred approach for confirming a diagnosis of XLA in male patients and identifying female carriers requires testing for the BTK protein expression on B cells by flow cytometry and genetic testing for a BTK variant. Patients can be screened for the presence of BTK protein by flow cytometry (BTK / Bruton Tyrosine Kinase [BTK], Protein Expression, Flow Cytometry, Blood); however, normal results by flow cytometry do not rule out the presence of a BTK variant with normal protein expression but aberrant protein function. The diagnosis is confirmed only in those individuals with appropriate clinical history who have a disease-causing variant identified within BTK by gene sequencing or who have male family members with hypogammaglobulinemia with absent or low B cells.

Useful For: Confirming a diagnosis of X-linked agammaglobulinemia in patients with a history of recurrent sinopulmonary infections, profound hypogammaglobulinemia, and less than 1% peripheral B cells, with or without abnormal Bruton tyrosine kinase (BTK) protein expression by flow cytometry
Evaluating for the presence of BTK variants in family members of affected individuals, including those who do not demonstrate carrier phenotype by BTK flow cytometry

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(4) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

BTK
89011

Bruton Tyrosine Kinase, Protein Expression, Flow Cytometry, Blood

Clinical Information: The differential diagnosis for patients with primary hypogammaglobulinemia of unclear etiology (after other secondary causes of hypogammaglobulinemia have been ruled out) includes common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA). CVID is the most common diagnosis of humoral immunodeficiency, particularly in adults but also in children over 4 years of age. However, men with XLA may be misdiagnosed with CVID. XLA is an independent humoral immunodeficiency and should not be regarded as a subset of CVID. The BTK gene is present on the long arm of the X-chromosome and encodes for a cytoplasmic tyrosine kinase with 5 distinct structural domains. While BTK gene sequencing is the gold standard for definitively identifying variants and confirming a diagnosis of XLA, it is labor intensive and expensive, and it may result in a variant of uncertain significance. Flow cytometry is a screening test for XLA and should be included in the evaluation of patients with possible CVID, particularly in male patients with less than 1% B cells. Bruton tyrosine kinase (BTK) is an intracellular protein, and absence of the BTK protein by flow cytometry provides a strong rationale for performing a BTK gene-sequencing test. However, 20% to 30% of patients with XLA may have intact or truncated BTK protein with abnormal function; therefore, genetic analysis remains the more definitive test for diagnosing XLA (besides other clinical and immunological parameters). X-linked agammaglobulinemia is a prototypical humoral immunodeficiency caused by variants in the BTK gene, which encodes BTK, a hematopoietic-specific tyrosine kinase. XLA is characterized by normal, reduced, or absent BTK expression in monocytes and platelets, a significant reduction or absence of circulating B cells in blood, and profound hypogammaglobulinemia of all isotypes (IgG, IgA, IgM, and IgE). The clinical presentation includes early onset of recurrent bacterial infections and absent lymph nodes and tonsils. BTK plays a critical role in B-cell differentiation. The defect in BTK may be "leaky" in some patients (ie, a consequence of variants in the gene that result in a milder clinical and laboratory phenotype), such that these patients may have some levels of IgG and/or IgM and a small number of B cells in blood.(1) The vast majority of patients with XLA are diagnosed in childhood (median age of diagnosis in patients with sporadic XLA is 26 months), although some patients are recognized in early adulthood or later in life. The diagnosis of XLA in both children and adults indicates that the disorder demonstrates considerable clinical phenotypic heterogeneity, depending on the position of the variants within the gene. Female patients are typically carriers and asymptomatic. Testing in women should be limited to those in their child-bearing years (<45 years). Carrier testing ideally should be confirmed by genetic testing since it is possible to have a normal flow cytometry test for protein expression in the presence of heterozygous (carrier) BTK gene variants. Flow cytometry is a preliminary screening test for XLA. It is important to keep in mind that this flow cytometry test is only a screening tool and approximately 20% to 30% of patients who have a variant within the BTK gene have normal protein expression (again related to the position of the variant in the gene and the antibody used for flow cytometric analysis). Therefore, in addition to clinical correlation, genetic testing is recommended to confirm a diagnosis of XLA. Furthermore, it is helpful to correlate gene and protein data with clinical history (genotype-phenotype correlation) in making a final diagnosis of XLA. Consequently, the preferred test for XLA is BTKSG / Bruton Tyrosine Kinase, BTK Full Gene Analysis, Varies. If a familial variant has already been identified, then FMTT / Familial Variant, Targeted Testing, Varies should be ordered.

Useful For: Preliminary screening for X-linked agammaglobulinemia, primarily in male patients (<65 years) or female carriers (child-bearing age: <45 years)

Interpretation: Results are reported as Bruton tyrosine kinase (BTK) protein expression present

(normal) or absent (abnormal) in monocytes and B cells if present. Additionally, mosaic BTK expression (indicative of a carrier) and reduced BTK expression (consistent with partial BTK protein deficiency) are reported when present and correlated with a healthy experimental control. BTK genotyping (BTKSG / Bruton Tyrosine Kinase, BTK Full Gene Analysis, Varies or FMTT / Familial Variant, Targeted Testing, Varies) should be performed in the following situations: -To confirm any abnormal flow cytometry result -In the rare patient with the clinical features of X-linked agammaglobulinemia, but normal BTK protein expression -In mothers of patients who do not show the classic carrier pattern of bimodal protein expression (to determine if there is maternal germinal mosaicism or skewed altered X-chromosome inactivation), or there is dominant expression of the normal protein in the presence of one copy of a genetic variant.

Reference Values:
Present

Clinical References: 1. Kanegane H, Futatani T, Wang Y, et al. Clinical and mutational characteristics of X-linked agammaglobulinemia and its carrier identified by flow cytometric assessment combined with genetic analysis. J Allergy Clin Immunol. 2001;108(6):1012-1020. doi:10.1067/mai.2001.120133 2. Kanegane H, Tsukada S, Iwata T, et al. Detection of Bruton's tyrosine kinase mutations in hypogammaglobulinemic males registered as common variable immunodeficiency (CVID) in the Japanese Immunodeficiency Registry. Clin Exp Immunol. 2000;120(3):512-517. doi:10.1046/j.1365-2249.2000.01244.x 3. Stewart DM, Tian L, Nelson DL. A case of X-linked agammaglobulinemia diagnosed in adulthood. Clin Immunol. 2001;99(1):94-99. doi:10.1006/clim.2001.5024 4. Futatani T, Miyawaki T, Tsukada S, et al. Deficient expression of Bruton's tyrosine kinase in monocytes from X-linked agammaglobulinemia as evaluated by a flow cytometric analysis and its clinical application to carrier detection. Blood. 1998;91(2):595-602 5. Kraft MT, Pyle R, Dong X, et al. Identification of 22 novel BTK gene variants in B cell deficiency with hypogammaglobulinemia. Clin Immunol. 2021;229:108788. doi:10.1016/j.clim.2021.108788 6. Chear CT, Ripen AM, Mohamed SAS, Dhaliwal JS. A novel BTK gene mutation creates a de-novo splice site in an X-linked agammaglobulinemia patient. Gene. 2015;560(2):245-248. doi:10.1016/j.gene.2015.02.019

BUCW
82727

Buckwheat, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to buckwheat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BDRP
82791

Budgerigar Droppings, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Budgerigar droppings Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the

concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BFTH
82779

Budgerigar Feathers, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Budgerigar feathers Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BPAB
606816

Bullous Pemphigoid, BP180 and BP230, IgG Antibodies, Serum

Clinical Information: Bullous pemphigoid (BP) is a chronic pruritic blistering disorder found mainly in aged persons, characterized by the development of tense blisters over an erythematous or urticarial base. IgG anti-basement membrane zone antibodies are found in the serum of patients, and linear IgG and complement component 3 sediment is found on the basement membrane zone of the lesion. Several well characterized variants exist including localized, mucous membrane predominant and pemphigoid gestationis, also referred to as herpes gestationis. Target antigens of the autoantibodies in BP patient serum are BP230 and BP180, also called BPAG1 and BPAG2. Molecular weight of these antigens is 230 kDa and 180 kDa, respectively. BP180 is thought to be the direct target of the autoantibody because of its location along the basement membranes, and the autoantibody against BP230 is thought to be secondarily produced.

Useful For: Initial screening test in the diagnosis of bullous pemphigoid and its variants
Complementing the standard serum test of indirect immunofluorescence utilizing primate esophagus substrate and primate salt-split skin substrate (CIFS / Cutaneous Immunofluorescence Antibodies [IgG], Serum)

Interpretation: Antibodies to bullous pemphigoid (BP) BP180 and BP230 have been shown to be present in most patients with pemphigoid. Adequate sensitivities and specificity for disease are documented and Mayo Clinic's experience demonstrates a very good correlation between BP180 and BP230 results and the presence of pemphigoid (see Supportive Data). However, in those patients strongly suspected to have pemphigoid, either by clinical findings or by routine biopsyor direct immunofluorescence, and in whom the BP180/BP230 assay is negative, follow-up testing by CIFS / Cutaneous Immunofluorescence Antibodies (IgG), Serum is recommended. Antibody titer may correlate with disease activity in some patients. Patients with severe disease may be expected to have high titers of antibodies to BP. Titers may decrease with clinical improvement.

Reference Values:
BULLOUS PEMPHIGOID 180:

<20 RU/mL (negative)
> or =20 RU/mL (positive)

BULLOUS PEMPHIGOID 230:
<20 RU/mL (negative)
> or =20 RU/mL (positive)

Clinical References: 1. Liu Z, Diaz LA, Troy JL, et al. A passive transfer model of the organ-specific autoimmune disease, bullous pemphigoid, using antibodies generated against the hemidesmosomal antigen, BP180. J Clin Invest. 1993;92(5):2480-2488 2. Matsumura K, Amagai M, Nishikawa T, Hashimoto T. The majority of bullous pemphigoid and herpes gestationes serum samples react with the NC16a domain of the e180-kD bullous pemphigoid antigen. Arch Dermatol Res. 1996;288(9):507-509 3. Stanley JR, Hawley-Nelson P, Yuspa SH, Shevach EM, Katz SI. Characterization of bullous pemphigoid antigen: a unique basement membrane protein of stratified aqueous epithelia. Cell. 1981;24(3):897-903 4. Hamada T, Nagata Y, Tomita M, Salmhofer W, Hashimoto T. Bullous pemphigoid sera react specially with various domains of BP230, most frequently with C-terminal domain, by immunblot analyses using bacterial recombinant proteins covering the entire molecule. Exp Dermatol. 2001;10(4):256-263 5. Rico MJ, Korman NJ, Stanley JR, Tanaka T, Hall RP. IgG antibodies from patients with bullous pemphigoid bind to localized epitopes on synthetic peptides encoded by bullous pemphigoid antigen cDNA. J Immunol. 1990;145(11):3728-3733 6. Wieland CN, Comfere NI, Gibson LE, Weaver AL, Krause PK, Murray JA. Anti-bullous pemphigoid 180 and 230 antibodies in a sample of unaffected subjects. Arch Dermatol. 2010;146(1):21-25 7. Montagnon CM, Tolkachjov SN, Murrell DF, Camilleri MJ, Lehman JS. Subepithelial autoimmune blistering dermatoses: Clinical features and diagnosis. J Am Acad Dermatol. 2021;85(1):1-14 8. Montagnon CM, Lehman JS, Murrell DF, Camilleri MJ, Tolkachjov SN. Subepithelial autoimmune bullous dermatoses: disease activity assessment and therapy. J Am Acad Dermatol. 2021;85(1):18-27

FMARC 75307 Bupivacaine (Marcaine)

Reference Values:
Reference Range: 0.1 - 4.0 ug/mL

BUPMX 65215 Buprenorphine and Norbuprenorphine, Chain of Custody, Random, Urine

Clinical Information: Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin.(1) Buprenorphine has a prolonged duration of activity. The combination of decreased clinical effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids.(1) Compared to morphine, buprenorphine is 25 to 40 times more potent.(1) As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist. Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4. Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one-fifth of the potency of its parent. The glucuronide metabolites are inactive.(1) The primary clinical utility of quantification of buprenorphine in urine is to identify patients that have

strayed from opioid dependence therapy. Chain of custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Monitoring of compliance of buprenorphine therapy Detection and confirmation of the illicit use of buprenorphine Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of buprenorphine above 5.0 ng/mL or norbuprenorphine above 2.5 ng/mL is a strong indicator that the patient has used buprenorphine.

Reference Values:

Negative
Positive results are reported with a quantitative result.

Cutoff concentrations:

Immunoassay Screen: 5 ng/mL

Liquid chromatography tandem mass spectrometry:
Buprenorphine: 5.0 ng/mL
Norbuprenorphine: 2.5 ng/mL

Clinical References: 1. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. Clin Pharmacokinet. 2005;44(7):661-680 2. Grimm D, Pauly E, Poschl J, Linderkamp O, Skopp G. Buprenorphine and norbuprenorphine concentrations in human breast milk samples determined by liquid chromatography-tandem mass spectrometry. Ther Drug Monit. 2005;27(4):526-530 3. Kacinko SL, Shakleya DM, Huestis MA. Validation and application of a method for the determination of buprenorphine, norbuprenorphine, and their glucuronide conjugates in human meconium. Anal Chem. 2008;80(1):246-252 4. Concheiro M, Shakleya DM, Huestis MA. Simultaneous quantification buprenorphine, norbuprenorphine, buprenorphine-glucuronide and norbuprenorphine-glucuronide in human umbilical cord by liquid chromatography tandem mass spectrometry. Forensic Sci Int. 2009;188(1-3):144-151 5. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 6. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 10th ed. Biomedical Publications; 2014:2211

BUPM
66200

Buprenorphine and Norbuprenorphine, Random, Urine

Clinical Information: Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin.(1) Buprenorphine has a prolonged duration of activity. The combination of decreased clinical effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids.(1) Compared to morphine, buprenorphine is 25 to 40 times more potent.(1) As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as

prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist. Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4 (CYP3A4). Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one-fifth of the potency of its parent. The glucuronide metabolites are inactive.(1) The primary clinical utility of quantification of buprenorphine in urine is to identify patients that have strayed from opioid dependence therapy.

Useful For: Monitoring of compliance utilizing buprenorphine Detection and confirmation of the illicit use of buprenorphine

Interpretation: The presence of buprenorphine above 5.0 ng/mL or norbuprenorphine above 2.5 ng/mL is a strong indicator that the patient has used buprenorphine.

Reference Values:
Negative (Positive results are reported with a quantitative result)

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Buprenorphine: 5.0 ng/mL
Norbuprenorphine: 2.5 ng/mL

Clinical References: 1. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. Clin Pharmacokinet. 2005;44(7):661-680 2. Grimm D, Pauly E, Poschl J, Linderkamp O, Skopp G. Buprenorphine and norbuprenorphine concentrations in human breast milk samples determined by liquid chromatography-tandem mass spectrometry. Ther Drug Monit. 2005;27(4):526-530 3. Kacinko SL, Shakleya DM, Huestis MA. Validation and application of a method for the determination of buprenorphine, norbuprenorphine, and their glucuronide conjugates in human meconium. Anal Chem. 2008;80(1):246-252 4. Concheiro M, Shakleya DM, Huestis MA. Simultaneous quantification buprenorphine, norbuprenorphine, buprenorphine-glucuronide and norbuprenorphine-glucuronide in human umbilical cord by liquid chromatography tandem mass spectrometry. Forensic Sci Int. 2009;188(1-3):144-151 5. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 6. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 10th ed. Biomedical Publications; 2014:2211

BUPR
63222

Buprenorphine Screen with Reflex, Random, Urine

Clinical Information: Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin.(1) Buprenorphine has a prolonged duration of activity. The combination of decreased clinical effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids.(1) Compared to morphine, buprenorphine is 25 to 40 times more potent.(1) As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist. Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4 (CYP 3A4). Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one fifth of the potency of its parent. The glucuronide metabolites are

inactive.(1) This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can produce a false-positive result due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also can produce a false-negative result due to the antibody's ability to cross-react with different drugs in the target class.

Useful For: Screening and confirmation for drug abuse or use of buprenorphine

Interpretation: If the screen result is negative, buprenorphine concentrations were not detected. If the screen result is positive, then confirmation by liquid chromatography tandem mass spectrometry will be performed. A positive interpretation will be given if either the buprenorphine result is greater than or equal to 5.0 ng/mL or the norbuprenorphine result is greater than or equal to 2.5 ng/mL. The presence of buprenorphine above 5.0 ng/mL or norbuprenorphine above 2.5 ng/mL is a strong indicator that the patient has used buprenorphine.

Reference Values:
Negative
Screening cutoff concentration:
Buprenorphine: 5 ng/mL

Clinical References: 1. Elkader A, Spuroule B. Buprenorphine clinical pharmacokinetics in the treatment of opioid dependence. Clin Pharmacokinet. 2005;44(7):661-680 2. Jannetto PJ, Bratanow NC, Clark WA, et al: Executive Summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline-Using Clinical Laboratory Tests to Monitor Drug Therapy in Pain Management Patients. J Appl Lab Med. 2018;2:489-526 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

BUPS
63119

Buprenorphine Screen, Random, Urine

Clinical Information: Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin.(1) Buprenorphine has a prolonged duration of activity. The combination of decreased clinical effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids.(1) Compared to morphine, buprenorphine is 25 to 40 times more potent.(1) As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist. Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4 (CYP 3A4). Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one fifth of the potency of its parent. The glucuronide metabolites are inactive.(1) This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can produce a false-positive result due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also can produce a false-negative result due to the antibody's ability to cross-react with different drugs in the target class.

Useful For: Screening for drug abuse or use of buprenorphine

Interpretation: This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography tandem mass spectrometry) must be used to obtain a confirmed analytical result.

Reference Values:
Negative
Screening cutoff concentration:
Buprenorphine: 5 ng/mL

Clinical References: 1. Elkader A, Spuroule B. Buprenorphine clinical pharmacokinetics in the treatment of opioid dependence. Clin Pharmacokinet 2005;44(7):661-680 2. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive summary: American association of clinical chemistry laboratory medicine practice guideline-using clinical laboratory tests to monitor drug therapy in pain management patients. J Appl Lab Med. 2018;2(4):489-526. doi:10.1373/jalm.2017.023341 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

FBUMT
75387

Bupropion and Metabolite, Serum

Interpretation:

Reference Values:
Reporting Limit determined each analysis.
Units: ng/mL

FBUS
91115

Buspirone (Buspar)

Reference Values:
Units: ng/mL

Therapeutic and toxic ranges have not been established.

Expected serum buspirone concentrations in patients taking recommended daily dosages: up to 10.00 ng/mL.

BUAUC
83188

Busulfan, Intravenous Dose, Area Under the Curve, Plasma

Clinical Information: Busulfan is an alkylating agent used to ablate bone marrow cells prior to hematopoietic stem cell transplantation for chronic myelogenous leukemia.(1) Busulfan is typically administered intravenously (IV) at the recommended dosage of 0.8 mg/kg of actual or ideal body weight (whichever is lower) and given once every 6 hours over 4 days for a total of 16 doses. Dose-limiting toxicity of busulfan includes veno-occlusive liver disease, seizures, and coma. To avoid toxicity while ensuring busulfan dose adequacy to completely ablate the bone marrow, IV dosing should be guided by a pharmacokinetic (PK) evaluation of the area under the curve and clearance after the first dose.(2) The PK evaluation should be carried out at the end of the first dose, with results of PK testing available to facilitate dose adjustment before beginning the fifth dose.

Useful For: Guiding dosage adjustments to achieve complete bone marrow ablation while minimizing dose-dependent toxicity

Interpretation: Results of the timed collections will be used to calculate a 6-hour area under the curve (AUC). If a different dosing or specimen collection protocol is used, or if different calculations are required, contact the Laboratory Director. The optimal result for AUC (6 hour) derived from this pharmacokinetic evaluation of IV busulfan is 1100 (mcmol/L)(min). Area under the curve results greater than 1500 (mcmol/L)(min) are associated with hepatic veno-occlusive disease. A dose reduction should be considered before the next busulfan infusion. Area under the curve results below 900 (mcmol/L)(min) are consistent with incomplete bone marrow ablation. A dose increase should be considered before the next busulfan infusion. Clearance of busulfan in patients with normal kidney function is usually in the range of 2.1 to 3.5 (mL/min)/kg. Elevated AUC is typically associated with clearance below 2.5 (mL/min)/kg, most frequently due to diminished activity of glutathione S-transferase A1-1 activity.(3)

Reference Values:
AREA UNDER THE CURVE
900-1500 (mcmol/L)(min)

CLEARANCE
2.1-3.5 (mL/minute)/kg

Clinical References: 1. Santos GW, Tutschka PJ, Brookmeyer R, et al. Marrow transplantation for acute nonlymphocytic leukemia after treatment with busulfan and cyclophosphamide. N Engl J Med. 1983;309(22):1347-1353 2. Slattery JT, Sanders JE, Buckner CD, et al. Graft-rejection and toxicity following bone marrow transplantation in relation to busulfan pharmacokinetics. Bone Marrow Transplant. 1995;16(1):31-42 3. Slattery JT, Risler LJ. Therapeutic monitoring of busulfan in hematopoietic stem cell transplantation. Ther Drug Monit. 1998;20(5):543-549 4. Czerwinski M, Gibbs M, Slattery JT. Busulfan conjugation by glutathione S-transferases alpha, mu, and pi. Drug Metab Dispos. 1996;24(9):1015-1019 5. Vassal G, Re M, Gouyette A. Gas chromatographic-mass spectrometric assay for busulfan in biological fluids using a deuterated internal standard. J Chromatogr. 1988;428(2):357-361 6. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 12th ed. Biomedical Publications; 2020 7. Busulfex. Package insert. Otsuka Pharmaceutical Co, Ltd; Updated January 2015. Accessed October 8, 2024. Available at www.accessdata.fda.gov/drugsatfda_docs/label/2015/020954s014lbl.pdf 8. Palmer J, McCune JS, Perales MA, et al. Personalizing busulfan-based conditioning: considerations from the American Society for Blood and Marrow Transplantation Practice Guidelines Committee. Biol Blood Marrow Transplant. 2016;22(11):1915-1925

BUTAS
8427

Butalbital, Serum

Clinical Information: Butalbital, a short-acting barbiturate with hypnotic properties, is used in combination with other drugs such as acetaminophen, salicylate, caffeine, and codeine.(1) Butalbital is administered orally. The duration of its hypnotic effect is about 3 to 4 hours. The drug distributes throughout the body, with a volume of distribution of 0.8 L/kg, and about 26% of a dose is bound to plasma proteins. The half-life of butalbital is about 35 to 88 hours. Excretion occurs mainly in the urine.(1,2)

Useful For: Monitoring butalbital therapy

Interpretation: Butalbital concentrations of 10 mcg/mL or greater have been associated with toxicity.

Reference Values:
Therapeutic concentration: <10 mcg/mL

Toxic concentration: > or =10 mcg/mL

Clinical References: 1. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:454-454.e484 2. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020 3. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453 4. Mihic SJ, Mayfield J. Hypnotics and sedatives. In: Brunton LL, Knollmann BC, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 14th ed. McGraw-Hill Education; 2023

FCPEU
75894

C-Peptide, 24-Hour Urine

Useful For: Urine C-peptide is measured when a continuous assessment of B-cell function is desired or frequent blood sampling is not practical (eg, in children). C-peptide excretion in urine has been used to access pancreatic function in gestational diabetes and in patients with unstable glycemic control in insulin-dependent diabetes mellitus (IDDM).

Reference Values:
C-Peptide, Urine: Not Established ng/mL
C-Peptide, Urine 24 hr: 17.2-181.0 ug/24 hr

CPR
8804

C-Peptide, Serum

Clinical Information: C-peptide (connecting peptide), a 31-amino-acid polypeptide, represents the midportion of the proinsulin molecule. Proinsulin resembles a hairpin structure, with an N-terminal and C-terminal, which correspond to the A and B chains of the mature insulin molecule, oriented parallel to each other and linked by disulfide bonds. The looped portion of the hairpin between the A and B chains is called C-peptide. During insulin secretion, C-peptide is enzymatically cleaved off and cosecreted in equimolar proportion with mature insulin molecules. Following secretion, insulin and C-peptide enter the portal circulation and are routed through the liver where at least 50% of the insulin binds to receptors, initiates specific hepatic actions (stimulation of hepatic glucose uptake and suppression of glycogenolysis, gluconeogenesis, and ketogenesis), and is subsequently degraded. Most of the insulin molecules that pass through the liver into the main circulation bind to peripheral insulin receptors, promoting glucose uptake, while the remaining molecules undergo renal elimination. Unlike insulin, C-peptide is subject to neither hepatic nor significant peripheral degradation but is mainly removed by the kidneys. As a result, C-peptide has a longer half-life than insulin (30-35 minutes versus 5-10 minutes), and the molar ratio of circulating insulin to circulating C-peptide is generally below 1, despite equimolar secretion. Until recently, C-peptide was thought to have no physiological function, but it now appears that there may be specific C-peptide cell-surface receptors (most likely belonging to the super-family of G-protein coupled receptors), which influence endothelial responsiveness and skeletal and renal blood flow. In most disease conditions associated with abnormal serum insulin levels, the changes in serum C-peptide levels parallel insulin-related alterations (insulin to C-peptide molar ratio < or =1). Both serum C-peptide and serum insulin levels are elevated in kidney failure and in disease states that lead to augmented primary endogenous insulin secretion (eg, insulinoma, sulfonylurea intoxication). Both also may be raised in any disease states that cause secondary increases in endogenous insulin secretion mediated through insulin resistance, primarily obesity, glucose intolerance, and early type 2 diabetes mellitus (DM), as well as endocrine disorders associated with hypersecretion of insulin-antagonistic hormones (eg, Cushing syndrome, acromegaly). Failing insulin secretion in type 1 DM and longstanding type 2 DM is associated with corresponding reductions in serum C-peptide levels. Discordant serum insulin and serum C-peptide abnormalities are mainly observed in 2 situations:

exogenous insulin administration and the presence of anti-insulin autoantibodies. Factitious hypoglycemia due to surreptitious insulin administration results in appropriate suppression of endogenous insulin and C-peptide secretion. At the same time, the peripherally administered insulin bypasses the hepatic first-pass metabolism. In these situations, insulin levels are elevated and C-peptide levels are decreased. In patients with insulin antibodies, insulin levels are increased because of the prolonged half-life of autoantibody-bound insulin. Some patients with anti-idiotypic anti-insulin autoantibodies experience episodic hypoglycemia caused by displacement of autoantibody-bound insulin.

Useful For: Diagnostic workup of hypoglycemia: -Diagnosis of factitious hypoglycemia due to surreptitious administration of insulin -Evaluation of possible insulinoma -Surrogate measure for the absence or presence of physiological suppressibility of endogenous insulin secretion during diagnostic insulin-induced hypoglycemia (C-peptide suppression test) Assessing insulin secretory reserve in selected diabetic patients (as listed below) who either have insulin autoantibodies or who are receiving insulin therapy: -Assessing residual endogenous insulin secretory reserve -Monitoring pancreatic and islet cell transplant function -Monitoring immunomodulatory therapy aimed at slowing progression of preclinical, or very early-stage type 1 diabetes mellitus

Interpretation: To compare insulin and C-peptide concentrations (ie, insulin to C-peptide ratio): -Convert insulin to pmol/L: insulin concentration in mcIU/mL x 6.945 = insulin concentration in pmol/L -Convert C-peptide to pmol/L: C-peptide concentration in ng/mL x 331 = C-peptide concentration in pmol/L Factitious hypoglycemia due to surreptitious insulin administration results in elevated serum insulin levels and low or undetectable C-peptide levels, with a clear reversal of the physiological molar insulin to C-peptide ratio (< or =1) to an insulin to C-peptide ratio of greater than 1. By contrast, insulin and C-peptide levels are both elevated in insulinoma and the insulin to C-peptide molar ratio is 1 or less. Sulfonylurea ingestion also is associated with preservation of the insulin to C-peptide molar ratio of 1 or less. In patients with insulin autoantibodies, the insulin to C-peptide ratio may be reversed to greater than 1, because of the prolonged half-life of autoantibody-bound insulin. Dynamic testing may be necessary in the workup of hypoglycemia; the C-peptide suppression test is most frequently employed. C-peptide levels are measured following induction of hypoglycemia through exogenous insulin administration. The test relies on the demonstration of the lack of suppression of serum C-peptide levels within 2 hours following insulin-induced hypoglycemia in patients with insulinoma. Reference intervals have not been formally verified in-house for pediatric patients. The published literature indicates that reference intervals for adult and pediatric patients are comparable.

Reference Values:

1.1-4.4 ng/mL

Reference interval applies to fasting patients.

Reference intervals have not been formally verified in-house for pediatric patients. The published literature indicates that reference intervals for adult and pediatric patients are comparable.

Clinical References: 1. Service FJ, O'Brien PC, Kao PC, Young WF Jr. C-peptide suppression test: effects of gender, age, and body mass index; implications for the diagnosis of insulinoma. J Clin Endocrinol Metab. 1992;74:204-210 2. Lebowitz MR, Blumenthal SA. The molar ratio of insulin to C-peptide. An aid to the diagnosis of hypoglycemia due to surreptitious (or inadvertent) insulin administration. Arch Int Med. 1993;153(5):650-655 3. Leighton E, Sainsbury CA, Jones GC. A practical review of C-peptide testing in diabetes. Diabetes Ther. 2017;8(3):475-487 4. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet.Med. 2013;30(7):803-817. doi:10.1111/dme.12159 5. Ahn CH, Kim LK, Lee JE, et al. Clinical implications of various criteria for the biochemical diagnosis of insulinoma. Endocrinol Metab (Seoul). 2014;29(4):498-504. doi:10.3803/EnM.2014.29.4.498 6. Young DS, Huth EJ. SI Units for Clinical Measurement. American College of Physicians; 1998

CRPRO
70409

C-Reactive Protein (CRP) Immunostain, Technical Component Only

Clinical Information: C-reactive protein (CRP) is an acute-phase reactant associated with host defense that promotes agglutination and complement fixation. CRP can be used with a panel of immunohistochemical markers (beta-catenin, liver fatty acid-binding protein, glutamine synthetase, and amyloid A) to distinguish hepatic adenoma from focal nodular hyperplasia and non-neoplastic liver. CRP, along with amyloid A, is overexpressed in inflammatory (type 3) hepatic adenoma. CRP may stain hepatocytes in nonneoplastic liver tissue in areas of nonspecific inflammation.

Useful For: Classification of hepatic adenomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Ma Y, Lu M, Deng Y, et al: The preparation of C-reactive protein immunosensor based on nano-mimetic enzyme Co3O4. J Biomed Nanotechnol. 2018;14(6):1169-1177 2. Wang M, Meng S, Gu M, et al. An enzyme-linked immunosorbent assay for c-reactive protein based on gold nanoparticles at metal porphyrin porous compound. J Biomed Nanotechnol. 2019;15(10):2100-2107 3. Yeh Y, Lei H, Chen M, et al. C-reactive protein (CRP) is a promising diagnostic immunohistochemical marker for intrahepatic cholangiocarcinoma and is associated with better prognosis. Am J Surg Pathol. 2017;41(12):1630-1641 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CRP
9731

C-Reactive Protein (CRP), Serum

Clinical Information: C-reactive protein (CRP) is one of the most sensitive acute-phase reactants for inflammation. CRP is synthesized by the liver and consists of 5 identical polypeptide chains that form a 5-membered ring with a molecular weight of 105,000 Da. Complexed CRP activates the classical complement pathway. The CRP response frequently precedes clinical symptoms, including fever. CRP elevations are nonspecific and may be useful for the detection of systemic inflammatory processes; to assess treatment of bacterial infections with antibiotics; to detect intrauterine infections with concomitant premature amniorrhexis; to differentiate between active and inactive forms of disease with concurrent infection, eg, in patients suffering from systemic lupus erythematosus or colitis ulcerosa; to therapeutically monitor rheumatic disease and assess antiinflammatory therapy; to determine the presence of postoperative complications at an early stage, such as infected wounds, thrombosis, and pneumonia; and to distinguish between infection and bone marrow rejection. Postoperative monitoring of CRP levels of patients can aid in the recognition of unexpected complications (persisting high or increasing levels). Measuring changes in the concentration of CRP provides useful diagnostic information about the level of acuity and severity of a disease. It also allows judgments about the disease genesis. Persistence of a high serum CRP concentration is usually a grave prognostic sign that generally indicates the presence of an uncontrolled infection.

Useful For: Detecting systemic inflammatory processes Detecting infection and assessing response to antibiotic treatment of bacterial infections Differentiating between active and inactive disease forms with concurrent infection

Interpretation: In normal healthy individuals, C-reactive protein (CRP) is a trace protein (<5 mg/L). Elevated values are consistent with an acute inflammatory process. After onset of an acute phase response, the serum CRP concentration rises rapidly (within 6-12 hours and peaks at 24-48 hours) and extensively. Concentrations above 100 mg/L are associated with severe stimuli such as major trauma and severe infection (sepsis).

Reference Values:

<5.0 mg/L

Reference values apply to all ages.

Clinical References: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

HSCRP
606909

C-Reactive Protein, High Sensitivity, Serum

Clinical Information: C-reactive protein (CRP) is a biomarker of inflammation. Serum CRP concentrations increase rapidly and dramatically (100-fold or more) in response to tissue injury or inflammation. High-sensitivity CRP (hs-CRP) is more precise than standard CRP when measuring baseline (ie, normal) concentrations and enables a measure of chronic inflammation. Atherosclerosis is an inflammatory disease and hs-CRP has been endorsed by multiple guidelines as a biomarker of atherosclerotic cardiovascular disease risk.(1-3) A large prospective clinical trial demonstrated significantly less cardiovascular risk for patients with hs-CRP less than 2.0 mg/L.(1) More aggressive treatment strategies may be warranted in patients with hs-CRP of 2.0 mg/L or higher.

Useful For: Assessment of risk of developing myocardial infarction in patients presenting with acute coronary syndromes Assessment of risk of developing cardiovascular disease or ischemic events in individuals who do not manifest disease at present

Interpretation: Values greater than 2.0 mg/L suggest an increased likelihood of developing cardiovascular disease or ischemic events.

Reference Values:

> or =18 years: <2.0 mg/L

Reference values have not been established for patients who are younger than 18 years.

Clinical References: 1. European Association for Cardiovascular Prevention and Rehabilitation, Reiner Z, Catapano AL, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32:1769-1818 2. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. Circulation. 2014;129:S49-S73 3. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. J Clin Lipidol. 2014;8:473-488 4. Cardiac C-Reactive Protein (Latex) High Sensitive. V 12.0. Package insert: Roche Diagnostics; 03/2019 5. Ridker PM, Danielson E, Fonseca FA, et al. Reduction in C-reactive protein and LDL-cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet. 2009;373:1175-1182 6. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2019;140:563-595 7. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease. Application to clinical and public health practice. A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107(3):499-511. doi:10.1161/01.cir.0000052939.59093.45

C1ES
8198

C1 Esterase Inhibitor Antigen, Serum

Clinical Information: C1 esterase inhibitor blocks the activation of C1 (first component of the complement cascade) to its active form. The deficiency of C1 esterase inhibitor results in the inappropriate activation of C1 and the subsequent release of an activation peptide from C2 with kinin-like activity. This kinin-like peptide enhances vascular permeability. C1 esterase inhibitor deficiency results in hereditary or acquired angioedema. This disease is an autosomal dominant inherited condition, in which exhaustion of the abnormally low levels of C1 esterase inhibitor results in C1 activation, breakdown of C2 and C4, and subsequent acute edema of subcutaneous tissue, the gastrointestinal tract, or the upper respiratory tract. The disease responds to attenuated androgens. Because 15% of C1 inhibitor deficiencies have nonfunctional protein, some patients will have abnormal functional results (C1INF / C1 Esterase Inhibitor, Functional, Serum) in the presence of normal (or elevated) antigen levels.

Useful For: Diagnosis of hereditary angioedema Monitoring levels of C1 esterase inhibitor in response to therapy

Interpretation: Abnormally low results are consistent with a heterozygous C1 esterase inhibitor deficiency and hereditary angioedema. Fifteen percent of hereditary angioedema patients have a normal or elevated level but nonfunctional C1 esterase inhibitor protein. Detection of these patients requires a functional measurement of C1 esterase inhibitor; C1INF / C1 Esterase Inhibitor, Functional, Serum. Measurement of C1q antigen levels (C1Q / Complement C1q, Serum) is key to the differential diagnoses of acquired or hereditary angioedema. Those patients with the hereditary form of the disease will have normal levels of C1q, while those with the acquired form of the disease will have low levels. Studies in children show that adult levels of C1 inhibitor are reached by 6 months of age.

Reference Values:
19-37 mg/dL

Clinical References: 1. Willrich MAV, Braun KMP, Moyer AM, Jeffrey DH, Frazer-Abel A. Complement testing in the clinical laboratory. Crit Rev Clin Lab Sci. 2021;58(7):447-478. doi:10.1080/10408363.2021.19072972 2. Drouet C, Lopez-Lera A, Ghannam A, et al. SERPING1 variants and C1-INH biological function: A close relationship with C1-INH-HAE. Front Allergy. 2022;3:835503. doi:10.3389/falgy.2022.835503 3. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507. doi:10.1007/s10875-022-01289-3 4. Brodszki N, Frazer-Abel A, Grumach AS, et al. European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA) Complement Guideline: Deficiencies, Diagnosis, and Management. J Clin Immunol. 2020;40(4):576-591. doi:10.1007/s10875-020-00754-1 5. Patel G, Pongracic JA. Hereditary and acquired angioedema. Allergy Asthma Proc. 2019;40(6):441-445. doi:10.2500/aap.2019.40.4267 6. Longhurst HJ, Tarzi MD, Ashworth F, et al. C1 inhibitor deficiency: 2014 United Kingdom consensus document [published correction appears in Clin Exp Immunol. 2015;182(3):346]. Clin Exp Immunol. 2015;180(3):475-483. doi:10.1111/cei.12584

C1INF
616906

C1 Esterase Inhibitor, Functional, Serum

Clinical Information: C1 esterase inhibitor (C1-INH) is a multispecific protease inhibitor that is present in normal human plasma and serum and regulates enzymes of the complement, coagulation, fibrinolytic, and kinin-forming systems. The enzymes (proteases) regulated by this protein include the C1r and C1s subunits of the activated first component of complement (the C1qrs complex), activated Hageman factor (factor XIa), kallikrein (Fletcher factor), and plasmin. A deficiency of functionally

active C1-INH may lead to life-threatening angioedema. Two major forms of C1- INH deficiency have been reported: the congenital form, termed hereditary angioedema (HAE), and the acquired form, which is associated with a variety of diseases, acquired angioedema (AAE). In HAE, there is insufficient C1-INH to negatively regulate bradykinin release and stop angioedema attacks from occurring. The mechanism of HAE attacks is distinct from an allergic angioedema as it is not mediated by histamine release via mast cell activation. Therefore, HAE patients are unresponsive to antihistamines or corticosteroids. There are 2 main types of HAE that are attributed to C1-INH deficiency (type I) or dysfunction (type II), resulting in C1-INH activity ranging from less than 20% to 50% of normal. Type I HAEs, representing approximately 85% of patients, are associated with low circulating concentrations of C1-INH, leading to a concomitant decrease in C1-INH function. In type II HAEs, normal or elevated concentrations of functionally inactive C1-INH are produced. The relative proportion of type I and type II HAE may differ based on geographical location. A third HAE subtype with unknown prevalence termed "HAE with normal C1-INH" has been described. Although poorly characterized, a minority of these patients is known to harbor a variant in Factor XII; the disease origin for the remainder of patients remains unknown. Factor XII is the zymogen form of Factor XIIa and plays a key role in bradykinin production as part of the contact system. Angioedema due to C1-INH deficiency can also be acquired during adulthood in the fifth decade of life or later. The prevalence of AAE is extremely low and is estimated at 10% of HAE. AAE is frequently associated with monoclonal gammopathies or lymphoproliferative disease as well as different types of cancer and autoimmune diseases. AAE may be caused by development of anti-C1-INH autoantibodies, which act to reduce the functional activity or increase the catabolism of C1-INH. For patients exhibiting symptoms associated with HAE, evaluation of pertinent family history in combination with laboratory results for C1-INH function and concentration, C4 concentration, and C1q concentration can assist in HAE diagnosis and determination of HAE type. Identification of low C1-INH function and low C4 concentration support the diagnosis of HAE and was found to have 98% specificity towards C1-INH deficiency and a negative predictive value of 95%. C4 is decreased owing to excessive consumption through the classical pathway in the absence of inhibition by C1-INH. Due to low disease prevalence, false-positive results are common and therefore, repeated testing is recommended to confirm findings.

Useful For: Diagnosing hereditary angioedema Monitoring response to C1 esterase inhibitor replacement therapy

Interpretation: The C1 esterase inhibitor (C1-INH) concentration assay can be used to distinguish type I hereditary angioedema (HAE), with low C1-INH concentration, from type II HAE characterized by normal or elevated concentration. Furthermore, serum C1q concentrations can be used to differentiate HAE from acquired angioedema (AAE) forms of angioedema as the latter is characterized by decreased C1q antigen concentration and autoantibodies against C1-INH. Genetic analysis for SERPING1 variants status may also help exclude HAE. -Nonfunctional C1-INH results are consistent with HAE -Patients with current attacks may also have low C2 and C4 concentrations due to C1 activation and complement activation of the classical pathway (consumption). -Patients with acquired C1-INH deficiency have a low C1q concentration and/or function in addition to low C1-INH. Table. Laboratory Features Consistent with Hereditary and Acquired Angioedema Subtypes Type I hereditary angioedema Type II hereditary angioedema Acquired angioedema C1 esterase inhibitor (C1-INH) concentration Low Normal/high Low C1-INH function Low Low Low/normal C4 concentration Low Low Low C1q concentration Normal Normal Low Anti-C1-INH antibodies Absent Absent Present C3 concentration Normal Normal Normal Family history Yes Yes No

Reference Values:
>67% normal (normal)
41-67% normal (equivocal)
<41% normal (abnormal)

Clinical References: 1. Stoppa-Lyonnet D, Tosi M, Laurent J, Sobel A, Lagrue G, Meo T. Altered C1 inhibitor genes in type I hereditary angioedema. N Engl J Med. 1987;317(1):1-6.

doi:10.1056/NEJM198707023170101 2. Frigas E. Angioedema with acquired deficiency of the C1 inhibitor: a constellation of syndromes. Mayo Clin Proc. 1989;64(10):1269-1275. doi:10.1016/s0025-6196(12)61290-7 3. Frazer-Abel A, Sepiashvili L, Mbughuni MM, Willrich MA. Overview of laboratory testing and clinical presentations of complement deficiencies and dysregulation. Adv Clin Chem. 2016;77:1-75. doi:10.1016/bs.acc.2016.06.001

C1QFX
83374

C1q Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classical pathway, 2) the alternative (or properdin) pathway, and 3) the lectin (or mannan binding lectin) pathway. The classical pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. A single IgM molecule or 2 IgG molecules are sufficient to trigger activation of the recognition complex initiated by C1q. The activation process triggers a cascade that includes an amplification loop. The amplification loop is mediated by C3, with cleavage of a series of proteins, and results in 3 main end products: 1) anaphylatoxins that promote inflammation (C3a, C5a), 2) opsonization peptides that are chemotactic for neutrophils (C3b) and facilitate phagocytosis, and 3) the membrane attack complex, which promotes cell lysis. There are 3 subunits that compose the C1 component, designated as C1q, C1r, and C1s. The C1q subunit recognizes and binds to immunoglobulin complexed to antigen and initiates the complement cascade. Congenital deficiencies of any of the early complement components (C1-C4) result in an inability to generate the peptides that are necessary to clear immune complexes and to attract neutrophils or generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease in which complement deficiency may be an etiologic factor. Inherited deficiency of C1 is rare. Just over 40 cases have been reported for C1q deficiency, and another 20 cases have been described for C1s and C1r deficiency. C1 deficiency is associated with increased incidence of immune complex disease (systemic lupus erythematosus [SLE], polymyositis, glomerulonephritis, and Henoch-Schonlein purpura), with SLE the most common manifestation of C1 deficiency. The SLE associated with C1 deficiency is similar to SLE without complement deficiency, but the age of onset is often prior to puberty. Low C1 levels have also been reported in patients with abnormal immunoglobulin levels (Bruton and common variable hypogammaglobulinemia and severe combined immunodeficiency), and this is most likely due to increased catabolism. Complement levels can be detected by antigen assays that quantitate the amount of the protein. For most of the complement proteins a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

Useful For: Diagnosis of C1 deficiency Investigation of a patient with an absent total complement level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). The measurement of C1q activity is an indicator of the amount of C1 present. Absent C1q levels in the presence of normal C3 and C4 values are consistent with a C1 deficiency. Low C1q levels in the presence of low C4 but normal C3 may indicate the presence of an acquired inhibitor (autoantibody) to C1 esterase inhibitor.

Reference Values:
34-63 U/mL

Clinical References: 1. Sonntag J, Brandenburg U, Polzehl D, et al. Complement systems in healthy term newborns: reference values in umbilical cord blood. Pediatr Dev Pathol. 1998;1(2):131-135 2. Prellner K, Sjoholm AG, Truedsson L. Concentrations of C1q, factor B, factor D

and properdin in healthy children, and the age-related presence of circulating C1r-C1s complexes. Acta Paediatr Scand. 1987;76(6):939-943 3. Davis ML, Austin C, Messmer BL, et al. IFCC-standardization pediatric reference intervals for 10 serum proteins using the Beckman Array 360 system. Clin Biochem. 1996;29(5):489-492 4. Gaither TA, Frank MM. Complement. In: Henry JB, ed. Clinical Diagnosis and Management by Laboratory Methods. 17th ed. WB Saunders Company: 1984:879-892 5. O'Neil KM. Complement deficiency. Clin Rev Allergy Immunol. 2000;19:83-108 6. Frank MM. Complement deficiencies. Pediatr Clin North Am. 2000;47(6):1339-1354 7. Brodszki N, Frazer-Abel A, Grumach AS, et al. European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA) Complement Guideline: Deficiencies, diagnosis, and management. J Clin Immunol. 2020;40(4):576-591 8. Willrich MAV, Braun KMP, Moyer AM, Jeffrey DH, Frazer-Abel A. Complement testing in the clinical laboratory. Crit Rev Clin Lab Sci. 2021;58(7):447-478. doi:10.1080/10408363.2021.1907297

C2FXN
32137

C2 Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classical pathway, 2) the alternative (or properdin) pathway, and 3) the lectin (or mannan binding lectin) pathway. The classical pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. A single IgM molecule or 2 IgG molecules are sufficient to trigger activation of the recognition complex initiated by C1q. This activation process triggers a cascade that includes an amplification loop. The amplification loop is mediated by C3, with cleavage of a series of proteins, and results in 3 main end products: 1) anaphylatoxins that promote inflammation (C3a, C5a), 2) opsonization peptides that are chemotactic for neutrophils (C3b) and facilitate phagocytosis, and 3) the membrane attack complex, which promotes cell lysis. The absence of early components (C1, C2, C3, C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate lytic activity or to clear immune complexes. They may also have symptoms that suggest autoimmune disease in which complement deficiency may be an etiologic factor. Although rare, C2 deficiency is the most common inherited complement deficiency. Homozygous C2 deficiency has an estimated prevalence ranging from 1 in 10,000 to 1 in 40,000 (the prevalence of heterozygotes is 1 in 100 to 1 in 50). Half of the homozygous patients are clinically normal. However, discoid lupus erythematosus or systemic lupus erythematosus (SLE) occurs in approximately one-third of patients with homozygous C2 deficiency. Patients with SLE and a C2 deficiency frequently have a normal anti-double-stranded DNA titer. Clinically, many have lupus-like skin lesions and photosensitivity, but immunofluorescence studies may fail to demonstrate immunoglobulin or complement along the epidermal-dermal junction. Other diseases reported to be associated with C2 deficiency include dermatomyositis, glomerulonephritis, vasculitis, atrophodema, cold urticaria, inflammatory bowel disease, and recurrent infections. The laboratory findings that suggest C2 deficiency include a hemolytic complement of nearly zero, with normal values for C3 and C4.

Useful For: Investigation of a patient with a low (absent) hemolytic complement

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent (or low) C2 levels in the presence of normal C3 and C4 values are consistent with a C2 deficiency. Low C2 levels in the presence of low C3 and C4 values are consistent with a complement-consumptive process. Low C2 and C4 values, in the presence of normal values for C3 is suggestive of C1 esterase inhibitor deficiency.

Reference Values:
25-47 U/mL

Clinical References: 1. Gaither TA, Frank MM. Complement. In: Henry JB, ed. Clinical Diagnosis and Management by Laboratory Methods. 17th ed. WB Saunders Company; 1984:879-892 2. Agnello V. Complement deficiency states. Medicine. 1978;57:1-23 3. Buckley D, Barnes L. Childhood subacute cutaneous lupus erythematosus associated with homozygous complement 2 deficiency. Pediatr Dermatol. 1995;12:327-330 4. Willrich MAV, Braun KMP, Moyer AM, Jeffrey DH, Frazer-Abel A. Complement testing in the clinical laboratory. Crit Rev Clin Lab Sci. 2021;58(7):447-478. doi:10.1080/10408363.2021.1907297

C2
81835

C2 Complement, Functional, with Reflex, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classical pathway, 2) the alternative (or properdin) pathway, and 3) the lectin (or mannan binding lectin) pathway. The classical pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. A single IgM molecule or 2 IgG molecules are sufficient to trigger activation of the recognition complex initiated by C1q. This activation process triggers a cascade that includes an amplification loop. The amplification loop in mediated by C3, with cleavage of a series of proteins, and results in 3 main end products: 1) anaphylatoxins that promote inflammation (C3a, C5a), 2) opsonization peptides that are chemotactic for neutrophils (C3b) and facilitate phagocytosis, and 3) the membrane attack complex, which promotes cell lysis. The absence of early components (C1, C2, C3, C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate lytic activity or to clear immune complexes. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease, of which complement deficiency may be an etiologic factor. Although rare, C2 deficiency is the most common inherited complement deficiency. Homozygous C2 deficiency has an estimated prevalence ranging from 1 in 10,000 to 1 in 40,000 (the prevalence of heterozygotes is 1 in 100 to 1 in 50). Half of the homozygous patients are clinically normal. However, discoid lupus erythematosus or systemic lupus erythematosus (SLE) occurs in approximately one-third of patients with homozygous C2 deficiency. Patients with SLE and a C2 deficiency frequently have a normal anti-double stranded DNA titer. Clinically, many have lupus-like skin lesions and photosensitivity, but immunofluorescence studies may fail to demonstrate immunoglobulin or complement along the epidermal-dermal junction. Other diseases reported to be associated with C2 deficiency include dermatomyositis, glomerulonephritis, vasculitis, atrophoderma, cold urticaria, inflammatory bowel disease, and recurrent infections. The laboratory findings that suggest C2 deficiency include a hemolytic complement of nearly zero, with normal values for C3 and C4.

Useful For: Investigation of a patient with a low (absent) hemolytic complement, with reflex testing to C3 and C4, if appropriate

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent (or low) C2 levels in the presence of normal C3 and C4 values are consistent with a C2 deficiency. Low C2 levels in the presence of low C3 and C4 values are consistent with a complement-consumptive process. Low C2 and C4 values, in the presence of normal values for C3 is suggestive of C1 esterase inhibitor deficiency.

Reference Values:
25-47 U/mL

Clinical References: 1. Gaither TA, Frank MM. Complement. In: Henry JB, ed. Clinical Diagnosis and Management by Laboratory Methods. 17th ed. WB Saunders Company; 1984:879-892 2.

O'Neil KM. Complement deficiency. Clin Rev Allergy Immunol. 2000;19:83-108 3. Frank MM. Complement deficiencies. Pediatr Clin North Am. 2000;47(6):1339-1354 4. Agnello V. Complement deficiency states. Medicine. 1978;57(1):1-23 5. Buckley D, Barnes L. Childhood subacute cutaneous lupus erythematosus associated with homozygous complement 2 deficiency. Pediatr Dermatol. 1995;12(4):327-330 6. Willrich MAV, Braun KMP, Moyer AM, Jeffrey DH, Frazer-Abel A. Complement testing in the clinical laboratory. Crit Rev Clin Lab Sci. 2021;58(7):447-478. doi:10.1080/10408363.2021.1907297

C3FX
81090

C3 Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classical pathway, 2) the alternative (or properdin) pathway, and 3) the lectin (or mannan-binding lectin) pathway. The classical pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. A single IgM molecule or 2 IgG molecules are sufficient to trigger activation of the recognition complex initiated by C1q. The activation process triggers a cascade that includes an amplification loop. The amplification loop is mediated by C3, with cleavage of a series of proteins, and results in 3 main end products: 1) anaphylatoxins that promote inflammation (C3a, C5a), 2) opsonization peptides that are chemotactic for neutrophils (C3b) and facilitate phagocytosis, and 3) the membrane attack complex (MAC), which promotes cell lysis. The absence of early components (C1-C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to clear immune complexes or to generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease in which complement deficiency may be an etiologic factor. The complement protein C3 is at the entry point for all 3 activation pathways to activate the MAC. C3 deficiency may result in severe and recurrent pneumococcal and neisserial infections. Deficiency is very rare, with less than 30 cases described. Complement levels can be detected by antigen assays that quantitate the amount of the protein (C3 / Complement C3, Serum). For most of the complement proteins, a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

Useful For: Diagnosis of C3 deficiency Investigation of a patient with undetectable total complement level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C3 levels in the presence of other normal complement values are consistent with a C3 deficiency.

Reference Values:
21-50 U/mL

Clinical References: 1. Davis ML, Austin C, Messmer BL, et al. IFCC-standardization pediatric reference intervals for 10 serum proteins using the Beckman Array 360 system. Clin Biochem. 1996;29(5):489-492 2. Gaither TA, Frank MM. Complement. In: Henry JB, ed. Clinical Diagnosis and Management by Laboratory Methods. 17th ed. WB Saunders Company; 1984:879-892 3. O'Neil KM. Complement deficiency. Clin Rev Allergy Immunol. 2000;19(2):83-108 4. Frank MM. Complement deficiencies. Pediatr Clin North Am. 2000;47(6):1339-1354 5. Brodszki N, Frazer-Abel A, Grumach AS, et al. European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA) Complement Guideline: Deficiencies, diagnosis, and management. J Clin Immunol. 2020;40(4):576-591 6. Willrich MAV, Braun KMP, Moyer AM, Jeffrey DH, Frazer-Abel A. Complement testing in the clinical laboratory. Crit Rev Clin Lab Sci. 2021;58(7):447-478. doi:10.1080/10408363.2021.1907297

FC3AR
75729

C3a Level By RIA

Reference Values:
0-780 ng/mL

C4U
88829

C4 Acylcarnitine, Quantitative, Random, Urine

Clinical Information: An isolated elevation of iso-/butyrylcarnitine (C4) in plasma or newborn screening blood spots is related to a diagnosis of either short chain acyl-CoA dehydrogenase (SCAD) deficiency or isobutyryl-CoA dehydrogenase (IBD) deficiency. Diagnostic testing by acylcarnitine analysis, including the evaluation of C4 excretion in urine, is necessary to differentiate the 2 clinical entities.(1) Patients with IBD deficiency excrete an abnormal amount of C4 acylcarnitine in urine, whereas patients with SCAD deficiency can have a normal excretion of this metabolite.

Useful For: Evaluation of patients with abnormal newborn screens showing elevations of iso-/butyrylcarnitine to aid in the differential diagnosis of short-chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies

Interpretation: Almost all patients with isobutyryl-CoA dehydrogenase deficiency excrete an abnormal amount of iso-/butyrylcarnitine (C4) in their urine. Some, but not all, affected individuals also excrete elevated levels of isobutyrylglycine. Conversely, patients with short-chain acyl-CoA dehydrogenase deficiency can have a normal excretion of C4.

Reference Values:
<3.00 millimoles/mole creatinine

Clinical References: 1. Miller MJ, Cusmano-Ozog K, Oglesbee D, Young S; ACMG Laboratory Quality Assurance Committee: Laboratory analysis of acylcarnitines, 2020 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(2):249-258 2. Oglesbee D, Vockley J, Ensenauer RE, et al. Ten cases of isobutyryl-CoA dehydrogenase (IBDH) deficiency detected by newborn screening. J Inherit Metab Dis. 2005;28(Suppl 1):13. doi: 10.1007/s10545-004-0001-x 3. Oglesbee D, He M, Majumder N, et al. Development of a newborn screening follow-up algorithm for the diagnosis of isobutyryl-CoA dehydrogenase deficiency. Genet Med. 2007;9(2):108-116

C4FX
83391

C4 Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classical pathway, 2) the alternative (or properdin) pathway, and 3) the lectin (or mannan-binding lectin) pathway. The classical pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. A single IgM molecule or 2 IgG molecules are sufficient to trigger activation of the recognition complex initiated by C1q. The activation process triggers a cascade that includes an amplification loop. The amplification loop is mediated by C3, with cleavage of a series of proteins, and results in 3 main end products: 1) anaphylatoxins that promote inflammation (C3a, C5a), 2) opsonization peptides that are chemotactic for neutrophils (C3b) and facilitate phagocytosis, and 3) the membrane attack complex, which promotes cell lysis. The absence of early components (C1-C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate the peptides that are necessary clear immune complexes and to attract neutrophils or to generate to lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms

that suggest autoimmune disease, of which complement deficiency may be an etiologic factor. Approximately 30 cases of homozygous C4 deficiency have been reported. Most of these patients have systemic lupus erythematosus (SLE) or glomerulonephritis, IgA nephropathy. Patients with C4 deficiency may also have frequent bacterial infections and may present with autoimmune diseases such as SLE and SLE-like syndromes or rheumatoid arthritis. C4 is coded by two different genes in the major histocompatibility complex on human chromosome 6. Seventy-five percent of the population has two C4A and two C4B genes. However, the total sum of C4A and C4B genes in an individual can range from zero to 8 or more copies, giving this protein a wide range of concentrations and an even wider range of function in the general population. Most of the partial C4 deficiencies are without consequence, although deficiency of C4A is associated with a 15% incidence of SLE. Complement levels can be detected by antigen assays that quantitate the amount of the protein (C4 / Complement C4, Serum). For most of the complement proteins, a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

Useful For: Diagnosis of C4 deficiency Investigation of a patient with an undetectable total complement level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C4 levels in the presence of normal C3 and C2 values are consistent with a C4 deficiency. Normal results indicate both normal C4 protein levels and normal functional activity. In hereditary angioedema, a disorder caused by C1 esterase inhibitor deficiency, absent or low C4 and C2 values are seen in the presence of normal C3 (due to activation and consumption of C4 and C2).

Reference Values:
22-45 U/mL

Clinical References: 1. Davis ML, Austin C, Messmer BL, et al. IFCC-standardization pediatric reference intervals for 10 serum proteins using the Beckman Array 360 system. Clin Biochem. 1996;29(5):489-492 2. Gaither TA, Frank MM. Complement. In: Henry JB, ed. Clinical Diagnosis and Management by Laboratory Methods. 17th ed. WB Saunders Company; 1984:879-892 3. O'Neil KM. Complement deficiency. Clin Rev in Allergy Immunol. 2000;19(2):83-108 4. Frank MM. Complement deficiencies. Pediatr Clin North Am. 2000;47(6):1339-1354 5. Brodszki N, Frazer-Abel A, Grumach AS, et al. European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA) Complement Guideline: Deficiencies, Diagnosis, and Management. J Clin Immunol. 2020;40(4):576-591 6. Willrich MAV, Braun KMP, Moyer AM, Jeffrey DH, Frazer-Abel A. Complement testing in the clinical laboratory. Crit Rev Clin Lab Sci. 2021;58(7):447-478. doi:10.1080/10408363.2021.1907297

FC4AL
75726

C4 Level by RIA

Reference Values:
0-2830 ng/mL

C5AG
9266

C5 Complement, Antigen, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: the classic pathway, the alternative (or properdin) pathway, and the lectin activation (mannan-binding protein: MBP) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for

neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). The absence of early components (C1-C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to clear immune complexes or to generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease, and complement deficiency may be an etiologic factor in the development of autoimmune disease. More than 30 cases of C5 deficiency have been reported. Most of these patients have neisserial infections.

Useful For: Diagnosis of C5 deficiency Investigation of a patient with an absent total complement (CH50) level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C5 levels in the presence of normal C3 and C4 values are consistent with a C5 deficiency. Absent C5 levels in the presence of low C3 and C4 values suggest complement consumption. A small number of cases have been described in which the complement protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency; for more information see C5FX / C5 Complement, Functional, Serum.

Reference Values:
10.6-26.3 mg/dL

Clinical References: 1. Sonntag J, Brandenburg U, Polzehl D, et al. Complement system in healthy term newborns: reference values in umbilical cord blood. Pediatr Dev Pathol. 1998;1(2):131-135 2. Prellner K, Sjoholm AG, Truedsson L. Concentrations of C1q, factor B, factor D and properdin in healthy children, and the age-related presence of circulating C1r-C1s complexes. Acta Paediatr Scand. 1987;76(6):939-943 3. Davis ML, Austin C, Messmer BL, Nichols WK, Bonin AP, Bennett MJ. IFCC-standardized pediatric reference intervals for 10 serum proteins using the Beckman Array 360 system. Clin Biochem. 1996;29(5):489-492 4. Gaither TA, Frank MM. Complement. In: Henry JB. Clinical Diagnosis and Management by Laboratory Methods. 17th ed. Saunders; 1984:879-892 5. O'Neil KM. Complement deficiency. Clin Rev Allergy Immunol. 2000;19(2):83-108 6. Frank MM. Complement deficiencies. Pediatr Clin North Am. 2000;47(6):1339-1354 7. Volokhina EB, van de Kar NC, Bergseth G, et al. Sensitive, reliable and easy-performed laboratory monitoring of eculizumab therapy in atypical hemolytic uremic syndrome. Clin Immunol. 2015;160(2):237-243. 8Andreguetto B, Murray D, Snyder M, Tostrud L, Willrich MA. Abstract 003: The impact of eculizumab in complement assays. Mol Immunol. 2015;67:119-120. doi:10.1016/j.molimm.2015.03.013

C5FX
83392

C5 Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classical pathway, 2) the alternative (or properdin) pathway, and 3) the lectin (mannan-binding lectin) pathway. The classical pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. A single IgM molecule or 2 IgG molecules are sufficient to trigger activation of the recognition complex initiated by C1q. The activation process triggers a cascade that includes an amplification loop. The amplification loop is mediated by C3, with cleavage of a series of proteins, and results in 3 main end products: 1) anaphylatoxins that promote inflammation (C3a, C5a), 2) opsonization peptides that are chemotactic for neutrophils (C3b) and facilitate phagocytosis, and 3) the membrane attack complex (MAC), which promotes cell lysis. Patients with deficiencies of the late

complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC and may have increased susceptibility to neisserial infections. There have been between 20 and 100 cases of C5 deficiency reported. Complement levels can be detected by antigen assays that quantitate the amount of the protein (C5AG / C5 Complement, Antigen, Serum). For most of the complement proteins, a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

Useful For: Diagnosis of C5 deficiency Investigation of a patient with an undetectable total complement level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C5 levels in the presence of normal C3 and C4 values are consistent with a C5 deficiency. Absent C5 levels in the presence of low C3 and C4 values suggest complement consumption. Normal results indicate both normal C5 protein levels and normal functional activity.

Reference Values:
29-53 U/mL

Clinical References: 1. Sonntag J, Brandenburg U, Polzehl D, et al. Complement systems in healthy term newborns: reference values in umbilical cord blood. Pediatr Dev Pathol. 1998;1(2):131-135 2. Prellner K, Sjoholm AG, Truedsson L. Concentrations of C1q, factor B, factor D and properdin in healthy children, and the age-related presence of circulating C1r-C1s complexes. Acta Paediatr Scand. 1987;76(6):939-943 3. Davis ML, Austin C, Messmer BL, et al. IFCC-standardization pediatric reference intervals for 10 serum proteins using the Beckman Array 360 system. Clin Biochem. 1996;29(5):489-492 4. Gaither TA, Frank MM: Complement. In: Henry JB, ed. Clinical Diagnosis and Management by Laboratory Methods. 17th ed. WB Saunders Company; 1984:879-892 5. O'Neil KM. Complement deficiency. Clin Rev Allergy Immunol. 2000;19(2):83-108 6. Frank MM. Complement deficiencies. Pediatr Clin North Am. 2000 Dec;47(6):1339-1354 7. Willrich MAV, Braun KMP, Moyer AM, Jeffrey DH, Frazer-Abel A. Complement testing in the clinical laboratory. Crit Rev Clin Lab Sci. 2021;58(7):447-478. doi:10.1080/10408363.2021.1907297

C5DCU
88831

C5-DC Acylcarnitine, Quantitative, Random, Urine

Clinical Information: An isolated elevation of glutarylcarnitine (C5-DC) in plasma or newborn screening blood spots is related to a diagnosis of glutaric aciduria type 1 (GA-1), also known as glutaric acidemia type 1. GA-1 is caused by a deficiency of glutaryl-CoA dehydrogenase. Diagnostic testing by acylcarnitine analysis, including the evaluation of C5DC in urine, is helpful to determine if a patient has GA1.(1) Urinary excretion of C5-DC is a specific biochemical marker of GA-1 that appears to be elevated even in low excretors, those patients who are affected but have normal levels of glutaric acid in urine. GA-1 is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by illness. Many affected individuals also have macrocephaly. Dietary treatment and aggressive interventions during time of illness are recommended to try to prevent or minimize neurologic injury, which is most likely to occur in infancy and early childhood. Prevalence is approximately 1 in 100,000 individuals. The American College of Medical Genetics and Genomics newborn screening work group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see the Practice Resources: ACT Sheets and Algorithms at www.acmg.net.

Useful For: Evaluation of patients with an abnormal newborn screen showing elevations of glutarylcarnitine Diagnosis of glutaric aciduria type 1 deficiency

Interpretation: Elevated excretion of glutarylcarnitine is a specific biochemical marker of glutaric aciduria type 1 that is elevated in affected patients, apparently even in low excretors, ie, those affected individuals with normal levels of glutaric acid in urine.

Reference Values:
<1.54 millimoles/mole creatinine

Clinical References:

C5OHU
88830

C5-OH Acylcarnitine, Quantitative, Random, Urine

Clinical Information: The differential diagnosis of an isolated elevation of 3-hydroxyisovaleryl-/2-methyl-3-hydroxy acylcarnitine (C5-OH) in plasma or (newborn screening) blood spots includes the following disorders: -3-Methylcrotonyl-CoA carboxylase deficiency (common name: 3-methylcrotonylglycinuria), either infantile or maternal -3-Hydroxy 3-methylglutaryl-CoA lyase deficiency -Beta-ketothiolase deficiency -2-Methyl 3-hydroxybutyryl-CoA dehydrogenase deficiency -3-Methylglutaconic aciduria type I -Biotinidase deficiency -Holocarboxylase deficiency Confirmatory and diagnostic testing are necessary to differentiate these clinical entities. This test can be used to differentiate patients with 3-methylcrotonylglycinuria and with 3-methylglutaconic aciduria as they typically excrete larger amounts of C5-OH in urine compared to patients with the other diagnoses. The American College of Medical Genetics and Genomics Newborn Screening Work Group published diagnostic algorithms for the follow-up of infants who had positive newborn screening results. For more information, see the Practice Resources: ACT Sheets and Algorithms at www.acmg.net.

Useful For: Evaluation of patients with an abnormal newborn screen showing elevations of 3-hydroxyisovaleryl-/2-methyl-3-hydroxybutyryl-carnitine

Interpretation: Preliminary data showed that an elevated excretion in urine and concentration in plasma of 3-hydroxyisovaleryl-/2-methyl-3-hydroxy acylcarnitine can be the only biochemical abnormalities in patients with 3-methylcrotonylglycinuria.

Reference Values:
<2.93 millimoles/mole creatinine

Clinical References: 1. Wolfe LA, Finegold DN, Vockley J, et al. Potential misdiagnosis of 3-methylcrotonyl-coenzyme A carboxylase deficiency associated with absent or trace urinary 3-methylcrotonylglycine. Pediatrics. 2007;120(5):e1335-1340 2. Miller MJ, Cusmano-Ozog K, Oglesbee D, Young S; ACMG Laboratory Quality Assurance Committee: Laboratory analysis of acylcarnitines, 2020 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(2):249-258

C6FX
83393

C6 Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classical pathway, 2) the alternative (or properdin) pathway, and 3) the lectin (mannan-binding lectin) pathway. The classical pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. A single IgM molecule or 2 IgG molecules are sufficient to trigger activation of the recognition complex initiated by C1q. The activation process triggers a cascade that includes an amplification loop. The amplification loop is mediated by C3, with cleavage of a series of proteins, and

results in 3 main end products: 1) anaphylatoxins that promote inflammation (C3a, C5a), 2) opsonization peptides that are chemotactic for neutrophils (C3b) and facilitate phagocytosis, and 3) the membrane attack complex (MAC), which promotes cell lysis. Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. Deficiency of C6 is relatively rare, over 50 cases have been described. Most of these patients have systemic meningococcal infection and some have had invasive gonococcal infections. Normal levels of C6 antigen have been reported in patients with dysfunctional C6 lytic activity, hence the recommendation of functional testing.

Useful For: Diagnosis of C6 deficiency Investigation of a patient with an undetectable total complement level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C6 levels in the presence of normal C3 and C4 values are consistent with a C6 deficiency. Absent C6 levels in the presence of low C3 and C4 values suggests complement consumption. Normal results indicate both normal C6 protein levels and normal functional activity.

Reference Values:
32-57 U/mL

Clinical References:

C7FX
81064

C7 Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classical pathway, 2) the alternative (or properdin) pathway, and 3) the lectin (mannan-binding lectin) pathway. The classical pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. A single IgM molecule or 2 IgG molecules are sufficient to trigger activation of the recognition complex initiated by C1q. The activation process triggers a cascade that includes an amplification loop. The amplification loop is mediated by C3, with cleavage of a series of proteins, and results in 3 main end products: 1) anaphylatoxins that promote inflammation (C3a, C5a), 2) opsonization peptides that are chemotactic for neutrophils (C3b) and facilitate phagocytosis, and 3) the membrane attack complex (MAC), which promotes cell lysis. Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. Deficiency of C7 is relatively rare, over 50 cases have been described. The majority of C7 deficiency cases have neisserial infections, but cases with systemic lupus erythematosus, rheumatoid arthritis, scleroderma, and pyoderma gangrenosum have also been reported. The pathogenesis of the rheumatic disease is not clear. Complement levels can be detected by antigen assays that quantitate the amount of the protein. For most of the complement proteins, a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

Useful For: Diagnosis of C7 deficiency Investigation of a patient with an undetectable total complement level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C7 levels in the presence of normal C3 and C4 values are consistent with a C7 deficiency. Absent C7 levels in the presence of low C3 and C4 values suggest complement consumption.

Reference Values:
36-60 U/mL

Clinical References:

C8FX
81065

C8 Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classical pathway, 2) the alternative (or properdin) pathway, and 3) the lectin (mannan-binding lectin) pathway. The classical pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. A single IgM molecule or 2 IgG molecules are sufficient to trigger activation of the recognition complex initiated by C1q. The activation process triggers a cascade that includes an amplification loop. The amplification loop is mediated by C3, with cleavage of a series of proteins, and results in 3 main end products: 1) anaphylatoxins that promote inflammation (C3a, C5a), 2) opsonization peptides that are chemotactic for neutrophils (C3b) and facilitate phagocytosis, and 3) the membrane attack complex (MAC), which promotes cell lysis. Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. Deficiency of C8 is relatively rare, over 50 cases have been described. The C8 protein is comprised of 3 subunits: alpha, beta, and gamma. However, variants leading to deficiency have not been reported in C8 gamma, and the majority are in the C8 beta subunit. C8 deficiency is characterized by recurrent neisserial infections, particularly meningitis. Autoimmune disease (systemic lupus erythematosus-like) has also been reported. Given the 3 subunits, it is possible to have a low-normal C8 concentration but a nonfunctional protein, therefore the recommendation for testing is the functional assay. Complement levels can be detected by antigen assays that quantitate the amount of the protein. For most of the complement proteins, a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

Useful For: Diagnosis of C8 deficiency Investigation of a patient with an undetectable total hemolytic complement level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C8 levels in the presence of normal C3 and C4 values are consistent with a C8 deficiency. Absent C8 levels in the presence of low C3 and C4 values suggests complement consumption. Normal results indicate both normal C8 protein levels and normal functional activity.

Reference Values:
33-58 U/mL

Clinical References:

C9FX
81066

C9 Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classical pathway, 2) the alternative (or properdin) pathway, and 3) the lectin (mannan-binding lectin) pathway. The classical pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. A single IgM molecule or 2 IgG molecules are sufficient to trigger activation of the recognition complex initiated by C1q. The activation process triggers a cascade that includes an

amplification loop. The amplification loop is mediated by C3, with cleavage of a series of proteins, and results in 3 main end products: 1) anaphylatoxins that promote inflammation (C3a, C5a), 2) opsonization peptides that are chemotactic for neutrophils (C3b) and facilitate phagocytosis, and 3) the membrane attack complex (MAC), which promotes cell lysis. Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. Deficiency of C9 is common in the Japanese population, (1:1000), but is otherwise rare. The lytic activity of C9-deficient serum is decreased. However, the assembly of C5b-C8 complexes will result in a transmembrane channel with minimal lytic activity. Many C9-deficient patients are asymptomatic. C9-deficient patients may, however, present with invasive neisserial infections. Complement levels can be detected by antigen assays that quantitate the amount of the protein. For most of the complement proteins, a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

Useful For: Diagnosis of C9 deficiency Investigation of a patient with a low total (hemolytic) complement level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C9 levels in the presence of normal C3 and C4 values are consistent with a C9 deficiency. Absent C9 levels in the presence of low C3 and C4 values suggests complement consumption. Normal results indicate both normal C9 protein levels and normal functional activity.

Reference Values:
37-61 U/mL

Clinical References:

C9ORF
35377

C9orf72 Hexanucleotide Repeat, Molecular Analysis, Varies

Clinical Information: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease affecting the upper and lower motor neurons. The disease is characterized by progressive spasticity, muscle wasting and paralysis, typically leading to death from respiratory failure. Frontotemporal dementia (FTD) is a dementia syndrome that predominantly involves the frontal and temporal lobes of the brain. Clinical presentation is variable and includes progressive changes in behavior and personality and language disturbances. Affected individuals may also exhibit extrapyramidal signs. Amyotrophic lateral sclerosis and FTD are now thought to represent an overlapping spectrum of disease. Recent literature has found that approximately 40% of familial ALS, 25% of familial FTD, and 90% of familial ALS/FTD cases have a large hexanucleotide repeat (GGGGCC) expansion in a noncoding region of C9orf72. At lower frequency, C9orf72 hexanucleotide repeat expansions have also been observed in individuals with sporadic ALS, FTD, and ALS/FTD. The vast majority of individuals affected with a C9orf72-related disorder (c9ALS, c9FTD, or c9ALS/FTD) have hexanucleotide repeat expansions in the hundreds to thousands, while unaffected individuals have repeat sizes less than 20. The significance of repeat sizes between 20 and 100 repeats is currently unclear as both healthy controls and individuals with ALS or FTD phenotypes have been reported with repeat sizes in this range.

Useful For: Molecular confirmation of clinically suspected cases of c9FTD/ALS, frontotemporal dementia (FTD), or amyotrophic lateral sclerosis (ALS) Presymptomatic testing for individuals with a family history of c9FTD/ALS and a documented expansion in the C9orf72 gene

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:

Normal alleles (reference):<20 GGGGCC repeats
Indeterminate alleles: 20-100 GGGGCC repeats
Pathogenic alleles: >100* GGGGCC repeats

*The exact cutoff for pathogenicity is currently undefined. Although additional studies are needed to confirm if 100 repeats is the cutoff for pathogenicity, most individuals affected with a C9orf72-related disorder have C9orf72 hexanucleotide repeat expansions with hundreds to thousands of repeats.

An interpretive report will be provided.

Clinical References: 1. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011;72(2):245-256 2. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 2011;72(2):257-268 3. Gijselinck I, Van Langenhove T, van der Zee J, et al. A C9orf72 promoter repeat expansion in a Flanders-Belgian cohort with disorders of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum: a gene identification study. Lancet Neuron. 2012;11(1):54-65 4. Majounie E, Renton AE, Mok K, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurol. 2012;11(4):323-330 5. Boeve BF, Boylan KB, Graff-Radford NR, et al. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. Brain. 2012;135(Pt 3):765-783 6. van Blitterswijk M, DeJesus-Hernandez M, Niemantsverdriet E, et al. Association between repeat sizes and clinical and pathological characteristics in carriers of C9ORF72 repeat expansions (Xpansize-72): a cross-sectional cohort study. Lancet Neurol. 2013;12(10):978-988 7. Nordin A, Akimoto C, Wuolikainen A, et al. Extensive size variability of the GGGGCC expansion in C9orf72 in both neuronal and non-neuronal tissues in 18 patients with ALS or FTD. Hum Mol Genet. 2015;24(11):3133-3142 8. Xi Z, van Blitterswijk M, Zhang M, et al. Jump from pre-mutation to pathologic expansion in C9orf72. Am J Hum Genet. 2015;96(6):962-970 9. Gami P, Murray C, Schottlaender L, et al. A 30-unit hexanucleotide repeat expansion in C9orf72 induces pathological lesions with dipeptide-repeat proteins and RNA foci, but not TDP-43 inclusions and clinical disease. Acta Neuropathol. 2015;130(4):599-601 10. Ng ASL, Tan EK. Intermediate C9orf72 alleles in neurological disorders: does size really matter? J Med Genet. 2017;54(9):591-597 11. Nordin A, Akimoto C, Wuolikainen A, et al. Sequence variations in C9orf72 downstream of the hexanucleotide repeat region and its effect on repeat-primed PCR interpretation: a large multinational screening study. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(3-4):256-264 12. Van Mossevelde S, van der Zee J, Cruts M, Van Broeckhoven. Relationship between C9orf72 repeat size and clinical phenotype. Curr Opin Genet Dev. 2017;44:117-124 13. Breevoort S, Gibson S, Figueroa K, Bromberg M, Pulst S. Expanding clinical spectrum of C9ORF72-related disorders and promising therapeutic strategies. A review. Neurol Genet. 2022;8(3):e670. 24;8(5):e200028

FCABB
57672

Cabbage IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:

Reference ranges have not been established for food-specific IgG tests.

CABB
86327

Cabbage, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cabbage Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

COCOA
60112

Cacao/Cocoa, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cacao/cocoa Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CDOMB
89539

Cadmium for Occupational Monitoring, Blood

Clinical Information: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; kidney dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Breathing the fumes of cadmium vapors leads to

nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting organic-based paints without a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. Tobacco smoke is another common source of cadmium exposure.

Useful For: Detecting exposure to cadmium, a toxic heavy metal, as a part of occupational monitoring

Interpretation: Normal blood cadmium is less than 5.0 mcg/L, with most results in the range of 0.5 to 2.0 mcg/L. Acute toxicity will be observed when the blood level exceeds 50 mcg/L.

Reference Values:
< 5.0 mcg/L
Reference values apply to all ages.

Clinical References: 1. Moreau T, Orssaud G, Lellouch J, Claude JR, Juguet B, Festy B. Blood cadmium levels in a general male population with special reference to smoking. Arch Environ Health. 1983;38(3):163-167 2. Occupational Safety and Health Administration, US Department of Labor: Cadmium . Accessed December 3, 2024. Available at www.osha.gov/cadmium 3. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

CDOU
608892

Cadmium Occupational Exposure, Random, Urine

Clinical Information: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; kidney dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid, also occur over a period of years and precede overt kidney failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. For nonsmokers, the primary source of cadmium exposure is from the food supply. In general, leafy vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium. For smokers, the most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary source of the metal, leading to reproductive toxicity in both male and female patients. Chronic exposure to cadmium causes accumulated kidney damage. The excretion of cadmium is proportional to creatinine except when kidney damage has occurred. Kidney damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. OSHA mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

Useful For: Detecting occupational exposure to cadmium using random urine specimens

Interpretation: Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. Results above 15 mcg/g creatinine are considered indicative of severe exposure

Reference Values:
Only orderable as part of profile. For more information see:
-CDUOE / Cadmium Occupational Exposure, Random, Urine
-HMUOE / Heavy Metal Occupational Exposure, with Reflex, Random, Urine

Biological exposure indices (BEI): <5.0 mcg/g creatinine

Clinical References: 1. de Burbure C, Buchet JP, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590 2. Schulz C, Angerer J, Ewers U, Heudorf U, Wilhelm M; Human Biomonitoring Commission of the German Federal Environment Agency. Revised and new reference values for environmental pollutants in urine or blood of children in Germany derived from the German Environmental Survey on Children 2003-2006(GerESIV). Int J Hyg Environ Health. 2009;212(6):637-647 3. Occupational Safety and Health Administration. Cadmium exposure and control. Updated 09/02/2008. Accessed August 30, 2024. US Department of Labor Available at osha.gov/SLTC/cadmium/evaluation.html 4. Agency for Toxic Substances and Disease Registry. Toxicological profile for cadmium. US Department of Health and Human Services. September 2012. Available at www.atsdr.cdc.gov/ToxProfiles/tp5.pdf 5. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44 6. Zhang H, Reynolds M. Cadmium exposure in living organisms: A short review. Sci Total Environ. 2019;678:761-767. doi:10.1016/j.scitotenv.2019.04.395 7. Wang M, Chen Z, Song W, Hong D, Huang L, Li Y. A review on cadmium exposure in the population and intervention strategies against cadmium toxicity. Bull Environ Contam Toxicol. 2021;106(1):65-74. doi:10.1007/s00128-020-03088-1

CDUOE
608896

Cadmium Occupational Exposure, Random, Urine

Clinical Information: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; kidney dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid, also occur over a period of years and precede overt kidney failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. For nonsmokers, the primary source of cadmium exposure is from the food supply. In general, leafy vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium. For smokers, the most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary source of the metal, leading to reproductive toxicity in both male and female patients. Chronic exposure to cadmium causes accumulated renal damage. The excretion of cadmium is proportional to creatinine except when kidney damage has occurred. Kidney damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. OSHA mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

Useful For: Detecting occupational exposure to cadmium, a toxic heavy metal, using random urine specimens

Interpretation: Urine cadmium levels primarily reflect total body burden of cadmium. Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. For occupational testing, the OSHA cadmium standard is below 3.0 mcg/g creatinine, and the biological exposure index is 5 mcg/g creatinine.

Reference Values:

Clinical References: 1. deBurbure C, Buchet J-P, Leroyer A, et al: Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: Evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006 Apr;114(4):584-590 2. Schulz C, Angerer J, Ewers U, et al: Revised and new reference values for environmental pollutants in urine or blood of children in Germany derived from the German Environmental Survey on Children

2003-2006(GerESIV) Int J Hyg Environ Health. 2009 Nov;212(6):637-647 3. Occupational Safety and Health Administration: Cadmium exposure and control. US Department of Labor; Updated 9/2/2008. Accessed July 17, 2020. Available at osha.gov/SLTC/cadmium/evaluation.html 4. Agency for Toxic Substances and Disease Registry: Toxicological profile for cadmium. US Department of Health and Human Services; September 2012. Available at www.atsdr.cdc.gov/ToxProfiles/tp5.pdf 5. Strathmann FG, Blum LM: Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44 6. Wang M, Chen Z, Song W, Hong D, Huang L, Li Y: A review on cadmium exposure in the population and intervention strategies against cadmium toxicity. Bull Environ Contam Toxicol. 2021 Jan;106(1):65-74. doi: 10.1007/s00128-020-03088-1 7. Zhang H, Reynolds M: Cadmium exposure in living organisms: A short review. Sci Total Environ. 2019 Aug 15;678:761-767. doi: 10.1016/j.scitotenv.2019.04.395

CDU
8678

Cadmium, 24 Hour, Urine

Clinical Information: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; kidney dysfunction with proteinuria and a slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid also occur over a period of years and precede overt kidney failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. For nonsmokers, the primary source of cadmium exposure is from the food supply. In general, leafy vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium. For smokers, the most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both men and women. The concentration of cadmium in the kidneys and urine is elevated in some patients exposed to cadmium.

Useful For: Detecting exposure to cadmium, a toxic heavy metal, in 24-hour urine specimens

Interpretation: Urine cadmium levels primarily reflect total body burden of cadmium. Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. For occupational testing, OSHA cadmium standard is less than 3.0 mcg/g creatinine, and the biological exposure index is 5.0 mcg/g creatinine. Collection of urine over 24 hours minimizes fluctuations of observed cadmium concentrations in random urine samples.

Reference Values:
0-17 years: Not established
> or =18 years: <0.7 mcg/24 h

Clinical References: 1. de Burbure C, Buchet JP, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590 2. Schulz C, Angerer J, Ewers U, Heudorf U, Wilhelm M; Human Biomonitoring Commission of the German Federal Environment Agency. Revised and new reference values for environmental pollutants in urine or blood of children in Germany derived from the German Environmental Survey on Children 2003-2006(GerESIV). Int J Hyg Environ Health. 2009;212(6):637-647 3. Occupational Safety and Health Administration. Cadmium exposure and control. Updated 09/02/2008. Accessed August 30, 2024. US Department of Labor Available at osha.gov/SLTC/cadmium/evaluation.html 4. Agency for Toxic Substances and Disease Registry. Toxicological profile for cadmium. US Department of Health and Human Services. September 2012. Available at www.atsdr.cdc.gov/ToxProfiles/tp5.pdf 5. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44 6. Zhang H, Reynolds M. Cadmium exposure in living organisms: A short review. Sci Total Environ. 2019;678:761-767.

doi:10.1016/j.scitotenv.2019.04.395

CDB
8682

Cadmium, Blood

Clinical Information: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; kidney dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting organic-based paints without a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. In addition, another common source of cadmium exposure is tobacco smoke.

Useful For: Detecting exposure to cadmium, a toxic heavy metal

Interpretation: Normal blood cadmium is less than 5.0 ng/mL, with most results in the range of 0.5 to 2.0 ng/mL. Acute toxicity will be observed when the blood level exceeds 50 ng/mL.

Reference Values:
<5.0 ng/mL
Reference values apply to all ages.

Clinical References: 1. Moreau T, Orssaud G, Lellouch J, Claude JR, Juguet B, Festy B. Blood cadmium levels in a general population with special reference to smoking. Arch Environ Health. 1983;38(3):163-167 2. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

CDUCR
608906

Cadmium/Creatinine Ratio, Random, Urine

Clinical Information: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; kidney dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid, also occur over a period of years and precede overt kidney failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. For nonsmokers, the primary source of cadmium exposure is from the food supply. In general, leafy vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium. For smokers, the most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary source of the metal leading to reproductive toxicity in both male and female patients. Chronic exposure to cadmium causes accumulated kidney damage. The excretion of cadmium is proportional to creatinine except when kidney damage has occurred. Kidney damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. Occupational Safety and Health Administration mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

Useful For: Detecting exposure to cadmium, a toxic heavy metal, using random urine specimens

Interpretation: Urine cadmium levels primarily reflect total body burden of cadmium. Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. For occupational testing, the Occupational Safety and Health Administration cadmium standard is less than 3.0 mcg/g

creatinine, and the biological exposure index is 5 mcg/g creatinine.

Reference Values:

CADMIUM/CREATININE:
0-17 years: Not established
> or =18 years: <0.6 mcg/g creatinine

CREATININE:
> or =18 years: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. deBurbure C, Buchet J-P, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: Evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590 2. Schulz C, Angerer J, Ewers U, et al. Revised and new reference values for environmental pollutants in urine or blood of children in Germany derived from the German Environmental Survey on Children 2003-2006(GerESIV) Int J Hyg Environ Health. 2009;212(6):637-647 3. Occupational Safety and Health Administration: Cadmium exposure and control. US Department of Labor; Updated 9/2/2008. Accessed July 17, 2020. Available at osha.gov/SLTC/cadmium/evaluation.html 4. Agency for Toxic Substances and Disease Registry: Toxicological profile for cadmium. US Department of Health and Human Services; September 2012. Available at www.atsdr.cdc.gov/ToxProfiles/tp5.pdf 5. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44 6. Wang M, Chen Z, Song W, Hong D, Huang L, Li Y. A review on cadmium exposure in the population and intervention strategies against cadmium toxicity. Bull Environ Contam Toxicol. 2021;106(1):65-74. doi:10.1007/s00128-020-03088-1

CDCU
608902

Cadmium/Creatinine Ratio, Urine

Clinical Information: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; kidney dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid, also occur over a period of years and precede overt kidney failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. For nonsmokers, the primary source of cadmium exposure is from the food supply. In general, leafy vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium. For smokers, the most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary source of the metal, leading to reproductive toxicity in both male and female patients. Chronic exposure to cadmium causes accumulated kidney damage. The excretion of cadmium is proportional to creatinine except when kidney damage has occurred. Kidney damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. OSHA mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

Useful For: Detecting exposure to cadmium using random urine specimens

Interpretation: Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. Results above15 mcg/g creatinine are considered indicative of severe exposure.

Reference Values:

Only orderable as part of profile. For more information, see:
-CDUCR / Cadmium/Creatinine Ratio, Random, Urine

-HMUCR / Heavy Metal/Creatinine Ratio, with Reflex, Random, Urine

0-17 years: Not established
> or =18 years: <0.6 mcg/g Creatinine

Clinical References: 1. de Burbure C, Buchet JP, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590 2. Schulz C, Angerer J, Ewers U, Heudorf U, Wilhelm M; Human Biomonitoring Commission of the German Federal Environment Agency. Revised and new reference values for environmental pollutants in urine or blood of children in Germany derived from the German Environmental Survey on Children 2003-2006(GerESIV). Int J Hyg Environ Health. 2009;212(6):637-647 3. Occupational Safety and Health Administration. Cadmium exposure and control. Updated 09/02/2008. Accessed August 30, 2024. US Department of Labor Available at osha.gov/SLTC/cadmium/evaluation.html 4. Agency for Toxic Substances and Disease Registry. Toxicological profile for cadmium. US Department of Health and Human Services. September 2012. Available at www.atsdr.cdc.gov/ToxProfiles/tp5.pdf 5. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44 6. Zhang H, Reynolds M. Cadmium exposure in living organisms: A short review. Sci Total Environ. 2019;678:761-767. doi:10.1016/j.scitotenv.2019.04.395

CAFF
8754

Caffeine, Serum

Clinical Information: Caffeine is used to treat apnea of prematurity that occurs in newborn infants, the most frequent complication seen in the neonatal nursery. In neonates, caffeine has a half-life that ranges from approximately 3 to 4 days, which is much longer than in adults (typically 4-6 hours) due to the immaturity of the neonatal liver. This requires that small doses be administered at much longer intervals than would be predicted based on adult pharmacokinetics. The volume of distribution of caffeine is 0.8 to 0.9 L/kg (infants) or 0.6 L/kg (adults) and the drug is approximately 36% protein bound. Toxicity observed in neonates is characterized by central nervous system and skeletal muscle stimulation and bradycardia. These symptoms are seen in adults at lower levels than in neonates, suggesting that neonates have much greater tolerance to the drug.

Useful For: Monitoring caffeine therapy in neonates Assessing caffeine toxicity in neonates

Interpretation: Optimal pharmacologic response occurs when the serum level is in the range of 8.0 to 20.0 mcg/mL. Toxicity in neonates and adults may be seen when the serum level is above 20.0 mcg/mL.

Reference Values:
Therapeutic: 8.0-20.0 mcg/mL
Critical value: > or =30.0 mcg/mL

Clinical References: 1. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453.e9 2. Brunton LL, Knollmann BC, eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 14th ed. McGraw-Hill Education; 2023 3. Ou CN, Frawley VL. Concurrent measurement of theophylline and caffeine in neonates by an interference-free liquid-chromatographic method. Clin Chem. 1983;29:1934-1936

CALCI
70368

Calcitonin (CALCI) Immunostain, Technical Component Only

Clinical Information: Calcitonin is a hormone involved in calcium metabolism. Staining for calcitonin produces fine granular, cytoplasmic staining of C cells of thyroid, medullary thyroid carcinomas, many atypical laryngeal carcinoids, and other neuroendocrine tumors. Amyloid deposits within medullary thyroid carcinoma may also exhibit varying degrees of calcitonin immunoreactivity.

Useful For: Aids in the identification of C cells of thyroid, medullary thyroid carcinomas, many atypical laryngeal carcinoids, and other neuroendocrine tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Costante G, Meringolo D. Calcitonin as a biomarker of C cell disease: recent achievements and current challenges. Endocrine. 2020;(67):273-280. doi: 10.1007/s12020-019-02183-6 2. Gambardella C, Offi C, Patrone R, et al. Calcitonin negative medullary thyroid carcinoma: a challenging diagnosis or a medical dilemma?. BMC Endocr Disord. 2019;(19):45. doi:10.1186/s12902-019-0367-2 3. Gambardella C, Offi C, Clarizia G, et al: Medullary thyroid carcinoma with double negative calcitonin and CEA: a case report and update of literature review. BMC Endocr Disord. 2019;(19):103. doi:10.1186/s12902-019-0435-7 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CATLN
61527

Calcitonin, Fine-Needle Aspiration Biopsy Needle Wash, Lymph Node

Clinical Information: Calcitonin is a polypeptide hormone secreted by the parafollicular cells (also referred to as calcitonin cells or C-cells) of the thyroid gland. Malignant tumors arising from thyroid C-cells (medullary thyroid carcinoma: MTC) usually produce elevated levels of calcitonin. MTC is an uncommon malignant thyroid tumor, comprising less than 5% of all thyroid malignancies. Measurement of serum calcitonin is used in the follow-up of patients who underwent surgical removal of the thyroid gland. Studies have reported that the measurement of calcitonin in fine-needle aspiration biopsy (FNAB)-needle washes improves the evaluation of suspicious lymph nodes in patients with a history of MTC when used in combination with cytology. Comparing the results of calcitonin in the needle rinse with serum calcitonin is highly recommended. An elevated calcitonin in the serum could falsely elevate calcitonin in the washings if the rinse is contaminated with blood. In these cases, only calcitonin values significantly higher than the serum should be considered as true-positive results. Cytologic examination and measurement of calcitonin can be performed on the same specimen. To measure calcitonin, the FNA needle is rinsed with a small volume of normal saline solution immediately after a specimen for cytological examination (for a smear or CytoTrap preparation) has been expelled from the needle. Calcitonin levels are measured in the needle wash.

Useful For: As an adjunct to cytologic examination of fine-needle aspiration specimens in athyrotic individuals treated for medullary thyroid carcinoma to confirm or exclude metastases in enlarged or ultrasonographically suspicious lymph nodes

Interpretation: In athyrotic patients with a history of medullary thyroid carcinoma, a fine-needle aspiration calcitonin value greater than or equal to 5.0 pg/mL is suggestive of the presence of metastatic

MTC in the biopsied lymph node. Calcitonin values less than 5.0 pg/mL suggest the lymph node does not contain medullary thyroid carcinoma. This result is dependent on accurate sampling and a total needle wash volume between 0.5 to 1.5 mL. This test should be interpreted in the context of the clinical presentation, imaging, and cytology findings. If the results are discordant with the clinical presentation, a sampling error at the time of biopsy should be considered.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Trimboli P, Rossi F, Baldelli R, et al. Measuring calcitonin in washout of the needle in patients undergoing fine needle aspiration with suspicious medullary thyroid cancer. Diagn Cytopathol. 2012;40(5):394-398 2. Boi F, Maurelli I, Pinna G, et al. Calcitonin measurement in wash-out fluid from fine needle aspiration of neck masses in patients with primary and metastatic medullary thyroid carcinoma. J Clin Endocrinol Metab. 2007;92(6):2115-2118 3. Kudo T, Miyauchi A, Ito Y, Takamura Y, Amino N, Hirokawa M. Diagnosis of medullary thyroid carcinoma by calcitonin measurement in fine-needle aspiration biopsy specimens. Thyroid. 2007;17(7):635-638 4. Trimboli P, D'Aurizio F, Tozzoli R, Giovanella L. Measurement of thyroglobulin, calcitonin, and PTH in FNA washout fluids. Clin Chem Lab Med. 2017;55(7):914-925

CATN
9160

Calcitonin, Serum

Clinical Information: Calcitonin is a polypeptide hormone secreted by the parafollicular cells (also referred to as calcitonin cells or C cells) of the thyroid gland. The main action of calcitonin is the inhibition of bone resorption by regulating the number and activity of osteoclasts. Calcitonin is secreted in direct response to serum hypercalcemia and may prevent large oscillations in serum calcium levels and excessive loss of body calcium. However, in comparison to parathyroid hormone and 1,25-dihydroxyvitamin D, the role of calcitonin in the regulation of serum calcium in humans is minor. Measurements of serum calcitonin levels are, therefore, not useful in the diagnosis of disorders of calcium homeostasis. Malignant tumors arising from thyroid C cells (medullary thyroid carcinoma: MTC) usually produce elevated levels of calcitonin. MTC is an uncommon malignant thyroid tumor, comprising less than 5% of all thyroid malignancies. Approximately 25% of these are familial cases, usually appearing as a component of multiple endocrine neoplasia type II (MENII, Sipple syndrome). MTC may also occur in families without other associated endocrine dysfunction, with similar autosomal dominant transmission as MENII, which is then called familial medullary thyroid carcinoma (FMTC). Variants in the RET proto-oncogene are associated with MENII and FMTC. Serum calcitonin concentrations are high in infants, decline rapidly, and are relatively stable from childhood through adulthood. In general, calcitonin serum concentrations are higher in men than in women due to the larger C-cell mass in men. Serum calcitonin concentrations may be increased in patients with chronic kidney failure, and other conditions such as hyperparathyroidism, leukemic and myeloproliferative disorders, Zollinger-Ellison syndrome, autoimmune thyroiditis, small cell and large cell lung cancers, breast and prostate cancer, mastocytosis, and various neuroendocrine tumors, in particular, islet cell tumors.

Useful For: Aids in the diagnosis and follow-up of medullary thyroid carcinoma Aids in the evaluation of multiple endocrine neoplasia type II and familial medullary thyroid carcinoma This test is not useful for evaluating calcium metabolic diseases.

Interpretation: Although most patients with sporadic medullary thyroid carcinoma (MTC) have high basal serum calcitonin concentrations, 30% of those with familial MTC or multiple endocrine neoplasia type II have normal basal levels. In completely cured cases following surgical therapy for MTC, serum calcitonin levels fall into the undetectable range over a variable period of several weeks. Persistently elevated postoperative serum calcitonin levels usually indicate incomplete cure. The

reasons for this can be locoregional lymph node spread or distant metastases. In most of these cases, imaging procedures are required for further workup. Those individuals who are then found to suffer only locoregional spread may benefit from additional surgical procedures. However, the survival benefits derived from such approaches are still debated. A rise in previously undetectable or very low postoperative serum calcitonin levels is highly suggestive of disease recurrence or spread and should trigger further diagnostic evaluations.

Reference Values:

Pediatric
1 month: < or =34 pg/mL
2 months: < or =31 pg/mL
3 months: < or =28 pg/mL
4 months: < or =26 pg/mL
5 months: < or =24 pg/mL
6 months: < or =22 pg/mL
7 months: < or =20 pg/mL
8 months: < or =19.0 pg/mL
9 months: < or =17.0 pg/mL
10 months: < or =16.0 pg/mL
11 months: < or =15.0 pg/mL
12-14 months: < or =14.0 pg/mL
15-17 months: < or =12.0 pg/mL
18-20 months: < or =10.0 pg/mL
21-23 months: < or =9.0 pg/mL
2 years: < or =8.0 pg/mL
3-9 years: < or =7.0 pg/mL
10-15 years: < or =6.0 pg/mL
16 years: < or =5.0 pg/mL

Adults
17 years and older:
Males: < or =14.3 pg/mL
Females: < or =7.6 pg/mL

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567-610 2. Griebeler ML, Gharib H, Thompson GB. Medullary thyroid carcinoma. Endocr Pract. 2013;19(4):703-711 3. Richards ML. Familial syndromes associated with thyroid cancer in the era of personalized medicine. Thyroid. 2010;20(7):707-713

CALU
610595

Calcium, 24 Hour, Urine

Clinical Information: Calcium is the fifth most common element in the body. It is a fundamental element necessary to form electrical gradients across membranes, an essential cofactor for many enzymes, and the main constituent in bone. Under normal physiologic conditions, the concentration of calcium in serum and in cells is tightly controlled. Calcium is excreted in both urine and feces. Ordinarily about 20% to 25% of dietary calcium is absorbed and 98% of filtered calcium is reabsorbed in the kidney. Traffic of calcium between the gastrointestinal tract, bone, and kidney is tightly controlled by a complex regulatory system that includes vitamin D and parathyroid hormone. Sufficient bioavailable calcium is essential for bone health. Excessive excretion of calcium in the urine is a common contributor to kidney stone risk.

Useful For: Evaluation of calcium oxalate and calcium phosphate kidney stone risk, and calculation of urinary supersaturation Evaluation of bone diseases, including osteoporosis and osteomalacia

Interpretation: Increased urinary calcium excretion (hypercalciuria) is a known contributor to kidney stone disease and osteoporosis. Many cases are genetic (often termed idiopathic). Previously such patients were often divided into fasting versus absorptive hypercalciuria depending on the level of urine calcium in a fasting versus fed state, but the clinical utility of this approach is now in question. Overall, the risk of stone disease appears increased when 24-hour urine calcium is above 250 mg in men and above 200 mg in women. Thiazide diuretics are often used to reduce urinary calcium excretion, and repeat urine collections can be performed to monitor the effectiveness of therapy. Known secondary causes of hypercalciuria include hyperparathyroidism, Paget disease, prolonged immobilization, vitamin D intoxication, and diseases that destroy bone (such as metastatic cancer or multiple myeloma). Urine calcium excretion can be used to gauge the adequacy of calcium and vitamin D supplementation, for example in states of gastrointestinal fat malabsorption that are associated with decreased bone mineralization (osteomalacia).

Reference Values:
Males: <250 mg/24 hours*
Females: <200 mg/24 hours*
*Values represent clinical cutoffs above which studies have demonstrated increased risk of kidney stone formation. These values were not determined in a reference range study.

Reference values have not been established for patients who are younger than 18 years of age.
Reference values apply to 24-hour collection.

Clinical References: 1. Fraser WD: Bone and mineral metabolism. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1438 2. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int. 2001;59(6):2290-2298 3. Metz MP. Determining urinary calcium/creatinine cut-offs for the pediatric population using published data. Ann Clin Biochem. 2006;43(Pt 5):398-401 4. Pak CY, Britton F, Peterson R, et al. Ambulatory evaluation of nephrolithiasis. Classification, clinical presentation and diagnostic criteria. Am J Med. 1980;69(1):19-30 5. Pak CY, Kaplan R, Bone H, Townsend J, Waters O. A simple test for the diagnosis of absorptive, resorptive and renal hypercalciurias. N Engl J Med. 1975;292(10):497-500

CAI
8378

Calcium, Ionized, Serum

Clinical Information: Ionized calcium, which accounts for 50% to 55% of total calcium, is the physiologically active form of calcium. Low ionized calcium values are often seen in kidney disease, critically ill patients, or patients receiving rapid transfusion of citrated whole blood or blood products. Increased serum ionized calcium concentrations may be seen with primary hyperparathyroidism, ectopic parathyroid hormone-producing tumors, excess intake of vitamin D, or various malignancies. Nomograms have been used to calculate ionized calcium from total calcium, albumin, and pH values. However, calculated ionized calcium results have proven to be unsatisfactory. A Mayo study of 114 patients found significant differences between ionized and total calcium in 26% of patients.

Useful For: Assessing calcium states during liver transplantation surgery, cardiopulmonary bypass, or any procedure requiring rapid transfusion of whole blood in neonates and critically ill patients Second-order test in the evaluation of patients with abnormal calcium values

Interpretation: Serum ionized calcium concentrations 50% below normal will result in severely reduced cardiac stroke work. With moderate to severe hypocalcemia, left ventricular function may be

profoundly depressed. Ionized calcium values are higher in children and young adults. Ionized calcium result has been adjusted to pH 7.40 to account for changes in specimen pH that may occur during transport. Ionized calcium concentration increases approximately 0.2 mg/dL per 0.1 pH unit decrease.

Reference Values:
IONIZED CALCIUM
< or =13 days old: Not established
14 days-<1 year: 5.21-5.99 mg/dL
1-<2 years: 5.04-5.84 mg/dL
2-<3 years: 4.87-5.67 mg/dL
3-23 years: 4.83-5.52 mg/dL
24-97 years: 4.57-5.43 mg/dL
> or =98 years: Not established

pH
< or =13 days old: Not established
14 days-97 years old: 7.35-7.48
> or =98 years old: Not established

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

CALC5
610591

Calcium, Random, Urine

Clinical Information: Calcium is the fifth most common element in the body. It is a fundamental element necessary to form electrical gradients across membranes, an essential cofactor for many enzymes, and the main constituent in bone. Under normal physiologic conditions, the concentration of calcium in serum and in cells is tightly controlled. Calcium is excreted in both urine and feces. Ordinarily about 20% to 25% of dietary calcium is absorbed, and 98% of filtered calcium is reabsorbed in the kidney. Traffic of calcium between the gastrointestinal tract, bone, and kidney is tightly controlled by a complex regulatory system that includes vitamin D and parathyroid hormone. Sufficient bioavailable calcium is essential for bone health. Excessive excretion of calcium in the urine is a common contributor to kidney stone risk.

Useful For: Measurement of calcium for the evaluation of calcium oxalate and calcium phosphate kidney stone risk, and calculation of urinary supersaturations Evaluation of bone diseases, including osteoporosis and osteomalacia

Interpretation: Increased urinary calcium excretion (hypercalciuria) is a known contributor to kidney stone disease and osteoporosis. Many cases are genetic (often termed "idiopathic"). Previously such patients were often divided into fasting versus absorptive hypercalciuria depending on the level of urine calcium in a fasting versus fed state, but the clinical utility of this approach is now in question. Overall, the risk of stone disease appears increased when 24-hour urine calcium is greater than 250 mg in men and greater than 200 mg in women. Thiazide diuretics are often used to reduce urinary calcium excretion and repeat urine collections can be performed to monitor the effectiveness of therapy. Known secondary causes of hypercalciuria include hyperparathyroidism, Paget disease, prolonged immobilization, vitamin D intoxication, and diseases that destroy bone (such as metastatic cancer or multiple myeloma). Urine calcium excretion can be used to gauge the adequacy of calcium and vitamin D supplementation, for example in states of gastrointestinal fat malabsorption that are associated with decreased bone mineralization (osteomalacia).

Reference Values:
Only orderable as part of a profile. For more information see CACR3 / Calcium/Creatinine Ratio, Random, Urine

1 month-<12 months: 0.03-0.81 mg/mg creatinine
12 months-<24 months: 0.03-0.56 mg/mg creatinine
24 months-<3 years: 0.02-0.50 mg/mg creatinine
3 years-<5 years: 0.02-0.41 mg/mg creatinine
5 years-<7 years: 0.01-0.30 mg/mg creatinine
7 years-<10 years: 0.01-0.25 mg/mg creatinine
10 years-<18 years: 0.01-0.24 mg/mg creatinine
18 years-83 years: 0.05-0.27 mg/mg creatinine
Reference values have not been established for patients who are younger than 1 month of age.
Reference values have not been established for patients who are older than 83 years of age.

Clinical References: 1. Fraser WD: Bone and mineral metabolism. In: Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier;2018:1438 2. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int. 2001;59(6):2290-2298 3. Metz MP. Determining urinary calcium/creatinine cut-offs for the pediatric population using published data. Ann Clin Biochem. 2006;43(Pt 5):398-401 4. Pak CY, Britton F, Peterson R, et al. Ambulatory evaluation of nephrolithiasis. Classification, clinical presentation and diagnostic criteria. AM J Med. 1980;69(1):19-30 5. Pak CY, Kaplan R, Bone H, et al, A simple test for the diagnosis of absorptive, resorptive and renal hypercalciurias. N Engl J Med. 1975;292(10):497-500

CA
601514

Calcium, Total, Serum

Clinical Information: The calcium content of an adult is somewhat over 1 kg (about 2% of the body weight). Of this, 99% is present as calcium hydroxyapatite in bones and less than 1% is present in the extra-osseous intracellular space or extracellular space (ECS). The calcium level in the ECS is in dynamic equilibrium with the rapidly exchangeable fraction of bone calcium. In serum, calcium is bound to a considerable extent to proteins (approximately 40%), 10% is in the form of inorganic complexes, and 50% is present as free or ionized calcium. Calcium ions affect the contractility of the heart and the skeletal musculature, and are essential for the function of the nervous system. In addition, calcium ions play an important role in blood clotting and bone mineralization. Hypocalcemia is due to the absence or impaired function of the parathyroid glands or impaired vitamin-D synthesis. Chronic renal failure is also frequently associated with hypocalcemia due to decreased vitamin-D synthesis as well as hyperphosphatemia and skeletal resistance to the action of parathyroid hormone (PTH). Characteristic symptoms of hypocalcemia are latent or manifest tetany and osteomalacia. Hypercalcemia is brought about by increased mobilization of calcium from the skeletal system or increased intestinal absorption. A majority of cases are due to primary hyperparathyroidism (pHPT) or bone metastasis of carcinoma of the breast, prostate, thyroid gland, or lung. Patients who have pHPT and bone disease, renal stones or nephrocalcinosis, or other signs or symptoms are candidates for surgical removal of the parathyroid glands. Severe hypercalcemia may result in cardiac arrhythmia. Calcium levels may also reflect abnormal vitamin D or protein levels.

Useful For: Diagnosis and monitoring of a wide range of disorders including diseases of bone, kidney, parathyroid gland, or gastrointestinal tract

Interpretation: Hypocalcemia: Long-term therapy must be tailored to the specific disease causing the hypocalcemia. The therapeutic endpoint is to achieve a serum calcium level of 8.0 to 8.5 mg/dL to prevent tetany. For symptomatic hypocalcemia, calcium may be administered intravenously.

Hypercalcemia: The level at which hypercalcemic symptoms occur varies from patient to patient. Symptoms are common when serum calcium levels are above 11.5 mg/dL, although patients may be asymptomatic at this level. Levels above 12.0 mg/dL are considered a critical value. Severe hypercalcemia (>15.0 mg/dL) is a medical emergency.

Reference Values:

<1 year: 8.7-11.0 mg/dL
1-17 years: 9.3-10.6 mg/dL
18-59 years: 8.6-10.0 mg/dL
> or =60 years: 8.8-10.2 mg/dL

Clinical References: 1. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018. 2. Baldwin TE, Chernow B: Hypocalcemia in the ICU. J Crit Illness. 1987;2:9-16 3. Estey MP, Cohen AH, Colantonio DA, et al: CLSI-based transference of the CALIPER database of pediatric reference intervals from Abbott to Beckman, Ortho, Roche and Siemens Clinical Chemistry Assays: direct validation using reference samples from the CALIPER cohort. Clin Biochem. 2013;46:1197-1219

CCTR
610592

Calcium/Creatinine Ratio, Random, Urine

Clinical Information: Calcium is the fifth most common element in the body. It is a fundamental element necessary to form electrical gradients across membranes, an essential cofactor for many enzymes, and the main constituent in bone. Under normal physiologic conditions, the concentration of calcium in serum and in cells is tightly controlled. Calcium is excreted in both urine and feces. Ordinarily about 20% to 25% of dietary calcium is absorbed, and 98% of filtered calcium is reabsorbed in the kidney. Traffic of calcium between the gastrointestinal tract, bone, and kidney is tightly controlled by a complex regulatory system that includes vitamin D and parathyroid hormone. Sufficient bioavailable calcium is essential for bone health. Excessive excretion of calcium in the urine is a common contributor to kidney stone risk.

Useful For: Calculation of calcium concentration per creatinine concentration

Interpretation: Increased urinary calcium excretion (hypercalciuria) is a known contributor to kidney stone disease and osteoporosis. Many cases are genetic (often termed "idiopathic"). Previously such patients were often divided into fasting versus absorptive hypercalciuria depending on the level of urine calcium in a fasting versus fed state, but the clinical utility of this approach is now in question. Overall, the risk of stone disease appears increased when 24-hour urine calcium is greater than 250 mg in men and greater than 200 mg in women. Thiazide diuretics are often used to reduce urinary calcium excretion, and repeat urine collections can be performed to monitor the effectiveness of therapy. Known secondary causes of hypercalciuria include hyperparathyroidism, Paget disease, prolonged immobilization, vitamin D intoxication, and diseases that destroy bone (such as metastatic cancer or multiple myeloma). Urine calcium excretion can be used to gauge the adequacy of calcium and vitamin D supplementation, for example in states of gastrointestinal fat malabsorption that are associated with decreased bone mineralization (osteomalacia).

Reference Values:

Only orderable as part of a profile. For more information see CACR3 / Calcium/Creatinine Ratio, Random, Urine

1 month-<12 months: 0.03-0.81 mg/mg creatinine
12 months-<24 months: 0.03-0.56 mg/mg creatinine
24 months-<3 years: 0.02-0.50 mg/mg creatinine
3 years-<5 years: 0.02-0.41 mg/mg creatinine

5 years-<7 years: 0.01-0.30 mg/mg creatinine
7 years-<10 years: 0.01-0.25 mg/mg creatinine
10 years-<18 years: 0.01-0.24 mg/mg creatinine
18 years-83 years: 0.05-0.27 mg/mg creatinine
Reference values have not been established for patients who are less than 1 month of age.
Reference values have not been established for patients who are greater than 83 years of age.

Clinical References: 1. Fraser WD. Bone and mineral metabolism. In: Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier;2018:1438 2. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int. 2001;59(6):2290-2298 3. Metz MP. Determining urinary calcium/creatinine cut-offs for the pediatric population using published data. Ann Clin Biochem. 2006;43(Pt 5):398-401 4. Pak CY, Britton F, Peterson R, et al. Ambulatory evaluation of nephrolithiasis. Classification, clinical presentation and diagnostic criteria. AM J Med. 1980;69(1):19-30 5. Pak CY, Kaplan R, Bone H, et al. A simple test for the diagnosis of absorptive, resorptive and renal hypercalciurias. N Engl J Med. 1975;292(10):497-500

CACR3
610594

Calcium/Creatinine Ratio, Random, Urine

Clinical Information: Calcium is the fifth most common element in the body. It is a fundamental element necessary to form electrical gradients across membranes, an essential cofactor for many enzymes, and the main constituent in bone. Under normal physiologic conditions, the concentration of calcium in serum and in cells is tightly controlled. Calcium is excreted in both urine and feces. Ordinarily about 20% to 25% of dietary calcium is absorbed, and 98% of filtered calcium is reabsorbed in the kidney. Traffic of calcium between the gastrointestinal tract, bone, and kidney is tightly controlled by a complex regulatory system that includes vitamin D and parathyroid hormone. Sufficient bioavailable calcium is essential for bone health. Excessive excretion of calcium in the urine is a common contributor to kidney stone risk.

Useful For: Evaluation of calcium oxalate and calcium phosphate kidney stone risk Calculation of urinary supersaturation Evaluation of bone diseases, including osteoporosis and osteomalacia

Interpretation: Increased urinary calcium excretion (hypercalciuria) is a known contributor to kidney stone disease and osteoporosis. Many cases are genetic (often termed "idiopathic"). Previously such patients were often divided into fasting versus absorptive hypercalciuria depending on the level of urine calcium in a fasting versus fed state, but the clinical utility of this approach is now in question. Overall, the risk of stone disease appears increased when 24-hour urine calcium is greater than 250 mg in men and greater than 200 mg in women. Thiazide diuretics are often used to reduce urinary calcium excretion and repeat urine collections can be performed to monitor the effectiveness of therapy. Known secondary causes of hypercalciuria include hyperparathyroidism, Paget disease, prolonged immobilization, vitamin D intoxication, and diseases that destroy bone (such as metastatic cancer or multiple myeloma). Urine calcium excretion can be used to gauge the adequacy of calcium and vitamin D supplementation, for example in states of gastrointestinal fat malabsorption that are associated with decreased bone mineralization (osteomalacia).

Reference Values:
1 month-<12 months: 0.03-0.81 mg/mg creatinine
12 months-<24 months: 0.03-0.56 mg/mg creatinine
24 months-<3 years: 0.02-0.50 mg/mg creatinine
3 years-<5 years: 0.02-0.41 mg/mg creatinine
5 years-<7 years: 0.01-0.30 mg/mg creatinine
7 years-<10 years: 0.01-0.25 mg/mg creatinine

10 years-<18 years: 0.01-0.24 mg/mg creatinine
18 years-83 years: 0.05-0.27 mg/mg creatinine
Reference values have not been established for patients who are less than 1 month of age.
Reference values have not been established for patients who are greater than 83 years of age.

Clinical References: 1. Fraser WD. Bone and mineral metabolism. In: Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1438 2. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int. 2001;59:2290-2298 3. Metz MP. Determining urinary calcium/creatinine cut-offs for the pediatric population using published data. Ann Clin Biochem. 2006;43:398-401 4. Pak CY, Britton F, Peterson R, et al. Ambulatory evaluation of nephrolithiasis. Classification, clinical presentation and diagnostic criteria. AM J Med. 1980;69:19-30 5. Pak CY, Kaplan R, Bone H, et al. A simple test for the diagnosis of absorptive, resorptive and renal hypercalciurias. N Engl J Med. 1975;292:497-500

CALD
70369

Caldesmon Immunostain, Technical Component Only

Clinical Information: Caldesmon is a smooth muscle specific protein that regulates smooth muscle contraction. This clone recognizes the high-molecular-weight variant (h-caldesmon) and does not react with the nonmuscle variant. Neither variant of caldesmon is present in skeletal muscle. Anti-h-caldesmon seems to be a reliable marker of smooth muscle differentiation and may assist in the diagnosis of smooth muscle tumors.

Useful For: As a marker of smooth muscle differentiation

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Wick MR, Hornick JL: Immunohistology of soft tissue and osseous neoplasms. In: Dabbs DJ, ed. Diagnostic Immunohistochemistry: Theranostic and Genomic Applications. 3rd ed. 2010:chap 4 2. Horita A, Kurata A, Maeda D,Fukayama M, Sakamoto A. Immunohistochemical characteristics of atypical polypoid adenomyoma with special reference to h-caldesmon. Int J Gynecol Pathol. 201130(1)64-70 3. Ordonez NG: Value of PAX8, PAX2, claudin-4, and h-caldesmon immunostaining in distinguishing peritoneal epithelioid mesotheliomas from serous carcinomas. Mod Path. 2013;26:553-562 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CAVPC
83900

California Virus (La Crosse) Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid

Clinical Information: California (La Crosse) virus is a member of the Bunyaviridae family, and it is one of the arthropod-borne encephalitides. It is transmitted by various Aedes and Culex mosquitoes and is found in such intermediate hosts as rabbits, squirrels, chipmunks, and field mice. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children and adolescents younger than 15 years, usually from rural areas. The incubation period is estimated to be 7 days, and acute illness lasts 10 days or less in most instances. Typically, the first

symptoms are nonspecific, lasting 1 to 3 days, and are followed by the appearance of central nervous system (CNS) signs and symptoms, such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those older than 18 years. The most important sequela of California virus encephalitis is epilepsy, which occurs in about 10% of children and almost always in patients who have had seizures during the acute illness. An estimated 2% of patients have persistent paresis. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (<2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the specific transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. Serious California (La Crosse) virus infections primarily involve children, especially boys. Men exposed to California viruses have high prevalence rates of antibody but usually show no serious illness. Infection among men is primarily due to working conditions and sports activities taking place where the vector is present.

Useful For: Aiding in the diagnosis of California (La Crosse) encephalitis using spinal fluid specimens

Interpretation: A positive result indicates intrathecal synthesis of antibody and is indicative of neurological infection.

Reference Values:
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

Clinical References: 1. Dolin R. California encephalitis, hantavirus pulmonary syndrome, hantavirus hemorrhagic fever with renal syndrome, and bunyavirus hemorrhagic fevers. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2169-2176 2. Piantadosi A, Kanjilal S. Diagnostic approach for arboviral infections in the United States. J Clin Microbiol. 2020;58(12):e01926-19. doi:10.1128/JCM.01926-19

CAVP
83153

California Virus (La Crosse) IgG and IgM, Serum

Clinical Information: California (La Crosse) virus is a member of the Bunyaviridae family and is one of the arthropod-borne encephalitides. It is transmitted by various Aedes and Culex mosquitoes and is found in such intermediate hosts as rabbits, squirrels, chipmunks, and field mice. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children and adolescents younger than 15 years, usually from rural areas. The incubation period is estimated to be 7 days, and acute illness lasts 10 days or less in most instances. Typically, the first symptoms are nonspecific, lasting 1 to 3 days, and are followed by the appearance of central nervous system signs and symptoms, such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those older than 18 years. The most important sequela of California virus encephalitis is epilepsy, which occurs in about 10% of children; almost always in patients who have had seizures during the acute illness. A few patients (estimated 2%) have persistent paresis. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (no more than 2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the specific transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals.

Once humans have been infected, the severity of the host response may be influenced by age. Serious California (La Crosse) virus infections primarily involve children, especially boys. Men exposed to California viruses have high prevalence rates of antibody but usually show no serious illness. Infection among men is primarily due to working conditions and sports activities taking place where the vector is present.

Useful For: Aiding the diagnosis of California (La Crosse) encephalitis using serum specimens

Interpretation: In patients infected with these or related viruses, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Single serum specimen IgG of 1:10 or greater indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicates recent infection.

Reference Values:
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

Clinical References: 1. Gonzalez-Scarano F, Nathanson N: Bunyaviruses. In: Fields BN, Knipe DM, eds. Fields Virology. Vol 1. 2nd ed. Raven Press; 1990:1195-1228 2. Donat JF, Rhodes KH, Groover RV, Smith TF, Etiology and outcome in 42 children with acute nonbacterial meningoencephalitis. Mayo Clin Proc. 1980;55(3):156-160 3. Tsai TF. Arboviruses. In: Murray PR, Baron EJ, Pfaller MA, et al, eds. Manual of Clinical Microbiology. 7th ed. American Society for Microbiology; 1999:1107-1124 4. Calisher CH. Medically important arboviruses of the United States and Canada. Clin Microbiol Rev. 1994;7(1):89-116 5. Dolin R. California encephalitis, hantavirus pulmonary syndrome, hantavirus hemorrhagic fever with renal syndrome, and bunyavirus hemorrhagic fevers. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2169-2176

CAMTA
603417

Calmodulin-Binding Transcription Activator 1 (CAMTA1), Immunostain, Technical Component Only

Clinical Information: Calmodulin-binding transcription activator 1 (CAMTA1) protein overexpression in the nucleus is the result of the WWTR1-CAMTA1 gene fusion, which is found in approximately 90% of epithelioid hemangioendotheliomas (EHE). CAMTA1 can be used to distinguish EHE from other tumors with epithelioid morphology.

Useful For: Aids in the diagnosis of epithelioid hemangioendotheliomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Shibuya R, Matsuyama A, Shiba E, et al: CAMTA1 is a useful immunohistochemical marker for diagnosing epithelioid haemangioendothelioma. Histopathology. 2015; 67:827-835. doi:10.1111/his.12713 2. Flucke U, Vogels RJ, de Saint Aubain Somerhausen N, et al.

Epithelioid Hemangioendothelioma: clinicopathologic, immunohistochemical, and molecular genetic analysis of 39 cases. Diagn Pathol. 2014;9:131 doi:10.1186/1746-1596-9-131 3. Doyle LA, Fletcher CD, Hornick JL. Nuclear expression of CAMTA1 distinguishes epithelioid hemangioendothelioma from histologic mimics. Am J Surg Pathol. 2016;40:94-102. doi:10.1097/PAS.0000000000000511 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CALPN 70370 Calponin Immunostain, Technical Component Only

Clinical Information: Calponin is a cytoskeleton-associated protein that can bind to actin, tropomyosin, troponin C, and calmodulin and is involved in modulation of smooth muscle contraction. Calponin expression has been demonstrated in smooth muscle cells of blood vessels and myoepithelial cells in the lobules, ducts, and galactophorous sinuses of normal human breast.

Useful For: Marker for myoepithelium when differentiating ductal carcinomas in situ from infiltrating breast carcinoma Characterization of tumors of smooth muscle or myoepithelial lineage

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Russell T D, Jindal S, Agunbiade S, et al. Myoepithelial cell differentiation markers in ductal carcinoma in situ progression. Am J Pathol. 2015;185(11):3076-3089. doi:10.1016/j.ajpath.2015.07.004 2. Gray E, Mitchell, E, Jindal S, Schedin P, Chang YH. A method for quantification of calponin expression in myoepithelial cells in immunohistochemical images of ductal carcinoma in situ. Proc IEEE Int Symp Biomed Imaging. 2018;2018:796-799. doi: 10.1109/isbi.2018.8363692 3. Liu R, Jin JP: Calponin isoforms CNN 1, CNN 2 and CNN 3: Regulators for actin cytoskeleton functions in smooth muscle and non-muscle cells. Gene. 2016;585(1):143-153. doi:10.1016/j.gene.2016.02.040 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CALPR 63016 Calprotectin, Feces

Clinical Information: Calprotectin, formed as a heterodimer of S100A8 and S100A9, is a member of the S100 calcium-binding protein family. It is expressed primarily by granulocytes and, to a lesser degree, by monocytes/macrophages and epithelial cells. In neutrophils, calprotectin comprises almost 60% of the total cytoplasmic protein content. Activation of the intestinal immune system leads to recruitment of cells from the innate immune system, including neutrophils. The neutrophils are then activated, which leads to release of cellular proteins, including calprotectin. Calprotectin is eventually translocated across the epithelial barrier and enters the lumen of the gut. As the inflammatory process progresses, the released calprotectin is absorbed by fecal material before it is excreted from the body. The amount of calprotectin present in the feces is proportional to the number of neutrophils within the gastrointestinal mucosa and can be used as an indirect marker of intestinal inflammation. Calprotectin is most frequently used as part of the diagnostic evaluation of patients with suspected inflammatory bowel disease (IBD). Patients with IBD may be diagnosed with Crohn disease or ulcerative colitis. Although distinct in their pathology and clinical manifestations, both are associated with significant intestinal inflammation. Elevated concentrations of fecal calprotectin may be useful in distinguishing IBD from functional gastrointestinal disorders, such as irritable bowel syndrome. When used for this differential

diagnosis, fecal calprotectin has sensitivity and specificity both of approximately 85%. However, it must be remembered that increases in fecal calprotectin are not diagnostic for IBD, as other disorders such as celiac disease, colorectal cancer, and gastrointestinal infections, may also be associated with neutrophilic inflammation.

Useful For: Evaluating patients suspected of having a gastrointestinal inflammatory process
Distinguishing inflammatory bowel disease from irritable bowel syndrome, when used in conjunction with other diagnostic modalities, including endoscopy, histology, and imaging

Interpretation: Calprotectin concentrations below 50.0 mcg/g are not suggestive of an active inflammatory process within the gastrointestinal system. For patients experiencing gastrointestinal symptoms, consider further evaluation for functional gastrointestinal disorders. Calprotectin concentrations between 50.0 and 120 mcg/g are borderline and may represent a mild inflammatory process, such as in treated inflammatory bowel disease (IBD) or associated with nonsteroidal anti-inflammatory drug or aspirin usage. For patients with clinical symptoms suggestive of IBD, retesting in 4 to 6 weeks may be indicated. Calprotectin concentrations above 120 mcg/g are suggestive of an active inflammatory process within the gastrointestinal system. Additional diagnostic testing to determine the etiology of the inflammation is suggested.

Reference Values:
<50.0 mcg/g (Normal)
50.0-120 mcg/g (Borderline)
>120 mcg/g (Abnormal)

Reference values apply to all ages.

Clinical References: 1. Gisbert JP, McNicholl AG. Questions and answers on the role of faecal calprotectin as a biological marker in inflammatory bowel disease. Digest Liver Dis. 2009;41(1):56-66 2. Campeotto F, Butel MJ, Kalach N, et al. High faecal calprotectin concentrations in newborn infants. Arch Dis Child Fetal Neonatal Ed. 2004;89(4):F353-F355 3. Dabritz J, Musci J, Foell D. Diagnostic utility of faecal biomarkers in patients with irritable bowel syndrome. World J Gastroenterol. 2014;20(2):363-375 4. Fagerberg UL, Loof L, Merzoug RD, Hansson LO, Finkel Y. Fecal calprotectin levels in healthy children studied with an improved assay. J Pediatr Gastroenterol Nutr. 2003;37(4):438-472 5. Sherwood RA, Walsham NE, Bjarnason I: Gastric, pancreatic, and intestinal function. In: Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1398-1420

CALFM
618654

CALR Mutation Analysis, Myeloproliferative Neoplasm (MPN), Bone Marrow

Clinical Information: Mutations in the JAK2, CALR and MPL genes are considered driver events in the BCR-ABL1 negative myeloproliferative neoplasms (MPN) including polycythemia vera (PV), primary myelofibrosis (PMF) and essential thrombocythemia (ET). The JAK2 V617F mutation occurs in 95% to 98% of patients with PV, 50% to 60% of patients with PMF and 50% to 60% of patients with ET respectively at diagnosis. Other JAK2 mutations in exon 12 to 15 occur in the remaining patients with PV. Mutations in the CALR gene occur in 20% to 30% of patients with PMF and 20% to 30% of patients with ET at diagnosis. A 52 base pairs (bp) deletion (53%) and a 5 bp deletion (32%) are the most common mutations in the CALR gene while other types of mutations may occur in the remaining cases. MPL exon 10 mutations occur in 5% to 10% of patients with PMF and 5% to 10% of patients with ET. Mutations in JAK2, CALR and MPL are mutually exclusive. The JAK2 V617F mutation is detected by quantitative polymerase chain reaction (qPCR). The CALR mutations are detected by PCR targeting the exon 9. The MPL mutations in exon 10 are detected by Sanger sequencing. All mutations in JAK2, CALR and MPL

can also be detected by next generation sequencing (NGS). In addition to the mutations in JAK2, CALR and MPL, mutations in many other genes including ASXL1, TET2, DNMT3A, SRSF2, SF3B1, U2AF1, ZRSR2, EZH2, IDH1, IDH2, CBL, KRAS, NRAS, STAG2, and TP53 can occur in MPN. These additional mutations are more frequent in PMF and advanced disease, as compared to PV and ET. It is known that mutations in the ASXL1, SRSF2, U2AF1, EZH2, IDH1 and IDH2 are correlated with a poor prognostic risk. While a single gene test on JAK2, CALR and MPL can be clinically useful, all above mentioned gene mutations can be detected by NGS.

Useful For: Diagnosis or differential diagnosis of myeloproliferative disorders by CALR gene sequencing using bone marrow specimens

Interpretation: The results will be reported as 1 of the 3 states if DNA amplification is successful (see Cautions): -Positive. A deletion-insertion-type mutation was detected in CALR, exon 9. -Negative. No deletion or insertion was detected in CALR, exon 9. -Equivocal. A small amplicon suspicious for a deletion-insertion type mutation was detected in CALR, exon 9. Positive mutation status is highly suggestive of a myeloid neoplasm but must be correlated with clinical and other laboratory and morphologic features for definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplastic disorders.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390 2. Rumi E, Pietra D, Ferretti V, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. Blood. 2014;123(10):1544-1551 3. Greenfield G, McMullin MF, Mills K. Molecular pathogenesis of the myeloproliferative neoplasms. J Hematol Oncol. 2021;14(1):103 4. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022;36(7):1703-1719. doi:10.1038/s41375-022-01613-1

CALX
36997

CALR Mutation Analysis, Myeloproliferative Neoplasm (MPN), Reflex, Varies

Clinical Information: The JAK2 (Janus kinase 2) gene codes for a tyrosine kinase (JAK2) associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR::ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). The JAK2 V617F is present in 95% to 98% of polycythemia vera, and 50% to 60% of primary myelofibrosis (PMF) and essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR::ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET). Mutations in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR mutation is associated with decreased risk of thrombosis in both ET and PMF and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

Useful For: Aiding in the distinction between a reactive cytosis and a chronic myeloproliferative disorder Evaluating mutations in CALR in an algorithmic process for the MPNR / Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies

Interpretation: An interpretation will be provided under the MPNR / Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies.

Reference Values:
Only orderable as a reflex. For more information see MPNR / Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies.

An interpretive report will be provided.

Clinical References: 1. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutation of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390 2. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutation in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med. 2013;369(25):2391-2405 3. Rumi E, Pietra D, Ferretti V, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. Blood. 2014;123(10):1544-1551 4. Rotunno G, Mannarelli C, Guglielmelli P, et al. Impact of calreticulin mutations on clinical and hematological phenotype and outcome in essential thrombocythemia. Blood. 2014;123(10):1552-1555 5. Tefferi A, Lasho TL, Finke CM, et al. CALR vs JAK2 vs MPL-mutated or triple-negative myelofibrosis: clinical, cytogenetic and molecular comparisons. Leukemia. 2014;28(7):1472-1477

CALR
62912

CALR Mutation Analysis, Myeloproliferative Neoplasm (MPN), Varies

Clinical Information: The most frequent genetic mutation in BCR-ABL1-negative myeloproliferative neoplasm (MPN), essential thrombocythemia (ET), and primary myelofibrosis (PMF) is the JAK2V617F alteration, which is present in approximately 50% to 60% of patients. It serves as a confirmatory molecular marker of these diseases. Mutations in the MPL gene are found in an additional 5% to 10% of ET and PMF cases. It was recently discovered that somatic mutation (insertions and deletions) in exon 9 of the CALR gene is the second most frequent somatic mutation after JAK2 in ET and PMF patients, and it is mutually exclusive of JAK2 and MPL mutations.(1,2) It has a frequency of approximately 49% to 88% in JAK2 and MPL-wild type (WT) ET and PMF and is not found in polycythemia vera (PV) patients.(1-4) Therefore, the CALR mutation serves as an important diagnostic molecular marker in ET and PMF. The CALR gene encodes for calreticulin, a multifunctional protein with a C-terminus rich in acidic amino acids and a KDEL endoplasmic reticulum (ER)-retention motif. All the disease-causing CALR mutations reported to date are out-of-frame insertion and/or deletions in exon 9, generating a 1 base pair (bp) frame shift and an altered protein with a novel C-terminus rich in basic amino acids and loss of the KDEL ER-retention signal. The most common mutation types are 52 bp-deletion (c.1092_1143del, L367fs*46) and 5-bp insertion (c.1154_1155insTTGCC, K385fs*47), and they comprise approximately 85% of CALR mutations in MPN.(1,2) CALR mutations have been found in hematopoietic stem and progenitor cells in MPN patients(2) and may activate the STAT5 signaling pathway.(1) They are associated with decreased risk of thrombosis in ET (1,3-5), and better survival in PMF compared to JAK2 mutations.(5)

Useful For: Rapid and sensitive detection of insertion and deletion-type mutations in exon 9 of CALR Aiding in distinguishing between reactive thrombocytosis and leukocytosis versus a myeloproliferative neoplasm (MPN), especially essential thrombocythemia (ET) and primary myelofibrosis (PMF), and is highly informative in cases in which JAK2 and MPL testing are negative Especially helpful to the pathologist in those bone marrow cases with ambiguous etiology of thrombocytosis, equivocal bone

marrow morphologic findings of MPN, and unexplained reticulin fibrosis Aiding in the prognostication of PMF and thrombosis risk assessment in ET

Interpretation: An interpretive report will be issued. The results will be reported as 1 of the 3 states if DNA amplification is successful (see Cautions): -Positive. A deletion-insertion-type mutation was detected in CALR, exon 9. -Negative. No deletion or insertion was detected in CALR, exon 9. -Equivocal. A small amplicon suspicious for a deletion-insertion type mutation was detected in CALR, exon 9. Positive mutation status is highly suggestive of a myeloid neoplasm but must be correlated with clinical and other laboratory and morphologic features for definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplastic disorders.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutation of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390 2. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutation in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med. 2013;369(25):2391-2405 3. Rumi E, Pietra D, Ferretti V, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. Blood. 2014;123(10):1544-1551 4. Rotunno G, Mannarelli C, Guglielmelli P, et al. Impact of calreticulin mutations on clinical and hematological phenotype and outcome in essential thrombocythemia. Blood. 2014;123(10):1552-1555 5. Tefferi A, Lasho TL, Finke CM, et al. CALR vs JAK2 vs MPL-mutated or triple-negative myelofibrosis: clinical, cytogenetic and molecular comparisons. Leukemia. 2014;28(7):1472-1477 6. Greenfield G, McMullin MF, Mils K. Molecular pathogenesis of the myeloproliferative neoplasms. J Hematol Oncol. 2021;14(1):103

CALJM 606806 CALR Variant Analysis, Myeloproliferative Neoplasm, Reflex, Bone Marrow

Clinical Information: The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide variant in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). JAK2 V617F is present in 95% to 98% of polycythemia vera and 50% to 60% of primary myelofibrosis (PMF) and essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome. Detection of JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 variant (20%-30% of PMF and ET) and MPL exon 10 variant (5%-10% of PMF and 3%-5% of ET). Variants in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR variant is associated with decreased risk of thrombosis in both ET and PMF and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

Useful For: Aiding in the distinction between a reactive cytosis and a chronic myeloproliferative disorder Evaluating for variants in CALR in an algorithmic process

Interpretation: The interpretive report includes an overview of the findings.

Reference Values:
Only orderable as a reflex. For more information see MPNJM / Myeloproliferative Neoplasm (MPN), JAK2 V617F with Reflex to CALR and MPL, Bone Marrow.

An interpretive report will be provided.

Clinical References: 1. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutation of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390. doi:10.1056/NEJMoa1311347 2. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutation in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med. 2013;369(25):2391-2405 3. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95(12):1599-1613 4. Luque Paz D, Kralovics R, Skoda RC. Genetic basis and molecular profiling in myeloproliferative neoplasms. Blood. 2023;141(16):1909-1921 5. Tefferi A, Vannucchi AM, Barbui T. Essential thrombocythemia: 2024 update on diagnosis, risk stratification, and management. Am J Hematol. 2024;99(4):697-718

CALRC
71486

Calreticulin ex9mut Immunostain, Technical Component Only

Clinical Information: The detection of calreticulin exon 9 frameshift alterations can assist in the diagnosis and prognostication of myeloproliferative diseases. Although these alterations are heterogeneous, they all result in a protein with a novel 36-amino acid C terminus the anticalreticulin CAL2 clone specifically identifies. Most patients with essential thrombocythemia or primary myelofibrosis not associated with Janus kinase 2 (JAK2) or MPL variants are associated with CALR exon 9 variants and primary myelofibrosis patients carrying CALR variants have a more indolent clinical course.

Useful For: Identifying the presence of CALR exon 9 frameshift alterations in myeloproliferative neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Vannucchi AM, Rotunno G, Bartalucci N, et al. Calreticulin mutation-specific immunostaining in myeloproliferative neoplasms: pathogenetic insight and diagnostic value. Leukemia. 2014;28(9):1811-1818. doi:10.1038/leu.2014.100 2. Stein H, Bob R, Durkop H, et al. A new monoclonal antibody (CAL2) detects CALRETICULIN mutations in formalin-fixed and paraffin-embedded bone marrow biopsies. Leukemia. 2016;30(1):131-135. doi:10.1038/leu.2015.192 3. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of Calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390. doi:10.1056/NEJMoa1311347 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CALNN
70371

Calretinin Immunostain, Technical Component Only

Clinical Information: Calretinin is expressed in benign and malignant mesothelial cells and strongly expressed in Leydig cells of the testis.

Useful For: Separating mesotheliomas from carcinomas which usually lack expression of calretinin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Arora R, Agarwal S, Mahur SR, Verma K, Iyer VK, Aron M. Utility of a limited panel of calretinin and Ber-EP4 immunocytochemistry on cytospin preparation of serous effusions: A cost-effective measure in resource-limited settings. Cytojournal. 2011;8:14 2. Musa ZA, Qasim BJ, Ghazi HF, Al Shaikhly AW. Diagnostic roles of calretinin in hirschsprung disease: A comparison to neuron-specific enolase. Saudi J Gastroentrol. 2017;23(1):60-66 3. Fakhry T, Samaka RM, Sheir M, Albatanony AA. Comparative study between use of calretinin and synaptophysin immunostaining in diagnosis of Hirschsprung disease. Int Surg J. 2019;6:(3):658-663. doi:10.18203/2349-2902.isj20190810 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CAMPC 606218 Campylobacter Culture, Feces

Clinical Information: Diarrhea may be caused by a number of agents, including bacteria, viruses, parasites, and chemicals; these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the healthcare provider determine the appropriate testing to be performed. Campylobacter enteritis is an important cause of acute diarrhea worldwide. The organism inhabits the intestinal tracts of a wide range of animal hosts, notably poultry; contamination from these sources can lead to foodborne disease that is typically caused by Campylobacter jejuni or Campylobacter coli. Campylobacter infection can also be transmitted via water-borne routes or direct contact with animals or animal products. Early symptoms (1-7 days after exposure) include abrupt onset of abdominal pain, diarrhea, and occasionally vomiting. The acute illness is characterized by cramping, abdominal pain, and diarrhea. Patients may report 10 or more bowel movements per day. Bloody feces may be observed. Diarrhea is typically self-limited, lasting around 7 days. Proper hydration is necessary. Antibiotics are not needed for most cases of Campylobacter gastroenteritis, except if patients experience severe disease or if they are immunocompromised.

Useful For: Determining whether Campylobacter species may be the cause of diarrhea Reflexive testing for Campylobacter species from nucleic acid amplification test-positive feces This test is generally not useful for patients hospitalized more than 3 days because the yield from specimens from these patients is very low, as is the likelihood of identifying a pathogen that has not been detected previously.

Interpretation: The growth of Campylobacter species identifies a potential cause of diarrhea.

Reference Values:
No growth of Campylobacter species.

Clinical References: 1. DuPont HL. Persistent diarrhea. A clinical review. JAMA. 2016;315(24):2712-2723. doi:10.1001/jama.2016.7833 2. Skirrow MB, Blaser MJ. Clinical aspects of Campylobacter infection. In: Nachamkin I, Blaser MJ, eds. Campylobacter. 2nd ed. ASM Press; 2000:69 3. Blaser MJ, Berkowitz ID, LaForce FM, et al. Campylobacter enteritis: clinical and

epidemiologic features. Ann Intern Med. 1979;91(2):179-1985

CFTH
82778

Canary Feathers, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to canary feathers Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CAGR
82829

Canary Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to canary grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CA25
9289

Cancer Antigen 125 (CA 125), Serum

Clinical Information: Cancer antigen 125 (CA 125) is a glycoprotein antigen normally expressed in tissues derived from coelomic epithelia (ovary, fallopian tube, peritoneum, pleura, pericardium, colon, kidney, stomach). Serum CA 125 is elevated in approximately 80% of women with advanced epithelial ovarian cancer, but the assay sensitivity is suboptimal in early disease stages. The average reported sensitivities are 50% for stage I and 90% for stage II or greater. Elevated serum CA 125 levels have been reported in individuals with a variety of nonovarian malignancies including cervical, liver, pancreatic, lung, colon, stomach, biliary tract, uterine, fallopian tube, breast, and endometrial carcinomas. Elevated serum CA 125 levels have been reported in individuals with a variety of benign conditions including: cirrhosis, hepatitis, endometriosis, first trimester pregnancy, ovarian cysts, and pelvic inflammatory disease. Elevated levels during the menstrual cycle also have been reported.

Useful For: Evaluating individuals' response to ovarian cancer therapy Predicting recurrent ovarian cancer This test is not useful for cancer detection screening in the normal population.

Interpretation: In monitoring studies, elevations of cancer antigen 125 (CA 125) above the reference interval after debulking surgery and chemotherapy indicate that residual disease is likely (>95% accuracy). However, normal levels do not rule out recurrence. A persistently rising CA 125 value suggests progressive malignant disease and poor therapeutic response. Physiologic half-life of CA 125 is approximately 5 days. In individuals with advanced disease who have undergone cytoreductive surgery and are on chemotherapy, a prolonged half-life (>20 days) may be associated with a shortened disease-free survival.

Reference Values:
Males: Not applicable
Females: <46 U/mL

Clinical References: 1. Zhang M, Cheng S, Jin Y, Zhao Y, Wang Y. Roles of CA125 in diagnosis, prediction, and oncogenesis of ovarian cancer. Biochim Biophys Acta Rev Cancer. 2021;1875(2):188503. doi:10.1016/j.bbcan.2021.188503 2. Charkhchi P, Cybulski C, Gronwald J, Wong FO, Narod SA, Akbari MR. CA125 and Ovarian Cancer: A Comprehensive Review. Cancers (Basel). 2020;12(12):3730. doi:10.3390/cancers12123730. PMID: 33322519; PMCID: PMC7763876 3. Sturgeon CM, Duffy MJ, Stenman UH, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate colorectal, breast, and ovarian cancers. Clin Chem. 2008;54(12):11-79 4. The Role of the Obstetrician-Gynecologist in the Early Detection of Epithelial Ovarian Cancer. American College of Obstetricians and Gynecologists. 2011. Committee Opinion Number 477

CA153
81607

Cancer Antigen 15-3 (CA 15-3), Serum

Clinical Information: Carcinoma of the breast is the most prevalent form of cancer in women. These tumors often produce mucinous antigens, which are large molecular weight glycoproteins with O-linked oligosaccharide chains. Tumor-associated antigens encoded by the human MUC-1 gene are known by several names, including MAM6, milk mucin antigen, cancer antigen (CA) 27.29, and CA 15-3. CA 15-3 assay values are not elevated in most normal individuals and are frequently elevated in sera from breast cancer patients. Nonmammary malignancies in which elevated CA 15-3 assay values have been reported include: lung, colon, pancreas, primary liver, ovary, cervix, and endometrium.

Useful For: Managing breast cancer patients when used in conjunction with clinical information and other diagnostic procedures Serial testing to assist in early detection of disease recurrence in previously treated stage II and III breast cancer patients Monitoring response to therapy in metastatic breast cancer patients This test is not useful as a cancer screening test.

Interpretation: Increasing and decreasing values show correlation with disease progression and regression, respectively.(1) Increasing cancer antigen 15-3 (CA 15-3) assay values in patients at risk for breast cancer recurrence after primary therapy may be indicative of recurrent disease before it can be detected clinically (2,3) and may be used as an indication that additional tests or procedures should be performed.

Reference Values:
Males: <30 U/mL (use not defined)
Females: <30 U/mL

Clinical References: 1. Molina R, Zanon G, Filella X, et al. Use of serial carcinoembryonic antigen and CA 15-3 assays in detecting relapses in breast cancer patients. Breast Cancer Res Treat. 1995;36(1):41-48 2. Geraghty JG, Coveney EC, Sherry F, O'Higgins NJ, Duffy MJ. CA 15-3 in patients with locoregional and metastatic breast carcinoma. Cancer. 1992;70(12):2831-2834 3. Kallioniemi OP, Oksa H, Aaran RK, Hietanen T, Lehtinen M, Koivula T. Serum CA 15-3 assay in the diagnosis and follow-up of breast cancer. Br J Cancer. 1988;58(2):213-215 4. Lin DC, Genzen JR. Concordance analysis of paired cancer antigen (CA) 15-3 and 27.29 testing. Breast Cancer Research and Treatment. 2018;167:269-276

FCARP 75447 Cancer-Associated Retinopathy Panel (CARP) by Immunoblot and IHC

Reference Values:
A final report will be provided.

CDAB 82690 Candida albicans (Monilia), IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Candida albicans (Monilia) Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with

the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FCANG
75605

Candida albicans IgG

Clinical Information: Although there have been many publications concerning the measurement of allergen-specific IgG, the clinical utility of such tests has not been established except in special situations. Thus, the quantitative IgG test should only be ordered by specialists who recognize the limitations of the test. The normal reference ranges reported represent the expected results for individuals who have no unusual exposure and have not been immunized with the indicated allergen. The ranges reported have no disease-associated significance.

Reference Values:
<52.0 mcg/mL

CAURS
607883

Candida auris Surveillance, Molecular Detection, PCR, Varies

Clinical Information: Candida auris can cause serious, and sometimes fatal, infections, is often resistant to one or more classes of antifungal drugs, and inappropriate treatment may occur as it can be misidentified in the laboratory. In addition, C auris appears to be more resistant to disinfection than other yeasts, leading to prolonged survival in the environment, increasing the possibility of transmission in hospitals and nursing homes. In December 2018, the Centers for Disease Control and Prevention (CDC) recommended that healthcare facilities implement routine surveillance screening of patients who have had an overnight stay in a healthcare facility outside of the US over the past year, particularly if the hospitalization was in a country with confirmed cases of C auris. The CDC also recommended considering screening of patients who have been hospitalized outside of the US and have a documented infection or colonization with a carbapenemase-producing gram-negative bacteria. These patients have frequently been found to have C auris colonization as well. A second group of people for whom screening is recommended includes healthcare workers who have been in close contact with patients who have

previously unrecognized C auris infection or colonization. The C auris polymerase chain reaction assay detects and identifies C auris combination groin/axilla surveillance swabs.

Useful For: Detecting Candida auris from surveillance swabs This test should not be used to determine cure or to monitor response to therapy.

Interpretation: A positive result indicates the presence of Candida auris DNA. A negative result indicates the absence of detectable C auris DNA.

Reference Values:
Not applicable

Clinical References: 1. Spivak ES, Hanson KE. Candida auris: an emerging fungal pathogen. J Clin Microbiol. 2018;56(2):e01588-17 2. Centers for Disease Control and Prevention (CDC) National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED): Candida auris. CDC; Updated July 31, 2023. Accessed September 22, 2023. Available at: www.cdc.gov/fungal/candida-auris/index.html 3. Navalkele BD, Revankar S, Chandrasekar P. Candida auris: a worrisome, globally emerging pathogen. Expert Rev Anti Infect Ther. 2017;15(9):819-827

CVRNA
620888

Candida Vaginitis, Nucleic Acid Amplification RNA, Vaginal

Clinical Information: This test is intended to aid in the diagnosis of vulvovaginal candidiasis from vaginal samples collected from symptomatic individuals. Vaginitis is characterized by a spectrum of signs and symptoms, including vaginal/vulvar irritation, odor, discharge, and pruritus. Vaginitis may develop as a result of mechanical and/or chemical irritants (eg, feminine hygiene products, contraceptive materials), or due to a dysbiosis of the microbiota in the vaginal tract. Up to 90% of vaginitis cases are infectious due to Bacterial vaginosis (BV), vulvovaginal candidiasis (Candida vaginitis, CV) and/or trichomoniasis (Trichomonas vaginalis, TV). BV, CV and TV individually account for 22% to 50%, 17% to 39%, and 4% to 35% of vaginitis cases, respectively. Candida vaginitis, commonly known as a yeast infection, is the second most frequent cause of vaginitis. CV is characterized by an overgrowth of Candida species in the vaginal tract and is associated with development of inflammation, abnormal vaginal discharge, vaginal soreness, pruritus, dyspareunia, and external dysuria. Up to 89% of CV cases are caused by C albicans, while non-albicans species may be responsible for 11%. C glabrata, which is responsible for the majority of non-albicans CV in the U.S., has decreased susceptibility to standard antifungal regiments for CV as compared to C albicans, which is why C glabrata is specifically reported by this assay.

Useful For: Aiding in the diagnosis of Candida vaginitis This test is not intended for use in medico-legal applications.

Interpretation: Candida species group (C albicans, C tropicalis, C parapsilosis, C dubliniensis): Positive: Candida albicans, C tropicalis, C parapsilosis and/or C dubliniensis RNA detected. Individual organisms are not identified or reported by this assay. Results should be interpreted alongside clinical presentation. Up to 21% of asymptomatic patients may be positive by this assay. Negative: No RNA detected from Candida albicans, C tropicalis, C parapsilosis or C dubliniensis. A negative result does not exclude infection. Inconclusive: Repeat testing on a new sample is recommended if clinically indicated. Candida glabrata: Positive: Candida glabrata RNA detected. Results should be interpreted alongside clinical presentation. Up to 9% of asymptomatic patients may be positive for C glabrata this assay. Negative: No RNA detected from Candida glabrata. A negative result does not exclude infection. Inconclusive: Repeat testing on a new sample is recommended if clinically indicated.

Reference Values:
Candida glabrata
Negative

Candida species group (C albicans, C tropicalis, C parapsilosis, C dubliniensis)
Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Huang SH, Hsu HC, Lee TF, et al. Prevalence, Associated Factors, and Appropriateness of Empirical Treatment of Trichomoniasis, Bacterial Vaginosis, and Vulvovaginal Candidiasis among Women with Vaginitis, 2023. American Society for Microbiology. 2023;11(3):e00161-23.doi:10.1128/spectrum.00161-23 3. Farr A, Effendy I, Frey Tirri B, Hof H, et al. Guideline: Vulvovaginal candidosis (AWMF 015/072, level S2k), 2021. Mycoses. 2021;64(6) 583-602. doi.org/10.1111/myc.13248

FCBDS 75527 Cannabidiol, Serum

Clinical Information: Mean peak CBD plasma concentrations at 3-4 hours post-dose with Sativex at a low dose (5.4 mg of Delta-9 THC and 5.0 mg of Cannabidiol) were 1.6 +/- 0.4 ng/mL and at a high dose (16 mg of Delta-9 THC and 15 mg of Cannabidiol) were 6.7 +/- 2.0 ng/mL. Following high dose 400 and 800 mg oral synthetic CBD in corn oil administration, mean peak CBD plasma concentrations occurred within 1.5-3 hours post-dose and were 181.2 +/- 39.8 and 221.1 +/- 35.6 ng/mL, respectively. The ratio of blood to serum or plasma concentration is unknown for this analyte.

Reference Values:
Reporting limit determined each analysis
Units: ng/mL

FMARI 75172 Cannabinoid Analysis, Whole Blood

Reference Values:

FCDU7 75782 Cannabinoids, Umbilical Cord Tissue

Reference Values:
Reporting limit determined each analysis.

Units: ng/g

Only orderable as part of a profile-see FCDSU.

CWAY 82493 Caraway, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to

allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to caraway Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CARBR
610048

Carbamazepine Hypersensitivity Pharmacogenomics, Varies

Clinical Information: Carbamazepine and oxcarbazepine are aromatic anticonvulsants, as are eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital. Carbamazepine is US Food and Drug Administration (FDA)-approved for the treatment of epilepsy, trigeminal neuralgia, and bipolar disorder. Oxcarbazepine is FDA-approved for the treatment of partial seizures. A minority of carbamazepine- or oxcarbazepine-treated persons have cutaneous adverse reactions that vary in prevalence and severity, with some forms associated with substantial morbidity and mortality. The most severe reactions, such as the Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN),

are characterized by a blistering rash affecting a variable percentage of the body-surface area. TEN is the rarest of these phenotypes and is associated with mortality of up to 30%. Drug reaction with eosinophilia and systemic symptoms (DRESS) and maculopapular exanthema (MPE) may also be related to carbamazepine exposure. According to the FDA-approved label for carbamazepine, the estimated incidence of SJS-TEN is 1 to 6 cases in 10,000 persons of European ancestry who are exposed to the drug. The rate of SJS-TEN as a result of carbamazepine exposure is about 10 times higher in some Asian countries. According to the FDA label for oxcarbazepine, the rate of TEN and SJS among individuals exposed to oxcarbazepine exceeds the background incidence by a factor of 3- to 10-fold, but this is expected to be an underestimate due to underreporting. The risk for a severe cutaneous adverse reaction is highest within the first few months of initiating therapy, but may not be absent, particularly if therapy is interrupted or reinitiated. Clinical studies have demonstrated associations between some human leukocyte antigen (HLA) genotypes and drug-associated cutaneous adverse reactions. The presence of the HLA-B*15:02 allele varies throughout Asia: 10% to 15% frequency in Chinese; 2% to 4% frequency in Southeast Asians and Indians; and less than 1% frequency in Japanese and Koreans. This allele may be found in other populations, but is rare. This allele is strongly associated with greater risk of SJS and TEN in patients treated with carbamazepine or oxcarbazepine and has also been associated with SJS/TEN with phenytoin use. There is limited evidence associating SJS/TEN/DRESS or MPE and other aromatic anticonvulsants, such as lamotrigine, in patients who are positive for HLA-B*15:02, but the FDA has not issued a formal warning. The HLA-A*31:01 allele, which has a prevalence of 2% to 5% in Northern European populations, 6% among Hispanic/South American populations, and 8% among Japanese populations, has been significantly associated with greater risk of MPE, DRESS, and SJS/TEN among patients treated with carbamazepine. In the absence of HLA-A*31:01, the risk for drug-associated cutaneous adverse reactions is 3.8%, but in the presence of this allele, the risk increases to 26%. The evidence linking other aromatic anticonvulsants with SJS/TEN in the presence of the HLA-A*31:01 allele is weaker; however, an alternative medication should be chosen with caution. The FDA-approved label for carbamazepine states that the screening of patients in genetically at-risk populations (ie, patients of Asian descent) for the presence of the HLA-B*15:02 allele should be carried out prior to initiating treatment with carbamazepine. The FDA-approved label also notes the association of HLA-A*31:01 allele with drug-associated cutaneous adverse reactions regardless of ancestry, but it does not specifically mandate screening of patients. The FDA-approved label for oxcarbazepine indicates that testing for the presence of the HLA-B*15:02 allele should be considered in patients with ancestry including genetically at-risk populations prior to initiation of therapy. According to the FDA label, patients who test positive for HLA-B*15:02 should not be treated with carbamazepine or oxcarbazepine unless the benefit clearly outweighs the risk. Similarly, the most recent Clinical Pharmacogenetic Implementation Consortium (CPIC) guideline, patients who are HLA-B*15:02 positive should not be prescribed carbamazepine or oxcarbazepine if alternative agents are available; however, caution should be used in selecting an alternative medication as there is weaker evidence that also links other aromatic anticonvulsants with SJS/TEN in patients positive for HLA-B*15:02. Furthermore, phenytoin and fosphenytoin are the subject of a separate CPIC guideline with recommendations to avoid phenytoin and fosphenytoin in HLA-B*15:02 positive individuals, along with additional recommendations based on CYP2C9 genotype. Patients who are HLA-A*31:01 positive should not be prescribed carbamazepine if alternative agents are available. Although very limited evidence links SJS/TEN/DRESS/MPE with other aromatic anticonvulsants when used by HLA-A*31:01-positive patients, caution is advised when selecting an alternative medication.

Useful For: Identifying individuals with increased risk of carbamazepine- or oxcarbazepine-associated cutaneous adverse reactions

Interpretation: The presence of the HLA-B*15:02 and/or HLA-A*31:01 allele confers increased risk for hypersensitivity to carbamazepine. The presence of the HLA-B*15:02 allele also confers increased risk for hypersensitivity to oxcarbazepine and phenytoin. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 Update. Clin Pharmacol Ther. 2018;103(4):574-581 2. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011;364:1134-1143 3. Amstutz U, Shear NH, Rieder MJ, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia. 2014;55:496-506 4. Karnes JH, Rettie AE, Somogyi AA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing: 2020 Update. Clin Pharmacol Ther. 2021;109(2):302-309. doi:10.1002/cpt.2008

CARTF
37037

Carbamazepine Profile, Serum

Clinical Information: Carbamazepine is a common antiepileptic drug. It is a first-line drug for treatment of partial seizures and trigeminal neuralgia. Carbamazepine is metabolized by the liver to carbamazepine-10,11-epoxide (CBZ10-11), which is pharmacologically active and potentially toxic. CBZ10-11 is, in turn, inactivated by hepatic conversion to a transdiol derivative. CBZ10-11 may be responsible for the congenital abnormalities that are sometimes associated with the use of carbamazepine during early pregnancy. There have been cases of severe seizures exacerbation when serum epoxide levels were increased. Toxic levels of CBZ10-11 can occur during: -Concomitant administration of other drugs that induce hepatic oxidizing enzymes (eg, most antiepileptic drugs [with the exception of valproic acid and the benzodiazepines], propoxyphene) -Concomitant administration of drugs that inhibit its breakdown such as valproic acid, felbamate, and lamotrigine -High-dose carbamazepine therapy, especially in combination with the above conditions

Useful For: Monitoring patients exhibiting symptoms of carbamazepine toxicity whose total serum carbamazepine concentration is within the therapeutic range, but who may be producing significant levels of the active metabolite epoxide Free carbamazepine concentration may also be useful to monitor in patients with altered or unpredictable protein binding capacity

Interpretation: The clinically acceptable serum concentration of carbamazepine-10,11-epoxide (CBZ10-11) is not well established, but 4.0 mcg/mL has often been used as an upper limit for its therapeutic range. The ratio of CBZ10-11 to carbamazepine is usually less than or equal to 0.2 mcg/mL in symptomatic adults and less than or equal to 0.3 mcg/mL in children. Clinical correlation is aided by comparing values obtained when the patient is symptomatic with those obtained when the patient has improved.

Reference Values:
CARBAMAZEPINE, TOTAL
Therapeutic: 4.0-12.0 mcg/mL
Critical value: > or =15.0 mcg/mL

CARBAMAZEPINE-10,11-EPOXIDE
Therapeutic: 0.4-4.0 mcg/mL
Toxic concentration: > or =8.0 mcg/mL

CARBAMAZEPINE, FREE
Therapeutic: 1.0-3.0 mcg/mL
Critical value: > or =4.0 mcg/mL

Clinical References: 1. Theodore WH, Narang PK, Holmes MD, et al: Carbamazepine and its epoxide: relation of plasma levels to toxicity and seizure control. Ann Neurol 1989;25:194-196 2. Tomson T, Almkvist O, Nilsson BY, et al: Carbamazepine-10, 11-epoxide in epilepsy. A pilot study. Arch Neurol 1990;47:888-892 3. McKauge L, Tyrer JH, Eadie MI: Factors influencing simultaneous concentrations of carbamazepine and its epoxide in plasma. Ther Drug Monit 1981;3:63-70 4. Brodie MJ, Forrest G, Rapeport WG: Carbamazepine-10,11-epoxide concentrations in epileptics of carbamazepine alone and in combination with other anticonvulsants. Br J Clin Pharmacol 1983;16:747-749 5. Shoeman JF, Elyas AA, Brett EM, Lascelles PT: Correlation between plasma carbamazepine-10,11-epoxide concentration and drug side-effects in children with epilepsy. Dev Med Child Neurol 1984;26:756-764

CARFT
37039

Carbamazepine, Free and Total, Serum

Clinical Information: Carbamazepine (Tegretol) is an effective treatment for complex partial seizures, with or without generalization to tonic-clonic seizures. It is frequently administered in conjunction with other antiepileptic agents, such as phenytoin and valproic acid. Under normal circumstances, 75% of the carbamazepine that circulates in blood is protein bound. In severe uremia, carbamazepine may be displaced from protein, resulting in a higher free (unbound) fraction of the drug circulating in blood. Since neurologic activity and toxicity are directly related to the circulating free fraction of drug, adjustment of dosage based on knowledge of the free carbamazepine level may be useful in patients with severe uremia.

Useful For: Monitoring carbamazepine (free and total) therapy in patients who are uremic

Interpretation: In patients with normal kidney function, optimal response is often associated with free (unbound) carbamazepine levels greater than 1.0 mcg/mL, and toxicity may occur when the free carbamazepine is greater than or equal to 4.0 mcg/mL. In uremic patients, the free carbamazepine level may be a more useful guide for dosage adjustments than the total level. In patients with severe uremia, subtherapeutic total carbamazepine levels in the range of 1.0 to 2.0 mcg/mL may be associated with therapeutic free levels. Toxicity may occur in these patients when the free carbamazepine level is greater than or equal to 4.0 mcg/mL (even though the total carbamazepine concentration is <15.0 mcg/mL). As with the serum levels of other anticonvulsant drugs, total and free carbamazepine levels should be correlated with the patient's clinical condition. They are best used as a guide in dose adjustment.

Reference Values:

CARBAMAZEPINE, TOTAL
Therapeutic: 4.0-12.0 mcg/mL
Critical value: > or =15.0 mcg/mL

CARBAMAZEPINE, FREE
Therapeutic: 1.0-3.0 mcg/mL
Critical value: > or =4.0 mcg/mL

Clinical References: 1. Svinarov DA, Pippenger CE. Relationships between carbamazepine-diol, carbamazepine-epoxide, and carbamazepine total and free steady-state concentrations in epileptic patients: the influence of age, sex, and comedication. Ther Drug Monit. 1996;18(6):660-665 2. Bernus I, Dickinson RG, Hooper WD, Eadie MJ. The mechanism of the carbamazepine-valproate interactions in humans. Br J Clin Phamacol. 1997;44(1):21-27 3. Dasgupta A, Volk A. Displacement of valproic acid and carbamazepine from protein binding in normal and uremic sera by tolmetin, ibuprofen, and naproxen: presence of inhibitor in uremic serum that blocks valproic acid-naproxen interactions. Ther Drug Monit. 1996;18(3):284-287 4. Moyer TP: Therapeutic drug monitoring. In: Burtis CA, Ashwood ER eds. Tietz Textbook of Clinical Chemistry. 4th ed. WB Saunders Company; 2005: 1237-1285 5. Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs-best practice guidelines for therapeutic drug monitoring: A

position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239-1276 6. Kanner A.M, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2018;91(2):74-81

CARF
37038

Carbamazepine, Free, Serum

Clinical Information: Carbamazepine (Tegretol) is an effective treatment for complex partial seizures, with or without generalization to tonic-clonic seizures.(1) It is frequently administered in conjunction with other antiepileptic agents, such as phenytoin and valproic acid.(2) Under normal circumstances, the carbamazepine that circulates in blood is 70% to 80% protein-bound;(3) only the free drug is able to enter the interstitial space in the brain where the pharmacological effects occur.(4) Patient management is best guided by monitoring free serum concentrations when protein binding is altered. Altered protein binding occurs in patients with hypoalbuminemia observed during pregnancy, in the malnourished, and liver disease. In patients with kidney disease, uremia may develop whose byproducts can displace bound carbamazepine increasing the unbound fraction. Administration of drugs that can compete for serum protein binding sites may also increase the unbound fraction of carbamazepine. Since neurologic activity and toxicity of carbamazepine are directly related to the circulating free fraction of drug, adjustment of dosage based on knowledge of the free carbamazepine concentration may be more useful in these patient populations.

Useful For: Monitoring unbound or free carbamazepine levels in patients where the total carbamazepine result is within the therapeutic range, but the patient is experiencing side effects
Monitoring carbamazepine (free) therapy in patients who are uremic

Interpretation: In patients with normal kidney function, optimal response is often associated with free (unbound) carbamazepine levels above 1.0 mcg/mL, and toxicity may occur when the free carbamazepine is greater than or equal to 4.0 mcg/mL. Under normal circumstances, 75% of the carbamazepine that circulates in blood is protein-bound. Therapies or conditions such as uremia that displace carbamazepine from protein cause a higher free (unbound) fraction of the drug circulating in blood. In uremia, the free carbamazepine level may be a more useful guide for dosage adjustments than the total level. In patients with severe uremia, subtherapeutic total carbamazepine levels in the range of 1.0 to 2.0 mcg/mL may be associated with therapeutic free carbamazepine levels. Toxicity may occur when the free carbamazepine level is greater than or equal to 4.0 mcg/mL (even though the total carbamazepine concentration is <15.0 mcg/mL). As with the serum levels of other anticonvulsant drugs, total and free carbamazepine levels should be correlated with the patient's clinical condition. Serum levels are best used as a guide in dose adjustment.

Reference Values:
Therapeutic concentration: 1.0-3.0 mcg/mL
Critical value: > or =4.0 mcg/mL

Clinical References: 1. Svinarov DA, Pippenger CE. Relationships between carbamazepine-diol, carbamazepine-epoxide, and carbamazepine total and free steady-state concentrations in epileptic patients: the influence of age, sex, and comedication. Ther Drug Monit. 1996;18(6):660-665 2. Bernus I, Dickinson RG, Hooper WD, Eadie MJ. The mechanism of the carbamazepine-valproate interactions in humans. Br J Clin Phamacol. 1997;44(1):21-27 3. Dasgupta A, Volk A. Displacement of valproic acid and carbamazepine from protein binding in normal and uremic sera by tolmetin, ibuprofen, and naproxen: presence of inhibitor in uremic serum that blocks valproic acid-naproxen interactions. Ther Drug Monit. 1996;18(3):284-287 4 Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs-best

practice guidelines for therapeutic drug monitoring: A position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239-1276 5. Kanner A.M, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2018;91(2):74-81

CARTA
37035

Carbamazepine, Total, Serum

Clinical Information: Carbamazepine (Tegretol) is used in the control of partial seizures with both temporal lobe and psychomotor symptoms as well as for generalized tonic-clonic seizures. It is also used for analgesia in trigeminal neuralgia. Carbamazepine exhibits a volume of distribution of 1.4 L/kg with an elimination half-life of 15 hours. Protein binding averages 70%. Carbamazepine-10,11-epoxide (CBZ10-11) is an active metabolite that represents the predominant form of the drug in children. The volume of distribution of CBZ10-11 is 1.1 L/kg, and the half-life is 5 to 8 hours. Aplastic anemia and agranulocytosis are rare side effects of treatment with carbamazepine; baseline hematologic data should be documented before treatment is initiated. Toxicity associated with carbamazepine overdose occurs when the blood level is 15.0 mcg/mL or higher and is typified by irregular breathing, muscle irritability, and hyperreflexia; followed by hyporeflexia, tachycardia, hypotension, and impaired consciousness with coma in severe toxicity. The higher the blood level, the more severe the symptoms.

Useful For: Monitoring therapy Determining compliance Assessing toxicity

Interpretation: Dosage adjustments are usually guided by monitoring blood levels. Most patients respond well when the serum concentration is in the range of 4.0 to 12.0 mcg/mL. Toxicity often occurs when levels are greater than or equal to 15.0 mcg/mL.

Reference Values:
Therapeutic: 4.0-12.0 mcg/mL
Critical value: > or =15.0 mcg/mL

Clinical References: 1. Cereghino JJ, Meter JC, Brock JT, Penry JK, Smith LD, White BG: Preliminary observations of serum carbamazepine concentration in epileptic patients. Neurology. 1973 Apr;23(4):357-366. doi: 10.1212/wnl.23.4.357 2. Patsalos PN, Berry DJ, Bourgeois BF, et al: Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008 Jul;49(7):1239-1276. doi: 10.1111/j.1528-1167.2008.01561.x 3. Scheuer ML, Pedley TA: The evaluation and treatment of seizures. N Engl J Med. 1990 Nov 22;323(21):1468-1474. 10.1056/NEJM199011223232107 4. Milone MC, Shaw LM: Therapeutic Drug Monitoring. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics. 8th ed. Saunders; 2019:549 5. Patsalos PN, Zugman M, Lake C, James A, Ratnaraj N, Sander JW. Serum protein binding of 25 antiepileptic drugs in a routine clinical setting: a comparison of free non-protein-bound concentrations. Epilepsia. 2017 Jul;58(7):1234-1243. doi: 10.1111/epi.13802

CARBG
37036

Carbamazepine-10,11-Epoxide, Serum

Clinical Information: Carbamazepine is a common antiepileptic drug. It is a first-line drug for treatment of partial seizures and trigeminal neuralgia. Carbamazepine is metabolized by the liver to carbamazepine-10,11-epoxide (CBZ10-11) which is pharmacologically active and potentially toxic. CBZ10-11 is, in turn, inactivated by hepatic conversion to a transdiol derivative. CBZ10-11 may be responsible for the congenital abnormalities that are sometimes associated with the use of carbamazepine

during early pregnancy. There have been cases of severe seizures exacerbation when serum epoxide levels were increased. Toxic levels of CBZ10-11 can occur during: -Concomitant administration of other drugs that induce hepatic oxidizing enzymes (eg, most antiepileptic drugs [with the exception of valproic acid and the benzodiazepines], propoxyphene) -Concomitant administration of drugs that inhibit its breakdown such as valproic acid, felbamate, and lamotrigine -High-dose carbamazepine therapy, especially in combination with the above conditions

Useful For: Monitoring patients exhibiting symptoms of carbamazepine toxicity whose total serum carbamazepine concentration is within the therapeutic range, but who may be producing significant levels of the active metabolite epoxide, which can accumulate to concentrations equivalent to carbamazepine

Interpretation: The clinically acceptable serum concentration of carbamazepine-10,11-epoxide (CBZ10-11) is not well established, but 4.0 mcg/mL has often been used as an upper limit for its therapeutic range. The ratio of CBZ10-11 to carbamazepine is usually < or =0.2 mcg/mL in symptomatic adults and < or =0.3 mcg/mL in children. Clinical correlation is aided by comparing values obtained when the patient is symptomatic with those obtained when the patient has improved.

Reference Values:
CARBAMAZEPINE, TOTAL
Therapeutic: 4.0-12.0 mcg/mL
Critical value: > or =15.0 mcg/mL

CARBAMAZEPINE-10,11-EPOXIDE
Therapeutic concentration: 0.4-4.0 mcg/mL
Toxic concentration: > or =8.0 mcg/mL

Clinical References: 1. Theodore WH, Narang PK, Holmes MD, et al: Carbamazepine and its epoxide: relation of plasma levels to toxicity and seizure control. Ann Neurol 1989;25:194-196 2. Tomson T, Almkvist O, Nilsson BY, et al: Carbamazepine-10, 11-epoxide in epilepsy. A pilot study. Arch Neurol 1990;47:888-892 3. McKauge L, Tyrer JH, Eadie MI: Factors influencing simultaneous concentrations of carbamazepine and its epoxide in plasma. Ther Drug Monit 1981;3:63-70 4. Brodie MJ, Forrest G, Rapeport WG: Carbamazepine-10,11-epoxide concentrations in epileptics of carbamazepine alone and in combination with other anticonvulsants. Br J Clin Pharmacol 1983;16:747-749 5. Shoeman JF, Elyas AA, Brett EM, Lascelles PT: Correlation between plasma carbamazepine-10,11-epoxide concentration and drug side-effects in children with epilepsy. Dev Med Child Neurol 1984;26:756-764

CRPCR 620176 Carbapenem Resistance Genes, Molecular Detection, PCR, Rectal Swab

Clinical Information: The global spread of carbapenemase-producing Enterobacterales, Pseudomonas aeruginosa, and Acinetobacter species (organisms not susceptible to carbapenem antimicrobials) is a critical public health issue. These bacteria are often resistant to all beta-lactam agents and, frequently, are also resistant to multiple classes of other antimicrobial agents leaving very few treatment options. Tracing the spread of organisms not susceptible to carbapenems is complicated by the diversity of carbapenem-hydrolyzing enzymes that have emerged and the ability of the genes to spread among multiple bacterial species.

Useful For: Detecting and differentiating the blaKPC, blaNDM, blaVIM, blaOXA-48, and blaIMP gene sequences associated with carbapenem intermediate or resistant results Aiding in infection control in the detection of gastrointestinal colonization of patients in healthcare settings with bacteria not

susceptible to carbapenems using rectal or perirectal swabs

Interpretation: A detected result is when blaKPC, blaNDM, blaVIM, blaOXA-48, or blaIMP target DNA is detected. This indicates the presence of gene sequences associated with carbapenem intermediate or resistant results. A not detected result is when blaKPC, blaNDM, blaVIM, blaOXA-48, and blaIMP target DNA is not detected. A not detected Xpert Carba-R Assay result does not preclude the presence of other carbapenem resistance mechanisms.

Reference Values:
Not detected

Clinical References: 1. McConville TH, Sullivan SB, Gomez-Simmonds A, Whittier S, Uhlemann AC. Carbapenem-resistant Enterobacteriaceae colonization (CRE) and subsequent risk of infection and 90-day mortality in critically ill patients, an observational study. PLoS One. 2017;12(10):e0186195 2. Tenover FC, Nicolau DP, Gill CM. Carbapenemase-producing Pseudomonas aeruginosa an emerging challenge. Emerg Microbes Infect. 2022;11(1):811-814 3. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. 11th ed. CLSI standard M07. CLSI; 2018

CARBI
620159

Carbapenem Resistance Genes, Molecular Detection, PCR, Varies

Clinical Information: The global spread of carbapenemase-producing Enterobacterales, Pseudomonas aeruginosa, and Acinetobacter baumannii (organisms not-susceptible to carbapenem antimicrobials) is a critical public health issue. These bacteria are often resistant to all beta-lactam agents and frequently also resistant to multiple classes of other antimicrobial agents, leaving very few treatment options. Tracing the spread of organisms not-susceptible to carbapenems is complicated by the diversity of carbapenem-hydrolyzing enzymes that have emerged and the ability of the genes to spread among multiple bacterial species.

Useful For: Detecting and differentiating blaKPC, blaNDM, blaVIM, blaOXA-48, and blaIMP gene sequences associated with carbapenem intermediate or resistant results Aiding in infection control in the detection of gastrointestinal colonization of patients in healthcare settings with bacteria not susceptible to carbapenems using bacterial isolates from rectal or perirectal swabs

Interpretation: A detected result is when blaKPC, blaNDM, blaVIM, blaOXA-48, or blaIMP target DNA is detected. This indicates the presence of gene sequences associated with carbapenem intermediate or resistant results. A not detected result is when blaKPC, blaNDM, blaVIM, blaOXA-48, and blaIMP target DNA is not detected. A not detected Xpert Carba-R Assay result does not preclude the presence of other carbapenem-resistance mechanisms.

Reference Values:
Not Detected

Clinical References: 1. Bush K, Bradford PA. Epidemiology of beta-lactamase-producing pathogens. Clin Microbiol Rev. 2020;33(2): e00047-19 2. Tenover FC, Nicolau DP, Gill CM. Carbapenemase-producing Pseudomonas aeruginosa - an emerging challenge. Emerg Microbes Infect. 2022;11(1):811-814 3. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. 11th ed. CLSI standard M07. CLSI; 2018

CARNB
35953

Carbapenemase Detection-Carba NP Test (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

CARNP
62606

Carbapenemase Detection-Carba NP Test, Varies

Clinical Information: Gram-negative bacilli (GNB) with acquired carbapenemases have disseminated worldwide, rendering them a global threat. The therapeutic armamentarium for infections caused by carbapenem-resistant Enterobacterales (CRE) is limited, and CRE infections have been associated with significant mortality. Enterobacterales harboring Klebsiella pneumoniae carbapenemase are endemic in some regions of the United States, and although still sporadic, GNB harboring New Delhi metallo-beta-lactamase have been reported from several states. Timely detection of these carbapenemases (along with emerging carbapenemases such as OXA-48 and VIM) is important. Detection is challenging since isolates may have only borderline reductions in susceptibility to carbapenems, and carbapenem resistance may be mediated by mechanisms other than carbapenemases (eg, AmpC or extended-spectrum beta-lactamase with decreased membrane permeability). While molecular methods are confirmatory, testing may not be immediately available and may be limited by the number of targets assayed. The Carba NP test is preferred over the mCIM (modified carbapenem inactivation method) test due to faster turnaround time. If an isolate is suspected to possess KPC or NDM carbapenemase (eg, due to local epidemiology), Carbapenem Resistance Genes, Molecular Detection, PCR, Varies (CARBI) may be preferred over the Carba NP test.

Useful For: Confirming carbapenemase production from pure isolates of Enterobacterales or Pseudomonas aeruginosa

Interpretation: A positive result indicates production of a carbapenemase by the isolate submitted for testing. A negative result indicates lack of production of a carbapenemase by the isolate submitted for testing.

Reference Values:
Negative

Clinical References: 1. Vasoo S, Cunningham SA, Kohner PC, et al. Comparison of a novel, rapid chromogenic biochemical assay, the Carba NP test, with the modified Hodge test for detection of carbapenemase-producing Gram-negative bacilli. J Clin Microbiol. 2013;51(9):3097-3101 2. Nordmann P, Poirel L, Dortet L. Rapid detection of carbapenemase-producing Enterobacteriaceae. Emerg Infect Dis. 2012;18(9):1503-1507 3. Clinical and Laboratory Standards Institute (CLSI): Performance Standards for Antimicrobial Susceptibility Testing. 33rd ed. CLSI Supplement M100, CLSI; 2023

199PC
89508

Carbohydrate Antigen 19-9 (CA 19-9), Pancreatic Cyst Fluid

Clinical Information: Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen that has been used as a tumor marker. Serum CA 19-9 concentrations may be elevated in patients with gastrointestinal malignancies, such as cholangiocarcinoma, colon cancer, or pancreatic cancer. While serum CA 19-9 is neither sensitive nor specific for pancreatic cancer, concentrations of CA 19-9 in pancreatic cyst fluid may help determine whether a pancreatic cyst is benign. Cystic lesions of the pancreas are of various types: Benign cysts: -Inflammatory cysts (pseudocysts) -Serous cysts (serous cystadenoma) Mucinous cysts: -Premalignant (mucinous cystadenoma) -Malignant (cystadenocarcinoma, intrapapillary mucinous neoplasia) Pancreatic cyst fluid CA 19-9 results should

be used in conjunction with imaging studies, cytology, and other cyst-fluid tumor markers, such as carcinoembryonic antigen and amylase.

Useful For: As an adjunct in the assessment of pancreatic cysts, when used in conjunction with carcinoembryonic antigen, amylase, imaging studies and cytology

Interpretation: Cyst fluid carbohydrate antigen 19-9 (CA19-9) concentrations less than 37 U/mL indicate a low risk for a mucinous cyst and are more consistent with serous cystadenoma or pseudocyst. The sensitivity and specificity are approximately 19% and 98%, respectively, at this concentration. Correlation of these test results with cytology and imaging is recommended.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Snozek CL, Jenkins SM, Bryant SC, et al: . Analysis of CEA, CA19-9 and amylase in pancreatic cyst fluid for diagnosis of pancreatic lesions. Clin Chem. 2008;54(6 Suppl S):A126-127 2. van der Waaij LA, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a polled analysis. Gastrointest Endosc. 2005;62(3):383-389 3. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol. 2007;102(10):2339-2349 4. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG clinical guideline: diagnosis and management of pancreatic cysts. Am J Gastroenterol. 2018;113(4):464-479. doi:10.1038/ajg.2018.14

199PT
61530

Carbohydrate Antigen 19-9 (CA 19-9), Peritoneal Fluid

Clinical Information: Malignancy accounts for approximately 7% of cases of ascites formation. Malignant disease can cause ascites by various mechanisms including peritoneal carcinomatosis (53%), massive liver metastasis causing portal hypertension (13%), peritoneal carcinomatosis plus massive liver metastasis (13%), hepatocellular carcinoma plus cirrhosis (7%), and chylous ascites due to lymphoma (7%). The evaluation and diagnosis of malignancy-related ascites is based on the patient clinical history, ascites fluid analysis, and imaging tests. The overall sensitivity of cytology for the detection of malignancy-related ascites ranges from 58% to 75%. Cytology examination is most successful in patients with ascites related to peritoneal carcinomatosis, as viable malignant cells are exfoliated into the ascitic fluid. However, only approximately 53% of patients with malignancy-related ascites have peritoneal carcinomatosis. Patients with other causes of malignancy-related ascites almost always have a negative cytology. Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen. CA 19-9 may be elevated in the serum patients with gastrointestinal malignancies, such as cholangiocarcinoma, pancreatic cancer, or colon cancer. Measurement of CA 19-9 in ascitic fluid is sometimes used in combination with cytology for detecting malignancy-related ascites.

Useful For: An adjunct to cytology to differentiate between malignancy-related ascites and benign causes of ascites formation

Interpretation: A peritoneal fluid carbohydrate antigen 19-9 (CA 19-9) concentration greater than 32 U/mL is suspicious, but not diagnostic, of a malignancy-related ascites. This clinical decision limit cutoff yielded 44% sensitivity and 93% specificity in a study of 137 patients presenting with ascites. However, ascites caused by malignancies not associated with increase serum CA 19-9 concentrations, including lymphoma, mesothelioma, leukemia, and melanoma, routinely had CA 19-9 concentrations less than 32 U/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a malignancy not associated with elevated CA 19-9 levels in serum.

Reference Values:

An interpretive report will be provided.

Clinical References: 1. Trape J, Molina R, Sant F. Clinical evaluation of the simultaneous determination of tumor markers in fluid and serum and their ratio in the differential diagnosis of serous effusions. Tumour Biol. 2004;25(5-6):276-281 2. Sari R, Yildirim B, Sevinc A, Bahceci F, Hilmioglu F. The importance of serum and ascites fluid alpha-fetoprotein, carcinoembryonic antigen, CA 19-9, and CA 15-3 levels in differential diagnosis of ascites etiology. Hepatogastroenterology. 2001;48(42):1616-1621 3. Block DR, Algeciras-Schimnich A. Body fluid analysis: clinical utility and applicability of published studies to guide interpretation of today's laboratory testing in serous fluids. Crit Rev Clin Lab Sci. 2013;50(4-5):107-124. doi:10.3109/10408363.2013.844679 4. Jain T, Ram S, Kumar H, Saroch A, Sharma V, Singh H. Ascitic and serum levels of tumor biomarkers (CA 72-4, CA 19-9, CEA AND CA 125) in discrimination of cause of ascites: A prospective study. Arq Gastroenterol. 2022;59(2):198-203. doi:10.1590/S0004-2803.202202000-37

PF199
60230

Carbohydrate Antigen 19-9 (CA 19-9), Pleural Fluid

Clinical Information: Pleural effusions occur as a consequence of either nonmalignant conditions (including congestive heart failure, pneumonia, pulmonary embolism, and liver cirrhosis) or malignant conditions (including lung, breast, and lymphoma cancers). Diagnosing the cause of an effusion can be difficult, requiring cytological examination of the fluid. Analysis of various tumor markers in pleural fluid has shown that these markers can differentiate between effusions caused by nonmalignant and malignant conditions and can enhance cytology findings. Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen. Healthy adults typically produce low to undetectable levels of CA 19-9. Serum concentrations of CA 19-9 may be elevated in patients with certain malignancies that secrete CA 19-9 into circulation, including cholangiocarcinoma, colorectal, stomach, bile duct, lung, ovarian, and pancreatic cancers. Pleural fluid concentrations of CA 19-9 have been reported to be elevated in patients with certain malignancies. Malignancies that can secrete CA 19-9 and elevate serum CA 19-9 concentrations, including cholangiocarcinoma, colorectal, stomach, bile duct, lung, ovarian, and pancreatic cancers, typically also elevate CA 19-9 in pleural fluid. In contrast, malignancies that do not secrete CA 19-9, including mesothelioma, lymphoma, leukemia, and melanoma, have low concentrations of CA 19-9 in pleural fluid comparable to concentrations observed in nonmalignant effusions. CA 19-9 results should be used in conjunction with cytological analysis of pleural fluid, imaging studies, and other clinical findings.

Useful For: An adjuvant to cytology and imaging studies to differentiate between nonmalignant and malignant causes of pleural effusions

Interpretation: A pleural fluid carbohydrate antigen 19-9 (CA 19-9) concentration of 20.0 U/mL or higher is suspicious, but not diagnostic, of a malignant source of the effusion. This cutoff yielded a sensitivity of 35%, specificity of 95%, and positive predictive value of 88% in a study of 200 patients presenting with effusion. CA 19-9 concentrations were significantly higher in effusions caused by CA 19-9-secreting malignancies, including cholangiocarcinoma, colorectal, stomach, bile duct, lung, ovarian, and pancreatic cancers. However, effusions caused by non-CA 19-9-secreting malignancies, including lymphoma, mesothelioma, leukemia, and melanoma, routinely had CA 19-9 concentrations below 20.0 U/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a non-CA 19-9-secreting malignancy. Correlation of all tumor marker results with cytology and imaging is highly recommended.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Shitrit D, Zingerman B, Shitrit ABG, Shlomi D, Kramer MR: Diagnostic

value of CYFRA 21-1, CEA, CA 19-9, CA 15-3, and CA 125 assays in pleural effusions: analysis of 116 cases and review of the literature. Oncologist. 2005 Aug;10(7):501-507 2. Hackbarth JS, Murata K, Reilly WM, Algeciras-Schimnich A: Performance of CEA and CA19-9 in identifying pleural effusions caused by specific malignancies. Clin Biochem. 2010 Sep;43(13-14):1051-1055 3. Block DR, Algeciras-Schimnich A: Body fluid analysis: clinical utility and applicability of published studies to guide interpretation of today's laboratory testing in serous fluids. Crit Rev Clin Lab Sci. 2013 Jul-Oct;50(4-5):107-124. doi: 10.3109/10408363.2013.844679 4. Yang Y, Liu YL, Shi HZ: Diagnostic accuracy of combinations of tumor markers for malignant pleural effusion: An updated meta-analysis. Respiration. 2017;94(1):62-69. doi: 10.1159/000468545

CA19
9288

Carbohydrate Antigen 19-9 (CA 19-9), Serum

Clinical Information: Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen. CA 19-9 may be elevated in patients with gastrointestinal malignancies such as cholangiocarcinoma, pancreatic cancer, or colon cancer. Benign conditions, such as cirrhosis, cholestasis, and pancreatitis, also result in elevated serum CA 19-9 concentrations, but in these cases, values are usually below 1000 U/mL. Individuals that are Lewis antigen negative (5%-7% of the population) do not express CA 19-9 due to the lack of the enzyme fucosyltransferase needed for CA 19-9 production. In these individuals, a low or undetectable serum CA 19-9 concentration is not informative regarding cancer recurrence.

Useful For: As a potential adjunct for diagnosis and monitoring of pancreatic cancer Potentially differentiating patients with cholangiocarcinoma and primary sclerosing cholangitis (PSC) from those with PSC alone

Interpretation: Serial monitoring of carbohydrate antigen 19-9 (CA 19-9) should begin prior to therapy to verify post therapy decreases in CA 19-9 and to establish a baseline for evaluating possible recurrence. Single values of CA 19-9 are less informative. Elevated values may be caused by a variety of malignant and nonmalignant conditions including cholangiocarcinoma, pancreatic cancer, and colon cancer.

Reference Values:
<35 U/mL

Clinical References: 1. Torok N, Gores GJ. Cholangiocarcinoma. Semin Gastrointest Dis. 2001;12(2):125-132 2. Scara S, Bottoni P, Scatena R. CA 19-9: Biochemical and clinical aspects. Adv Exp Med Biol. 2015;867:247-260. doi:10.1007/978-94-017-7215-0_15

CDG
89891

Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum

Clinical Information: Glycosylation is the post-translational modification of proteins and lipids by the addition of glycans (sugars and sugar chains) in a complex stepwise fashion in the endoplasmic reticulum, Golgi apparatus, cytosol and sarcolemmal membrane. Congenital disorders of glycosylation (CDG) are a group of over 150 inherited metabolic disorders characterized by abnormal protein and lipid glycosylation. There are 2 main groups of CDG: type I, characterized by defects in the assembly or transfer of the dolichol-linked glycan in either the cytosol or endoplasmic reticulum (ER) and type II, involving processing defects of the glycan in the ER and Golgi apparatus. In addition, there are 2 main categories of glycosylation: N-glycosylation where N-linked glycans are attached to a protein backbone via an asparagine residue on the protein, and O-glycosylation where O-glycans are attached to the

hydroxyl group of threonine or serine. Apolipoprotein CIII (Apo-CIII) isoforms, with a single core 1 mucin type O-glycosylate protein, is a complementary evaluation for the CDG type II profile. This analysis will evaluate mucin type O-glycosylation, a defect involving the Golgi apparatus, which is detected biochemically by the change in ratios of the 3 isoforms. CDG typically present as multi-systemic disorders with a broad clinical spectrum including, but not limited to, developmental delay, hypotonia, with or without neurological abnormalities, abnormal magnetic resonance imaging findings, skin manifestations, and coagulopathy. There is considerable variation in the severity of this group of diseases ranging from a mild presentation in adults and children to severe multi-organ dysfunctions causing infant lethality. In some subtypes, phosphomannose isomerase-CDG (MPI-CDG or CDG-Ib) in particular, intelligence is not compromised. CDG should be suspected in all patients with neurological abnormalities including developmental delay and seizures, brain abnormalities such as cerebellar atrophy or hypoplasia as well as unexplained liver dysfunction. Abnormal subcutaneous fat distribution and chronic diarrhea each may or may not be present. The differential diagnosis of abnormal transferrin patterns also includes liver disease not related to CDG including galactosemia, hereditary fructose intolerance in acute crisis, and liver disease of unexplained etiology. Transferrin and apolipoprotein CIII isoform analysis are the initial screening tests for CDG. The results of the transferrin and apolipoprotein CIII isoform analysis should be correlated with the clinical presentation to determine the most appropriate follow-up testing strategy including enzyme, molecular, and research-based testing. Enzymatic analysis for phosphomannomutase and phosphomannose isomerase in leukocytes (PMMIL / Phosphomannomutase and Phosphomannose Isomerase, Leukocytes) should be performed if either PMM2-CDG (CDG-Ia) or MPI-CDG (CDG-Ib) is suspected. Other glycosylation pathways, in addition to N- and O-glycosylation, have been elucidated, in particular glycophosphatidylinositol (GPI)-anchored protein glycosylation disorders in which there is absent or decreased expression of all the GPI-linked antigens, and alpha-dystroglycanopathies caused by impaired synthesis of O-mannose glycans. Neither class of disorders are picked up by CDG analysis in serum but are typically diagnosed using molecular methods (CDGGP / Congenital Disorders of Glycosylation Gene Panel, Varies).

Useful For: Screening for congenital disorders of glycosylation This test is not useful for screening patients for chronic alcohol abuse.

Interpretation: Positive test results could be due to a genetic or nongenetic condition; additional confirmatory testing is required. In serum, the bi-antennary transferrin (di-oligo) fraction is the most abundant transferrin isoform. Congenital disorders of glycosylation (CDG)-I generally show increases in mono-oligo- and/or a-oligo transferrin isoforms whereas CDG-II shows elevated increased transferrin with truncated glycans of varying degree depending on the type of defect.(1) Results are reported as the mono-oligosaccharide/di-oligosaccharide transferrin ratio, the a-oligosaccharide/di-oligosaccharide transferrin ratio, the tri-sialo/di-oligosaccharide transferrin ratio, and the apolipoprotein CIII-1/apolipoprotein CIII-2 ratio, and the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio. The report will include the quantitative results and an interpretation. The congenital disorders of glycosylation (CDG) profiles are categorized into 5 types: 1. CDG type I profile. Mono-oligosaccharide/di-oligosaccharide transferrin ratio and/or the a-oligosaccharide/di-oligosaccharide transferrin ratio are abnormal. This group should have the apolipoprotein C-III profile within the normal ranges, because the Golgi system is not affected in CDG type I. 2. CDG type II profile. The tri-sialo/di-oligosaccharide transferrin ratio is abnormal. In this category, the apolipoprotein C-III profile will have 2 scenarios: A. The apolipoprotein CIII-1/apolipoprotein CIII-2 ratio and/or the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio will be abnormal. In this case, the defect is most likely glycan processing in the Golgi apparatus; therefore, a CDG (conserved oligomeric Golgi [COG]) defect or defect that alters the Golgi apparatus is likely. B. The apolipoprotein CIII-1/apolipoprotein CIII-2 ratio and/or the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio are normal. In this case, the defects most likely do not involve the Golgi system, thus the molecular defect is different. 3. CDG mixed type profile (type I and II together). In this type of profile one can have abnormal tri-sialo/di-oligosaccharide transferrin ratio with the mono-oligosaccharide/di-oligosaccharide transferrin ratio and/or the a-oligosaccharide/di-oligosaccharide transferrin ratio abnormal and may have the apolipoprotein CIII-1/apolipoprotein CIII-2 ratio and the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio normal or abnormal, depending on if the defects

involve Golgi apparatus. 4. CDG with normal transferrin and apolipoprotein profile. Some CDG (eg, PGM3, some ALG13, MOGS, NGLY1, SLC35C1, Fut8) pose a problem for their detection. Thus, a careful medical history, physical exam, and analysis of other protein status may be informative for general protein glycosylation defects. If suspicious for either NGLY1- or MOGS-CDG, specific oligosaccharides in urine can be detected (OLIGU / Oligosaccharide Screen, Random, Urine). 5. When the profile cannot be categorized following the above classification, the abnormalities will be reported descriptively according to the molecular mass of the glycan isoform structures. Reports of abnormal results will include recommendations for additional biochemical and molecular genetic studies to identify the correct form of CDG more precisely. If applicable, treatment options, the name and telephone number of contacts who may provide studies, and a telephone number for one of the laboratory directors (if the referring physician has additional questions) will be provided. For more information, see Transferrin and Lipoprotein-CIII Isoform Analysis.

Reference Values:

Ratio	Normal	Indeterminate	Abnormal
Transferrin mono-oligo/di-oligo ratio	< or =0.06	0.07-0.09	> or =0.10
Transferrin A-oligo/di-oligo ratio	< or =0.011	0.012-0.021	> or =0.022
Transferrin tri-sialo/di-oligo ratio	< or =0.05	0.06-0.12	> or =0.13
Apo CIII-1/Apo CIII-2 ratio	< or =2.91	2.92-3.68	> or =3.69
Apo CIII-0/Apo CIII-2 ratio	< or =0.48	0.49-0.68	> or =0.69

Clinical References: 1. Lefeber DJ, Morava E, Jaeken J. How to find and diagnose a CDG due to defective N-glycosylation. J Inherit Metab Dis. 2011;34(4):849-852 2. Peanne R, de Lonlay P, Foulquier F, et al. Congenital disorders of glycosylation (CDG): Quo vadis? Eur J Med Genet. 2018;61(11):643-663 3. Freeze HH, Eklund EA, Ng BG, Patterson MC. Neurology of inherited glycosylation disorders. Lancet Neurol. 2012;11(5):453-466 4. Hennet T, Cabalzar J. Congenital disorders of glycosylation: a concise chart of glycocalyx dysfunction. Trends Biochem Sci. 2015;40(7):377-384 5. Freeze HH, Chong JX, Bamshad MJ, Ng BG. Solving glycosylation disorders: fundamental approaches reveal complicated pathways. Am J Hum Genet. 2014;94(2):161-175 6. Sparks SE, Krasnewich DM. Congenital disorders of N-linked glycosylation and multiple pathway overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2005. Updated January 12, 2017. Accessed January 8, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1332/ 7. Ng BG, Freeze HH. Human genetic disorders involving glycosylphosphatidylinositol (GPI) anchors and glycosphingolipids (GSL). J Inherit Metab Dis. 2015;38(1):171-178. doi:10.1007/s10545-014-9752-1 8. Bouchet-Seraphin C, Vuillaumier-Barrot S, Seta N. Dystroglycanopathies: About numerous genes involved in glycosylation of one single glycoprotein. J Neuromuscul Dis. 2015;2(1):27-38

CDTA
82425

Carbohydrate Deficient Transferrin, Adult, Serum

Clinical Information: Chronic alcoholism causes a transient change in the glycosylation pattern of transferrin where the relative amounts of disialo- and asialotransferrin (carbohydrate deficient transferrin: [CDT]) are increased over the amount of normally glycosylated tetrasialotransferrin. This recognition led

to the use of CDT in serum as a marker for chronic alcohol abuse. CDT typically normalizes within several weeks of abstinence of alcohol use. However, it is important to recognize that there are other causes of abnormal CDT levels, which include congenital disorders of glycosylation and other genetic and nongenetic causes of acute or chronic liver disease. CDT testing alone is not recommended for general screening for alcoholism; however, when combined with other methods (ie, gamma-glutamyltransferase, mean corpuscular volume, patient self-reporting, ethylglucuronide analysis), clinicians can expect to identify the majority of patients who consume a large amount of alcohol.

Useful For: Indicating chronic alcohol abuse This test is not appropriate for screening patients for congenital disorders of glycosylation.

Interpretation: Patients with chronic alcoholism may develop abnormally glycosylated transferrin isoforms (ie, carbohydrate deficient transferrin: CDT >0.12). CDT results from 0.11 to 0.12 are considered indeterminate. Patients with liver disease due to genetic or nongenetic causes may also have abnormal results.

Reference Values:
< or =0.10
0.11-0.12 (indeterminate)

Clinical References: 1. De Giovanni N, Cittadini F, Martello S. The usefulness of biomarkers of alcohol abuse in hair and serum carbohydrate-deficient transferrin: a case report. Drug Test Anal. 2015;7(8):703-707 2. Fleming MF, Anton RF, Spies CD. A review of genetic, biological, pharmacological, and clinical factors that affect carbohydrate-deficient transferrin levels. Alcohol Clin Exp Res. 2004;28(9):1347-1355 3. Gough G, Heathers L, Puckett D, et al. The Utility of Commonly Used Laboratory Tests to Screen for Excessive Alcohol Use in Clinical Practice. Alcohol Clin Exp Res. 2015;39(8):1493-1500 4. Shibamoto A, Namisaki T, Suzuki J, et al. Clinical significance of gamma-glutamyltranspeptidase combined with carbohydrate-deficient transferrin for the assessment of excessive alcohol consumption in patients with alcoholic cirrhosis. Medicines (Basel). 2021;8(7):39 5. Torrente MP, Freeman WM, Vrana KE. Protein biomarkers of alcohol abuse. Expert Rev Proteomics. 2012;9(4):425-436

CHOU 9255 Carbohydrate, Urine

Clinical Information: Carbohydrates are a group of mono-, di-, and oligosaccharides of endogenous and exogenous sources. Their presence frequently reflects dietary consumption but can indicate specific pathology if either a particular saccharide or a particular excretory pattern is present. Most saccharides (except glucose) have low renal thresholds and are readily excreted in the urine. The identification and quantitation of carbohydrates, in particular galactose and fructose, is useful to screen for inborn errors of galactose and fructose metabolism such as galactosemia and hereditary fructose intolerance. Additionally, xylose may also be detected in individuals with hereditary pentosuria, a benign trait with high frequency among individuals with Ashkenazi Jewish ancestry. This test is useful as an initial screen. To establish any diagnosis, abnormal results require confirmation by enzyme assay, molecular genetic analysis, or correlation with other laboratory testing.

Useful For: Screening for conditions associated with increased excretion of carbohydrates, including inborn errors of fructose and galactose metabolism. This test is not recommended as a follow up test for abnormal newborn screening for galactosemia.

Interpretation: When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations, if any, for additional biochemical testing, and a phone

number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

Reducing Substances: Negative Quantitative results are reported as mmol/mol creatinine. Age range		12 months-18 years	> or =19 years
Xylose	< or =13	< or =38	< or =9
Fructose	< or =32	< or =31	< or =16
Galactose	< or =117	< or =32	< or =5
Glucose	< or =139	< or =15	< or =22
Sucrose	< or =27	< or =46	< or =20
Lactose	< or =160	< or =18	< or =5
Maltose	< or =5	< or =1	< or =2
Raffinose	< or =1	< or =1	< or =1

Clinical References: 1. Hastings J, Owen G, Dekker A, et al. ChEBI in 2016: Improved services and an expanding collection of metabolites. Nucleic Acids Res. 2016;44(D1):D1214-D1219. doi:10.1093/nar/gkv1031 2. Steinmann B, Gitzelmann R, Van den Berghe G. Disorders of fructose metabolism. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Accessed February 21, 2025. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225080452 3. OMIM. #260800 Pentosuria; PNTSU. Johns Hopkins University; 1986. Updated July 9, 2016. Accessed February 21, 2025. Available at https://omim.org/entry/260800 4. Gaughan S, Ayres L, Baker P II. Hereditary fructose intolerance. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2015. Updated February 18, 2021. Accessed February 21, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK333439

FCMEB
75880

Carbon Monoxide Exposure, Blood

Interpretation:

Reference Values:
Reporting limit determined each analysis.

CAIX
606251

Carbonic Anhydrase IX (CA-IX) Immunostain, Technical Component Only

Clinical Information: Carbonic anhydrase IX (CA-IX) is a hypoxia-induced protein expressed in the gastrointestinal tract, mainly in the stomach. Expression of CA-IX is useful in the diagnosis of clear cell renal cell carcinoma and clear cell papillary renal cell carcinoma. It can assist in distinguishing clear cell carcinoma from chromophobe carcinoma, oncocytoma, and several other renal cell carcinomas.

Useful For: Diagnosis of clear cell renal cell carcinoma and clear cell papillary renal cell carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Alshenawy HA. Immunohistochemical panel for differentiating renal cell carcinoma with clear and papillary features. J Microsc Ultrastruct. 2015;3(2):68-74 2. Genega EM, Ghebremichael M, Najarian R, et al. Carbonic anhydrase IX expression in renal neoplasms: correlation with tumor type and grade. Am J Clin Pathol. 2010;134(6):873-879 3. Stillebroer AB, Mulders PF, Boerman OC, Oyen WJ, Oosterwijk E. Carbonic anhydrase IX in renal cell carcinoma: implications for prognosis, diagnosis, and therapy. Euro Urol. 2010;58(1):75-83 4. Bing Z, Lal P, Lu S, Ziober A, Tomaszewski JE. Role of carbonic anhydrase IX, a-methylacyl coenzyme a racemase, cytokeratin 7, and galectin-3 in the evaluation of renal neoplasms: a tissue microarray immunohistochemical study. Ann Diag Pathol. 2013;17(1):58-62 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CEAPC
89509

Carcinoembryonic Antigen (CEA), Pancreatic Cyst Fluid

Clinical Information: Cystic lesions of the pancreas are of various types including: Benign cysts: -Inflammatory cysts (pseudocysts) -Serous cysts (serous cystadenoma) Mucinous cysts: -Premalignant (mucinous cystadenoma) -Malignant (cystadenocarcinoma, intrapapillary mucinous neoplasia) The diagnosis of pancreatic cyst type is often difficult and may require correlating imaging studies with results of cytological examination and tumor marker testing performed on cyst aspirates. Various tumor markers have been evaluated to distinguish non-mucinous, nonmalignant pancreatic cysts from mucinous cysts, which have a high likelihood of malignancy. Carcinoembryonic antigen (CEA) has been found to be the most reliable tumor marker for identifying pancreatic cysts that are likely mucinous. In cyst aspirates, CEA concentrations of 200 ng/mL and above are highly suspicious for mucinous cysts. The greater the CEA concentration, the greater the likelihood the mucinous cyst is malignant. However, CEA testing does not reliably distinguish between benign, premalignant, or malignant mucinous cysts. CEA test results should be correlated with the results of imaging studies, cytology, other cyst fluid tumor markers (ie, amylase and CA [carbohydrate antigen] 19-9), and clinical findings for diagnosis.

Useful For: When used in conjunction with imaging studies, cytology, and other pancreatic cyst fluid tumor markers: -Distinguishing between mucinous and nonmucinous pancreatic cysts -Determining the likely type of malignant pancreatic cyst

Interpretation: A pancreatic cyst fluid carcinoembryonic antigen (CEA) concentration greater than or equal to 200 ng/mL is very suggestive for a mucinous cyst but is not diagnostic. The sensitivity and specificity for mucinous lesions are approximately 62% and 93%, respectively, at this concentration. Cyst fluid CEA concentrations less than 5 ng/mL indicate a low risk for a mucinous cyst and are more consistent with serous cystadenoma, fluid collections complicating pancreatitis, cystic neuroendocrine tumor, or metastatic lesions. CEA values between these extremes have limited diagnostic value.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, et al. Diagnosis of

pancreatic cystic neoplasms: a report of cooperative pancreatic cyst study. Gastroenterology. 2004;126(5):1330-1336 2. Snozek CL, Jenkins SM, Bryant SC, et al.: Analysis of CEA, CA 19-9, and amylase in pancreatic cyst fluid for diagnosis of pancreatic lesions. Clin Chem. 2008;54(Suppl S):A126-127 3. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol. 2007;102(10):2339-2349 4. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG clinical guideline: diagnosis and management of pancreatic cysts. Am J Gastroenterol. 2018;113(4):464-479. doi:10.1038/ajg.2018.14

CEAPT
61528

Carcinoembryonic Antigen (CEA), Peritoneal Fluid

Clinical Information: Malignancy accounts for approximately 7% of cases of ascites formation. Malignant disease can cause ascites by various mechanisms including peritoneal carcinomatosis (53%), massive liver metastasis causing portal hypertension (13%), peritoneal carcinomatosis plus massive liver metastasis (13%), hepatocellular carcinoma plus cirrhosis (7%), and chylous ascites due to lymphoma (7%). The evaluation and diagnosis of malignancy-related ascites is based on the patient clinical history, ascites fluid analysis, and imaging tests. The overall sensitivity of cytology for the detection of malignancy-related ascites ranges from 58% to 75%. Cytology examination is most successful in patients with ascites related to peritoneal carcinomatosis as viable malignant cells are exfoliated into the ascitic fluid. However, only approximately 53% of patients with malignancy-related ascites have peritoneal carcinomatosis. Patients with other causes of malignancy-related ascites almost always have a negative cytology. Carcinoembryonic antigen (CEA) is a glycoprotein that is shed from the surface of malignant cells. Measurement of CEA in ascitic fluid has been proposed as a helpful test in detecting malignancy-related ascites given the limited sensitivity of cytology.

Useful For: An adjunct to cytology to differentiate between malignancy-related and benign causes of ascites formation

Interpretation: A peritoneal fluid carcinoembryonic antigen (CEA) concentration greater than 6.0 ng/mL is suspicious, but not diagnostic, of malignancy-related ascites. This clinical decision limit cutoff yielded 48% sensitivity and 99% specificity in a study of 137 patients presenting with ascites. CEA concentrations were significantly higher in ascites caused by malignancies known to be associated with elevated serum CEA levels, including lung, breast, ovarian, gastrointestinal, and colorectal cancers. However, ascites caused by other malignancies, such as lymphoma, mesothelioma, leukemia, and melanoma and hepatocellular carcinoma, routinely had CEA concentrations less than 6.0 ng/mL. Therefore, negative results should be interpreted with caution, especially in patients who have, or are suspected of having, a malignancy not associated with elevated CEA levels in serum.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Torresini RJ, Prolla JC, Diehl AR, Morais EK, Jobim LF. Combined carcinoembryonic antigen and cytopathologic examination in ascites. Acta Cytol. 2000;44(5):778-782 2. Tuzun Y, Yilmaz S, Dursun M, et al. How to increase the diagnostic value of malignancy-related ascites: discriminative ability of the ascitic tumour markers. J Int Med Res. 2009;37(1):87-95 3. Kaleta EJ, Tolan NV, Ness KA, O'Kane D, Algeciras-Schimnich A. CEA, AFP and CA 19-9 analysis in peritoneal fluid to differentiate causes of ascites formation. Clin Biochem. 2013;46(9):814-818. doi:10.1016/j.clinbiochem.2013.02.010 4. Trape J, Sant F, Montesinos J, et al. Comparative assessment of two strategies for interpreting tumor markers in ascitic effusions. In Vivo. 2020;34(2):715-722. doi:10.21873/invivo.11829

PFCEA
83742

Carcinoembryonic Antigen (CEA), Pleural Fluid

Clinical Information: Pleural effusions occur as a consequence of either nonmalignant conditions (including congestive heart failure, pneumonia, pulmonary embolism, and liver cirrhosis) or malignant conditions (including lung, breast, and lymphoma cancers). Diagnosing the cause of an effusion can be difficult, often requiring cytological examination of the pleural fluid and imaging studies of the pleural tissue. Analysis of various tumor markers in pleural fluid has shown that these markers can differentiate between effusions caused by nonmalignant and malignant conditions and can enhance cytology and imaging findings. Carcinoembryonic antigen (CEA) is a glycoprotein produced during fetal development. Nonsmoking, healthy adults typically produce low to undetectable levels of CEA. Serum concentrations of CEA may be elevated in patients with certain malignancies that secrete CEA into circulation, including medullary thyroid carcinoma and breast, gastrointestinal tract, colorectal, liver, lung, ovarian, pancreatic, and prostate cancers. Pleural fluid concentrations of CEA have been reported to be elevated in patients with certain malignancies. Malignancies that can secrete CEA and elevate serum CEA concentrations, including lung, breast, ovarian, gastrointestinal, and colorectal cancers, typically also elevate CEA in pleural fluid. In contrast, malignancies that do not secrete CEA, including mesothelioma, lymphoma, leukemia, and melanoma, have low concentrations of CEA in pleural fluid comparable to concentrations observed in non-malignant effusions. Elevated CEA concentrations in pleural fluid have also been reported with certain nonmalignant conditions, including liver cirrhosis, pancreatitis, complicated parapneumonic effusions and empyemas, and rarely with tuberculosis. CEA results should be used in conjunction with cytological analysis of pleural fluid, imaging studies, and other clinical findings.

Useful For: An adjuvant to cytology and imaging studies to differentiate between nonmalignant and malignant causes of pleural effusions

Interpretation: A pleural fluid carcinoembryonic antigen (CEA) concentration of 3.5 ng/mL or higher is suspicious but not diagnostic of a malignant source of the effusion. This cutoff yielded a sensitivity of 52%, specificity of 95%, and part per volume of 93% in a study of 200 patients presenting with effusion. CEA concentrations were significantly higher in effusions caused by CEA-secreting malignancies, including lung, breast, ovarian, gastrointestinal, and colorectal cancers. However, effusions caused by non-CEA-secreting malignancies, including lymphoma, mesothelioma, leukemia, and melanoma, routinely had CEA concentrations below 3.5 ng/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a non-CEA-secreting malignancy. Correlation of all tumor marker results with cytology and imaging is highly recommended.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Shitrit D, Zingerman B, Shitrit ABG, Shlomi D, Kramer MR: Diagnostic value of CYFRA 21-1, CEA, CA 19-9, CA 15-3, and CA 125 assays in pleural effusions: analysis of 116 cases and review of the literature. Oncologist. 2005 Aug;10(7):501-507 2. Hackbarth JS, Murata K, Reilly WM, Algeciras-Schimnich A: Performance of CEA and CA19-9 in identifying pleural effusions caused by specific malignancies. Clin Biochem. 2010 Sep;43(13-14):1051-1055 3. Garcia-Pachon E, Padilla-Navas I, Dosda MD, Miralles-Llopis A: Elevated level of carcinoembryonic antigen in nonmalignant pleural effusions. Chest. 1997 Mar;111(3):643-647 4. Hackner K, Errhalt P, Handzhiev S: Ratio of carcinoembryonic antigen in pleural fluid and serum for the diagnosis of malignant pleural effusion. Ther Adv Med Oncol. 2019 May 22;11:1758835919850341. doi: 10.1177/1758835919850341 5. Tozzoli R, Basso SMM, D'Aurizio F, Metus P, Lumachi F: Evaluation of predictive value of pleural CEA in patients with pleural effusions and histological findings: A prospective study and literature review. Clin Biochem. 2016 Nov;49(16-17):1227-1231. doi: 10.1016/j.clinbiochem.2016.08.006

CEA
8521

Carcinoembryonic Antigen (CEA), Serum

Clinical Information: Carcinoembryonic antigen (CEA) is a glycoprotein normally found in embryonic entodermal epithelium. Increased levels may be found in patients with primary colorectal cancer or other malignancies including medullary thyroid carcinoma and breast, gastrointestinal tract, liver, lung, ovarian, pancreatic, and prostatic cancers. Serial monitoring of CEA should begin prior to therapy to verify post therapy decrease in concentration and to establish a baseline for evaluating possible recurrence. Levels generally return to normal within 1 to 4 months after removal of cancerous tissue.

Useful For: Monitoring colorectal cancer and selected other cancers such as medullary thyroid carcinoma May be useful in assessing the effectiveness of chemotherapy or radiation treatment This test is not useful for screening the general population for undetected cancers.

Interpretation: Grossly elevated carcinoembryonic antigen (CEA) concentrations (>20 ng/mL) in a patient with compatible symptoms are strongly suggestive of the presence of cancer and suggest metastasis. Most healthy subjects (97%) have values less than or equal to 3.0 ng/mL. After removal of a colorectal tumor, the serum CEA concentration should return to normal by 6 weeks, unless there is residual tumor. Increases in test values over time in a patient with a history of cancer suggest tumor recurrence.

Reference Values:
Nonsmokers: < or =3.0 ng/mL
Some smokers may have elevated CEA, usually <5.0 ng/mL.
Serum markers are not specific for malignancy, and values may vary by method.

Clinical References: 1. Sturgeon C: Tumor markers. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:436-478 2. Locker, GY, Hamilton S, Harris J, et al: ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol. 2006;24:5313-5327 3. Moertel CG, Fleming TR, Macdonald JS, et al: An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with resected colon cancer. JAMA. 1993;270:943-947

CEASF
90695

Carcinoembryonic Antigen (CEA), Spinal Fluid

Clinical Information: Carcinoembryonic antigen (CEA) normally is present in cerebrospinal fluid (CSF) in very low concentrations. Elevations in serum CEA can cause passive transfer to CSF. Tumors of the brain, especially metastatic tumors, can elevate CSF CEA.

Useful For: Detecting meningeal carcinomatosis and intradural or extradural infiltration Differentiating brain parenchymal metastasis from adenocarcinoma or squamous-cell carcinoma

Interpretation: Increased values are seen in approximately 60% of patients with meningeal carcinomatosis.

Reference Values:
<0.6 ng/mL
Tumor markers are not specific for malignancy, and values may vary by method.

Clinical References: 1. Klee GG, Tallman RD, Goellner JR, Yanagihara T: Elevation of carcinoembryonic antigen in cerebrospinal fluid among patients with meningeal carcinomatosis. Mayo Clin Proc. 1986 Jan;61(1):9-13 2. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen C: An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with resected colon cancer. JAMA. 1993 Aug 25;270(8):943-947 3. Duffy MJ: Carcinogenic antigen as a

marker for colorectal cancer: is it clinically useful? Clin Chem. 2001 Apr;47(4):624-630 4. Block DR, Algeciras-Schimnich A: Body fluid analysis: clinical utility and applicability of published studies to guide interpretation of today's laboratory testing in serous fluids. Crit Rev Clin Lab Sci. 2013 Jul-Oct;5(4-5):107-124

MCEA
70506

Carcinoembryonic Antigen, Monoclonal Immunostain, Technical Component Only

Clinical Information: In tissue sections of normal colon, carcinoembryonic antigen (CEA) is mainly localized at the apical border of the epithelial cells. Monoclonal CEA antibodies label the epithelium of colonic adenocarcinoma, normal adult colonic mucosa, and normal gastric foveolar mucus-producing cells.

Useful For: Marker of epithelial cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Costa MJ, Kenny MB, Judd R. Adenocarcinoma and adenosquamous carcinoma of the uterine cervix. Histologic and immunohistochemical features with clinical correlation. Int J Surg Pathol. 1994;1:181-189 2. Sheahan K, O'Brien MJ, Burke B, et al. Differential reactivities of carcinoembryonic antigen (CEA) and CEA-related monoclonal and polyclonal antibodies in common epithelial malignancies. Am J Clin Pathol. 1990;94:157-164 3. Sumitoma S, Kumasa S, Mitani H, Mori M. Comparison of CEA distribution in lesions and tumors of salivary glands as determined with monoclonal and polyclonal antibodies. Circhows Arch B. 1987;53:133-139 4. Wong HH, Chu P: Immunohistochemical features of the gastrointestinal tract tumors. J Gastrointest Oncol. 2012;3(3):262-284 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PCEAI
70535

Carcinoembryonic Antigen, Polyclonal Immunostain, Technical Component Only

Clinical Information: Polyclonal carcinoembryonic antigen (pCEA) labels normal and neoplastic epithelium of the small and large intestine, stomach, and pancreatic ducts. The polyclonal antibody also reacts with biliary canaliculi and granulocytes

Useful For: Marker of epithelial cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

CRMP1
616727

Cardiovascular Risk Marker Panel, Serum

Clinical Information: Lipoprotein cholesterol measures are essential in managing risk for atherosclerotic cardiovascular disease (ASCVD). Atherosclerosis is defined by a buildup of plaque within arterial walls. ASCVD includes coronary heart disease, strokes, and peripheral artery disease. ASCVD develops over decades and is often asymptomatic until the patient experiences a life-threatening event such as a heart attack, stroke, or aneurysm. Cholesterol is a lipid that is synthesized in most tissues and actively absorbed from the diet. There is a strong association between serum cholesterol concentrations and cardiovascular disease. Cholesterol is carried in the blood by lipoproteins. Some lipoproteins carry a stronger risk of cardiovascular disease while others are associated with reduced cardiovascular risk. Total cholesterol concentration includes the sum of all "good" and "bad" cholesterol. Therefore, total cholesterol is recommended to be interpreted in context of a lipid panel that includes high-density lipoprotein cholesterol (HDL-C) and triglyceride measures. Low-density lipoprotein cholesterol (LDL-C) is the primary lipoprotein responsible for atherogenic plaque. Very low-density lipoprotein cholesterol (VLDL-C) is also atherogenic and the combination of LDL-C and VLDL-C is called non-HDL-C and often referred to as "bad" cholesterol. Serum total cholesterol, LDL-C and non-HDL-C are all directly associated with risk for ASCVD. HDL-C is associated with lower risk of cardiovascular disease. Excess cholesterol is actively pumped into HDL to be carried in the blood circulation and cleared by the liver in a process known as reverse cholesterol transport. For these reasons, HDL-C is often referred to as "good" cholesterol. Triglycerides are oily lipids carried in the blood by lipoproteins. Triglycerides are primarily carried by VLDL, chylomicrons and remnant lipoproteins. Recent evidence supports triglycerides as an independent risk factor for ASCVD. Several conditions are associated with increased plasma triglycerides, including obesity, pregnancy, physical inactivity, excess alcohol intake, kidney disease, and diabetes. Elevated triglycerides are often associated with reduced HDL-C, insulin resistance, hypertension, fatty liver disease, and increased waist circumference. In addition to cardiovascular risk, elevated triglycerides confer a risk for acute pancreatitis. Apolipoprotein B (ApoB), high-sensitivity C-reactive protein (hsCRP), and lipoprotein (a) (Lp[a]) are serological risk factors endorsed by multiple international guidelines for use in cardiovascular disease risk assessment. Several recent guidelines have suggested that clinicians utilize ApoB, hsCRP, and Lp(a) in selected persons to augment risk classification, guide intensity of risk-reduction therapy, and modulate clinical judgment when making therapeutic decision.(1-3)

Useful For: Assessment for risk of developing cardiovascular disease, major adverse cardiovascular events, or ischemic cerebrovascular events

Interpretation: Maintaining desirable concentrations of lipids lowers atherosclerotic cardiovascular disease risk. Establishing appropriate treatment strategies and lipid goals require that blood lipid values be considered in context with other risk factors including, age, sex, smoking status, and medical history of hypertension, diabetes, and cardiovascular disease. Triglycerides results of 500 mg/dL or above are severely elevated increasing the risk of pancreatitis. Triglycerides can be lowered by increasing physical activity, low-fat diet, weight loss and/or triglyceride lowering pharmaceuticals. Low high-density lipoprotein cholesterol (HDL-C) is a risk factor for cardiovascular disease. HDL-C can be increased by the same lifestyle changes that reduce risk for cardiovascular disease; physical activity, smoking cessation, and eating healthier. However, medications that specifically increase HDL levels have failed to reduce cardiovascular disease. Extremely low HDL values (<20 mg/dL) may indicate liver disease or inherited dyslipidemia. Low-density lipoprotein cholesterol results of 190 mg/dL or above in adults (> or =160 mg/dL in children) are severely elevated and may indicate familial hypercholesterolemia. For non-HDL cholesterol results of 220 mg/dL or above, consider possible inherited hyperlipidemia.

Reference Values:

Age	2-17 years	> or =18 years
CALCULATED NON-HDL CHOLESTEROL (mg/dL)	** Acceptable: or =145	* Desirable: or =220 mg/dL
CALCULATED LDL CHOLESTEROL (mg/dL)	** Acceptable: or =130	*** Desirable: or =190
HDL CHOLESTEROL (mg/dL)	** Low: 45	*** Males: > or =40 Females: > or =50
TOTAL CHOLESTEROL (mg/dL)	** Acceptable: or =200	

Clinical References: 1. Grundy SM, Stone NJ, Bailey AL, et al: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Jun 18;139(25):e1082-e1143 2. Jacobson TA, Ito MK, Maki KC, et al: National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1-executive summary. J Clin Lipidol. 2014 Sep-Oct;8(5):473-488. doi: 10.1016/j.jacl.2014.07.007 3. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics. 2011 Dec;128 Suppl 5(Suppl 5):S213-S256. doi: 10.1542/peds.2009-2107C 4. Sampson M, Ling C, Sun Q, et al: A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia. JAMA Cardiol. 2020 May 1;5(5):540-548

FCRDE 57524 Carmine Dye/Red Dye Cochineal (Dactylopius coccus) IgE (Red # 4)

Interpretation:

Reference Values:
<0.35 kU/L

CARN 8802 Carnitine, Plasma

Clinical Information: Carnitine and its esters are required for normal energy metabolism and serve 4 primary functions: -Importing long-chain fatty acids into the mitochondria -Exporting naturally-occurring short-chain acyl-CoA groups from the mitochondria -Maintaining the ratio of free CoA to esterified CoA -Removing potentially toxic acyl-CoA groups from the cells and tissues Evaluation of carnitine in serum, plasma, and urine is a biochemical screening test for suspected primary disorders of the carnitine cycle or secondary disturbances in carnitine levels as a result of organic acidemias and fatty acid oxidation disorders. In the latter, acyl-CoA groups accumulate and are excreted into the urine and bile as carnitine derivatives, resulting in a secondary carnitine deficiency. More than 100 such primary and secondary disorders have been described. Collectively, their incidence is approximately 1 in 1000 live births. Primary carnitine deficiency has an incidence of approximately 1 in 21,000 live births based on Minnesota newborn screening data. Other conditions that could cause an abnormal carnitine level include neuromuscular diseases, gastrointestinal disorders, familial cardiomyopathy,

renal tubulopathies and chronic renal failure (dialysis), and prolonged treatment with steroids, antibiotics (pivalic acid), anticonvulsants (valproic acid), and total parenteral nutrition. Follow-up testing is required to differentiate primary and secondary carnitine deficiencies and to elucidate the exact cause.

Useful For: Evaluation of patients with a clinical suspicion of a wide range of conditions including organic acidemias, fatty acid oxidation disorders, and primary carnitine deficiency using plasma specimens

Interpretation: When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

	Total carnitine (TC)	Free carnitine (FC)	Acylcarnitine (AC)	AC/FC Ratio
Age Group	Range*	Range*	Range*	Range
< or =1 day	23-68	12-36	7-37	0.4-1.7
2-7 days	17-41	10-21	3-24	0.2-1.4
8-31 days	19-59	12-46	4-15	0.1-0.7
32 days-12 months	38-68	27-49	7-19	0.2-0.5
13 months-6 years	35-84	24-63	4-28	0.1-0.8
7-10 years	28-83	22-66	3-32	0.1-0.9
11-17 years	34-77	22-65	4-29	0.1-0.9
> or =18 years	34-78	25-54	5-30	0.1-0.8

Clinical References: 1. Magoulas PL, El-Hattab AW. Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2012;18;7:68 2. Longo N, Amat di San Filippo C, Pasquali M. Disorders of carnitine transport and the carnitine cycle. Am J Med Genet C Semin Med Genet. 2006;142C(2):77-85 3. Zammit VA, Ramsay RR, Bonomini M, Arduini A. Carnitine, mitochondrial function and therapy. Adv Drug Deliv Rev. 2009;61(14):1353-1362 4. El-Hattab AW. Systemic primary carnitine deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2012. Updated November 3, 2016. Accessed November 27, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK84551/ 5. Longo N., Frigeni M., Pasquali M. Carnitine transport and fatty acid oxidation. Biochim. Biophys. Acta. 2016;1863:2422-2435 6. Almannai M, Alfadhel M, El-Hattab AW: Carnitine inborn errors of metabolism. Molecules. 2019;24(18):3251

CARNU
81123

Carnitine, Random, Urine

Clinical Information: Carnitine and its esters are required for normal energy metabolism and serve 4 primary functions: -Importing long-chain fatty acids into the mitochondria -Exporting naturally occurring short-chain acyl-CoA groups from the mitochondria -Maintaining the ratio of free CoA to esterified CoA -Removing potentially toxic acyl-CoA groups from the cells and tissues Evaluation of carnitine in serum, plasma, and urine is a biochemical screening test for suspected primary disorders of the carnitine cycle or

for secondary disturbances in carnitine levels as a result of organic acidemias and fatty acid oxidation disorders. In the latter, acyl-CoA groups accumulate and are excreted into the urine and bile as carnitine derivatives, resulting in a secondary carnitine deficiency. More than 100 such primary and secondary disorders have been described. Collectively, their incidence is approximately 1 in 1000 live births. Primary carnitine deficiency has an incidence of approximately 1 in 21,000 live births based on Minnesota newborn screening data. Other conditions that could cause an abnormal carnitine level include neuromuscular diseases, gastrointestinal disorders, familial cardiomyopathy, renal tubulopathies and chronic kidney failure (dialysis), and prolonged treatment with steroids, antibiotics (pivalic acid), anticonvulsants (valproic acid), and total parenteral nutrition. Follow-up testing is required to differentiate primary and secondary carnitine deficiencies and to elucidate the exact cause.

Useful For: Evaluation of patients with a clinical suspicion of a wide range of conditions including organic acidemias and fatty acid oxidation disorders Monitoring carnitine treatment

Interpretation: When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
FREE CARNITINE:
77-214 nmol/mg of creatinine

TOTAL CARNITINE:
180-412 nmol/mg of creatinine

RATIO:
Acylcarnitine to free carnitine: 0.7-3.4

Clinical References: 1. Magoulas PL, El-Hattab AW. Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2012; 18;7:68 2. Longo N, Amat di San Filippo C, Pasquali M. Disorders of carnitine transport and the carnitine cycle. Am J Med Genet C Semin Med Genet. 2006 15;142C(2):77-85 3. Zammit VA, Ramsay RR, Bonomini M, Arduini A. Carnitine, mitochondrial function and therapy. Adv Drug Deliv Rev. 2009;61(14):1353-1362 4. El-Hattab AW: Systemic primary carnitine deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2012. Updated November 3, 2016. Accessed November 27, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK84551/ 5. Almannai M, Alfadhel M, El-Hattab AW. Carnitine inborn errors of metabolism. Molecules. 2019;24(18):3251 6. Longo N., Frigeni M., Pasquali M. Carnitine transport and fatty acid oxidation. Biochim. Biophys. Acta. 2016;1863(10):2422-2435

CARNS
60449

Carnitine, Serum

Clinical Information: Carnitine and its esters are required for normal energy metabolism and serve 4 primary functions: -Importing long-chain fatty acids into the mitochondria -Exporting naturally-occurring short-chain acyl-CoA groups from the mitochondria -Maintaining the ratio of free CoA to esterified CoA -Removing potentially toxic acyl-CoA groups from the cells and tissues Evaluation of carnitine in serum, plasma, and urine is a biochemical screening test for suspected primary disorders of the carnitine cycle or secondary disturbances in carnitine levels as a result of organic acidemias and fatty acid oxidation disorders. In the latter disorders, acyl-CoA groups accumulate and are excreted into the urine and bile as carnitine derivatives, resulting in a secondary carnitine deficiency. More than 100 such primary and secondary disorders have been described. Collectively, their incidence is

approximately 1 in 1000 live births. Primary carnitine deficiency has an incidence of approximately 1 in 21,000 live births based on Minnesota newborn screening data. Other conditions that could cause an abnormal carnitine level include neuromuscular diseases, gastrointestinal disorders, familial cardiomyopathy, renal tubulopathies and chronic renal failure (dialysis), and prolonged treatment with steroids, antibiotics (pivalic acid), anticonvulsants (valproic acid), and total parenteral nutrition. Follow-up testing is required to differentiate primary and secondary carnitine deficiencies and to elucidate the exact cause.

Useful For: Evaluation of patients with a clinical suspicion of a wide range of conditions including organic acidemias, fatty acid oxidation disorders, and primary carnitine deficiency using serum specimens

	Total carnitine (TC)	Free carnitine (FC)	Acylcarnitine (AC)	AC/FC Ratio
Age Group	Range*	Range*	Range*	Range
< or =1 day	23-68	12-36	7-37	0.4-1.7
2-7 days	17-41	10-21	3-24	0.2-1.4
8-31 days	19-59	12-46	4-15	0.1-0.7
32 days-12 months	38-68	27-49	7-19	0.2-0.5
13 months-6 years	35-84	24-63	4-28	0.1-0.8
7-10 years	28-83	22-66	3-32	0.1-0.9
11-17 years	34-77	22-65	4-29	0.1-0.9
> or =18 years	34-78	25-54	5-30	0.1-0.8

Clinical References: 1. Magoulas PL, El-Hattab AW. Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2012;18;7:68 2. Longo N, Amat di San Filippo C, Pasquali M. Disorders of carnitine transport and the carnitine cycle. Am J Med Genet C Semin Med Genet. 2006;142C(2):77-85 3. Zammit VA, Ramsay RR, Bonomini M, Arduini A. Carnitine, mitochondrial function and therapy. Adv Drug Deliv Rev. 2009;61(14):1353-1362 4. El-Hattab AW: Systemic primary carnitine deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2012. Updated November 3, 2016. Accessed November 27, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK84551/ 5. Longo N., Frigeni M., Pasquali M. Carnitine transport and fatty acid oxidation. Biochim. Biophys. Acta. 2016;1863:2422-2435 6. Almannai M, Alfadhel M, El-Hattab AW. Carnitine inborn errors of metabolism. Molecules. 2019;24(18):3251

CAROB
82368

Carob, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant

allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to carob Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FCATB
75927

Carotene, Beta

Useful For: Confirming the diagnosis of carotenoderma Detecting fat malabsorption Depressed carotene levels may be found in cases of steatorrhea.

Interpretation: High levels are useful to rule out steatorrhea but lower values lack specificity. There is poor sensitivity. High levels are found in the serum of individuals ingesting large amounts of vegetables.

Reference Values:
3-91 ug/dL

CSFP
608336

Carrier Screen, Focused Panel, Varies

Clinical Information: Because an individual can be a carrier for an autosomal recessive condition without showing signs or symptoms, there is often no family history of such disorders. Therefore, without a family history, a reproductive couple may not know if they have an increased risk to have a child with a given genetic disorder. Carrier screening either before or during a pregnancy can help a reproductive couple further understand their risk to have a child with a genetic condition. Carrier screening for genetic variants associated with cystic fibrosis (CF) and spinal muscular atrophy (SMA) are considered standard of care by American College of Obstetricians and Gynecologists and American College of Medical Genetics and Genomics.(1,2) However, screening for CF and SMA alone would miss other common conditions. This focused test screens for select variants associated with the following conditions: alpha thalassemia, beta thalassemia, cystic fibrosis, fragile X syndrome, sickle cell anemia, and spinal muscular atrophy. It is recommended that screening tests be offered to all couples regardless of their ancestry.(2) If there is a history of a genetic condition in the family, it is recommended that the at-risk partner be tested for the known variant in the family. In order to confirm that the familial variant is covered by this test, contact the laboratory to facilitate testing; call 800-533-1710.

Useful For: Expanded carrier screening for reproductive risk assessment purposes This test is not useful for clinical diagnosis of an affected individual.

Interpretation: All reported variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Finucane B, Abrams L, Cronister A, Archibald AD, Bennett RL, McConkie-Rosell A. Genetic counseling and testing for FMR1 gene mutations: Practice Guidelines of the National Society of Genetic Counselors. J Genet Couns. 2012;21(6):752-760 2. Carrier Testing for Cystic Fibrosis. Cystic Fibrosis Foundation; Accessed April 1, 2025. Available at www.cff.org/What-is-CF/Testing/Carrier-Testing-for-Cystic-Fibrosis/ 3. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30 4. Langfelder-Schwind E, Karczeki B, Strecker MN, et al. Molecular testing for cystic fibrosis carrier status practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2014; 23:5-15 5. Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med. 2004;6 (5):387-391 6. Monaghan K, Lyon E, Spector E. ACMG Standards and Guidelines for fragile X testing: a revision to the disease-specific supplements to the Standards and Guidelines for Clinical Genetics Laboratories of the American College of Medical Genetics and Genomics. Genet Med. 2013;15(7):575-586 7. Committee Opinion No. 691: Carrier screening for genetic conditions. Obstet Gynecol. 2017;129(3):e41-e55. doi:10.1097/AOG.0000000000001952 8. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet. 2012;20(1):27-32. doi:10.1038/ejhg.2011.134 9. Deignan JL, Astbury C, Cutting GR, et al. CFTR variant testing: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22(8):1288-1295. doi:10.1038/s41436-020-0822-5

FCRTG
57630

Carrot IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

CROT
82742

Carrot, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to carrot Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FCASG
57555

Casein IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

CASE
82895

Casein, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to casein Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FCCA3
75556

Cashew Component rAna o 3

Clinical Information:

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.10 kU/L

Clinical References:

CASHX
618846

Cashew Component, IgE, Serum

Clinical Information: Allergies to tree nuts are relatively prevalent and can result in severe reactions. The main culprits in tree nut allergies include walnut, almond, pistachio, cashew, pecan, hazelnut, macadamia, Brazil nut, and pine nuts. Tree nut allergy often appears in young children and estimates of prevalence range from 0.1 % to greater than 5% of the population, dependent on geographical region. In the case of nut-induced allergic reactions, as with many other foods, symptoms usually present within minutes of ingestion. Over 80% of reactions to tree nuts involve allergy related respiratory symptoms. Tree nut allergies are one of the most dangerous types of allergic reaction with 20% to 40% of cases of related anaphylaxis, and 70% to 90% of fatalities attributable to nut exposure, including peanut exposure. Ana o 3 is a heat and digestion stable storage protein found in high abundance in cashew nuts. Approximately 80% of those with cashew allergy exhibit reactivity to the Ana o 3 component. Cashew nut allergy is often associated with severe reactions. Sensitization with Ana o 3 is associated with anaphylaxis in system reactions. Severe reactions in those with cashew nut allergy occur at a higher frequency than in those with peanut allergy. Cashews can be found in Asian cuisines, pesto, and nut butter. Cooking will not destroy the allergenic potential of Ana o 3 f. In addition to being severe, cashew nut allergy is persistent and can manifest early in life. Co-sensitization has been

repeated between pistachio, walnuts, and, to a lesser extent, hazelnut.

Useful For: Evaluation of patients with suspected cashew allergy to component Ana o 3

Interpretation: When detectable total cashew IgE antibody is present (> or =0.10 IgE kUa/L), additional specific component IgE antibody testing will be performed. If a potential specific allergenic cashew component IgE is detectable (> or =0.10 IgE kUa/L), an interpretive report will be provided. When the sample is negative for total cashew IgE antibody (<0.10 IgE kUa/L), further testing for specific cashew component IgE antibodies will not be performed. A negative IgE result for total cashew antibody may indicate a lack of sensitization to the potential cashew allergenic component.

Reference Values:

Only orderable as a reflex. For more information see CASHR / Cashew, IgE, with Reflex to Cashew Component, IgE, Serum Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/Equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Salo PM, Arbes SJ Jr, Jaramillo R, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol. 2014;134(2):350-359 2. Waserman S, Watson W. Food allergy. Allergy Asthma Clin Immunol. 2011;7 Suppl 1(Suppl 1):S7 3. Abrams EM, Sicherer SH. Diagnosis and management of food allergy. CMAJ. 2016;188(15):1087-1093 4. Weinberger T, Sicherer S. Current perspectives on tree nut allergy: a review. J Asthma Allergy. 2018;11:41-51 5. Lomas JM, Jarvinen KM. Managing nut-induced anaphylaxis: challenges and solutions. J Asthma Allergy. 2015;8:115-123 6. Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. J Allergy Clin Immunol. 2008;122(1):145-151 7. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. Pediatrics. 1998;102(1):e6 8. Crespo JF, James JM, Fernandez-Rodriguez C, Rodriguez J. Food allergy: nuts and tree nuts. Br J Nutr. 2006;96 Suppl 2:S95-S102 9. Yang L, Clements S, Joks R. A retrospective study of peanut and tree nut allergy: Sensitization and correlations with clinical manifestations [published online ahead of print, 2015 Feb 27]. Allergy Rhinol (Providence). 2015;doi:10.2500/ar.20105.6.0108 10. Masthoff LJ, Hoff R, Verhoeckx KC, et al. A systematic review of the effect of thermal processing on the allergenicity of tree nuts. Allergy. 2013;68(8):983-993 11. Davoren M, Peake J. Cashew nut allergy is associated with a high risk of anaphylaxis. Arch Dis Child. 2005;90(10):1084-1085 12. Robotham JM, Wang F, Seamon V, et al. Ana o 3, an important cashew nut (Anacardium occidentale L.) allergen of the 2S albumin family. J Allergy Clin

Immunol. 2005;115(6):1284-1290 13. Clark AT, Anagnostou K, Ewan PW. Cashew nut causes more severe reactions than peanut: case-matched comparison in 141 children. Allergy. 2007;62(8):913-916 14. Mendes C, Costa J, Vicente AA, Oliveira MBPP, Mafra I. Cashew nut allergy: Clinical relevance and allergen characterisation. Clin Rev Allergy Immunol. 2019;57(1):1-22 15. Blazowski L, Majak P, Kurzawa R, Kuna P, Jerzynska J. Food allergy endotype with high risk of severe anaphylaxis in children-Monosensitization to cashew 2S albumin Ana o 3. Allergy. 2019;74(10):1945-1955 16. Bastiaan-Net S, Batstra MR, Aazamy N, et al. IgE cross-reactivity measurement of cashew nut, hazelnut and peanut using a novel IMMULITE inhibition method. Clin Chem Lab Med. 2020;58(11):1875-1883

FCASH
57687

Cashew IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

CASHR
618845

Cashew, IgE with Reflex to Cashew Component, IgE, Serum

Clinical Information: Allergies to tree nuts are relatively prevalent and can result in severe reactions. The main culprits in tree nut allergies include walnut, almond, pistachio, cashew, pecan, hazelnut, macadamia, Brazil nut, and pine nuts. Tree nut allergy often appears in young children and estimates of prevalence range from 0.1% to greater than 5% of the population, dependent on geographical region. In the case of nut-induced allergic reactions, as with many other foods, symptoms usually present within minutes of ingestion. Over 80% of reactions to tree nuts involve allergy related respiratory symptoms. Tree nut allergies are one of the most dangerous types of allergic reaction with 20% to 40% of cases of related anaphylaxis and 70% to 90% of fatalities attributable to nut exposure, including peanut exposure. Ana o 3 is a heat and digestion stable storage protein found in high abundance in cashew nuts. Approximately 80% of those with cashew allergy exhibit reactivity to the Ana o 3 component. Cashew nut allergy is often associated with severe reactions. Sensitization with Ana o 3 is associated with anaphylaxis in system reactions. Severe reactions in those with cashew nut allergy occur at a higher frequency than in those with peanut allergy. Cashews can be found in Asian cuisines, pesto, and nut butter. Cooking will not destroy the allergenic potential of Ana o 3 f. In addition to being severe, cashew nut allergy is persistent and can manifest early in life. Co-sensitization has been repeated between pistachio, walnuts, and, to a lesser extent, hazelnut.

Useful For: Evaluation of patients with suspected cashew allergy

Interpretation: When detectable total cashew IgE antibody is present (> or =0.10 IgE kUa/L), additional specific component IgE antibody testing will be performed. If a potential specific allergenic cashew component IgE is detectable (> or =0.10 IgE kUa/L), an interpretive report will be provided. When the sample is negative for total cashew IgE antibody (<0.10 IgE kUa/L), further testing for specific cashew component IgE antibodies will not be performed. A negative IgE result for total cashew antibody may indicate a lack of sensitization to the potential cashew allergenic component.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/Equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Salo PM, Arbes SJ Jr, Jaramillo R, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol. 2014;134(2):350-359 2. Waserman S, Watson W. Food allergy. Allergy Asthma Clin Immunol. 2011;7 Suppl 1(Suppl 1):S7 3. Abrams EM, Sicherer SH. Diagnosis and management of food allergy. CMAJ. 2016;188(15):1087-1093 4. Weinberger T, Sicherer S. Current perspectives on tree nut allergy: a review. J Asthma Allergy. 2018;11:41-51 5. Lomas JM, Jarvinen KM. Managing nut-induced anaphylaxis: challenges and solutions. J Asthma Allergy. 2015;8:115-123 6. Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. J Allergy Clin Immunol. 2008;122(1):145-151 7. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. Pediatrics. 1998;102(1):e6 8. Crespo JF, James JM, Fernandez-Rodriguez C, Rodriguez J. Food allergy: nuts and tree nuts. Br J Nutr. 2006;96 Suppl 2:S95-S102 9. Yang L, Clements S, Joks R. A retrospective study of peanut and tree nut allergy: Sensitization and correlations with clinical manifestations [published online ahead of print, 2015 Feb 27]. Allergy Rhinol (Providence). 2015;doi:10.2500/ar.20105.6.0108 10. Masthoff LJ, Hoff R, Verhoeckx KC, et al. A systematic review of the effect of thermal processing on the allergenicity of tree nuts. Allergy. 2013;68(8):983-993 11. Davoren M, Peake J. Cashew nut allergy is associated with a high risk of anaphylaxis. Arch Dis Child. 2005;90(10):1084-1085 12. Robotham JM, Wang F, Seamon V, et al. Ana o 3, an important cashew nut (Anacardium occidentale L.) allergen of the 2S albumin family. J Allergy Clin Immunol. 2005;115(6):1284-1290 13. Clark AT, Anagnostou K, Ewan PW. Cashew nut causes more severe reactions than peanut: case-matched comparison in 141 children. Allergy. 2007;62(8):913-916 14. Mendes C, Costa J, Vicente AA, Oliveira MBPP, Mafra I. Cashew nut allergy: Clinical relevance and allergen characterisation. Clin Rev Allergy Immunol. 2019;57(1):1-22 15. Blazowski L, Majak P, Kurzawa R, Kuna P, Jerzynska J. Food allergy endotype with high risk of severe anaphylaxis in children-Monosensitization to cashew 2S albumin Ana o 3. Allergy. 2019;74(10):1945-1955 16. Bastiaan-Net S, Batstra MR, Aazamy N, et al. IgE cross-reactivity measurement of cashew nut, hazelnut and peanut using a novel IMMULITE inhibition method. Clin Chem Lab Med. 2020;58(11):1875-1883

CASH
82881

Cashew, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In

individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cashew Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CASRG
618058

CASR Full Gene Sequencing with Deletion/Duplication, Varies

Clinical Information: The extracellular G-protein-coupled calcium-sensing receptor (CASR) is an essential component of calcium homeostasis. CASR is expressed at high levels in the parathyroid glands and kidneys. In the parathyroid glands, an increase in serum calcium results in downregulation of gene expression of the main short-term regulator of calcium homeostasis, parathyroid hormone (PTH), as well as diminished secretion of already synthesized PTH. At the same time, kidney calcium excretion is upregulated, and sodium chloride excretion is downregulated.(1) Both activating and inactivating genetic variants have been described in CASR and result in altered calcium sensing and subsequent inappropriate PTH release relative to serum calcium concentration. Inactivating (loss-of-function) CASR variants result in undersensing of calcium concentrations and consequent PTH overproduction.

This leads to either autosomal dominant familial hypocalciuric hypercalcemia (FHH), autosomal dominant primary hyperparathyroidism, or autosomal recessive neonatal severe primary hyperparathyroidism (NSPHT), depending on the severity of the functional impairment.(1) In FHH, serum calcium levels are mildly-to-moderately elevated, PTH may be normal or only modestly elevated, phosphate is normal or slightly low, and urinary calcium excretion is low for the degree of hypercalcemia.(1) Unlike patients with primary hyperparathyroidism, the majority of FHH patients do not seem to experience adverse long-term effects from hypercalcemia and elevated PTH levels. On the other hand, NSPHT is usually caused by homozygous or compound heterozygous inactivating CASR variants but can occasionally be caused by dominant-negative heterozygous variants.(1) NSPHT presents at birth, or shortly thereafter, with severe hypercalcemia requiring urgent parathyroidectomy. Activating (gain-of-function) CASR variants lead to oversensing of calcium, resulting in suppression of PTH secretion and consequently hypoparathyroidism and hypocalcemia. This disorder is referred to as autosomal dominant hypocalcemia or autosomal dominant hypoparathyroidism. To date, all activating variants described are functionally dominant and inheritance is therefore autosomal dominant. However, sporadic (no known genetic etiology) cases also occur. Autosomal dominant hypoparathyroidism caused by CASR variants may account for many cases of idiopathic hypoparathyroidism. In addition, while the majority of patients exhibit only hypoparathyroidism, a small subgroup has extreme gain-of-function variants. These individuals may present with additional symptoms that are consistent with type V Bartter syndrome, including hypokalemic metabolic alkalosis, hyperreninemia, hyperaldosteronism, and hypomagnesemia.(1-2)

Useful For: Providing a genetic evaluation of individuals with a personal or family history of familial hypocalciuric hypercalcemia, neonatal severe primary hyperparathyroidism, or autosomal dominant hypoparathyroidism (autosomal dominant hypocalcemia) Establishing a diagnosis of familial hypocalciuric hypercalcemia, neonatal severe primary hyperparathyroidism, or autosomal dominant hypoparathyroidism (autosomal dominant hypocalcemia) As a part of the workup for patients with primary hyperparathyroidism, idiopathic hypoparathyroidism, and Bartter syndrome

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Vahe C, Benomar K, Espiard S, et al. Diseases associated with calcium-sensing receptor. Orphanet J Rare Dis. 2017 Jan 25;12(1):19. doi:10.1186/s13023-017-0570-z 2. Roszko KL, Bi RD, Mannstadt M. Autosomal dominant hypocalcemia (hypoparathyroidism) Types 1 and 2. Front Physiol. 2016;7:458. doi:10.3389/fphys.2016.00458 3. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

CAT
82665

Cat Epithelium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In

individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cat epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CATPF
616093

Cat Epithelium, IgE, with Reflex to Cat Epithelium Components, IgE, Serum

Clinical Information: Overall, allergies to common pets, such as cats and dogs, may afflict up to 20% of the world's population, and the prevalence appears to be increasing over time. A large multicenter study survey in European adults reported an 8.8% sensitization rate to cat (feline, Felis catus [domesticus]) allergens. The assessment of allergy to cats is dependent upon the presence of compatible clinical symptoms in the context of exposure, with support from identification of potential canine specific IgE allergen antibodies either by skin testing or in vitro serology testing. In vitro testing has generally focused on assessing for the presence of IgE antibodies to total cat dander (which contains

epithelial proteins) allergen extract. There is a correlation between total cat IgE allergen antibodies and an increased likelihood of a clinical allergic response. Allergic symptoms can include rhinitis, asthma, and atopic dermatitis. Once an elevated antibody response to total cat dander IgE extract is established, assessment for the presence of IgE antibodies to the most common cat allergenic components will be performed, which can yield additional, potentially useful, information for clinical assessment of allergy and sensitization. During cat component allergen IgE antibody testing, the presence of IgE antibodies specific for potentially allergenic individual proteins, namely Fel d1, Fel d2, Fel d4, and Fel d7, are individually assessed. The determination of the relative amount of IgE antibody to specific components can aid in assessment of the potential strength and type of allergenic response. Co-sensitization to some components, such as Fel d 1 and Fel d 4 may be associated with asthma symptoms.(1) Fel d 1 is the most clinically important, prevalent, and specific feline component allergen. Fel d 1 IgE antibodies have been observed in up to 95% of individuals with cat allergy. Measuring IgE antibodies to Fel d 1 may have prognostic value in evaluating cat allergy severity. Sixty to 90% of all IgE reactivity to cat dander is against the Fel d 1. Fel d 1 can be readily found in the fur and epidermis of a cat, may become airborne very easily, and can persist in the surrounding environment for several months. In 140 cat allergic patients, where all subjects were suffering from asthma and/or rhinoconjunctivitis, 95.6% of children and 94.4% of adults had IgE against Fel d 1. The IgE levels found in asthmatic children may be higher than the levels in children suffering from rhinoconjunctivitis. Consider avoidance to cat or other environmental exposure to Fel d 1 as well as allergen immunotherapy (AIT). All domestic cats produce Fel d 1. This allergen is also found in other feline species, such as cougar, tiger, and lion. Sensitization to the serum albumin Fel d 2 cat allergen is associated with increased risks of asthma and allergic rhinitis. Serum albumins are a minor allergen in animal dander and may be most associated with rhinitis but can play a significant role as cross-reacting allergens. Pork/cat syndrome (allergy to cat dander and pork meat) can be mediated by cross-reactive antibodies against pork serum albumin and cat serum albumin (Fel d 2). Less than 20% of individuals with known cat allergy are reactive to Fel d 2. Individuals sensitized to Fel d 2 may show cross reactivity to canine Can f 3 albumin antigen and potentially to other albumins from human, pig, cattle, sheep, horse, mouse, and rat. Fel d 4 and Fel d 7 are proteins that are members of the lipocalin protein family and are the cat allergens most associated with symptoms of asthma. In the case of Fel d 4, 62.96% (17 of 27) of individuals with cat allergy symptoms had detectable serum IgE antibody to the Fel d 4 antigen. Lipocalin proteins are found in many animal species, and Fel d 4 may cross react with Can d 6 and Equ c 1, while Fel d 7 may cross react with the major dog allergen Can f 1. Fel d 4 and Fel d 7 are produced in all cats. Table. Specific Cat Epithelium Allergens Allergen Most common reaction type Selected potential cross-reactivity with other allergens Fel d 1 (uteroglobin) The major cat allergen. Sensitivity is associated systemic rhinitis and asthma Fel d 1 is a cat-specific marker of sensitization. For individuals with clinical allergy symptoms to cats, the majority show antibody reactivity to Fel d1. The presence of IgE Fel d 1 antibodies indicates an increased risk of allergic response when exposed to cat skin, dander and/or saliva. No major cross reactivity to Fed d 1 has been reported. Fel d 1 is a cat-specific marker of sensitization. However, cat allergic patients with IgE to Fel d 1 have also reacted to different feline species, such as puma (cougar), tiger, and lion. Fel d 2 (albumin) Fel d 2 is rarely of significant clinical importance, however, sensitization to Fel d 2 may be associated with increased risks of allergic rhinitis and asthma. Serum albumins are a minor allergen in animal dander, but can play a significant role as cross-reacting allergens Sensitization to Fel d 2 may contribute to pork-cat syndrome. Serum IgE antibodies against this component may indicate cross-reactivity associated with canine Can f 3 albumin antigen as well as albumins from humans, pigs, cattle, sheep, horses, mice, and rats. Fel d 4 (lipocalin) Sensitization to lipocalins, such as Fel d 4, may be associated with asthma Increased sensitization to Fel d 4 is associated with an increased risk of asthma when exposed to cat dander. Potential for lipocalin cross-reactivity including dog Can f 6, dog Can f 4, and horse Equ c 1 allergens. Fel d 7 (lipocalin) Sensitization to lipocalins, such as Fel d 7, may be associated with asthma Increased sensitization to Fel d 7 is associated with an increased risk of asthma when exposed to cat dander. Potential for lipocalin cross-reactivity is present most notably with dog Can f 1 allergen.

Useful For: Evaluating patients with suspected cat allergy

Interpretation: When detectable total cat epithelium IgE antibody is present (> or =0.10 IgE kUa/L),

additional specific component IgE antibody testing will be performed. If at least one potential specific allergenic cat component IgE is detected (> or =0.10 IgE kUa/L), an interpretative report will be provided. When the sample is negative for total cat epithelium IgE antibody (<0.10 IgE kUa/L), additional testing for specific cat component IgE antibodies will not be performed. Negative IgE results for total cat epithelium antibody may indicate a lack of sensitization to potential cat allergenic components.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Gronlund H, Adedoyin J, Reininger R, et al: Higher immunoglobulin E antibody levels to recombinant Fel d 1 in cat-allergic children with asthma compared with rhinoconjunctivitis. Clin Exp Allergy. 2008 Aug;38(8):1275-1281. doi: 10.1111/j.1365-2222.2008.03003.x 2. Nwaru BI, Suzuki S, Ekerljung L, et al: Furry animal allergen component sensitization and clinical outcomes in adult asthma and rhinitis. J Allergy Clin Immunol Pract. 2019 Apr;7(4):1230-1238.e4. 3. Davila I, Dominguez-Ortega J, Navarro-Pulido A, et al: Consensus document on dog and cat allergy. Allergy. 2018 Jun;73(6):1206-1222. doi: 10.1111/all.13391 4. Bjerg A, Winberg A, Berthold M, Mattsson L, Borres MP, Ronmark E: A population-based study of animal component sensitization, asthma, and rhinitis in schoolchildren. Pediatr Allergy Immunol. 2015 Sep;26(6):557-563 5. Konradsen JR, Fujisawa T, van Hage M, et al: Allergy to furry animals: New insights, diagnostic approaches, and challenges. J Allergy Clin Immunol. 2015;135(3):616-625 6. de Groot H, van Swieten P, Aalberse RC: Evidence for a Fel d I-like molecule in the "big cats" (Felidae species). J Allergy Clin Immunol. 1990;86(1):107-116 7. Bonnet B, Messaoudi K, Jacomet F, et al: An update on molecular cat allergens: Fel d 1 and what else? Chapter 1: Fel d 1, the major cat allergen. Allergy Asthma Clin Immunol. 2018 Apr 10;14:14. doi: 10.1186/s13223-018-0239-8 8. Bousquet PJ, Chinn S, Janson C, et al: Geographical variation in the prevalence of positive skin tests to environmental aeroallergens in the European Community Respiratory Health Survey I. Allergy. 2007;62(3):301-309 9. Satyaraj E, Wedner HJ, Bousquet J: Keep the cat, change the care pathway: A transformational approach to managing Fel d 1, the major cat allergen. Allergy. 2019;74(S107):5-17 . doi: 10.1111/all.14013 10. Drouet M, Boutet S, Lauret MG, et al: [The pork-cat syndrome or crossed allergy between pork meat and cat epithelia (1)]. Allerg Immunol (Paris). 1994 May;26(5):166-168, 71-72 11. Huang Z, Zhu H, Lin R, et al: Serum albumin as a cross-reactive component in furry animals may be related to the allergic symptoms of patients with rhinitis. J Asthma Allergy. 2021 Oct 21;14:1231-1242. doi: 10.2147/JAA.S334195 12. Smith W, Butler AJ, Hazell LA, et al: Fel d 4, a cat lipocalin allergen. Clin Exp Allergy 2004;34(11):1732-8

COMTQ
610049

Catechol-O-Methyltransferase (COMT) Genotype, Varies

Clinical Information: Catechol-O-methyltransferase (COMT) is involved in phase II (conjugative) metabolism of catecholamines and catechol drugs, such as dopamine, as well as the catechol-estrogens. COMT transfers a donor methyl-group from S-adenosylmethionine to acceptor hydroxy groups on catechol structures (aromatic ring structures with vicinal hydroxy-groups).(1) Bioactive catecholamine metabolites are metabolized by COMT in conjunction with monoamine oxidase (MAO): -Norepinephrine is methylated by COMT forming normetanephrine. -Epinephrine is methylated by COMT forming metanephrine. -Dopamine is converted to homovanillic acid through the combined action of MAO and COMT. Parkinsonism patients receiving levodopa (L-Dopa) therapy are frequently also prescribed a COMT inhibitor to minimize metabolism of L-Dopa by COMT, thereby prolonging L-Dopa action. Catechol-O-methyltransferase is also involved in the inactivation of estrogens. Estradiol can be hydroxylated forming the catechol estrogens 2-hydroxyestradiol and 4-hydroxyestradiol.(2) These hydroxylated estradiols are methylated by COMT, forming the corresponding methoxyestradiols. The gene encoding COMT is transcribed from alternative promoters to produce 2 forms of the enzyme, a soluble short form of the enzyme and a membrane-bound long form. Variants in the COMT gene are therefore designated in the literature by the position of the amino acid change in both the short and long form of the enzyme. A single nucleotide variant in exon 4 of the gene produces an amino acid change from valine to methionine (Val108/158Met). The presence of methionine at this position reduces the maximum activity of the variant enzyme by 25% and also results in significantly less immunoreactive COMT protein, resulting in a 3-fold to 4-fold decrease in activity compared to wild type (valine at this position). This variant has been associated with prediction of response and risk of relapse when using nicotine replacement therapy for smoking cessation.(3) The following information outlines the relationship between the polymorphism detected in this assay and the effect on the activity of the enzyme produced by that allele: Amino acid change cDNA nucleotide change (NM_000754.3) Effect on enzyme activity/metabolism None (wild-type) None (wild type) Normal activity p.Val158Met (known as Val108Met) c.472G>A Reduced activity

Useful For: Prediction of response to nicotine replacement therapy for smoking cessation Investigation of inhibitor dosing for decreasing levodopa metabolism Research use for assessing estrogen metabolism

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Weinshilboum RM, Otterness DM, Szumlanski CL. Methylation pharmacogenetics: catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. Annu Rev Pharmacol Toxicol. 1999;39:19-52. doi:10.1146/annurev.pharmtox.39.1.19 2. Sun H, Guo S, Chen D, et al. Association of functional COMT Val108/Met polymorphism with smoking cessation in a nicotine replacement therapy. J Neural Transm (Vienna). 2012;119(12):1491-1498. doi:10.1007/s00702-012-0841-8 3. Herman AI, Jatlow PI, Gelernter J, Listman JB, Sofuoglu M. COMT Val158Met modulates subjective responses to intravenous nicotine and cognitive performance in abstinent smokers. Pharmacogenomics J. 2013;13(6):490-497. doi:10.1038/tpj.2013.1 4. Worda C, Sator MO, Schneeberger C, Jantschev T, Ferlitsch K, Huber JC. Influence of the catechol-O-methyltransferase (COMT) codon 158 polymorphism on estrogen levels in women. Hum Reprod. 2003;18(2):262-266. doi:10.1093/humrep/deg059 5. Shield AJ, Thomae BA, Eckloff BW, Wieben ED, Weinshilboum RM. Human catechol O-methyltransferase genetic variation: gene resequencing and functional characterization of variant allozymes. Mol Psychiatry. 2004;9(2):151-160. doi:10.1038/sj.mp.4001386 6. Crews KR, Monte AA, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther. 2021;110(4):888-896. doi:10.1002/cpt.2149

CATU 9276 Catecholamine Fractionation, Free, 24 Hour, Urine

Clinical Information: The catecholamines (dopamine, epinephrine, and norepinephrine) are derived from tyrosine via a series of enzymatic conversions. All 3 catecholamines are important neurotransmitters in the central nervous system and play crucial roles in the autonomic regulation of many homeostatic functions, namely vascular tone, intestinal and bronchial smooth muscle tone, cardiac rate and contractility, and glucose metabolism. Their actions are mediated via alpha- and beta-adrenergic receptors and dopamine receptors, all existing in several subforms. The 3 catecholamines overlap but also differ in their receptor activation profile and consequent biological actions. The systemically circulating fraction of the catecholamines is derived almost exclusively from the adrenal medulla, with small contributions from sympathetic ganglia. They are normally present in the plasma in minute amounts, but levels can increase dramatically and rapidly in response to change in posture, environmental temperature, physical and emotional stress, hypovolemia, blood loss, hypotension, hypoglycemia, and exercise. In patients with pheochromocytoma, a potentially curable tumor of catecholamine-producing cells of the adrenal medulla, or less commonly of sympathetic ganglia (paraganglioma), urine catecholamine levels may be elevated. This results in episodic or sustained hypertension and often in intermittent attacks of palpitations, cardiac arrhythmias, headache, sweating, pallor, anxiety, tremor, and nausea ("spells"). Elevations of the urine levels of 1 or several of the catecholamines may also be observed in patients with neuroblastoma and related tumors (ganglioneuroblastomas and ganglioneuromas) and, very occasionally, in other neuroectodermal tumors. At the other end of the spectrum, inherited and acquired syndromes of autonomic dysfunction/failure and autonomic neuropathies are characterized by either inadequate production of 1 or several of the catecholamines or by insufficient release of catecholamines upon appropriate physiological stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress).

Useful For: An auxiliary test to fractionated plasma and urine metanephrine measurements in the diagnosis of pheochromocytoma and paraganglioma An auxiliary test to urine vanillylmandelic acid and homovanillic acid determination in the diagnosis and follow-up of patients with neuroblastoma and related tumors This test is not useful as a first-line test for pheochromocytoma.

Interpretation: Diagnosis of Pheochromocytoma: This test should not be used as the first-line test for pheochromocytoma. PMET / Metanephrines, Fractionated, Free, Plasma (the most sensitive assay) and METAF / Metanephrines, Fractionated, 24 Hour, Urine (almost as sensitive and highly specific) are the recommended first-line laboratory tests for pheochromocytoma. However, urine catecholamine measurements can still be useful in patients whose plasma or urine metanephrine measurements do not completely exclude the diagnosis. In such cases, urine catecholamine specimens have an 86% diagnostic sensitivity when cutoff levels of greater than 80 mg/24 hours for norepinephrine and greater than 20 mg/24 hours for epinephrine are employed. Unfortunately, the specificity of these cutoff levels for separating tumor patients from other patients with similar symptoms is only 88%. When more specific (98%) decision levels of greater than 170 mg/24 hours for norepinephrine or greater than 35 mg/24 hours for epinephrine are used, the assay's sensitivity falls to about 77%. Diagnosis of Neuroblastoma: Vanillylmandelic acid, homovanillic acid, and sometimes urine catecholamine measurements using either random urine or 24-hour urine collections are the mainstay of biochemical diagnosis and follow-up of neuroblastoma; 1 or more of these analytes may be elevated.

Reference Values:

Norepinephrine <1 year: <11 mcg/24 h
1 year: 1-17 mcg/24 h
2-3 years: 4-29 mcg/24 h
4-6 years: 8-45 mcg/24 h
7-9 years: 13-65 mcg/24 h
> or =10 years: 15-80 mcg/24 h

Epinephrine
<1 year: <2.6 mcg/24 h
1 year: <3.6 mcg/24 h

2-3 years: <6.1 mcg/24 h
4-9 years: 0.2-10.0 mcg/24 h
10-15 years: 0.5-20.0 mcg/24 h
> or =16 years: <21 mcg/24 h

Dopamine
<1 year: <86 mcg/24 h
1 year: 10-140 mcg/24 h
2-3 years: 40-260 mcg/24 h
> or =4 years: 65-400 mcg/24 h

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Young WF Jr. Pheochromocytoma and primary aldosteronism. In: Arnold A, ed. Endocrine Neoplasms. Kluwer Academic Publishers; 1997:239-261. Cancer Treatment And Research. Vol 89 2. Pacak K, Linehan WM, Eisenhofer G, Walther MM, Goldstein DS. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med. 2001;134(4):315-329 3. Alexander F. Neuroblastoma. Urol Clin North Am. 2000;27(3):383-vii. doi:10.1016/s0094-0143(05)70087-2 4. McDougall AJ, McLeod JG. Autonomic neuropathy, I. Clinical features, investigation, pathophysiology, and treatment. J Neurol Sci. 1996;137(2):79-88 5. Lenders JW, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best?. JAMA. 2002;287(11):1427-1434. doi:10.1001/jama.287.11.1427 6. Pussard E, Neveux M, Guigueno N. Reference intervals for urinary catecholamines and metabolites from birth to adulthood. Clin Biochem. 2009;42(6):536-539 7. Ji C, Li W, Ren XD, et al. Diethylation labeling combined with UPLC/MS/MS for simultaneous determination of a panel of monoamine neurotransmitters in rat prefrontal cortex microdialysates. Anal Chem. 2008;80(23):9195-9203 8. Ellis AG, Zeglinski PT, Coleman KE, Whiting MJ. Dilute, derivatise and shoot: Measurement of urinary free metanephrines and catecholamines as ethyl derivatives by LC-MSMS. Clin Mass Spec. 2017;4-5:34-41

CATP
8532

Catecholamine Fractionation, Free, Plasma

Clinical Information: The catecholamines (dopamine, epinephrine, and norepinephrine) are derived from tyrosine via a series of enzymatic conversions. All 3 catecholamines are important neurotransmitters in the central nervous system and play a crucial role in the autonomic regulation of many homeostatic functions, namely, vascular tone, intestinal and bronchial smooth muscle tone, cardiac rate and contractility, and glucose metabolism. Their actions are mediated via alpha- and beta-adrenergic and dopamine receptors, all existing in several subforms. The 3 catecholamines overlap but differ in their receptor activation profile and consequent biological actions. The systemically circulating fraction of the catecholamines is derived almost exclusively from the adrenal medulla, with small contributions from sympathetic ganglia. Catecholamines are normally present in the plasma in minute amounts, but levels can increase dramatically and rapidly in response to change in posture, environmental temperature, physical and emotional stress, hypovolemia, blood loss, hypotension, hypoglycemia, and exercise. In patients with pheochromocytoma (a potentially curable tumor of catecholamine-producing cells of the adrenal medulla) or, less commonly, paraganglioma (a tumor of the sympathetic ganglia that also produces catecholamine), plasma catecholamine levels may be continuously or episodically elevated. This results in episodic or sustained hypertension and intermittent attacks of palpitations, cardiac arrhythmias, headache, sweating, pallor, anxiety, tremor, and nausea. Intermittent or continuous elevations of the plasma levels of one or several of the catecholamines may be observed in patients with neuroblastoma and related tumors (ganglioneuroblastomas and ganglioneuromas) and, very occasionally, in other neuroectodermal tumors. At the other end of the spectrum, inherited and acquired syndromes of autonomic dysfunction or failure and autonomic neuropathies are characterized by either inadequate production of one or several of the catecholamines or by insufficient release of catecholamines upon

appropriate physiological stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress).

Useful For: Diagnosing pheochromocytoma and paraganglioma, as an auxiliary test to fractionated plasma and urine metanephrine measurements Diagnosis follow-up of patients with neuroblastoma and related tumors, as an auxiliary test to urine vanillylmandelic acid and homovanillic acid measurements Evaluation of patients with autonomic dysfunction or failure or autonomic neuropathy

Interpretation: Diagnosis of Pheochromocytoma: This test should not be used as the first-line test for pheochromocytoma, as plasma catecholamine levels may not be continuously elevated but only secreted during a "spell." By contrast, production of metanephrines (catecholamine metabolites) appears to be increased continuously. The recommended first-line laboratory tests for pheochromocytoma are: -PMET / Metanephrines, Fractionated, Free, Plasma: the most sensitive assay -METAF / Metanephrines, Fractionated, 24 Hour, Urine: highly specific and almost as sensitive as PMET However, plasma catecholamine measurements can be useful in patients whose plasma metanephrine or urine metanephrine measurements do not completely exclude the diagnosis. In such cases, plasma catecholamine specimens, if collected during a "spell," have a 90% to 95% diagnostic sensitivity when cutoffs of 750 pg/mL for norepinephrine and 110 pg/mL for epinephrine are employed. A lower value during a "spell," particularly when plasma or urinary metanephrine measurements were also normal, essentially rules out pheochromocytoma. Unfortunately, the specificity of these high-sensitivity cutoff levels is not adequate for separating tumor patients from other patients with similar symptoms. When more specific (95%) decision levels of 2000 pg/mL for norepinephrine or 200 pg/mL for epinephrine are used, the assay's sensitivity falls to about 85%. Diagnosis of Neuroblastoma: Vanillylmandelic acid, homovanillic acid, and, sometimes, urine catecholamine measurements using random urine or 24-hour urine collections are the mainstay of biochemical diagnosis and follow-up of neuroblastoma. Plasma catecholamine levels can aid diagnosis in some cases, but diagnostic decision levels are not well established. The most useful finding is disproportional elevations in 1 of the 3 catecholamines, particularly dopamine, which may be observed in these tumors. Diagnosis of Autonomic Dysfunction or Failure and Autonomic Neuropathy: Depending on the underlying cause and pathology, autonomic dysfunction or failure and autonomic neuropathies are associated with subnormal resting norepinephrine levels or an absent rise of catecholamine levels in response to physiological release stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress), or both. In addition, there may be significant abnormalities in the ratios of the plasma values of the catecholamines to each other (normal: norepinephrine>epinephrine>dopamine). This is observed most strikingly in the inherited dysautonomic disorder dopamine-beta-hydroxylase deficiency, which results in markedly elevated plasma dopamine levels and a virtually total absence of plasma epinephrine and norepinephrine.

Reference Values:

NOREPINEPHRINE
Supine: 70-750 pg/mL
Standing: 200-1700 pg/mL

EPINEPHRINE
Supine: <111 pg/mL
Standing: <141 pg/mL

DOPAMINE
<30 pg/mL (no postural change)

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Jain A, Baracco R, Kapur G. Pheochromocytoma and paraganglioma-an update on diagnosis, evaluation, and management. Pediatr Nephrol. 2020;35(4):581-594.

doi:10.1007/s00467-018-4181-2 2. Bergmann ML, Schmedes A. Highly sensitive LC-MS/MS analysis of catecholamines in plasma. Clin Biochem. 2020;82:51-57. doi:10.1016/j.clinbiochem.2020.03.006 3. Cheshire WP Jr, Goldstein DS. Autonomic uprising: the tilt table test in autonomic medicine. Clin Auton Res. 2019;29(2):215-230. doi:10.1007/s10286-019-00598-9 4. Smith MD, Maani CV. Norepinephrine. In: StatPearls [Internet]. StatPearls Publishing; 2022. Accessed June 15, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK537259

CTP10
33861

Catecholamine Fractionation, Standing, Plasma, Free

Clinical Information: The catecholamines (dopamine, epinephrine, and norepinephrine) are derived from tyrosine via a series of enzymatic conversions. All 3 catecholamines are important neurotransmitters in the central nervous system and also play a crucial role in the autonomic regulation of many homeostatic functions, namely, vascular tone, intestinal and bronchial smooth muscle tone, cardiac rate and contractility, and glucose metabolism. Their actions are mediated via alpha and beta adrenergic and dopamine receptors, all existing in several subforms. The 3 catecholamines overlap but differ in their receptor activation profile and consequent biological actions. The systemically circulating fraction of the catecholamines is derived almost exclusively from the adrenal medulla, with small contributions from sympathetic ganglia. Catecholamines are normally present in the plasma in minute amounts but levels can increase dramatically and rapidly in response to change in posture, environmental temperature, physical and emotional stress, hypovolemia, blood loss, hypotension, hypoglycemia, and exercise. In patients with pheochromocytoma (a potentially curable tumor of catecholamine producing cells of the adrenal medulla), or less commonly, paraganglioma (a tumor of the sympathetic ganglia that also produces catecholamine), plasma catecholamine levels may be continuously or episodically elevated. This results in episodic or sustained hypertension and in intermittent attacks of palpitations, cardiac arrhythmias, headache, sweating, pallor, anxiety, tremor, and nausea. Intermittent or continuous elevations of the plasma levels of 1 or several of the catecholamines may be observed in patients with neuroblastoma and related tumors (ganglioneuroblastomas and ganglioneuromas) and, very occasionally, in other neuroectodermal tumors. At the other end of the spectrum, inherited and acquired syndromes of autonomic dysfunction/failure and autonomic neuropathies are characterized by either inadequate production of 1 or several of the catecholamines or by insufficient release of catecholamines upon appropriate physiological stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress).

Useful For: Diagnosis of pheochromocytoma and paraganglioma in specimens collected from individuals in a standing position, as an auxiliary test to fractionated plasma and urine metanephrine measurements Diagnosis and follow-up of patients with neuroblastoma and related tumors, as an auxiliary test to urine vanillylmandelic acid and homovanillic acid measurements Evaluation of patients with autonomic dysfunction/failure or autonomic neuropathy

Interpretation: Diagnosis of Pheochromocytoma: This test should not be used as the first-line test for pheochromocytoma, as plasma catecholamine levels may not be continuously elevated, but only secreted during a "spell." By contrast, production of metanephrines (catecholamine metabolites) appears to be increased continuously. The recommended first-line laboratory tests for pheochromocytoma are: -PMET / Metanephrines, Fractionated, Free, Plasma: the most sensitive assay -METAF / Metanephrines, Fractionated, 24 Hour, Urine: highly specific and almost as sensitive as PMET However, plasma catecholamine measurements can be useful in patients whose plasma metanephrine or urine metanephrine measurements do not completely exclude the diagnosis. In such cases, plasma catecholamine specimens, if drawn during a "spell," have a 90% to 95% diagnostic sensitivity when cutoffs of 750 pg/mL for norepinephrine and 110 pg/mL for epinephrine are employed. A lower value during a "spell," particularly when plasma and/or urinary metanephrine measurements were also normal, essentially rules out pheochromocytoma. Unfortunately, the specificity of these high-sensitivity cutoff levels is not good for separating tumor patients from other patients with similar symptoms. When more specific (95%) decision levels of 2000 pg/mL for norepinephrine or 200 pg/mL for epinephrine are used, the assay's sensitivity falls to about 85%. Diagnosis of Neuroblastoma: Vanillylmandelic acid, homovanillic acid, and

sometimes urine catecholamine measurements using random urine or 24-hour urine collections are the mainstay of biochemical diagnosis and follow-up of neuroblastoma. Plasma catecholamine levels can aid diagnosis in some cases, but diagnostic decision levels are not well established. The most useful finding is disproportional elevations in 1 of the 3 catecholamines, particularly dopamine, which may be observed in these tumors. Diagnosis of Autonomic Dysfunction/Failure and Autonomic Neuropathy: Depending on the underlying cause and pathology, autonomic dysfunction/failure and autonomic neuropathies are associated with subnormal resting norepinephrine levels, or an absent rise of catecholamine levels in response to physiological release stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress), or both. In addition, there may be significant abnormalities in the ratios of the plasma values of the catecholamines to each other (normal: norepinephrine>epinephrine>dopamine). This is observed most strikingly in the inherited dysautonomic disorder dopamine-beta-hydroxylase deficiency, which results in markedly elevated plasma dopamine levels and a virtually total absence of plasma epinephrine and norepinephrine.

Reference Values:

Only orderable as part of a profile. For more information see CATPA / Catecholamine, Endocrine Study, Plasma.

Clinical References: 1. Jain A, Baracco R, Kapur G. Pheochromocytoma and paraganglioma-an update on diagnosis, evaluation, and management. Pediatr Nephrol. 2020;35(4):581-594. doi:10.1007/s00467-018-4181-2 2. Bergmann ML, Schmedes A. Highly sensitive LC-MS/MS analysis of catecholamines in plasma. Clin Biochem. 2020;82:51-57. doi:10.1016/j.clinbiochem.2020.03.006 3. Cheshire WP Jr, Goldstein DS. Autonomic uprising: the tilt table test in autonomic medicine. Clin Auton Res. 2019;29(2):215-230. doi:10.1007/s10286-019-00598-9 4. Smith MD, Maani CV. Norepinephrine. In: StatPearls [Internet]. StatPearls Publishing; 2022. Accessed November 13, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK537259

CTP0 33860 Catecholamine Fractionation, Supine, Plasma, Free

Clinical Information: The catecholamines (dopamine, epinephrine, and norepinephrine) are derived from tyrosine via a series of enzymatic conversions. All 3 catecholamines are important neurotransmitters in the central nervous system and also play a crucial role in the autonomic regulation of many homeostatic functions, namely, vascular tone, intestinal and bronchial smooth muscle tone, cardiac rate and contractility, and glucose metabolism. Their actions are mediated via alpha and beta adrenergic and dopamine receptors, all existing in several subforms. The 3 catecholamines overlap but differ in their receptor activation profile and consequent biological actions. The systemically circulating fraction of the catecholamines is derived almost exclusively from the adrenal medulla, with small contributions from sympathetic ganglia. Catecholamines are normally present in the plasma in minute amounts but levels can increase dramatically and rapidly in response to change in posture, environmental temperature, physical and emotional stress, hypovolemia, blood loss, hypotension, hypoglycemia, and exercise. In patients with pheochromocytoma (a potentially curable tumor of catecholamine producing cells of the adrenal medulla), or less commonly, paraganglioma (a tumor of the sympathetic ganglia that also produces catecholamine), plasma catecholamine levels may be continuously or episodically elevated. This results in episodic or sustained hypertension and in intermittent attacks of palpitations, cardiac arrhythmias, headache, sweating, pallor, anxiety, tremor, and nausea. Intermittent or continuous elevations of the plasma levels of 1 or several of the catecholamines may be observed in patients with neuroblastoma and related tumors (ganglioneuroblastomas and ganglioneuromas) and, very occasionally, in other neuroectodermal tumors. At the other end of the spectrum, inherited and acquired syndromes of autonomic dysfunction/failure and autonomic neuropathies are characterized by either inadequate production of 1 or several of the catecholamines or by insufficient release of catecholamines upon appropriate physiological stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress).

Useful For: Diagnosis of pheochromocytoma and paraganglioma in specimens collected from individuals in a supine position, as an auxiliary test to fractionated plasma and urine metanephrine measurements Diagnosis and follow-up of patients with neuroblastoma and related tumors, as an auxiliary test to urine vanillylmandelic acid and homovanillic acid measurements Evaluation of patients with autonomic dysfunction/failure or autonomic neuropathy

Interpretation: Diagnosis of Pheochromocytoma: This test should not be used as the first-line test for pheochromocytoma, as plasma catecholamine levels may not be continuously elevated, but only secreted during a "spell." By contrast, production of metanephrines (catecholamine metabolites) appears to be increased continuously. The recommended first-line laboratory tests for pheochromocytoma are: -PMET / Metanephrines, Fractionated, Free, Plasma: the most sensitive assay -METAF / Metanephrines, Fractionated, 24 Hour, Urine: highly specific and almost as sensitive as PMET However, plasma catecholamine measurements can be useful in patients whose plasma metanephrine or urine metanephrine measurements do not completely exclude the diagnosis. In such cases, plasma catecholamine specimens, if drawn during a "spell," have a 90% to 95% diagnostic sensitivity when cutoffs of 750 pg/mL for norepinephrine and 110 pg/mL for epinephrine are employed. A lower value during a "spell," particularly when plasma and/or urinary metanephrine measurements were also normal, essentially rules out pheochromocytoma. Unfortunately, the specificity of these high-sensitivity cutoff levels is not good for separating tumor patients from other patients with similar symptoms. When more specific (95%) decision levels of 2000 pg/mL for norepinephrine or 200 pg/mL for epinephrine are used, the assay's sensitivity falls to about 85%. Diagnosis of Neuroblastoma: Vanillylmandelic acid, homovanillic acid, and sometimes urine catecholamine measurements using random urine or 24-hour urine collections are the mainstay of biochemical diagnosis and follow-up of neuroblastoma. Plasma catecholamine levels can aid diagnosis in some cases, but diagnostic decision levels are not well established. The most useful finding is disproportional elevations in 1 of the 3 catecholamines, particularly dopamine, which may be observed in these tumors. Diagnosis of Autonomic Dysfunction/Failure and Autonomic Neuropathy: Depending on the underlying cause and pathology, autonomic dysfunction/failure and autonomic neuropathies are associated with subnormal resting norepinephrine levels, or an absent rise of catecholamine levels in response to physiological release stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress), or both. In addition, there may be significant abnormalities in the ratios of the plasma values of the catecholamines to each other (normal: norepinephrine>epinephrine>dopamine). This is observed most strikingly in the inherited dysautonomic disorder dopamine-beta-hydroxylase deficiency, which results in markedly elevated plasma dopamine levels and a virtually total absence of plasma epinephrine and norepinephrine.

Reference Values:
Only orderable as part of a profile. For more information see CATPA / Catecholamine, Endocrine Study, Plasma.

Clinical References: 1. Jain A, Baracco R, Kapur G. Pheochromocytoma and paraganglioma-an update on diagnosis, evaluation, and management. Pediatr Nephrol. 2020;35(4):581-594. doi:10.1007/s00467-018-4181-2 2. Bergmann ML, Schmedes A. Highly sensitive LC-MS/MS analysis of catecholamines in plasma. Clin Biochem. 2020;82:51-57. doi:10.1016/j.clinbiochem.2020.03.006 3. Cheshire WP Jr, Goldstein DS. Autonomic uprising: the tilt table test in autonomic medicine. Clin Auton Res. 2019;29(2):215-230. doi:10.1007/s10286-019-00598-9 4. Smith MD, Maani CV. Norepinephrine. In: StatPearls [Internet]. StatPearls Publishing; 2022. Accessed November 13, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK537259

CATPA
33859

Catecholamine, Endocrine Study, Plasma

Clinical Information: The catecholamines (dopamine, epinephrine, and norepinephrine) are derived from tyrosine via a series of enzymatic conversions. All 3 catecholamines are important neurotransmitters

in the central nervous system and also play a crucial role in the autonomic regulation of many homeostatic functions, namely, vascular tone; intestinal and bronchial smooth muscle tone; cardiac rate and contractility; and glucose metabolism. Their actions are mediated via alpha and beta adrenergic and dopamine receptors, all existing in several subforms. The 3 catecholamines overlap, but differ in their receptor activation profile and consequent biological actions. The systemically circulating fraction of the catecholamines is derived almost exclusively from the adrenal medulla, with small contributions from sympathetic ganglia. Catecholamines are normally present in the plasma in minute amounts, but levels can increase dramatically and rapidly in response to change in posture, environmental temperature, physical and emotional stress, hypovolemia, blood loss, hypotension, hypoglycemia, and exercise. In patients with pheochromocytoma (a potentially curable tumor of catecholamine producing cells of the adrenal medulla), or less commonly, paraganglioma (a tumor of the sympathetic ganglia that also produces catecholamine), plasma catecholamine levels may be continuously or episodically elevated. This results in episodic or sustained hypertension and in intermittent attacks of palpitations, cardiac arrhythmias, headache, sweating, pallor, anxiety, tremor, and nausea. Intermittent or continuous elevations of the plasma levels of 1 or several of the catecholamines may be observed in patients with neuroblastoma and related tumors (ganglioneuroblastomas and ganglioneuromas) and, very occasionally, in other neuroectodermal tumors. At the other end of the spectrum, inherited and acquired syndromes of autonomic dysfunction/failure and autonomic neuropathies are characterized by either inadequate production of 1 or several of the catecholamines or by insufficient release of catecholamines upon appropriate physiological stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress).

Useful For: Diagnosis of pheochromocytoma and paraganglioma in specimens collected from individuals in both supine and standing positions, as an auxiliary test to fractionated plasma and urine metanephrine measurements Diagnosis and follow-up of patients with neuroblastoma and related tumors, as an auxiliary test to urine vanillylmandelic acid and homovanillic acid measurements Evaluation of patients with autonomic dysfunction/failure or autonomic neuropathy

Interpretation: Diagnosis of Pheochromocytoma: This test should not be used as the first-line test for pheochromocytoma, as plasma catecholamine levels may not be continuously elevated, but only secreted during a "spell." By contrast, production of metanephrines (catecholamine metabolites) appears to be increased continuously. The recommended first-line laboratory tests for pheochromocytoma are: -PMET / Metanephrines, Fractionated, Free, Plasma: the most sensitive assay -METAF / Metanephrines, Fractionated, 24 Hour, Urine: highly specific and almost as sensitive as PMET However, plasma catecholamine measurements can be useful in patients whose plasma metanephrine or urine metanephrine measurements do not completely exclude the diagnosis. In such cases, plasma catecholamine specimens, if drawn during a "spell," have a 90% to 95% diagnostic sensitivity when cutoffs of 750 pg/mL for norepinephrine and 110 pg/mL for epinephrine are employed. A lower value during a "spell," particularly when plasma and/or urinary metanephrine measurements were also normal, essentially rules out pheochromocytoma. Unfortunately, the specificity of these high-sensitivity cutoff levels is not good for separating tumor patients from other patients with similar symptoms. When more specific (95%) decision levels of 2,000 pg/mL for norepinephrine or 200 pg/mL for epinephrine are used, the assay's sensitivity falls to about 85%. Diagnosis of Neuroblastoma: Vanillylmandelic acid, homovanillic acid, and sometimes urine catecholamine measurements using random urine or 24-hour urine collections are the mainstay of biochemical diagnosis and follow-up of neuroblastoma. Plasma catecholamine levels can aid diagnosis in some cases, but diagnostic decision levels are not well established. The most useful finding is disproportional elevations in 1 of the 3 catecholamines, particularly dopamine, which may be observed in these tumors. Diagnosis of Autonomic Dysfunction/Failure and Autonomic Neuropathy: Depending on the underlying cause and pathology, autonomic dysfunction/failure and autonomic neuropathies are associated with subnormal resting norepinephrine levels, or an absent rise of catecholamine levels in response to physiological release stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress), or both. In addition, there may be significant abnormalities in the ratios of the plasma values of the catecholamines to each other (normal: norepinephrine>epinephrine>dopamine). This is observed most strikingly in the

inherited dysautonomic disorder dopamine-beta-hydroxylase deficiency, which results in markedly elevated plasma dopamine levels and a virtually total absence of plasma epinephrine and norepinephrine.

Reference Values:
NOREPINEPHRINE
Supine: 70-750 pg/mL
Standing: 200-1,700 pg/mL

EPINEPHRINE
Supine: Undetectable-110 pg/mL
Standing: Undetectable-140 pg/mL

DOPAMINE
<30 pg/mL (no postural change)

Clinical References: 1. Jain A, Baracco R, Kapur G. Pheochromocytoma and paraganglioma-an update on diagnosis, evaluation, and management. Pediatr Nephrol. 2020;35(4):581-594. doi:10.1007/s00467-018-4181-2 2. Bergmann ML, Schmedes A. Highly sensitive LC-MS/MS analysis of catecholamines in plasma. Clin Biochem. 2020;82:51-57. doi:10.1016/j.clinbiochem.2020.03.006 3. Cheshire WP Jr, Goldstein DS. Autonomic uprising: the tilt table test in autonomic medicine. Clin Auton Res. 2019;29(2):215-230. doi:10.1007/s10286-019-00598-9 4. Smith MD, Maani CV. Norepinephrine. In: StatPearls [Internet]. StatPearls Publishing; 2022. Accessed June 15, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK537259

CPVTG
617211

Catecholaminergic Polymorphic Ventricular Tachycardia Gene Panel, Varies

Clinical Information: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic cardiac arrhythmia condition characterized by polymorphic and bidirectional ventricular tachycardia induced by physical or emotional stress. CPVT can result in or present with palpitations, syncope, sudden cardiac arrest, or sudden cardiac death. Symptoms typically present in childhood, however, if left untreated, there is an estimated 30% to 50% mortality rate by 40 years of age.(1) CPVT has an estimated prevalence of 1:5000 to 1:10,000 and is caused by disease-causing variants in genes that encode proteins of the sacroplasmic reticulum calcium release complex.(1,2) It is estimated that six genes (RYR2, CASQ2, TRDN, CALM1, CALM2, CALM3) account for up to 75% of cases of CPVT, with gain-of-function variants in the RYR2 gene being the most common genetic etiology in patients with confirmed CPVT.(1) More recently, disease-causing variants in the TECRL gene have been associated with a mixed arrhythmia phenotype exhibiting characteristics of CPVT and long QT syndrome.(3) CPVT can follow autosomal dominant and autosomal recessive patterns of inheritance. Genetic testing in CPVT is recommended to confirm the clinical diagnosis, assist with risk stratification, guide management, and identify at-risk family members.(4) Even individuals without overt symptoms of CPVT may still be at risk for a cardiac event and sudden cardiac death.(4)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of catecholaminergic polymorphic ventricular tachycardia (CPVT) Establishing a diagnosis of CPVT

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:

An interpretive report will be provided.

Clinical References: 1. Wleklinski MJ, Kannankeril PJ, Knollmann BC: Molecular and tissue mechanisms of catecholaminergic polymorphic ventricular tachycardia. J Physiol. 2020 Jul;598(14):2817-2834. doi: 10.1113/JP276757 2. Kim CW, Aronow WS, Dutta T, Frenkel D, Frishman WH: Catecholaminergic polymorphic ventricular tachycardia. Cardiol Rev. Nov/Dec 2020;28(6):325-331. doi: 10.1097/CRD.0000000000000302 3. Webster G, Aburawi EH, Chaix MA, et al. Life-threatening arrhythmias with autosomal recessive TECRL variants. Europace. 2021 May;23(5):781-788. doi: 10.1093/europace/euaa376 4. Napolitano C, Priori SG, Bloise R, et al: Catecholaminergic polymorphic ventricular tachycardia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 2004. Updated June 23, 2022. Accessed July 14, 2022. Available from: www.ncbi.nlm.nih.gov/books/NBK1289/ 5. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424. doi: 10.1038/gim.2015.30.

FCATE
57554

Catfish (Siluriformes spp) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 17.50-49.99 Very High Positive 5 50.00-99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

FCLPF
75676

Cathartic Laxatives Profile, Stool

Interpretation: Magnesium: Magnesium concentrations in stool water above the normal levels of 0.7-1.2 mg/mL have been indicative of surreptitious abuse of magnesium containing laxatives. NMS Labs Calculated Normal: approximately 0.5-10 mg/g (Based on the reported range of magnesium eliminated per day in stool and the range of stool mass per day in adults). Phosphorus: Phosphorus concentration in stool water averaged 1.8 +/- 0.3 mg/mL (ranged from 0.3-4.2 mg/mL) following administration of 105 mmol of sodium phosphate. NMS Labs calculated normal: approximately 1.4-22 mg/g (Based on the reported range of phosphorus eliminated per day in stool and the range of stool mass per day in adults).

Reference Values:
Reporting limit determined each analysis.
Units: mg/g

CTSK
607887

Cathepsin K Immunostain, Technical Component Only

Clinical Information: Cathepsin K is a protease whose expression is driven by microphthalmia transcription factor in osteoclasts. Cathepsin K is also expressed in renal perivascular epithelioid cell neoplasms (PEComas), alveolar soft part sarcoma, and most MiT family translocation renal cell carcinomas. This includes most transcription factor EB- (TFEB) rearranged renal cell carcinomas, those with amplifications of TFEB, and renal cell carcinomas that harbor various TFE3 gene fusions.

Useful For: Evaluation for perivascular epithelioid cell neoplasms (PEComas), alveolar soft part

sarcoma, and translocation-associated renal cell carcinomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Martignoni G, Bonetti F, Chilosi M, et al. Cathepsin K expression in the spectrum of perivascular epithelioid cell (PEC) lesions of the kidney. Mod Pathol. 2012;25(1):100-111. doi:10.1038/modpathol.2011.136 2. Rao Q, Cheng L, Xia QY, et al. Cathepsin K expression in a wide spectrum of pervascular epithelioid cell neoplasms (PEComas): a clinicopathological study emphasizing external PEComas. Histol. 2013;62(4):642-650. doi:10.1111/his.12059 3. Martignoni G, Gobbo S, Camparo P, et al. Differential expression of cathepsin K in neoplasms harboring TFE3 gene fusions. Mod Pathol. 2011;24(10):1313-1319. doi:10.1038/modpathol.2011.93 4. Rao Q, Wang Y, Xia Q, et al. Cathepsin K in the immunohistochemical diagnosis of melanocytic lesions. Int J Clin Exp Pathol. 2014;7(3):1132-1139 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FCAFG
57680

Cauliflower IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

CALFL
82617

Cauliflower, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to cauliflower Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical

sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

IN16Q
610266

CBFB::MYH11 Inversion(16), Quantitative Detection and Minimal Disease Risk Monitoring, qRT-PCR, Varies

Clinical Information: CBFB::MYH11 minimal residual disease (MRD) monitoring in patients with acute myeloid leukemia (AML) with inv(16) or t(16;16) is useful for evaluating disease response after therapy and identifying individuals with increased risk of relapse. Quantitative real-time reverse transcription polymerase chain reaction testing in neoplasms with known clonal genetic markers can achieve highly sensitive detection of neoplastic cells in peripheral blood or bone marrow specimens. It is one of the most mature technologies available for this purpose. In this assay, inversion or translocation of chromosome 16 resulting in fusion of two genes, CBFB and MYH11, will be evaluated. Quantitative results will provide physicians with an accurate and precise measurement of disease burden to guide patient intervention decisions. This assay can be used for post-therapy MRD monitoring as well as detection of CBFB::MYH11 fusion in AML patients at the time of diagnosis.

Useful For: Detection of CBFB::MYH11 gene fusion in patients recently diagnosed with acute myeloid leukemia (AML) Minimal residual disease monitoring during the clinical and therapeutic course of patients with AML

Interpretation: The assay is reported in the form of a normalized ratio of CBFB::MYH11 fusion transcript to the control gene ABL1 expressed as a percentage, which is an estimate of the level of CBFB::MYH11 fusion RNA present in the specimen, expressed in relation to the level of RNA from an

internal control gene (ABL1). The normalized ratio has no units but is directly related to the level of CBFB::MYH11 detected (ie, larger numbers indicate higher relative levels of CBFB::MYH11, and smaller numbers indicate lower levels). A relative expression value minimizes variability in the RNA levels and cell numbers measured in separate specimens tested at different times. The precision of the quantitative assay is excellent, but interassay variability can occur such that result changes should not be considered significant if 2 single measurements differ by less than 0.5 log. More critical results, such as a change in the status of positivity or greater or equal to 1 log increase between 2 positive samples should be repeated on a separate specimen with appropriate time interval to verify the result.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Krauter J1, Hoellge W, Wattjes MP, et al. Detection and quantification of CBFB/MYH11 fusion transcripts in patients with inv(16)-positive acute myeloblastic leukemia by real-time RT-PCR. Genes Chromosomes Cancer. 2001;30(4):342-348. doi:10.1002/gcc.1100 2. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447. doi:10.1182/blood-2016-08-733196 3. O'Donnell MR, Tallman MS, Abboud CN, et al. Acute Myeloid Leukemia, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(7):926-957. doi:10.6004/jnccn.2017.0116 4. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European Leukemia Net MRD Working Party. Blood. 2018;131(12):1275-1291. doi:10.1182/blood-2017-09-801498 5. Jourdan E, Boissel N, Chevret S, et al. Prospective evaluation of gene mutations and minimal residual disease in patients with core binding factor acute myeloid leukemia. Blood. 2013;121(12):2213-2223. doi:10.1182/blood-2012-10-462879 6. Lane S, Saal R, Mollee P, et al. A > or =1 log rise in RQ-PCR transcript levels defines molecular relapse in core binding factor acute myeloid leukemia and predicts subsequent morphologic relapse. Leuk Lymphoma. 2008;49(3):517-523. doi:10.1080/10428190701817266 7. Yin JA, O'Brien MA, Hills RK, Daly SB, Wheatley K, Burnett AK. Minimal residual disease monitoring by quantitative RT-PCR in core binding factor AML allows risk stratification and predicts relapse: results of the United Kingdom MRC AML-15 trial. Blood. 2012;120(14):2826-2835. doi:10.1182/blood-2012-06-435669 8. Corbacioglu A, Scholl C, Schlenk RF, et al. Prognostic impact of minimal residual disease in CBFB-MYH11-positive acute myeloid leukemia. J Clin Oncol. 2010;28(23):3724-3729. doi: 10.1200/JCO.2010.28.6468

CD10
70373

CD10 Immunostain, Technical Component Only

Clinical Information: CD10 is a cell surface glycoprotein present on bone marrow B precursors (hematogones) and myeloid cells (including neutrophils), follicle center B cells, and a subset of follicular T helper cells. CD10 is also expressed in the brush border of the upper part of the intestinal tract, bile canaliculi, kidney (glomerular and proximal tubular cells), pulmonary alveolar cells, myoepithelial cells of breast, prostate glandular cells, placental trophoblastic cells, endometrial stromal cells, some endothelial cells, and a minority of (myo-)fibroblasts (stromal cells). CD10 is most useful in the diagnosis of B-precursor-acute lymphoblastic leukemia, Burkitt lymphoma, and lymphomas of follicle cell center origin (follicular lymphoma, subset of large B-cell lymphomas).

Useful For: Phenotyping leukemias and lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Al-Masri M, Darwazeh G, Sawalhi S et al. Phyllodes tumor of the breast: role of CD10 in predicting metastasis. Ann Surg Oncol. 2012;19:1181-1184. doi:10.1245/s10434-011-2076-6 2. Taghizadeh-Kermani Ali, Jafarian AH, Ashabymin R, et al. The stromal overexpression of CD10 in invasive breast cancer and its association with clincophathologic factors. Iran J Cancer Prev. Winter 2014;7(1):17-21 3. Lloyd J, Owens S. CD10 immunohistochemistry stains enteric mucosa, but negative staining is unreliable in the setting of active enteritis. Mod Pathol. 2011;24(12):1627-1632. doi:10.1038/modpathol.2011.122 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD103
70372

CD103 Immunostain, Technical Component Only

Clinical Information: CD103, also known as integrin alpha E, is an integrin subunit protein, which is widely expressed on T cells. CD103 is a useful diagnostic tool in the diagnosis of hairy cell leukemia.

CD11C
70412

CD11c Immunostain, Technical Component Only

Clinical Information: CD11c is a member of the leukocyte specific integrin family, involved in adherence to activated endothelial cells and complement-mediated phagocytosis. CD11c is normally expressed on histiocytes and monocytes, and weakly expressed on granulocytes. CD11c is also expressed on certain B cell neoplasms, including hairy cell leukemia and splenic marginal zone lymphoma.

Useful For: Aiding in the diagnosis of hematological malignancies and identification of cells of the macrophage/dendritic cell lineage within tissues

Interpretation: This test does not include pathologist interpretation; only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Wu J, Wu H, An J, Ballantyne CM, Cyster JG. Critical role of integrin CD11c in splenic dendritic cell capture of missing-self CD47 cells to induce adaptive immunity. Proc Natl Acad Sci USA. 2018; 115(26), 6786-6791 2. Troussard X, Cornet E: Hairy cell leukemia 2018. Update on diagnosis, risk-stratification, and treatment. Am J Hematol. 2017; 92(12), 1382-1390 3. Devin J, Kassambara A, Bruyer A, Moreaux J, Bret C. Phenotypic characterization of diffuse large B-cell lymphoma cells and prognostic impact. J Clin Med. 2019; 8(7), 1074 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD123
70413

CD123 Immunostain, Technical Component Only

Clinical Information: In normal lymphoid tissues, CD123 (cluster of differentiation 123) is expressed in plasmacytoid monocytes and mast cells in interfollicular regions. In bone marrow, it is expressed in hematopoietic precursors, mast cells, and megakaryocytes. CD123 is part of the IL3 receptor complex, involved in cellular growth and differentiation. Certain reactive lymph nodes show

increased numbers of plasmacytoid monocytes (eg, Kikuchi lymphadenitis). CD123 is characteristically expressed in blastic plasmacytoid dendritic cell neoplasm, aiding in its distinction from acute monocytic leukemia.

Useful For: Marker of plasmacytoid monocytes, mast cells, and megakaryocytes

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Arai N, Homma M, Abe M, et al. Impact of CD123 expression, analyzed by immunohistochemistry, on clinical outcomes in patients with acute myeloid leukemia. Int J Hematol. 2019;109(5):539-544 2. Testa U, Pelosi E, Frankel A. CD 123 is a membrane biomarker and a therapeutic target in hematologic malignancies. Biomark Res. 2014;2(1):4 3. Rollins-Raval M, Pillai R, Mitsuhashi-Warita T, et al. CD123 immunohistochemical expression in acute myeloid leukemia is associated with underlying FLT3-ITD and NPM1 mutations. Appl Immunohistochem Mol Morphol. 2013;21(3);212-217 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD13
70374

CD13 Immunostain, Technical Component Only

Clinical Information: CD13 (cluster of differentiation 13) plays roles in peptide metabolism (brush border membranes of small intestine, renal proximal tubules, and placenta), cell growth and differentiation, and phagocytosis. CD13 is normally expressed on myeloid lineage cells, including granulocytes and monocytes. It is also expressed on non-hematolymphoid cells including endothelial cells and fibroblasts and is present in a soluble form in plasma. This immunostain may be useful as a marker of myeloid lineage in acute leukemias.

Useful For: Marker of myeloid lineage

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Yamanaka C, Wada H, Eguchi H, et al. Clinical significance of CD13 and epithelial mesenchymal transition (EMT) markers in hepatocellular carcinoma. Jpn J Clin Oncol. 2018;48(1):52-60 2. Kessler T, Baumeier A, Brand C, et al. Aminopeptidase N (CD13): expression, prognostic impact, and use as therapeutic target for tissue factor induced tumor vascular infarction in soft tissue sarcoma. Transl Oncol. 2018;11(6):1271-1282 3. Dominguez JM, Perez-Chacon G, Guillen MJ, et al. CD13 as a new tumor target for antibody-drug conjugates: validation with the conjugate MI130110. J Hematol Oncol. 2020;13(1):32 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD138
70414

CD138 (Syndecan) Immunostain, Technical Component Only

Clinical Information: CD138 (cluster of differentiation 138) is expressed on plasma cells and can be useful in the diagnosis of plasma cell neoplasms. Epithelial cells and endothelial cells may also express CD138. In normal tonsil tissue, CD138 strongly stains the membranes of mature plasma cells and squamous epithelial cells.

Useful For: Marker of plasma cells and squamous epithelial cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chen Y, Fang R, Luo Y, Luo C. Analysis of the diagnostic value of CD138 for chronic endometritis, the risk factors for the pathogenesis of chronic endometritis and the effect of chronic endometritis on pregnancy: a cohort study. BMC Women's Health. 2016;16(1):60 2. Waisberg J, Theodoro TR, Matos LL, et al. Immunohistochemical expression of heparanase isoforms and syndecan-1 proteins in colorectal adenomas. Eur J Histochem. 2016;60(1):2590 3. Kind S, Merenkow C, Buscheck F, et al: Prevalence of syndecan-1 (CD138) expression in different kinds of human tumors and normal tissues. Dis Markers. 2019;2019:4928315 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD14I
70375

CD14 Immunostain, Technical Component Only

Clinical Information: CD14 (cluster of differentiation 14) is a glycosylphosphatidylinositol-linked glycoprotein that is preferentially expressed by mature cells of monocytic lineage (monocytes, macrophages, Langerhans cells) and follicular dendritic cells. Neutrophils exhibit lower levels of expression. This antibody may be useful as a marker of histiocytic/monocytic lineage in acute leukemias.

Useful For: Marker of histiocytic and monocytic lineage and follicular dendritic cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Heiskala M, Leidenius M, Joensuu K, Heikkila P. High expression of CCL2 in tumor cells and abundant infiltration with CD14 positive macrophages predict early relapse in breast cancer. Virchows Arch. 2019;474(1);3-12. doi:10.1007/s00428-018-2461-7 2. Smeltzer JP, Jones JM, Ziesmer SC, et al. Pattern of CD14+ follicular dendritic cells and PD1+ T cells independently predicts time to transformation in follicular lymphoma. Clin Cancer Res. 2014;20(11):2862-2872. doi:10.1158/1078-0432.CCR-13-2367 3. Li M, Zhang G, Zhang X, et al. Overexpression of B7-H3 in CD14+ monocytes is associated with renal cell carcinoma progression. Med Oncol. 2014;31(12);349. doi:10.1007/s12032-014-0349-1 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD15
70376

CD15 Immunostain, Technical Component Only

Clinical Information: CD15 (cluster of differentiation 15) is expressed in granulocytes and can be expressed in malignant lymphomas and acute myeloid leukemias. The Reed-Sternberg cells of classical Hodgkin lymphoma are characteristically positive for CD15 and CD30.

Useful For: Phenotyping leukemias and lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Benharroch D, Pilosof S, Gopas J, Levi I. Primary refractory and relapsed classical hodgkin lymphoma - significance of differential CD15 expression in Hodgkin-Reed-Sternberg cells. J Cancer. 2012;3:322-327 2. Roge R, Nielsen S, Vyberg M. Carb-3 is the superior antiCD15 monoclonal antibody for immunohistochemistry. Appl Immunohistochem Mol Morphol. 2014;22(6):449-458 3. Venkataraman G, Raffeld M, Pittaluga S, et al. CD15-expressing nodular lymphocyte-predominant hodgkin lymphoma. Histopathology. 2011;58(5):803-805 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD163
70415

CD163 Immunostain, Technical Component Only

Clinical Information: CD163 (cluster of differentiation 163) is a scavenger receptor for the hemoglobin-haptoglobin complex. CD163 is a marker of monocytic/histiocytic lineage, expressed late in maturation. It has superior specificity for monocytic/histiocytic lineage compared to CD68. In normal lymphoid tissues, staining of histiocytes in the paracortex and follicle center (tingible body macrophages) is seen. CD163 is usually negative in immature monocytic/histiocytic tumors (acute myeloid leukemia with monocytic differentiation).

Useful For: Identification of cells of monocytic/histiocytic lineage, expressed late in maturation

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Ma C, Horlad H, Ohnishi K, et al. CD163-positive cancer cells are potentially associated with high malignant potential in clear cell renal cell carcinoma. Med Mol Morphol. 2018;51(1):13-20 2. Garton T, Keep RF, Hua Y, Xi G. CD163, a hemoglobin/haptoglobin scavenger receptor, after intracerebral hemorrhage: functions in microglia/macrophages versus neurons. Trans Stroke Res. 2017;8(6):612-616 3. Yuan X, Zhang J, Li D, et al. Prognostic significance of tumor-associated macrophages in ovarian cancer: A meta-analysis. Gynecol Oncol. 2017;147(1):181-187 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

C19BM
603205

CD19 Immunostain, Bone Marrow, Technical Component Only

Clinical Information: CD19 is expressed by normal and neoplastic B cells but is not expressed by T cells, monocytes, or granulocytes. CD19 protein appears early during B-cell maturation and is found during all stages of B-cell maturation, including plasma cells. CD19 is useful as an additional marker of B cell lineage in leukemias and lymphomas. Expression of CD19 may be seen in some acute myeloid leukemias.

Useful For: Identification of normal and neoplastic B cells

Interpretation:

Clinical References: 1. Masir N, Marafioti T, Jones M, et al. Loss of CD19 expression in B-cell neoplasms. Histopathology 2006;48:239-246 2. Kirk CM, Lewin D, Lazarchick J, et al. Primary hepatic B-cell lymphoma of mucosa-associated lymphoid tissue. Arch Pathol Lab Med 1999;123:716-719 3. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD19I
70377

CD19 Immunostain, Technical Component Only

Clinical Information: CD19 is expressed by normal and neoplastic B cells but is not expressed by T cells, monocytes, or granulocytes. CD19 protein appears early during B-cell maturation and is found during all stages of B-cell maturation, including plasma cells. CD19 is useful as an additional marker of B cell lineage in leukemias and lymphomas. Expression of CD19 may be seen in some acute myeloid leukemias.

Useful For: Identification of normal and neoplastic B cells

Interpretation:

Clinical References: 1. Wang H, Zu Y. Diagnostic algorithm of common mature B-cell lymphomas by immunohistochemistry. Arch Pathol Lab Med. 2017;141(9):1236-1246 2. O'Malley DP, Auerbach A, Weiss LM. Practical applications in immunohistochemistry: evaluation of diffuse large B-cell lymphoma and related large B-cell lymphomas. Arch Pathol Lab Med. 2015;139(9):1094-1107 3. Wang K, Wei G, Liu D. CD19: a biomarker for B cell development, lymphoma diagnosis and therapy. Exp Hematol Oncol. 2012;1(1):36 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD1A
70378

CD1a Immunostain, Technical Component Only

Clinical Information: CD1a is a membrane surface glycoprotein that is expressed in Langerhans cells and immature T cells. CD1a expression is useful in phenotyping acute lymphoblastic leukemia/lymphoma of T-cell lineage and in the diagnosis of Langerhans cell histiocytosis.

Useful For: Marker of Langerhans cells and immature T cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Nasiri S, Bidari Zerehpoosh F, Abdollahimajd F, Younespour S, Esmaili Azad M. A comparative immunohistochemical study of epidermal and dermal/perifollicular Langerhans cell concentration in discoid lupus erythematosus and lichen planopilaris: a cross-sectional study. Lupus. 2018;27(14):2200-2205. doi:10.1177/0961203318808587 2. Wang P, Peng X, Deng X, Gao L, Zhang X, Feng Y. Diagnostic challenges in T-lymphoblastic lymphoma, early T-cell precursor acute lymphoblastic leukemia or mixed phenotype acute leukemia: A case report. Medicine (Baltimore). 2018;97(41):e12743. doi:10.1097/MD.0000000000012743 3. Kim HK, Park CJ, Jang S, et al. Bone marrow involvement of Langerhans cell histiocytosis: immunohistochemical evaluation of bone marrow for CD1a, Langerin, and S100 expression. Histopathology. 2014;65(6):742-748. doi:10.1111/his.12481 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD2B
603203

CD2 Immunostain, Bone Marrow, Technical Component Only

Clinical Information: CD2 is a pan T-cell antigen, expressed on normal and neoplastic T cells and natural killer cells. In normal tonsil, the T cells predominate in interfollicular regions. CD2 immunostaining is useful in determining T-cell lineage in cases of T-cell lymphoma.

Useful For: Determining T-cell lineage

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Campbell AM, Peters SB, Zirwas MJ, et al. Immunophenotypic diagnosis of primary cutaneous lymphomas. A review for the practicing dermatologist. J Clin Aesthet Dermatol 2010;3(10):21-25 2. Jordan JH, Walchshofer S, Jurecka W, et al, Immunohistochemical properties of bone marrow mast cells in systemic mastocytosis: evidence for expression of CD2, CD117/Kit, and bcl-x(L). Hum Pathol 2001;32(5):545-552 3. Went P, Agostinelli C, Gallamini A, et al, Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. J Clin Oncol 2006;24(16):2472-2479 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD2
70384

CD2 Immunostain, Technical Component Only

Clinical Information: CD2 is a pan T-cell antigen that is expressed on normal and neoplastic T cells and natural killer cells. CD2 immunostaining is useful in determining T-cell lineage in cases of T-cell lymphoma.

Useful For: Determining T-cell lineage

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Campbell AM, Peters SB, Zirwas MJ, et al. Immunophenotypic diagnosis of primary cutaneous lymphomas. A review for the practicing dermatologist. J Clin Aesthet Dermatol. 2010;3(10):21-25 2. Rai MP, Bedi PS, Marinas EB, Khan NNS. Angioimmunoblastic T-cell lymphoma: a rare subtype of peripheral T-cell lymphoma. Clin Case Rep. 2018;6(4):750-752. doi:10.1002/ccr3.1388 3. Stenman L, Persson M, Enlund F, Clasen-Linde E, Stenman G, Heegaard S. Primary orbital precursor T-cell lymphoblastic lymphoma: Report of a unique case. Mol Clin Oncol. 2016;5(5):593-595. doi:10.3892/mco.2016.1008 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CEE20 CD20 Cell Expression Evaluation, Varies

65660

Clinical Information: Monoclonal antibodies are critical tools for detecting cellular antigens in various hematologic diseases and are used to provide critical prognostic information (CD49d). Monoclonal antibodies are also used as therapeutic agents in a variety of hematologic diseases. For example: -Anti-CD20 (Rituxan): B-cell malignant lymphomas and multiple myeloma -Anti-CD52 (Campath-1H): B-cell chronic lymphocytic leukemia and T-cell disorders This list will undoubtedly expand over time to include other antibodies. It may be necessary to document expression of these markers by the malignant cells prior to initiating the respective monoclonal antibody therapy. Expression of these markers may also be required for follow-up to monitor the impact of treatment on residual normal counterparts (eg, CD20-positive lymphocytes in patients treated with anti-CD20). The distribution of these cellular antigens is well established in normal, reactive, and in various malignant disorders. The laboratory has several years of experience with therapeutic antibody monitoring of Mayo Clinic patients as part of the routine B-cell, T-cell, or acute immunophenotyping panels.

Useful For: Detecting cell-surface antigens on malignant cells that are potential therapeutic antibody targets, specifically CD20 Determining the eligibility of patients for monoclonal antibody therapies Monitoring response to the therapeutic antibody

Interpretation: The immunophenotyping report will summarize the pattern of antigenic expression on malignant cells and, if appropriate, the normal cellular counterparts that correspond to the therapeutic monoclonal antibody target.

Reference Values:
Normal individuals have B lymphocytes, T lymphocytes, or myeloid cells that express the corresponding cell-surface antigens in question.

Clinical References: 1. Salles G, Barrett M, Foa R, et al. Rituximab in B-cell hematologic malignancies: A review of 20 years of clinical experience. Adv Ther. 2017;34(10):2232-2273. doi:10.1007/s12325-017-0612-x. 2. Braun T, von Jan J, Wahnschaffe L, Herling M. Advances and Perspectives in the Treatment of T-PLL. Curr Hematol Malig Rep. 2020;15(2):113-124. doi:10.1007/s11899-020-00566-5. 3. Piccaluga PP, Cascianelli C, Inghirami G. Tyrosine kinases in nodal peripheral T-cell lymphomas. Front Oncol. 2023;13:1099943. Published 2023 Feb 8. doi:10.3389/fonc.2023.10999434. Amhaz G, Bazarbachi A, El-Cheikh J. Immunotherapy in indolent Non-Hodgkin's Lymphoma. Leuk Res Rep. 2022;17:100325. Published 2022 May 18. doi:10.1016/j.lrr.2022.100325 5. Tissino E, Pozzo F, Benedetti D, et al. CD49d promotes disease progression in chronic lymphocytic leukemia: new insights from CD49d bimodal expression. Blood. 2020;135(15):1244-1254. doi:10.1182/blood.2019003179

CD20I CD20 Immunostain, Technical Component Only

70379

Clinical Information: CD20 is a phosphorylated protein preferentially expressed by mature B lymphocytes. CD20 is not expressed by most normal plasma cells. It is one of the most specific B-cell lineage-associated antigens used in the diagnosis of B-cell lymphomas.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Choi CH, Park YH, Lim JH, et al. Prognostic implication of semi-quantitative immunohistochemical assessment of CD20 expression in diffuse large B-cell lymphoma. J Pathol Transl Med. 2016;50(2):96-103. doi:10.4132/jptm.2016.01.12 2. Duman BB, Sahin B, Ergin M, Guvenc B. Loss of CD20 antigen expression after rituximab therapy of CD20 positive B cell lymphoma (diffuse large B cell extranodal marginal zone lymphoma combination): A case report and review of the literature. Med Oncol. 2012;29(2):1223-1226. doi:10.1007/s12032-011-9955-3 3. Cang S, Mukhi N, Wang K, Liu D. Novel CD20 monoclonal antibodies for lymphoma therapy. J Hematol Oncol. 2012;5:64. doi:10.1186/1756-8722-5-64 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD20B
89584

CD20 on B Cells, Blood

Clinical Information: CD20 (cluster of differentiation 20) is a protein that is expressed on the surface of B cells, starting at the pre-B cell stage and on mature B cells in the bone marrow and in the periphery. CD20 is not expressed on hematopoietic stem cells, pro-B cells, or normal plasma cells.(1) Plasmablasts and stimulated plasma cells may express CD20.(2) CD20 is generally coexpressed on B cells with CD19, another B-cell differentiation marker. CD20 appears to play a role in B-cell development, differentiation, B-cell receptor (BCR) signaling, and cell-cycle initiation events.(3) CD20 is not shed from the surface of B cells and does not internalize on binding with anti-CD20 antibody, nor is it typically present as a soluble free antigen in circulation.(3) Certain primary humoral immunodeficiencies, such as X-linked agammaglobulinemia and autosomal recessive agammaglobulinemia, are characterized by a complete absence or profound reduction of peripheral B cells, expressing both CD20 and CD19. Variants in the CD19 gene have been shown to be associated with a primary humoral immunodeficiency, sometimes classified as common variable immunodeficiency (CVID).(4) This defect accounts for less than 1% of CVID patients and appears to be inherited as an autosomal recessive defect.(4) Since these patients have normal numbers of B cells with absent CD19 expression on the cell surface (4), CD20 can be used as a marker to help identify these patients. Genetic CD20 deficiency (autosomal recessive) is also associated with a primary humoral immunodeficiency. In this disease, B cells can be identified by CD19 expression.(5) Similarly, patients receiving anti-CD19 monoclonal antibody therapeutics, such as inebilizumab (6) may show loss of CD19 staining as well. A contrasting situation exists for patients with genetic defects in CD20 (5) or receiving rituximab, ofatumumab, and other anti-CD20 monoclonal antibodies that are used to treat certain cancers, autoimmune diseases, or for B-cell depletion to prevent humoral rejection in positive crossmatch kidney transplantation. These agents block available CD20-binding sites and, therefore, the antibody used for this flow cytometric assay cannot recognize the CD20 molecule on B cells. The concomitant use of the CD19 marker provides information on the extent of B-cell depletion when using this particular treatment strategy. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have

demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day.(6) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(7-9) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(7) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening(10), and during summer compared to winter.(11) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Evaluation of patients with a suspected CD19 deficiency (humoral immunodeficiency) Confirming complete absence of B cells in suspected primary humoral immunodeficiencies using both CD19 and CD20 markers Assessing therapeutic B-cell depletion quantitatively (absolute counts of cells/mcL) in any clinical context, including malignancies, autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and membranous glomerulonephritis among others, and treatment or prevention of acute humoral rejection in positive crossmatch renal transplant recipients This test is not useful for assessing whether B cells express the target molecule (CD20) in the context of initiating therapeutic monoclonal anti-CD20 antibody therapy (rituximab, ofatumumab, and tositumomab) for any of the hematological malignancies, or in other clinical contexts, such as autoimmunity.

Interpretation: The presence of CD20+ B cells with corresponding absence of CD19 staining in individuals not receiving anti-CD20 monoclonal antibody treatment or with clinical features of variable primary humoral immunodeficiency may suggest an underlying CD19 deficiency which should be further evaluated. Absence of both CD20 and CD19 markers on B cells in blood from individuals not on anti-CD20 monoclonal antibody treatment is consistent with complete mature and immature peripheral B-cell depletion, which may be due to an underlying primary immunodeficiency. Patients receiving B-cell depleting therapy with anti-CD20 antibodies can show unusual populations of B cells on reconstitution that express either CD19 or CD20 due to a phenomenon known as trogocytosis.

Reference Values:

%CD19 B Cells
> or =19 years: 4.6-22.1%

CD19 Absolute
> or =19 years: 56.6-417.4 cells/mcL

%CD20 B Cells
> or =19 years: 5.0-22.3%

CD20 Absolute
> or =19 years: 74.4-441.1 cells/mcL

CD45 Absolute
18-55 years: 0.99-3.15 thou/mcL
>55 years: 1.00-3.33 thou/mcL

Clinical References: 1. Nadler LM, Ritz J, Hardy R, Pesando JM, Schlossman SF, Stashenko P. A unique cell-surface antigen identifying lymphoid malignancies of B-cell origin. J Clin Invest. 1981;67(1):134 2. Robillard N, Avet-Loiseau H, Garand R, et al. CD20 is associated with a small mature plasma cell morphology and t(11;14) in multiple myeloma. Blood. 2003;102(3):1070-1071 3. Pescovitz MD. Rituximab, an anti-CD20 monoclonal antibody: history and mechanism of action. Am J Transplant. 2006;6(5 Pt 1):859-866 4. van Zelm MC, Reisli I, van der Burg M, et al. An antibody-deficiency syndrome due to mutations in the CD19 gene. N Engl J Med. 2006;354(18):1901-1912 5.

Kuijpers TW, Bende RJ, Baars PA, et al. CD20 deficiency in humans results in impaired T cell-independent antibody responses. J Clin Invest. 2010;120(1):214-222. doi:10.1172/JCI40231 6.Carmichael KF, Abayomi A. Analysis of diurnal variation of lymphocyte subsets in healthy subjects and its implication in HIV monitoring and treatment. 15th International Conference on AIDS, Bangkok, Thailand, 2004, Abstract B11052 7. Dimitrov S, Benedict C, Heutling D, Westermann J, Born J, Lange T. Cortisol and epinephrine control opposing circadian rhythms in T-cell subsets. Blood. 2009;113(21):5134-5143 8. Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating antigen presenting cells regulated by sleep. Sleep. 2007;30(4):401-411 9. Kronfol Z, Nair M, Zhang Q, Hill EE, Brown MB. Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Psychosom Med. 1997;59(1):42-50 10. Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS. Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J Acquir Immune Defic Syndr (1988). 1990;3(2):144-151 11. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994;34(6):512-516 12. Engel ER, Walter JE. Rituximab and eculizumab when treating nonmalignant hematologic disorders: infection risk, immunization recommendations, and antimicrobial prophylaxis needs. Hematology Am Soc Hematol Educ Program. 2020;2020(1):312-318. doi:10.1182/hematology.2020000171 13. Cree BAC, Kim HJ, Weinshenker BG, et al. Safety and efficacy of inebilizumab for the treatment of neuromyelitis optica spectrum disorder: end-of-study results from the open-label period of the N-MOmentum trial Lancet Neurol. 2024;23(6):588-602. doi:10.1016/S1474-4422(24)00077-2

CD200
619517

CD200 (OX2) Immunostain, Technical Component Only

Clinical Information: CD200 (OX2) is a type I immunoglobulin superfamily membrane glycoprotein that exhibits membranous and cytoplasmic staining within multiple cell types (B cells, subset of T cells, dendritic cells, endothelial cells and in the peripheral/central nervous system). CD200 (OX2) is a diagnostic marker to distinguish small lymphocytic lymphoma versus mantle cell lymphoma; hairy cell leukemia versus splenic marginal zone lymphoma and primary mediastinal large B-cell lymphoma versus large B-cell lymphoma not otherwise specified.

Useful For: Identifying the presence of CD200 (OX2) protein within chronic lymphocytic leukemia, small lymphocytic lymphoma, hairy cell leukemia, and primary mediastinal large B-cell lymphoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Pillai V, Pozdnyakova O, Charest K, et al. CD200 flow cytometric assessment and semiquantitative immunohistochemical staining distinguishes hairy cell leukemia from hairy cell leukemia-variant and other B-cell lymphoproliferative disorders. Am J Clin Pathol. 2013;140:536-543 2. Dorfman DM, Shahsafaei A, and Alonso MA. Utility of CD200 immunostaining in the diagnosis of primary mediastinal large B cell lymphoma: comparison with MAL, CD23, and other markers. Mod Pathol. 2012;25:1637-1643 3. Dorfman, DM and Shahsafaei A. CD200 (OX-2 membrane glycoprotein) expression in B cell-derived neoplasms. Am J Clin Pathol. 2010;134:726-733 4. Palumbo GA, Parrinello N, Fargione G, et. Al. CD200 expression may help in differential diagnosis between mantle cell lymphoma and B-cell chronic lymphocytic leukemia. Leuk Res. 2009;33:1212-1216

CD21
70380

CD21 Immunostain, Technical Component Only

Clinical Information: CD21 strongly stains the cytoplasm and membranes of the follicular dendritic cells and the membranes of a subset of the mantle zone lymphocytes. Follicular dendritic cells form a basket-weave meshwork in the germinal centers of lymphoid follicles, where they present antigens to B cells. Diagnostically, CD21 may be useful to support a diagnosis of follicular dendritic cell sarcoma, or to confirm the presence of lymphoid follicles.

Useful For: Identification of follicular dendritic cells and a subset of mantle zone lymphocytes

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Fujihara M. Study of CD21-positive FDC-like structures in MALT lymphoma: Does it provide helpful information for histopathological diagnosis? Pathol Int. 2010;60(9):642-643 2. Kurshumliu F, Sadiku-Zehri F, Qerimi A, et al. Divergent immunohistochemical expression of CD21 and CD23 by follicular dendritic cells with increasing grade of follicular lymphoma. World J Surg Oncol. 2019;17(1):115. doi: 10.1186/s12957-019-1659-8 3. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD22I
70381

CD22 Immunostain, Technical Component Only

Clinical Information: CD22 is expressed on B lymphocytes. It can be used as an alternative B-cell marker to CD20 or CD79a. Diagnostically, CD22 is useful to confirm B-cell lineage in malignant lymphomas.

Useful For: Determining B-cell lineage

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Kreitman RJ, Arons E. Update on hairy cell leukemia. Clin Adv Hematol Oncol. 2018;16(3):205-215 2. Pop LM, Barman S, Shao C, et al. A reevaluation of CD22 expression in human lung cancer. Cancer Res. 2014;74(1):263-271. doi:10.1158/0008-5472.CAN-13-1436 3. Remon J, Abedallaa N, Taranchon-Clermont E, et al. CD52, CD22, CD26, EG5 and IGF-1R expression in thymic malignancies. Lung Cancer. 2017;108:168-172. doi:10.1016/j.lungcan.2017.03.019 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD23
70382

CD23 Immunostain, Technical Component Only

Clinical Information: CD23 (cluster of differentiation 23) strongly stains the cytoplasm and membranes of follicular dendritic cells and the membranes of a subset of follicular mantle zone B-lymphocytes. Typically, B-cell small lymphocytic lymphoma/chronic lymphocytic leukemias are CD5 positive and CD23 positive, while mantle cell lymphoma is CD5 positive and CD23 negative.

Antibodies to CD23 are diagnostically useful in the classification of low-grade B-cell lymphomas.

Useful For: Identification of follicular dendritic cells Classification of low-grade B-cell lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. van den Brand M, van Krieken JH. Small cell B-cell lymphoma. Diagn Histopathol. 2015;21(10):383-390 2. Zhang XM, Aguilera N. New immunohistochemistry for B-cell lymphoma and Hodgkin lymphoma. Arch Pathol Lab Med. 2014;138(12):1666-1672 3. Gualco G, Natkunam Y, Bacchi CE. The spectrum of B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma: a description of 10 cases. Mod Pathol. 2012;25(5):661-674 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD25
70383

CD25 Immunostain, Technical Component Only

Clinical Information: CD25 (cluster of differentiation 25) is the receptor for IL2 and is expressed on activated T cells, B cells, and macrophages. It will stain only scattered cells in normal tonsil. CD25 is expressed in certain types of B-cell lymphoma (hairy cell leukemia) and T-cell lymphoma (adult T-cell lymphoma/leukemia [ATLL]). An anti-CD25 therapy can be used in patients who have lymphomas that express CD25.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Kageyama Y, Miwa H, Arakawa R, et al. Expression of CD25 fluctuates in the leukemia-initiating cell population of CD25-positive AML. PLoS One. 2018;13(12):e0209295. doi:10.1371/journal.pone.0209295 2. deLeeuw RJ, Kroeger DR, Kost SE, Chang PP, Webb JR, Nelson BH. CD25 identifies a subset of CD4+FoxP3- TIL that are exhausted yet prognostically favorable in human ovarian cancer. Cancer Immunol Res. 2015;3(3):245-253. doi:10.1158/2326-6066.CIR-14-0146 3. Zhang W, Pan Y, Gou P, et al. Effect of xanthohumol on Th1/Th2 balance in a breast cancer mouse model. Oncol Rep. 2018;39(1):280-288. doi:10.3892/or.2017.6094 4. Liu Y, Zhang H, Wang Z, Wu P, Gong W. 5-Hydroxytryptamine1a receptors on tumour cells induce immune evasion in lung adenocarcinoma patients with depression via autophagy/pSTAT3. Eur J Cancer. 2019;114:8-24. doi:10.1016/j.ejca.2019.03.017 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD273
601986

CD273 (PD-L2) Immunostain, Technical Component Only

Clinical Information: CD273, also known as programmed cell death 1-ligand 2 (PD-L2) regulates T-cell activation in addition to immune responses and is a member of the B7 family of cell surface ligands. CD273 (PD-L2) is useful in the distinction of primary mediastinal large B cell lymphoma from diffuse large B cell lymphoma.

Useful For: Differentiation of primary mediastinal large B-cell lymphoma from diffuse large B cell-lymphoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chong LC, Twa DDW, Mottok A, et al. Comprehensive characterization of programmed death ligand structural rearrangements in B-cell non-Hodgkin lymphomas. Blood. 2016;128(9):1206-1213 2. Shin S, Jeon YK, Kim P, et al. Clinicopathologic analysis of PD-L1 and PD-L2 expression in renal cell carcinoma: association with oncogenic proteins status. Ann Surg Oncol. 2016;23:694-702 3. Shi M, Roemer MGM, Chapuy B, et al. Expression of programmed cell death 1 ligand 2 (PD-L2) is a distinguishing feature of primary mediastinal (thymic) large B-cell lymphoma and associated with PDCD1LG2 copy gain. Am J Surg Pathol. 2014;38(12):1715-1723 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD279
70417

CD279 (PD-1) Immunostain, Technical Component Only

Clinical Information: CD279 (cluster of differentiation 279 or programmed cell death 1: [PD-1]) is an immunoregulatory receptor highly expressed by follicular T helper cells. Its expression has also been shown in the neoplastic counterpart of this T-cell subset, angioimmunoblastic T-cell lymphoma. This molecule interacts with programmed cell death ligand 1 (PD-L1), also known as B7 homolog 1 (B7H1), expressed on follicular dendritic cells and other cell types, which serves to attenuate T-cell activation. In the appropriate histologic context, a background rich in CD279-positive T cells can support a diagnosis of nodular lymphocyte-predominant Hodgkin lymphoma.

Useful For: Identification of follicular T helper cells Phenotyping of angioimmunoblastic T-cell lymphoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Wada DA, Wilcox RA, Harrington SM, Kwon ED, Ansell SM, Comfere NI. Programmed death 1 is expressed in cutaneous infiltrates of mycosis fungoides and Sezary syndrome. Am J Hematol. 2011;86:325-327 doi: 10.1002/ajh.21960 2. Steele KE, Brown C. Multiplex immunohistochemistry for image analysis of tertiary lymphoid structures in cancer. Methods Mol Biol. 2018;1845:87-98 doi: 10.1007/978-1-4939-8709-2_6 3. Cogbill CH, Swerdlow SH, Gibson SE. Utility of CD279/PD-1 immunohistochemistry in the evaluation of benign and neoplastic T-cell-rich bone marrow infiltrates. Am J Clin Pathol. 2014;142(1):88-98 doi: 10.1309/AJCPWF77VOGNOVZU 4. Cetinozman F, Jansen PM, Willemze R. Expression of programmed death-1 in primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma, cutaneous pseudo-T-cell lymphoma,

and other types of cutaneous T-cell lymphoma. Am J Surg Pathol. 2012;36(1):109-116 doi:10.1097/PAS.0b013e318230df87 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD3I
70391

CD3 Immunostain, Technical Component Only

Clinical Information: CD3 (cluster of differentiation 3) is part of the T-cell antigen receptor complex found on the surface of T lymphocytes. In paraffin sections, antibodies to CD3 will also react with a subset of natural killer cells that express the cytoplasmic epsilon chain of CD3. In normal tonsil tissue, T cells predominate in the interfollicular regions. Diagnostically, antibodies to CD3 are useful in demonstrating T-cell lineage of malignant lymphomas.

Useful For: Demonstrating T-cell lineage

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Cooper R, Papworth NJ, Harris C, et al. Counting intraepithelial lymphocytes: A comparison between routine staining and CD3 immunohistochemistry. Int J Surg Pathol. 2020;28(4):367-370. doi:10.1177/1066896919894644 2. Toki MI, Merritt CR, Wong PF, et al. High-plex predictive marker discovery for melanoma immunotherapy-treated patients using digital spatial profiling. Clin Cancer Res. 2019;25(18):5503-5512. doi:10.1158/1078-0432.CCR-19-0104 3. Moradi-Kalbolandi S, Sharifi-K A, Darvishi B, et al. Evaluation the potential of recombinant anti-CD3 nanobody on immunomodulatory function. Mol Immunol. 2020;118:174-181. doi:10.1016/j.molimm.2019.12.017 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD30
70385

CD30 Immunostain, Technical Component Only

Clinical Information: CD30 (cluster of differentiation 30) is a member of the tumor necrosis factor receptor superfamily. Expression of CD30 can also be seen in embryonal carcinomas, malignant melanomas, mesenchymal tumors, and activated T and B lymphocytes and plasma cells. Reed-Sternberg cells of classic Hodgkin lymphoma, as well as the neoplastic cells of anaplastic large cell lymphoma, express CD30.

Useful For: Identification of CD30 expression in a variety of neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If an interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Goyal A, Patel S, Goyal K, Morgan EA, Foreman RK. Variable loss of

CD30 expression by immunohistochemistry in recurrent cutaneous CD30+ lymphoid neoplasms treated with brentuximab vedotin. J Cutan Pathol. 2019;46(11):823-829. doi:10.1111/cup.13545 2. Bossard C, Dobay MP, Parrens M, et al. Immunohistochemistry as a valuable tool to assess CD30 expression in peripheral T-cell lymphomas: high correlation with mRNA levels. Blood. 2014;124(19):2983-2986. doi:10.1182/blood-2014-07-584953 3. Sabattini E, Pizzi M, Tabanelli V, et al. CD30 expression in peripheral T-cell lymphomas. Haematologica. 2013;98(8):e81-e82 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD303
607891

CD303 (BDCA-2) Immunostain, Technical Component Only

Clinical Information: CD303 (BDCA-2) is a highly specific marker for normal and neoplastic plasmacytoid dendritic cells and may be useful as a specific marker for the diagnosis of blastic plasmacytoid dendritic cell neoplasm. CD303 (BDCA-2) is expressed in the cytoplasm/membrane of plasmacytoid dendritic cells.

Useful For: Diagnosis of blastic plasmacytoid dendritic cell neoplasm

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

CD31
70386

CD31 Immunostain, Technical Component Only

Clinical Information: CD31 (cluster of differentiation 31) is expressed on endothelial cells, showing some membrane and occasional cytoplasmic staining. It is not expressed on discontinuous endothelium (eg, splenic red pulp). It is also expressed on megakaryocytes, histiocytes, plasma cells, and T-cell subsets. Tonsil sections will exhibit endothelial positivity in vessels primarily located in connective tissue areas around follicles and near the epithelial borders. Diagnostically, CD31 expression can confirm a diagnosis of angiosarcoma, a neoplasm of endothelial cells.

Useful For: Marker of endothelial cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Patel SD, Peterson A, Bartczak A, et al. Primary cardiac angiosarcoma - a review. Med Sci Monit. 2014;20:103-109. doi:10.12659/MSM.889875 2. Sullivan HC, Edgar MA, Cohen C, Kovach CK, Hookim K, Reid MD. The utility of ERG, CD31 and CD34 in the cytological diagnosis of angiosarcoma: an analysis of 25 cases. J Clin Pathol. 2014;68(1):44-50. doi:10.1136/jclinpath-2014-202629 3. Rao P, Lahat G, Arnold C, et al. Angiosarcoma: a tissue microarray study with diagnostic implications. Am J Dermatopathol. 2013;35(4):432-437. doi:10.1097/DAD.0b013e318271295a 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An

introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD33
70387

CD33 Immunostain, Technical Component Only

Clinical Information: CD33 (cluster of differentiation 33) is a transmembrane protein that is a member of the sialic acid-binding immunoglobulin-like lactic (Siglec) family. The exact function of CD33 is not known, but it may be involved in cell-to-cell adhesion. It is not expressed on hematopoietic stem cells but is expressed on maturing myelomonocytic cells. As granulocytes mature, there is progressive down regulation of CD33. Monocytes and macrophage/histiocytic cells maintain strong expression of CD33. In normal bone marrow, weak to moderate CD33 staining is seen on granulocytic and monocytic precursors, with strong staining in scattered mast cells. CD33 staining is useful for diagnosis of myeloid neoplasms and classification of acute leukemias. A therapeutic antibody targeting CD33 (gemtuzumab/Myelotarg) is available.

Useful For: Classification of myeloid neoplasms and acute leukemias

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Soeno T, Katoh H, Ishii S, et al. CD33+ immature myeloid cells critically predict recurrence in advanced gastric cancer. J Surg Res. 2020;245:552-563 2. Wadai GM, Hussain TA, Hussain MJ. Detect the level of expression of cluster differentiation (CD) marker (CD13 and CD33) in acute myeloid leukemia Iraqi patients. Al-Kufa Univers J Biol. 2016;Special Second International Scientific Conference for the Life Sciences:113-116 3. Kenderian SS, Ruella M, Shestova O, et al. CD33-specific chimeric antigen receptor T cells exhibit potent preclinical activity against human acute myeloid leukemia. Leukemia. 2015;29(8):1637-1647 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD34I
70388

CD34 Immunostain, Technical Component Only

Clinical Information: CD34 (cluster of differentiation 34) is 115 kDa membrane-associated antigen found on human hematopoietic progenitor cells and vascular endothelial cells. In normal tonsil sections, antibodies to CD34 strongly stain vascular endothelial cells. CD34 is used as a marker of immaturity in the setting of acute myeloid leukemia or B-cell lymphoblastic leukemia. It is also useful in the diagnosis of gastrointestinal stromal tumors, solitary fibrous tumors, and angiosarcomas.

Useful For: A marker of immaturity in the setting of acute myeloid leukemia or B-cell lymphoblastic leukemia Diagnosis of gastrointestinal stromal tumors, solitary fibrous tumors, and angiosarcomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Lopez-Nunez O, Surrey LF, Alaggio R, Fritchie KJ, John I. Novel PPP1CB-ALK fusion in spindle cell tumor defined by S100 and CD34 coexpression and distinctive stromal and perivascular hyalinization. Genes Chromosomes Cancer. 2020;59(8):495-499. doi:10.1002/gcc.22844 2. Matoso A, Epstein JI. Epithelioid angiosarcoma of the bladder: A series of 9 cases. Am J Surg Pathol. 2015;39(10):1377-1382. doi:10.1097/PAS.0000000000000444 3. Stanek J, Abdaljaleel M. CD34 immunostain increases the sensitivity of placental diagnosis of fetal vascular malperfusion in stillbirth. Placenta. 2019;77:30-38. doi:10.1016/j.placenta.2019.02.001 4. Sardina LA, Piliang M, Bergfeld WF. Diagnostic value of CD34 and calretinin immunostaining in the diagnosis of proliferating tricholemmal tumor and trichoblastoma. Int J Dermatol. 2020;59(1):99-102. doi:10.1111/ijd.14461 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD35
70389

CD35 Immunostain, Technical Component Only

Clinical Information: CD35 (cluster of differentiation 35) stains the membrane and cytoplasm of follicular dendritic cells and granulocytes. Follicular dendritic cells form a basketweave meshwork in the germinal centers of lymphoid follicles, where they present antigens to B cells. CD35 is useful in the diagnosis of follicular dendritic-cell sarcoma.

Useful For: Identification of follicular dendritic cells and granulocytes

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Durham BH. Molecular characterization of the histiocytoses: Neoplasia of dendritic cells and macrophages. Semin Cell Dev Biol. 2019;86:62-76. doi:10.1016/j.semcdb.2018.03.002 2. Duan GJ, Wu YL, Sun H, Lang L, Chen ZW, Yan XC. Primary follicular dendritic cell sarcoma of the urinary bladder: the first case report and potential diagnostic pitfalls. Diagn Pathol. 2017;12(1):35. doi:10.1186/s13000-017-0625-4 3. Liu H, Xiang C, Wu M, Hu S. Follicular dendritic cell sarcoma with co-expression of CD4 and CD30 mimics anaplastic large cell lymphoma. Front Oncol. 2020;10:876. doi:10.3389/fonc.2020.00876 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD38
70390

CD38 Immunostain, Technical Component Only

Clinical Information: CD38 (cluster of differentiation 38) is expressed in a variety of cell types, including hematopoietic precursors, plasma cells, germinal center B cells (weakly), a subset of T and NK cells, erythrocytes, platelets, prostatic epithelium, and smooth and striated muscle cells. Its expression maybe useful in the diagnosis of lymphoproliferative and plasma cell proliferative disorders.

TCD4
84348

CD4 Count for Immune Monitoring, Blood

Clinical Information: Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer cells. There are various subsets of each of these

individual populations with specific cell-surface markers and function. This assay provides absolute (cells/mcL) and relative (%) quantitation for total T cells and CD4+ and CD8+ T-cell subsets, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of 1 or more cell surface markers. The CD3 antigen is a pan-T-cell marker, and T cells can be further divided into 2 broad categories based on the expression of CD4 or CD8 coreceptors. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells increase between 8:30 a.m. and noon with no change between noon and afternoon.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening(5) and during summer compared to winter.(6) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of CD3, CD4, and CD8 T cells have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T lymphocytes in patients infected with HIV is associated with increased infections and complications. The US Public Health Service has recommended that all patients who are HIV-positive be tested every 3 to 6 months for the level of CD4 T lymphocytes. Basic T-cell subset quantitation is also very useful in the evaluation of patients of all ages with primary cellular immunodeficiencies, including follow-up for newborn screening for severe combined immunodeficiency and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, or any other relevant clinical condition where immunomodulatory treatment is used, and the T-cell compartment is specifically affected. It is also helpful as a preliminary screening assay for gross quantitative anomalies in T cells, whether related to malignancies or infection.

Useful For: Serial monitoring of CD4 T cell count in patients who are HIV-positive Follow-up and diagnostic evaluation of primary cellular immunodeficiencies, including severe combined immunodeficiency T-cell immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of T-cell immune reconstitution post hematopoietic cell transplantation Early screening of gross quantitative anomalies in T cells in infection or malignancies This assay should not be used for diagnosing T-lymphocytic malignancies or evaluation of T-cell lymphocytosis of unknown etiology.

Interpretation: HIV treatment guidelines from the US Department of Health and Human Services and the International Antiviral Society USA Panel recommend antiviral treatment in all patients with HIV infection, regardless of CD4 T-cell count.(7,8) Additionally, antibiotic prophylaxis for Pneumocystis jiroveci infection is recommended for patients with CD4 counts below 200 cells/mcL. For other opportunistic infections, see the recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.(9)

Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References: 1. Carmichael KF, Abayomi A. Analysis of diurnal variation of lymphocyte subsets in healthy subjects and its implication in HIV monitoring and treatment. 15th Intl Conference on AIDS, Bangkok, Thailand, 2004, Abstract B11052 2. Dimitrov S, Benedict C, Heutling D, Westermann J, Born J, Lange T. Cortisol and epinephrine control opposing circadian rhythms in T-cell subsets. Blood. 2009;113(21):5134-5143 3. Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating antigen presenting cells regulated by sleep. Sleep. 2007;30(4):401-411 4. Kronfol Z, Nair M, Zhang Q, Hill EE, Brown MB. Circadian immune measures in healthy volunteers: relationship to

hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Psychosom Med. 1997;59(1):42-50 5. Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS. Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J Acquir Immune Defic Syndr. 1990;3(2):144-151 6. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994;34(6):512-516 7. Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services; Updated January 20, 2022. Accessed April 4, 2022. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/guidelines-adult-adolescent-arv.pdf 8. Thompson MA, Horberg MA, Agwu AL, et al. Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. [published correction appears in Clin Infect Dis. 2022 May 30;74(10):1893-1898. doi: 10.1093/cid/ciab801] [published correction appears in Clin Infect Dis. 2022 Nov 30;75(11):2052. doi: 10.1093/cid/ciac474]. Clin Infect Dis. 2021;73(11):e3572-e3605 9. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Department of Health and Human Services; Updated February 17, 2022. Accessed April 4, 2022. Available at https://clinicalinfo.hiv.gov/en/guidelines

CD4NY
28334

CD4 Count for Monitoring, New York, Blood

Clinical Information: Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/mcL) and relative (%) quantitation for total T cells and CD4+ and CD8+ T-cell subsets, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of 1 or more cell surface markers. The CD3 antigen is a pan T-cell marker, and T cells can be further divided into 2 broad categories, based on the expression of CD4 or CD8 coreceptors. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells increase between 8:30 a.m. and noon with no change between noon and afternoon.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening(5) and during summer compared to winter.(6) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of CD3, CD4, and CD8 T cells have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T lymphocytes in patients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all patients who are HIV-positive be tested every 3 to 6 months for the level of CD4 T lymphocytes. Basic T-cell subset quantitation is also very useful in the evaluation of patients with primary cellular immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, or any other relevant clinical condition where immunomodulatory treatment is used, and the T-cell compartment is specifically affected. It is also helpful as a preliminary screening assay for gross quantitative anomalies in T cells, whether related to malignancies or infection.

Useful For: Only orderable by New York clients Serial monitoring of CD4 T-cell count in patients who are HIV-positive Follow-up and diagnostic evaluation of primary cellular immunodeficiencies, including severe combined immunodeficiency T-cell immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of T-cell immune reconstitution post hematopoietic cell transplantation Early screening of gross quantitative anomalies in T cells in infection or malignancies This assay should not be used for diagnosing T-lymphocytic malignancies or evaluation of T-cell lymphocytosis of unknown etiology.

Interpretation: HIV treatment guidelines from the US Department of Health and Human Services and the International Antiviral Society-USA Panel recommend antiviral treatment in all patients with HIV infection, regardless of CD4 T-cell count.(7,8) Additionally, antibiotic prophylaxis for Pneumocystis jiroveci infection is recommended for patients with a CD4 count below 200 cells/mcL. For other opportunistic infections, see the recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.(9)

Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References: 1. Carmichael KF, Abayomi A. Analysis of diurnal variation of lymphocyte subsets in healthy subjects and its implication in HIV monitoring and treatment. 15th Intl Conference on AIDS, Bangkok, Thailand, 2004, Abstract # B11052. Afr J Med Med Sci. 2006;35(1):53-57 2. Dimitrov S, Benedict C, Heutling D, et al Cortisol and epinephrine control opposing circadian rhythms in T-cell subsets. Blood. 2009;113(21):5134-5143 3. Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating antigen presenting cells regulated by sleep. Sleep. 2007;30(4):401-411 4. Kronfol Z, Nair M, Zhang Q, Hill EE, Brown MB.: Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Psychosom Med.1997;59(1):42-50 5. Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS.Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J AIDS. 1990;(3):144-151 6. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion. 199;34(6):512-516 7. Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services; Updated February 27, 2024. Accessed August 20, 2024. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf 8. Thompson MA, Horberg MA, Agwu AL, et al. Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. [published correction appears in Clin Infect Dis. 2022 May 30;74(10):1893-1898. doi: 10.1093/cid/ciab801] [published correction appears in Clin Infect Dis. 2022 Nov 30;75(11):2052. doi: 10.1093/cid/ciac474]. Clin Infect Dis. 2021;73(11):e3572-e3605 9. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Department of Health and Human Services; Updated August 15, 2024. Accessed August 19, 2024. Available at https://clinicalinfo.hiv.gov/en/guidelines

CD4I
70393

CD4 Immunostain, Technical Component Only

Clinical Information: CD4 (cluster of differentiation 4) is expressed on a subset of T cells (T helper cells), histiocytes, and monocytes. In normal tonsil, the T cells predominate in interfollicular regions. This immunostain is also used to support T cell or histiocytic lineage in hematolymphoid neoplasms.

Useful For: Identification of T helper cells, histiocytes, and monocytes

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Kristensen LK, Frohlich C, Christensen C, et al. CD4(+) and CD8a (+) PET imaging predicts response to novel PD-1 checkpoint inhibitor: studies of Sym021 in syngeneic mouse cancer models. Theranostics. 2019;9(26):8221-8238. doi:10.7150/thno.37513 2. Prat A, Navarro A, Pare L, et al. Immune-related gene expression profiling after PD-1 blockade in non-small cell lung carcinoma, head and neck squamous cell carcinoma, and melanoma. Cancer Res. 2017;77(13):3540-3550. doi:10.1158/0008-5472.CAN-16-3556 3. Sharma A, Subudhi SK, Blando J, et al. Anti-CTLA-4 immunotherapy does not deplete FOXP3(+) regulatory T cells (Tregs) in human cancers. Clin Cancer Res. 2019;25(4):1233-1238. doi:10.1158/1078-0432.CCR-18-0762 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD4RT
89504

CD4 T-Cell Recent Thymic Emigrants, Blood

Clinical Information: Naive T cells are generated in the thymus and exported to peripheral blood to form the peripheral T-cell repertoire. There is a decrease in naive T cells derived from the thymus with age due to age-related decline in thymic output. Recent thymic emigrants (RTE) typically refers to those populations of naive T cells that have not diluted their TREC (T-cell receptor excision circles) copies by homeostatic or antigen-driven cell division. Naive T cells can be long-lived in the periphery and postpuberty, and in adults, peripheral T-cell homeostasis is maintained by a balance of thymic output and peripheral T-cell expansion, this proportion changes with age. In infants and prepubertal children, the T-cell repertoire is largely maintained by thymic-derived naive T cells. RTE express TREC indicative of naive T cells derived from the thymus.(1) In the CD4 T-cell compartment, it has been shown that naive CD45RA+ T cells coexpressing CD31 had a higher frequency of TREC compared to T cells lacking CD31.(2) The higher proportion of TREC+ naive T cells indicate a more recent thymic ontogeny since TREC can be diluted by cell division (since they are extrachromosomal). It has been shown that CD31+CD4+ T cells continue to possess a relatively higher proportion of TREC despite an age-related 10-fold reduction after the neonatal period.(3) CD4 RTE (CD31+CD4+CD45RA+) have longer telomeres and higher telomerase activity, which, along with the increased frequency of TREC positivity, suggests a population of T cells with low replicative history.(3) The same study has also shown that CD31+ CD4+ T cells are an appropriate cell population to evaluate thymic reconstitution in lymphopenic children post-hematopoietic cell transplant.(3) A Mayo study (unpublished) shows that the CD31 marker correlates with TREC-enriched T cells across the spectrum of age and correlates with thymic recovery in adults after autologous hematopoietic cell transplantation.(4) CD31+ CD4 RTE have also been used to evaluate T-cell homeostatic anomalies in patients with relapsing-remitting multiple sclerosis.(5) For patients with DiGeorge syndrome (DGS)-a cellular immunodeficiency associated with other congenital problems including cardiac defects, facial dysmorphism, hypoparathyroidism, and secondary hypocalcemia, and chromosome 22q11.2 deletion (in a significant proportion of patients)-measurement of thymic function provides valuable information on the functional phenotype, ie, complete DGS (associated with thymic aplasia in a minority of patients) or partial DGS (generally well-preserved thymic function seen the in the majority of patients). Thymus transplants have been performed in patients with complete DGS but are typically not required in partial DGS. There can be change in peripheral T-cell counts in DGS patients with age.(6)

Useful For: Evaluating thymic reconstitution in patients following hematopoietic cell transplantation,

chemotherapy, immunomodulatory therapy, and immunosuppression Evaluating thymic recovery in patients who are HIV-positive and on highly active antiretroviral therapy Evaluating thymic output in patients with DiGeorge syndrome or other cellular immunodeficiencies Assessing the naive T-cell compartment in a variety of immunological contexts (autoimmunity, cancer, immunodeficiency, and transplantation) Identification of thymic remnants post-thymectomy for malignant thymoma or as an indicator of relapse of disease (malignant thymoma) or other contexts of thymectomy

Interpretation: The absence or reduction of CD31+CD4 recent thymic emigrants (RTE) generally correlates with loss or reduced thymic output and changes in the naive CD4 T-cell compartment, especially in infancy and prepubertal children. The CD4RTE result must be interpreted more cautiously in adults due to age-related decline in thymic function and correlated with total CD4 T cell count and other relevant immunological data. CD4 RTE measured along with TREC (TRECS / T-Cell Receptor Excision Circles Analysis, Blood) provides a comprehensive assessment of thymopoiesis but should not be used in adults over the sixth decade of life as clinically meaningful information on thymic function is limited in the older population due to a physiological decline in thymic activity. To evaluate immune reconstitution or recovery of thymopoiesis post-T-cell depletion due to post-hematopoietic cell transplant, immunotherapy, or other clinical conditions, it is helpful to systematically (serially) measure CD4RTE and TREC copies in the appropriate age groups.

Reference Values:

CD4 Absolute
Males
1 month-17 years: 153-1745 cells/mcL
18-70 years: 290-1,175 cells/mcL
Reference values have not been established for patients that are younger than 30 days of age.
Reference values have not been established for patients that are older than 70 years of age.

Females
1 month-17 years: 582-1630 cells/mcL
18-70 years: 457-1,766 cells/mcL
Reference values have not been established for patients that are younger than 30 days of age.
Reference values have not been established for patients that are older than 70 years of age.

CD4 RTE %
Males
1 month-17 years: 19.4-60.9%
18-25 years: 6.4-51.0%
26-55 years: 6.4-41.7%
> or =56 years: 6.4-27.7%
Reference values have not been established for patients that are younger than 30 days of age.
Reference values have not been established for patients that are older than 70 years of age.

Females
1 month-17 years: 25.8-68.0%
18-25 years: 6.4-51.0%
26-55 years: 6.4-41.7%
> or =56 years: 6.4-27.7%
Reference values have not been established for patients that are younger than 30 days of age.
Reference values have not been established for patients that are older than 70 years of age.

CD4 RTE Absolute
Males
1 month-17 years: 50.0-926.0 cells/mcL
18-70 years: 42.0-399.0 cells/mcL

Reference values have not been established for patients that are younger than 30 days of age.
Reference values have not been established for patients that are older than 70 years of age.

Females
1 month-17 years: 170.0-1007.0 cells/mcL
18-70 years: 42.0-832.0 cells/mcL
Reference values have not been established for patients that are younger than 30 days of age.
Reference values have not been established for patients that are older than 70 years of age.

Clinical References: 1. Hassan J, Reen DJ. Human recent thymic emigrants-identification, expansion, and survival characteristics. J Immunol. 2001;167(4):1970-1976 2. Kimmig S, Przybylski GK, Schmidt CA, et al. Two subsets of naive T-helper cells with distinct T-cell receptor excision circle content in human adult peripheral blood. J Exp Med. 2002;195(6):789-794 3. Junge S, Kloeckener-Gruissem B, Zufferey R, et al. Correlation between recent thymic emigrants and CD31+ (PECAM-1) CD4 T-cells in normal individuals during aging and in lymphopenic children. Eur J Immunol. 2007;37(11):3270-3280 4. Dong X, Hoeltzle MV, Abraham RS. Evaluation of CD4 and CD8 recent thymic emigrants in healthy adults and children. Unpublished data 2008 5. Duszczyszyn DA, Beck JD, Antel J, et al. Altered naiveCD4 and CD8 T-cell homeostasis in patients with relapsing-remitting multiple sclerosis: thymic versus peripheral (non-thymic) mechanisms. Clin Exp Immunol. 2006;143(2):305-313 6. Nain E, Kiykim A, Ogulur I, et al. Immune system defects in DiGeorge syndrome and association with clinical course. Scand J Immunol. 2019;90(5):e12809. doi:10.1111/sji.12809

CD43
70392

CD43 Immunostain, Technical Component Only

Clinical Information: CD43 (cluster of differentiation 43) is expressed by T lymphocytes and myeloid cells including granulocytes and precursors, monocytes, macrophages, histiocytes, plasma cells and megakaryocytes. In normal tonsil, CD43 will mainly show staining in T lymphocytes, histiocytes and plasma cells.

Useful For: Identification of T lymphocytes, monocytes, macrophages, granulocytes, plasma cells, and a subset of B lymphocytes

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Zargaran M, Baghaei F, Moghimbeigi A, Baghai F. Explanation for different behavior of peripheral and central giant cell granuloma by CD44 and CD34 immunostaining. J Investig Clin Dent. 2019;10(4):e12451. doi:10.1111/jicd.12451 2. Xiong B, Nie Y, Tang Z, Xue M, Zuo X. Prognostic evaluation of ALIP and CD34 immunostaining in IPSS-R subgroups of myelodysplastic syndromes. Pathology. 2017;49(5):526-533. doi:10.1016/j.pathol.2017.05.001 3. Sardina LA, Piliang M, Bergfeld WF. Diagnostic value of CD34 and calretinin immunostaining in the diagnosis of proliferating tricholemmal tumor and trichoblastoma. Int J Dermatol. 2020;59(1):99-102. doi:10.1111/ijd.14461 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD45I
70348

CD45 Leukocyte Common Antigen (LCA) Immunostain,

Technical Component Only

Clinical Information: CD45 (cluster of differentiation 45) is also called leukocyte common antigen given its shared expression in the vast majority of cells of hematolymphoid lineage. The CD45 antibody used is a cocktail of 2 clones, PD7/26 (detects the CD45RB isoform), and 2B11 (detects a common CD45 protein). CD45 expression is very specific and quite sensitive for cells of hematolymphoid lineage, thus, distinguishing lymphoma/leukemia from other neoplasms. The main exception is classical Hodgkin lymphoma, in which CD45 expression is absent.

Useful For: Aiding in distinguishing lymphoma/leukemia from other neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. D'Cruze L, Dutta R, Rao S, Anuradha R, Varadarajan S, Kuruvilla S. The role of immunohistochemistry in the analysis of the spectrum of small round cell tumours at a tertiary care centre. J Clin Diagn Res. 2013;7(7):1377-1382. doi:10.7860/JCDR/2013/5127.3132 2. O'Malley DP, Auerbach A, Weiss LM. Practical applications in immunohistochemistry: Evaluation of diffuse large B-cell lymphoma and related large B-cell lymphomas. Arch Path Lab Med. 2015;139(9):1094-1107. doi:10.5858/arpa.2014-0451-CP 3. Wang H-Y, Zu Y. Diagnostic algorithm of common mature B-cell lymphomas by immunohistochemistry. Arch Pathol Lab Med. 2017;141(9):1236-1246. doi:10.5858/arpa.2016-0521-RA 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CEE49
65658

CD49d Cell Expression Evaluation, Varies

Clinical Information: Monoclonal antibodies are critical tools for detecting cellular antigens in various hematologic diseases and are used to provide critical prognostic information (CD49d). Monoclonal antibodies are also used as therapeutic agents in a variety of hematologic diseases. For example: -Anti-CD20 (Rituxan): B-cell malignant lymphomas and multiple myeloma -Anti-CD52 (Campath-1H): B-cell chronic lymphocytic leukemia and T-cell disorders This list will undoubtedly expand over time to include other antibodies. It may be necessary to document expression of these markers by the malignant cells prior to initiating the respective monoclonal antibody therapy. Expression of these markers may also be required for follow-up to monitor the impact of treatment on residual normal counterparts (eg, CD20-positive lymphocytes in patients treated with anti-CD20). The distribution of these cellular antigens is well established in normal, reactive, and in various malignant disorders. The laboratory has several years of experience with therapeutic antibody monitoring of Mayo Clinic patients as part of the routine B-cell, T-cell, or acute immunophenotyping panels.

Useful For: Detecting cell-surface antigens on malignant cells that are potential therapeutic antibody targets, specifically CD49d Determining the eligibility of patients for monoclonal antibody therapies Monitoring response to the therapeutic antibody

Interpretation: The immunophenotyping report will summarize the pattern of antigenic expression on malignant cells and, if appropriate, the normal cellular counterparts that correspond to the therapeutic monoclonal antibody target.

Reference Values:

Normal individuals have B lymphocytes, T lymphocytes, or myeloid cells that express the corresponding cell-surface antigens in question.

Clinical References: 1. Salles G, Barrett M, Foa R, et al. Rituximab in B-cell hematologic malignancies: A review of 20 years of clinical experience. Adv Ther. 2017;34(10):2232-2273. doi:10.1007/s12325-017-0612-x. 2. Braun T, von Jan J, Wahnschaffe L, Herling M. Advances and Perspectives in the Treatment of T-PLL. Curr Hematol Malig Rep. 2020;15(2):113-124. doi:10.1007/s11899-020-00566-5. 3. Piccaluga PP, Cascianelli C, Inghirami G. Tyrosine kinases in nodal peripheral T-cell lymphomas. Front Oncol. 2023;13:1099943. Published 2023 Feb 8. doi:10.3389/fonc.2023.10999434. Amhaz G, Bazarbachi A, El-Cheikh J. Immunotherapy in indolent Non-Hodgkin's Lymphoma. Leuk Res Rep. 2022;17:100325. Published 2022 May 18. doi:10.1016/j.lrr.2022.100325 5. Tissino E, Pozzo F, Benedetti D, et al. CD49d promotes disease progression in chronic lymphocytic leukemia: new insights from CD49d bimodal expression. Blood. 2020;135(15):1244-1254. doi:10.1182/blood.2019003179

CD5
70396

CD5 Immunostain, Technical Component Only

Clinical Information: CD5 (cluster of differentiation 5) is expressed normally on all T cells (one of the pan T-cell antigens). It can be aberrantly expressed by B-cell lymphomas (most commonly mantle-cell lymphoma, B-cell small lymphocytic lymphoma). Expression of CD5 is useful to support T-cell lineage in T-cell lymphomas or to help subclassify B-cell lymphomas.

Useful For: Marker of T-cell lineage Phenotyping B-cell lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Selves J, Long-Mira E, Mathieu MC, Rochaix P, Ilie M. Immunohistochemistry for diagnosis of metastatic carcinomas of unknown primary site. Cancer (Basel). 2018;10(4):108. doi:10.3390/cancers10040108 2. Haninger D, Slone S The utility of immunohistochemical staining for CD5 in urothelial carcinoma. American Journal of Clinical Pathology. 2012;138(2):A036 3. Li Y, Hu S, Zuo Z, et al. CD5-positive follicular lymphoma: clinicopathologic correlations and outcome in 88 cases. Mod Pathol. 2015;28(6):787-798 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of imunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CEE52
65659

CD52 Cell Expression Evaluation, Varies

Clinical Information: Monoclonal antibodies are critical tools for detecting cellular antigens in various hematologic diseases and are used to provide critical prognostic information (eg, CD49d). Monoclonal antibodies are also used as therapeutic agents in a variety of hematologic diseases. For example: -Anti-CD20 (Rituxan): B-cell malignant lymphomas and multiple myeloma -Anti-CD52 (Campath-1H): B-cell chronic lymphocytic leukemia and T-cell disorders This list will undoubtedly expand over time to include other antibodies. It may be necessary to document expression of these markers by the malignant cells prior to initiating the respective monoclonal antibody therapy. Expression of these markers may also be required for follow-up to monitor the impact of treatment on residual normal counterparts (eg, CD20-positive lymphocytes in patients treated with anti-CD20). The distribution of these cellular antigens is well established in normal, reactive, and in various malignant

disorders. The laboratory has several years of experience with therapeutic antibody monitoring of Mayo Clinic patients as part of the routine B-cell, T-cell, or acute immunophenotyping panels.

Useful For: Detecting cell-surface antigens on malignant cells that are potential therapeutic antibody targets, specifically CD52 Determining the eligibility of patients for monoclonal antibody therapies Monitoring response to the therapeutic antibody

Interpretation: The immunophenotyping report will summarize the pattern of antigenic expression on malignant cells and, if appropriate, the normal cellular counterparts that correspond to the therapeutic monoclonal antibody target.

Reference Values:
Normal individuals have B lymphocytes, T lymphocytes, or myeloid cells that express the corresponding cell-surface antigens in question.

Clinical References: 1. Salles G, Barrett M, Foa R, et al. Rituximab in B-cell hematologic malignancies: A review of 20 years of clinical experience. Adv Ther. 2017;34(10):2232-2273. doi:10.1007/s12325-017-0612-x 2. Bachy E, Seymour JF, Feugier P, et al. Sustained progression-free survival benefit of rituximab maintenance in patients with follicular lymphoma: Long-term results of the PRIMA study. J Clin Oncol. 2019;37(31):2815-2824. doi:10.1200/JCO.19.01073 3. Cross M, Dearden C. B and T cell prolymphocytic leukaemia. Best Pract Res Clin Haematol. 2019;32(3):217-228. doi:10.1016/j.beha.2019.06.001 4. Braun T, von Jan J, Wahnschaffe L, Herling M. Advances and perspectives in the treatment of T-PLL. Curr Hematol Malig Rep. 2020;15(2):113-124. doi:10.1007/s11899-020-00566-5 5. Strati P, Parikh SA, Chaffee KG, et al. CD49d associates with nodal presentation and subsequent development of lymphadenopathy in patients with chronic lymphocytic leukaemia. Br J Haematol. 2017;178(1):99-105. doi:10.1111/bjh.14647

CD56
70394

CD56 Immunostain, Technical Component Only

Clinical Information: CD56 (cluster of differentiation 56) is an adhesion molecule mediating homophilic and heterophilic adhesion in neurons, natural killer cells, and a small subset of CD4- and CD8-positive T cells. It is expressed in tumors with neuroendocrine differentiation (small cell lung carcinoma and neural-derived tumors) or natural killer cell lineage (subset of lymphomas). In normal small intestine, the ganglion cells in the muscle wall and nerves will show strong staining. Scattered lymphocytes may also be positive.

Useful For: Aiding in the identification of tumors with neuroendocrine differentiation Aiding in the identification of natural killer cell lineage in a subset of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Kerekes D, Visscher DW, Hoskin TL, et al. CD56+ immune cell infiltration and MICA are decreased in breast lobules with fibrocystic changes. Breast Cancer Res Treat. 2018;167(3):649-658. doi:10.1007/s10549-017-4558-0 2. Skaria PE, Ahmed AA, Yin H, Nicol K, Reid KJ, Singh V. Expression of HBME-1 and CD56 in follicular variant of papillary carcinoma in children: An immunohistochemical study and their diagnostic utility. Pathol Res Pract. 2019;215(5):880-884. doi:10.1016/j.prp.2019.01.031 3. Moritz AW, Schlumbrecht MP, Nadji M, Pinto A. Expression of neuroendocrine markers in non-neuroendocrine endometrial carcinomas. Pathology. 2019;51(4):369-374.

doi:10.1016/j.pathol.2019.02.003 4. Alshenawy HA. Utility of immunohistochemical markers in diagnosis of follicular cell derived thyroid lesions. Pathol Oncol Res. 2014;20(4):819-828. doi:10.1007/s12253-014-9760-3 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD57
70395

CD57 Immunostain, Technical Component Only

Clinical Information: CD57 (cluster of differentiation 57) is present in tumors of neuroectodermal origins: small cell lung carcinoma, carcinoid tumors, adenocarcinomas of the prostate. It is also expressed in normal and hyperplastic prostatic epitheliums as well as in natural killer (NK) cells and a subset of T cells.

Useful For: Marker of natural killer cells and a subset of follicular T helper cells Aiding in the identification of tumors of neuroectodermal origin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Fang J, Li X, Ma D, et al. Prognostic significance of tumor infiltrating immune cells in oral squamous cell carcinoma. BMC Cancer. 2017;17(1):375 2. Greenberg SA, Pinkus JL, Amato AA, Kristensen T, Dorfman DM. Association of inclusion body myositis with T cell large granular lymphocytic leukaemia. Brain. 2016;139(Pt 5):1348-1360 3. David JA, Huang JZ. Diagnostic utility of flow cytometry analysis of reactive T cells in nodular lymphocyte-predominant Hodgkin lymphoma. Am J Clin Pathol. 2016;145(1):107-115 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD61
70397

CD61 Immunostain, Technical Component Only

Clinical Information: Cluster of differentiation 61 (CD61) shows cytoplasmic staining of normal and abnormal megakaryocytes and occasional endothelial cells. Antibodies to CD61 are most useful in recognizing micromegakaryocytes, cytologically abnormal megakaryocytes, and megakaryoblasts in cases of acute megakaryoblastic leukemia, myeloproliferative disorders, and myelodysplastic syndromes.

Useful For: Identification of micromegakaryocytes, cytologically abnormal megkaryocytes, and megakaryoblasts

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

CDKPB
603209

CD68 (KP1) Immunostain, Bone Marrow, Technical Component Only

Clinical Information: In normal tissues, CD68 KP-1 stains the cytoplasm of the granulocytes and myeloid progenitors in the bone marrow, monocytes, and macrophages, and osteoclasts. KP-1 reacts against a carbohydrate moiety of CD68. Although CD68 KP-1 is primarily used as a histiocytic marker, it is not specific for histiocytes. It can also be expressed in malignant melanoma, granular cell tumors, peripheral nerve sheath tumors, malignant fibrous histiocytoma, and other mesenchymal neoplasms and rare carcinomas.

Useful For: Aiding in the identification of histocytic and myeloid lineage cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Sanchez-Espiridion B, Martin-Moreno AM, Montalban C, et al: Immunohistochemical markers for tumor associated macrophages and survival in advanced classical Hodgkin's lymphoma. Haematologica. 2012 Jul;97:1080-1084 2. Tan KL, Scott DW, Hong F, et al: Tumor-associated macrophages predict inferior outcomes in classic Hodgkin lymphoma: a correlative study from the E2496 Intergroup trial. Blood. 2012 Oct 18;120(16):3280-3287 3. Mehra N, Schnatiwinkel C, Ergon L, et al: Comparison of multiplexed imaging mass cytometry in FFPE tissue to monoplex immunohistochemistry. Tumor Biology. 2018;78(13):3037

CDKP1
70486

CD68 (KP1) Immunostain, Tissue, Technical Component Only

Clinical Information: In normal tissues, CD68 KP-1 stains the cytoplasm of the granulocytes and myeloid progenitors in the bone marrow, monocytes and macrophages, and osteoclasts. KP-1 reacts against a carbohydrate moiety of CD68. Although CD68 KP-1 is primarily used as a histiocytic marker, it is not specific for histiocytes. It can also be expressed in malignant melanoma, granular cell tumors, peripheral nerve sheath tumors, malignant fibrous histiocytoma, and other mesenchymal neoplasms, and rare carcinomas.

Useful For: Aiding in the identification of histocytic and myeloid lineage cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Sanchez-Espiridion B, Martin-Moreno AM, Montalban C, et al. Immunohistochemical markers for tumor associated macrophages and survival in advanced classical Hodgkin's lymphoma. Haematologica. 2012;97:1080-1088 2. Tan KL, Scott DW, Hong F, et al. Tumor-associated macrophages predict inferior outcomes in classic Hodgkin lymphoma. A correlative study from the E2496 intergroup Trial. Blood. 2012;120(18):3280-3287 3. Mehra N, Schnatiwinkel C, Ergon L, et al. Comparison of multiplexed imaging mass cytometry in FFPE tissue to monoplex immunohistochemistry.

Tumor Biology. 2018;78(13):3037 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PGM1
70536

CD68 (PG-M1) Immunostain, Technical Component Only

Clinical Information: In normal tissues, CD68 (cluster of differentiation) PG-M1 stains monocytes, macrophages and, to a lesser extent, neutrophils in a cytoplasmic granular staining pattern. It has greater specificity for monocytes and macrophages than does KP-1 but its immunohistochemical staining pattern in non-hematolymphoid tumors has not been studied as extensively as CD68 KP-1. Diagnostically, CD68 PG-M1 is usually applied to cases of acute leukemia to demonstrate monocytic differentiation and to cases of hematolymphoid neoplasms that are suspected to represent histiocytic sarcomas.

Useful For: Identification of monocytic differentiation Phenotyping hematolymphoid neoplasms that are suspected to represent histiocytic sarcomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Sanchez-Espiridion B, Martin-Moreno AM, Montalban C, et al. Immunohistochemical markers for tumor associated macrophages and survival in advanced classical Hodgkin's lymphoma. Haematologica. 2012;97:1080-1084 2. Tan KL, Scott DW, Hong F, et al. Tumor-associated macrophages predict inferior outcomes in classic Hodgkin lymphoma. A correlative study from the E2496 intergroup trial. Blood. 2012;120(18):3280-3287 3. Wobser M, Roth S, Reinartz T, Rosenwald A, Goebeler M, Geissinger E. CD68 expression is a discriminative feature of indolent cutaneous CD8-positive lymphoid proliferation and distinguishes this lymphoma subtype from other CD8-positive cutaneous lymphomas. Br J Dermatol. 2015;172(6):1573-1580. doi:10.1111/bjd.13628 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD7
70399

CD7 Immunostain, Technical Component Only

Clinical Information: CD7 (cluster of differentiation) is expressed normally on all T cells and natural killer cells. Expression of CD7 can be aberrantly lost in T-cell lymphomas, providing support for a diagnosis of T-cell lymphoma.

Useful For: Identification of T cells and natural killer cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chu PG, Arber DA, Weiss LM. Expression of T/NK-cell and plasma cell antigens in non hematopoietic epithelioid neoplasms. An Immunohistochemical Study of 447 Cases.

Am J Clin Pathol. 2003;120:64-70 2. Dunphy CH: Applications of flow cytometry and immunohistochemistry to diagnostic hematopathology. Arch Pathol Lab Med. 2004;128:1004-1022 3. Higgins RA, Blankenship JE, Kinney MC. Application of immunohistochemistry in the diagnosis of non-Hodgkin and Hodgkin lymphoma. Archives of Pathology and Laboratory Medicine 2008;132(3):441-461 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD71
70398

CD71 Immunostain, Technical Component Only

Clinical Information: The transferrin receptor, CD71 (cluster of differentiation 71), is highly expressed on the surface of cells of the erythroid lineage and mediates the uptake of transferrin-iron complexes. Transferrin receptor expression levels are highest in early erythroid precursors through the intermediate normoblast phase, expression then decreases through the reticulocyte phase.

Useful For: Assessment of erythroid lineage

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Luchini C, Parcesepe P, Nottegar A, et al. CD71 in gestational pathology: A versatile immunohistochemical marker with new possible applications. Appl Immunohistochem Mol Morph. 2016;24(3):215-220 2. Menon V, Thomas R, Elgueta C, et al. Comprehensive cell surface antigen analysis identifies transferrin receptor protein-1 (CD71) as a negative selection marker for human neuronal cells. Stem Cells. 2019;37(10):1293-1306 3. Chan KT, Choi MY, Lai KK, et al. Overexpression of transferrin receptor CD71 and its tumorigenic properties in esophageal squamous cell carcinoma. Oncol Rep. 2014;31(3):1296-1304 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD79
70418

CD79a Immunostain, Technical Component Only

Clinical Information: CD79a (cluster of differentiation 79a) stains the cytoplasm and membrane of B lymphocytes and megakaryocytes. CD79a is a protein expressed on the surface of B lymphocytes at all stages of maturation, from B-lymphocyte precursors through plasma cells. Its function is to transduce the signal of antigen binding to immunoglobulin into the cytoplasm of the B lymphocyte initiating intracellular signaling. Antibodies to CD79a are diagnostically useful to demonstrate B-cell lineage of acute lymphoblastic leukemia, malignant lymphomas, and chronic lymphoproliferative disorders.

Useful For: Phenotyping leukemias and lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Khurana S, Melody ME, Ketterling RP, et al. Molecular and phenotypic

characterization of an early T-cell precursor acute lymphoblastic lymphoma harboring PICALM-MLLT10 fusion with aberrant expression of B-cell antigens. Cancer Genet. 2020;240:40-44. doi:10.1016/j.cancergen.2019.11.002 2. Menter T, Lundberg P, Wenzel F, et al. RUNX1 mutations can lead to aberrant expression of CD79a and PAX5 in acute myelogenous leukemias: A potential diagnostic pitfall. Pathobiology. 2019;86(2-3):162-166. doi:10.1159/000493688 3. Matnani RG, Stewart RL, Pulliam J, Jennings CD, Kesler M. Peripheral T-cell lymphoma with aberrant expression of CD19, CD20, and CD79a: Case report and literature review..Case Rep Hematol. 2013;2013:183134. doi:10.1155/2013/183134 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CD8I
70400

CD8 Immunostain, Technical Component Only

Clinical Information: CD8 (cluster of differentiation 8) is expressed in a subset of T cells (cytotoxic T cells). Antibodies to CD8 are useful diagnostically to demonstrate cytotoxic T-lymphocyte lineage of lymphomas and chronic lymphoproliferative disorders.

Useful For: Identification of cytotoxic T cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Tewari N, Zaitoun AM, Arora A, Madhusudan S, Ilyas M, Lobo DN: The presence of tumour-associated lymphocytes confers a good prognosis in pancreatic ductal adenocarcinoma: an immunohistochemical study of tissue microarrays. BMC Cancer. 2013;13:436 2. Oguejiofor K, Hall J, Slater C, et al. Stromal infiltration of CD8 T cells is associated with improved clinical outcome in HPV-positive oropharyngeal squamous carcinoma. Br J Cancer. 2015;113(6):886-893 3. Paulson KG, Iyer JG, Simonson WT, et al. CD8+ lymphocyte intratumoral infiltration as a stage-independent predictor of Merkel cell carcinoma survival: a population-based study. Am J Clin Pathol. 2014;142(4):452-458 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

GLICP
89369

CD8 T-Cell Immune Competence Panel, Global, Whole Blood

Clinical Information: CD8 T cells play an important role in the immune response to viral or intracellular infectious agents, as well as antitumor immunity and immune surveillance. Upon activation, CD8 T cells mediate a variety of effector functions, including cytokine secretion and cytotoxicity. Interferon-gamma (IFN-gamma) is one of the early cytokines produced by CD8 T cells; it is released within a few hours of activation.(1) The cytotoxic function is mediated by the contents of the cytolytic granules.(1) Cell-surface mobilization of the cytolytic granule components, CD107a and CD107b, also known as lysosome-associated membrane proteins LAMP-1 and LAMP-2, occurs when CD8 T cells mediate their cytolytic function and degranulate.(2) CD8 T-cell activation occurs either through the T-cell receptor peptide major histocompatibility complex or by use of a mitogen (eg, phorbol myristate acetate and the calcium ionophore ionomycin). Mitogen-mediated activation is antigen nonspecific. Impairment of global CD8 T-cell activation (due to inherent cellular immunodeficiency or as a consequence of over-immunosuppression by therapeutic agents) results in reduced production of IFN-gamma and other cytokines, reduced cytotoxic function, and increased risk

for developing infectious complications. Agents associated with over-immunosuppression include the calcineurin inhibitors (eg, cyclosporine A, FK506 [Prograf/tacrolimus], and rapamycin [sirolimus]), antimetabolites (eg, mycophenolate mofetil), and thymoglobulin. Immunosuppression is most commonly used for allograft maintenance in solid-organ transplant recipients, to prevent graft-versus-host disease in allogeneic hematopoietic stem cell transplant patients, and to treat patients with autoimmune diseases. In these settings, reducing the risk for developing infectious complications as a result of over-immunosuppression is a clinical challenge. Therapeutic drug monitoring is routinely used in the transplant practice to avoid overtreatment and to determine patient compliance. However, the levels of drugs measured in blood specimens do not directly correlate with the administered dose due to individual pharmacokinetic differences.(3) Furthermore, drug levels may not necessarily correlate with biological activity of the drug. Consequently, it may be beneficial to consider modification of the immunosuppression regimen based on the patient's level of functional immune competence. This assay provides a means to evaluate over-immunosuppression within the CD8 T-cell compartment (global CD8 T-cell function). Intracellular IFN-gamma expression is a marker for CD8 T-cell activation. Surface CD107a and CD107b are markers for cytotoxic function. This test may be most useful when ordered at the end of induction immunosuppression and 2 to 3 months after maintenance immunosuppression to ensure that global CD8 T-cell function is not compromised. The test may also provide value when immunosuppression is increased to halt or prevent graft rejection, to provide information on a balance between over-immunosuppression with subsequent infectious comorbidities and under-immunosuppression with resultant graft rejection. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8.30 a.m. and noon with no change between noon and afternoon. Natural killer-cell counts, on the other hand, are constant throughout the day.(4) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(5-7) In fact, cortisol and catecholamine concentrations control distribution and therefore, numbers of naive versus effector CD4 and CD8 T cells.(5) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening(8) and during summer compared to winter.(9) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Determining over immunosuppression within the CD8 T-cell compartment, when used on transplant recipients and patients with autoimmune disorders receiving therapy with immunosuppressant agents

Interpretation: Interferon-gamma (IFN-gamma) and CD107a and CD107b expression below the defined reference range are consistent with a global impairment in CD8 T-cell function, most likely due to over immunosuppression. IFN-gamma, CD107a, and CD107b levels greater than the defined reference range are unlikely to have any clinical significance.

Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References: 1. Betts MR, Casaza JP, Patterson BA, et al. Putative immunodominant human immunodeficiency virus-specific CD8(+) T-cell responses cannot be predicted by MHC class I haplotype. J Virol. 2000;74(19):9144-9151. doi:10.1128/jvi.74.19.9144-9151.2000 2. Peters PJ, Borst J, Oorschot V, et al. Cytotoxic T-lymphocyte granules are secretory lysosomes, containing both perforin and granzymes. J Exp Med. 1991;173(5):1099-1109. doi:10.1084/jem.173.5.1099 3. Venkataramanan R, Shaw LM, Sarkozi L, et al. Clinical utility of monitoring tacrolimus blood concentrations in liver transplant patients. J Clin Pharmacol. 2001;41(5):542-551. doi:10.1177/00912700122010429 4. Carmichael KF, Abayomi A. Analysis of diurnal variation of lymphocyte subsets in healthy subjects and its implication in HIV monitoring and treatment. 15th Intl Conference on AIDS, Bangkok, Thailand, 2004, Abstract # B11052 5. Dimitrov S, Benedict C, Heutling D, Westermann J, Born J, Lange T. Cortisol and epinephrine control

opposing circadian rhythms in T cell subsets. Blood. 2009;113(21):5134-5143. doi:10.1182/blood-2008-11-190769 6. Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating human antigen presenting cells regulated by sleep. Sleep. 2007;30(4):401-411. doi:10.1093/sleep/30.4.401 7. Kronfol Z, Nair M, Zhang Q, Hill EE, Brown MB. Circadian immune measures in healthy volunteers: Relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Pyschosom Med. 1997;59(1):42-50. doi:10.1097/00006842-199701000-00006 8. Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS. Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J Acquir Immune Defic Syndr (1988). 1990;3(2):144-151 9. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994;34(6):512-516 10. Cabral-Marques O, Schimke LF, de Oliveira EB Jr, et al. Flow cytometry contributions for the diagnosis and immunopathological characterization of primary immunodeficiency diseases with immune dysregulation. Front Immunol. 2019;10:2742. doi:10.3389/fimmu.2019.02742 11. Meesing A, Abraham RS, Razonable RR. Clinical correlation of cytomegalovirus infection with CMV-specific CD8+ T-cell immune competence score and lymphocyte subsets in solid organ transplant recipients. Transplantation. 2019;103(4):832-838. doi:10.1097/TP.0000000000002396

GLIC
89317

CD8 T-Cell Immune Competence, Global, Blood

Clinical Information:

Useful For: Determining overimmunosuppression within the CD8 T-cell compartment, when used on transplant recipients and patients with autoimmune disorders receiving therapy with immunosuppressant agents

Interpretation: Interferon-gamma (IFN-gamma) and CD107a and CD107b expression below the defined reference range are consistent with a global impairment in CD8 T-cell function, most likely due to overimmunosuppression. The IFN-gamma and CD107a and CD107b levels greater than the defined reference range are unlikely to have any clinical significance.

Reference Values:

Interferon-gamma (IFN-gamma) expression (as % CD8 T cells): 10.3-56.0%

CD107a/b expression (as % CD8 T cells): 8.5-49.1%

Reference values have not been established for patients who are <19 years of age.

Clinical References: 1. Betts MR, Casaza JP, Patterson BA, et al. Putative immunodominant human immunodeficiency virus-specific CD8 T-cell responses cannot be predicted by MHC class I haplotype. J Virol. 2000;74(19):9144-9151 2. Peters PJ, Borst J, Oorschot V, et al. Cytotoxic T-lymphocyte granules are secretory lysosomes, containing both perforin and granzymes. J Exp Med. 1991;173(5):1099-1109 3. Venkataramanan R, Shaw LM, Sarkozi L, et al. Clinical utility of monitoring tacrolimus blood concentrations in liver transplant patients. J Clin Pharmacol. 2001;41(5):542-551 4. Carmichael KF, Abayomi A. Analysis of diurnal variation of lymphocyte subsets in healthy subjects in the Caribbean, and its implication in HIV monitoring and treatment. Afr J Med Med Sci. 2006;35(1):53-57 5. Dimitrov S, Benedict C, Heutling D, et al. Cortisol and epinephrine control opposing circadian rhythms in T-cell subsets. Blood. 2009;113(21):5134-5143 6. Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating antigen presenting cells regulated by sleep. Sleep. 2007;30(4):401-411 7. Kronfol Z, Nair M, Zhang Q, Hill EE, Brown MB: Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Pyschosom Med. 1997;59(1):42-50 8. Malone JL, Simms TE, Gray GC,

et al. Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J AIDS. 1990;3(2):144-151 9. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion 1994;34:512-516 10. Cabral-Marques O, Schimke LF, de Oliveira EB Jr, et al. Flow cytometry contributions for the diagnosis and immunopathological characterization of primary immunodeficiency diseases with immune dysregulation. Front Immunol. 2019 26;10:2742. doi:10.3389/fimmu.2019.02742 11. Meesing A, Abraham RS, Razonable RR. Clinical correlation of cytomegalovirus infection With CMV-specific CD8+ T-cell immune competence score and lymphocyte subsets in solid organ transplant recipients. Transplantation. 2019;103(4):832-838. doi:10.1097/TP.0000000000002396

CD99
70508

CD99 (MIC-2) Immunostain, Technical Component Only

Clinical Information: CD99 (cluster of differentiation 99) is the product of the MIC2 gene. It is expressed in normal tissues including some lymphocytes, pancreatic islet cells, granulosa cells of the ovary, Sertoli cells of the testis, and ependymal cells of the central nervous system. It is strongly expressed in Ewing sarcoma/primitive neuroectodermal tumor, distinguishing it from other small round blue cell tumors of childhood and adolescence.

Useful For: Identification of Ewing sarcoma and primitive neuroectodermal tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Nunez J, Veloda C, Liu Y, Wakely PE Jr, Silverman JF. Utility of an immunohistochemical panel to distinguish nonductal pancreatic neoplasms in surgical pathology. Am J Clin Pathol. 2013;140:A181. doi:10.1093/ajcp/140.suppl1.181 2. Karikari IO, Mehta AI, Nimjee S, et al. Primary intradural extraosseous Ewing sarcoma of the spine: Case report and literature review. Neurosurgery. 2011;69(4):E995-999. doi:10.1227/NEU.0b013e318223b7c7 3. Romero-Rojas AE, Diaz-Perez JA, Ariza-Serrano LM. CD99 is expressed in chordoid glioma and suggests ependymal origin. Virchows Arch. 2012;460(1):119-122. doi:10.1007/s00428-011-1170-2 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CDKZ
35385

CDKN1C Gene, Full Gene Analysis, Varies

Clinical Information:

Useful For:

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. DeBaun MR, Niemitz EL, McNeil DE, Brandenburg SA, Lee MP, Feinberg AP. Epigenetic alterations of H19 and LIT1 distinguish patients with Beckwith-Wiedemann syndrome with cancer and birth defects. Am J Hum Genet. 2002;70(3):604-611 3. Shuman C, Kalish JM, Weksberg R. Beckwith-Wiedemann Syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews[Internet], University of Washington, Seattle; 1993-2025. Updated September 21.2023. Accessed April 17, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1394/ 4. Brioude F, Netchine I, Praz F, et al. Mutations of the Imprinted CDKN1C Gene as a Cause of the Overgrowth Beckwith-Wiedemann Syndrome: Clinical Spectrum and Functional Characterization. Hum Mutat. 2015;36(9):894-902. doi:10.1002/humu.22824 5. Binder G, Ziegler J, Schweizer R, et al. Novel mutation points to a hot spot in CDKN1C causing Silver-Russell syndrome. Clin Epigenetics. 2020;12(1):152. Published 2020 Oct 19. doi:10.1186/s13148-020-00945-y 6. Schrier Vergano SA, Deardorff MA. IMAGe Syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews[Internet]. University of Washington, Seattle; 1993-2025. Updated August 5,2021. Accessed April 17, 2025. Available at: www.ncbi.nlm.nih.gov/books/NBK190103/

CDX2
70401

CDX2 Immunostain, Technical Component Only

Clinical Information: Caudaltype homeobox 2 (CDX2) is a transcription factor belonging to the caudal type homeobox gene family. It is involved in regulating the proliferation and differentiation of intestinal epithelial cells.

Useful For: Identification of carcinoma of intestinal origin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Cecchini MJ, Walsh JC, Parfitt J, et al. CDX2 and Muc2 immunohistochemistry as prognostic markers in stage II colon cancer. Hum Pathol. 2019;90:70-79. doi:10.1016/j.humpath.2019.05.005 2. Chiesa-Vottero A. CDX2, SATB2, GATA3, TTF1, and PAX8 immunohistochemistry in Krukenberg tumors. Int J Gynecol Pathol. 2020;39(2):170-177. doi:10.1097/PGP.0000000000000582 3. Masood MA, Loya A, Yusuf MA. CDX2 as a prognostic marker in gastric cancer. Acta Gastroenterol Belg. 2016;79(2):197-200 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FRCE
57952

Cedar Red (Juniperus virginiana) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 5 6 17.50-49.99 50.0-99.99 >99.99 Very High Positive Very High Positive Very High Positive

Reference Values:
<0.35 kU/L

CEDR
82482

Cedar, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cedar Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FCELG
57638

Celery IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

CELY
82766

Celery, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to celery Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CELI
88906

Celiac Associated HLA-DQ Alpha 1 and DQ Beta 1 DNA Typing, Blood

Clinical Information: Celiac disease (gluten-sensitive enteropathy) is mediated by T lymphocytes in patients with genetic susceptibility. This genetic association is with certain HLA genes in the class II region (DQ alpha 1, DQ beta 1).

Useful For: Assessing risk of celiac disease

Interpretation: Most (90%-95%) patients with celiac disease have 1 or 2 copies of HLA-DQ2 haplotype (see below), while the remainder have HLA-DQ8 haplotype. Rare exceptions to these associations have occasionally been seen. In one study of celiac disease, only 0.7% of patients with celiac disease lacked the HLA alleles mentioned above. Results are based on the absence or presence of permissive genes and reported as Celiac gene pairs present: No, Yes, or Equivocal. It is important to realize that these genes are also present in about 20% of people without celiac disease. Therefore, the mere presence of these genes does not prove the presence of celiac disease or that genetic susceptibility to celiac disease is present. The HLA-DQ molecule is composed of 2 chains: DQ alpha (encoded by HLA-DQA1 gene) and DQ beta (encoded by HLA-DQB1 gene). HLA-DQ typing can be performed by serological or molecular methods. Currently, most laboratories perform typing by molecular methods. HLA-DQ2 and DQ8, as typed by serology, are usually based on the molecular typing of the DQB1 chain only. The current molecular method allows typing for both the DQB1 and DQA1 chains. This has shown that there are different haplotypes of HLA-DQ2 and DQ8. Typing of these haplotypes is important in celiac disease as they carry different risk association. There are 2 common haplotypes of DQ2: 1. DQA1*05:01 with DQB1*02:01, also called DQ2.5 in celiac literature 2. DQA1*02:01 with DQB1*02:02, also called DQ2.2 in celiac literature A single haplotype (heterozygote) of DQ2.5 is permissive for presence of celiac genes. However, only a double haplotype (homozygous) of DQ2.2 is permissive for presence of celiac genes. There are few reports where a single haplotype of DQ2.2 is considered to be an equivocal risk. In some cases, the DQ2.2 haplotype may be present with a DQ7.5 haplotype (DQA1*05:05 with DQB1*03:01). In this case, a DQ2.5 molecule can be formed by the combination of DQB1*02:02 from one chromosome and DQA1*05:05 from the other chromosome. These cases fall in the same category as the DQ2.5 heterozygote. There are 3 common haplotypes of DQ8: 1. DQA1*03:01 with DQB1*03:02 2. DQA1*03:02 with DQB1*03:02 3. DQA1*03:03 with DQB1*03:02 Any single haplotype (heterozygote) of DQ8 is permissive for celiac. Therefore, the gene pairs permissive for celiac are: 1. Heterozygote (single copy) -DQA1*05:XX with DQB1*02:01 -DQA1*05:XX with DQB1*02:02 -DQA1*03:XX with DQB1*03:02 2. Homozygous (2 copies) -DQA1*02:01 with DQB1*02:02 Gene pairs equivocal for celiac are: 1. Heterozygote (single copy) -DQA1*02:01 with DQB1*02:02 2. Rare allele types of DQ2 and DQ8 other than those listed above All other gene pair combinations are considered nonpermissive for celiac. There are reports that specific HLA-DQ2 and DQ8 combinations may confer different risks for the development of celiac disease.(1) A recent publication from our group demonstrated that risk gradient of tissue transglutaminase (tTG) IgA positivity depends on specific HLA-DQ2 and DQ8 combinations.(2) For more information see Tissue Transglutaminase IgA positivity.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Pietzak MM, Schofield TC, McGinniss MJ, Nakamura RM. Stratifying risk for celiac disease in a large at-risk United States population by using HLA alleles. Clin Gastroenterol

Hepatol. 2009;7(9):966-971. doi:10.1016/j.cgh.2009.05.028 2. Choung RS, Mills JR, Snyder MR, Murray JA, Gandhi MJ. Celiac disease risk stratification based on HLA-DQ heterodimer (HLA-DQA1 approximately DQB1) typing in a large cohort of adults with suspected celiac disease. Hum Immunol. 2020;81(2-3):59-64. doi:10.1016/j.humimm.2020.01.006 3. Hurley CK, Kempenich J, Wadsworth K, et al. Common, intermediate and well-documented HLA alleles in world populations: CIWD version 3.0.0. HLA. 2020;95(6):516-531. doi:10.1111/tan.13811 4. Polvi A, Arranz E, Fernandez-Arequero M, et al. HLA-DQ2-negative celiac disease in Finland and Spain. Hum Immunol. 1998;59(3):169-175 5. Husby S, Murray JA, Katzka DA. AGA Clinical Practice Update on Diagnosis and Monitoring of Celiac Disease-Changing Utility of Serology and Histologic Measures: Expert Review. Gastroenterology. 2019;156(4):885-889. doi:10.1053/j.gastro.2018.12.010 6. Raiteri A, Granito A, Giamperoli A, Catenaro T, Negrini G, Tovoli F. Current guidelines for the management of celiac disease: A systematic review with comparative analysis. World J Gastroenterol. 2022;28(1):154-175. doi:10.3748/wjg.v28.i1.154

CDCOM 89201 Celiac Disease Comprehensive Cascade, Serum and Whole Blood

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals.(1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations, including ataxia and peripheral neuropathy, and are at increased risk for developing non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Individuals with family members who have celiac disease are at increased risk of developing the disease.(2) Genetic susceptibility is related to specific human leukocyte antigen (HLA) markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers compared to approximately 40% of the general population. For this reason, HLA-DQ2 and HLA-DQ8 are considered genetic risk factors for celiac disease and are required, but not sufficient, for the disease process to occur. HLA testing is not required for diagnosis in all cases but can be useful in situations where histology and serology are discrepant or for individuals who have started a gluten free diet before evaluation.(3) A definitive diagnosis of celiac disease requires a duodenal biopsy demonstrating villous atrophy.(3) Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, individuals with positive laboratory results may be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial antibody, tissue transglutaminase (tTG), and deamidated gliadin antibodies.(4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic test is tTG IgA isotype in individuals who produce sufficient total IgA. For individuals who are IgA deficient, testing for tTG and deamidated gliadin IgG antibodies is required. A recent multi-cohort international study found that a tTG IgA titer of 10 or more times the upper limit of normal (ULN) had a positive predictive value of 95% in an adult population.(5) In addition, several prospective studies have shown that a biopsy-free approach to a celiac disease diagnosis may be possible in children with a tTG titer 10 or more times the ULN who meet certain criteria.(6-9) Given this evidence, the American College of Gastroenterology now suggests that a positive tTG IgA result greater than 10 times the ULN with a positive endomysial antibody in a separate

blood sample may be sufficient for a diagnosis of celiac disease in children.(3) The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, concentrations of associated autoantibodies decline, which is sometimes accompanied by reconstitution of the small intestinal villi. In most patients, an improvement in clinical symptoms is observed. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, antibody titers may take up to 1 year to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease. It should be noted that HLA typing is not required to establish a diagnosis of celiac disease. Consider ordering CDSP / Celiac Disease Serology Cascade, Serum if HLA typing is not desired or has been previously performed. For the recommended approach to a patient suspected of celiac disease, see Celiac Disease Diagnostic Testing Algorithm. For monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm

Useful For: Evaluating patients suspected of having celiac disease, including patients with compatible symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disease) Comprehensive algorithmic evaluation including human leukocyte antigen typing

Interpretation: Immunoglobulin A: Total IgA levels below the age-specific reference range suggest either a selective IgA deficiency or a more generalized immunodeficiency. For individuals with a low or high IgA level, additional clinical and laboratory evaluation is recommended. Some individuals may have a partial IgA deficiency in which the IgA levels are detectable but fall below the age-adjusted reference range. For these individuals both IgA and IgG isotypes for tissue transglutaminase (tTG) and deamidated gliadin antibodies are recommended for the evaluation of celiac disease; tTG IgA, tTG IgG, deamidated gliadin IgA, and deamidated gliadin IgG antibody assays are performed in this cascade. For individuals who have selective IgA deficiency with undetectable levels of IgA, only -tTG IgG and -deamidated gliadin IgG antibody assays are performed. HLA-DQ Typing: Approximately 90% to 95% of patients with celiac disease have the HLA-DQ2 allele; most of the remaining patients with celiac disease have the HLA-DQ8 allele. Individuals who do not carry either of these alleles are unlikely to have celiac disease. However, individuals with these alleles may not, during their lifetime, develop celiac disease. Therefore, the presence of DQ2 or DQ8 does not conclusively establish a diagnosis of celiac disease. Individuals with DQ2 and/or DQ8 alleles, in the context of positive serology and compatible clinical symptoms, should be referred for small intestinal biopsy. HLA typing may be especially helpful for those patients who have begun to follow a gluten-free diet prior to a confirmed diagnosis of celiac disease. tTG IgA/IgG Antibodies: Individuals positive for tTG antibodies of the IgA isotype likely have celiac disease, and a small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for tTG antibodies of the IgG isotype is performed. In these individuals, a positive tTG IgG antibody result suggests a diagnosis of celiac disease. However, just as with the tTG IgA antibody, a biopsy should be performed to confirm the diagnosis. Negative tTG IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Deamidated Gliadin IgA/IgG Antibodies: Positivity for deamidated gliadin antibodies of the IgA isotype is suggestive of celiac disease, and a small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for deamidated gliadin antibodies of the IgG isotype is performed. In these individuals, a positive deamidated gliadin IgG antibody result suggests a diagnosis of celiac disease. However, just as with the deamidated gliadin IgA antibody, a biopsy should be performed to confirm the diagnosis. Negative deamidated gliadin IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Endomysial Antibody, IgA: Positivity for endomysial antibodies (EMA) of the IgA isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, evaluation of EMA antibodies is not indicated. Negative EMA antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet.

Reference Values:

IMMUNOGLOBULIN A (IgA)
0-<5 months: 7-37 mg/dL
5-<9 months: 16-50 mg/dL
9-<15 months: 27-66 mg/dL
15-<24 months: 36-79 mg/dL
2-<4 years: 27-246 mg/dL
4-<7 years: 29-256 mg/dL
7-<10 years: 34-274 mg/dL
10-<13 years: 42-295 mg/dL
13-<16 years: 52-319 mg/dL
16-<18 years: 60-337 mg/dL
> or =18 years: 61-356 mg/dL

HLA-DQ TYPING
Presence of HLA-DQ2 or HLA-DQ8 alleles associated with celiac disease

Clinical References: 1. Rubin JE, Crowe SE. Celiac disease. Ann Int Med. 2020;172(1):ITC1-ITC16 2. Lebwohl B, Rubio-Tapia A. Epidemiology, presentation, and diagnosis of celiac disease. Gastroenterology. 2021;160(1):63-75 3. Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology guidelines update: Diagnosis and management of celiac disease. Am J Gastroenterol. 2023;118(1):59-76. doi:10.14309/ajg.0000000000002075 4. Penny HA, Raju SA, Sanders DS. Progress in the serology-based diagnosis and management of adult celiac disease. Expert Rev Gastroenterol Hepatol. 2020;14(3):147-154 5. Penny HA, Raju SA, Lau MS, et al. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. Gut. 2021;70(5):876-883. doi:10.1136/gutjnl-2020-320913 6. Ylonen V, Lindfors K, Repo M, et al. Non-biopsy serology-based diagnosis of celiac disease in adults is accurate with different commercial kits and pre-test probabilities. Nutrients. 2020;12(9):2736 7. Werkstetter KJ, Korponay-Szabo IR, Popp A, et al. Accuracy in diagnosis of celiac disease without biopsies in clinical practice. Gastroenterology. 2017;153(4):924-935. doi:10.1053/j.gastro.2017.06.002 8. Wolf J, Petroff D, Richter T, et al. Validation of antibody-based strategies for diagnosis of pediatric celiac disease without biopsy. Gastroenterology. 2017;153(2):410-419.e17. doi:10.1053/j.gastro.2017.04.023 9. Ho SS, Keenan JI, Day AS. Role of serological tests in the diagnosis of coeliac disease in children in New Zealand. J Paediatr Child Health. 2020;56(12):1906-1911. doi:10.1111/jpc.15076

CDGF
89200

Celiac Disease Gluten-Free Cascade, Serum and Whole Blood

Clinical Information:

Useful For: Evaluating patients suspected of having celiac disease who are currently (or were recently) on a gluten-free diet

Interpretation: HLA-DQ Typing: Approximately 90% to 95% of patients with celiac disease have the HLA-DQ2 allele; most of the remaining patients with celiac disease have the HLA-DQ8 allele. Individuals who do not carry either of these alleles are unlikely to have celiac disease. For these individuals, no further serologic testing is required. However, individuals with these alleles may not, during their lifetime, develop celiac disease. Therefore, the presence of DQ2 or DQ8 does not conclusively establish a diagnosis of celiac disease. For individuals with DQ2 and/or DQ8 alleles, in the context of positive serology and compatible clinical symptoms, small intestinal biopsy is recommended. Immunoglobulin A: Total IgA levels below the age-specific reference range suggest either a selective IgA deficiency or a more generalized immunodeficiency. For individuals with a low or high IgA level, additional clinical and laboratory evaluation is recommended. Some individuals may have a partial IgA

deficiency in which the IgA levels are detectable but fall below the age-adjusted reference range. For these individuals, both IgA and IgG isotypes for tissue transglutaminase (tTG) and deamidated gliadin antibodies are recommended for the evaluation of celiac disease. tTG IgA/IgG Antibodies: Individuals positive for tTG antibodies of the IgA and/or IgG isotype may have celiac disease, and a small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for tTG antibodies of the IgG isotype is indicated. In these individuals, a positive tTg IgG antibody result suggests a diagnosis of celiac disease. However, just as with the tTG IgA antibody, a biopsy should be performed to confirm the diagnosis. Negative tTG IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Deamidated Gliadin IgA/IgG Antibodies: Positivity for deamidated gliadin antibodies of the IgA and/or IgG isotype is suggestive of celiac disease, and a small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for deamidated gliadin antibodies of the IgG isotype is indicated. In these individuals, a positive deamidated gliadin IgG antibody result suggests a diagnosis of celiac disease. However, just as with the deamidated gliadin IgA antibody, a biopsy should be performed to confirm the diagnosis. Negative deamidated gliadin IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet.

Reference Values:

HLA-DQ TYPING

Presence of HLA-DQ2 or HLA-DQ8 alleles associated with celiac disease

Clinical References: 1. Rubin JE, Crowe SE. Celiac disease. Ann Int Med. 2020;172(1):ITC1-ITC16 2. Lebwohl B, Rubio-Tapia A. Epidemiology, presentation, and diagnosis of celiac disease. Gastroenterology. 2021;160(1):63-75 3. Rubio-Tapia A, Hill, ID, Semrad, C, Kelly CP, Greer, KB, Limketkai, BN, Lebwohl B, American College of Gastroenterology Guidelines update: Diagnosis and management of celiac disease. Am J Gastroenterol. 2023;118(1):59-76. doi:10.14309/ajg.0000000000002075 4. Penny HA, Raju SA, Sanders DS. Progress in the serology-based diagnosis and management of adult celiac disease. Exp Rev Gastroenterol Hepatol. 2020;14(3):147-154 5. Penny HA, Raju SA, Lau MS, Marks LJ, et.al. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. Gut. 2021;70(5):876-883. doi:10.1136/gutjnl-2020-320913 6. Ylonen, V., Lindfors, K., Repo M, et al. Non-biopsy serology-based diagnosis of celiac disease in adults is accurate with different commercial kits and pre-test probabilities. Nutrients. 2020:12(9):1736. doi:10.3390/nu12092736 7. Werkstetter KJ, Korponay-Szabo IR, Popp A, et al. Accuracy in diagnosis of celiac disease without biopsies in clinical practice. Gastroenterology. 2017;153(4):924-935. doi:10.1053/j.gastro.2017.06.002 8. Wolf J, Petroff D, Richter T, et al. Validation of antibody-based strategies for diagnosis of pediatric celiac disease without biopsy. Gastroenterology. 2017;153(2):410-419.e17. doi:10.1053/j.gastro.2017.04.023 9. Ho SS, Keenan JI, Day AS. Role of serological tests in the diagnosis of coeliac disease in children in New Zealand. J Paediatr Child Health. 2020;56(12):1906-1911. doi:10.1111/jpc.15076

CDSP
89199

Celiac Disease Serology Cascade, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals.(1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations, including ataxia and peripheral neuropathy, and are at increased risk for

development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Individuals with family members who have celiac disease are at increased risk of developing the disease.(2) Genetic susceptibility is related to specific human leukocyte antigen (HLA) markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared with approximately 40% of the general population. For this reason, HLA-DQ2 and HLA-DQ8 are considered genetic risk factors for celiac disease and are required, but not sufficient, for the disease process to occur. HLA testing is not required for diagnosis in all cases but can be useful in situations where histology and serology are discrepant or for individuals who have started a gluten free diet before evaluation.(3) A definitive diagnosis of celiac disease requires a duodenal biopsy demonstrating villous atrophy.(3) Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, individuals with positive laboratory results may be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial antibody, tissue transglutaminase (tTG), and deamidated gliadin antibodies.(4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic test is tTG IgA isotype, in individuals who produce sufficient total IgA. For Individuals who are IgA deficient, testing for tTG and deamidated gliadin IgG antibodies is required. A recent multi-cohort international study found that a tTG IgA titer of 10 or more times the upper limit of normal (ULN) had a positive predictive value of 95% in an adult population.(5) In addition, several prospective studies have shown that a biopsy free approach to celiac disease diagnosis may be possible in children with a tTG titer 10 or more times the ULN who meet certain criteria.(6-9) Given this evidence, the American College of Gastroenterology now suggests that a positive TTG IgA result greater than 10 times the ULN with a positive endomysial antibody in a separate blood sample may be sufficient for a diagnosis celiac disease in children.(3) The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, concentrations of associated autoantibodies decline, which is sometimes also accompanied by reconstitution of the small intestinal villi. In most patients, an improvement in clinical symptoms is observed. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease. See Celiac Disease Diagnostic Testing Algorithm for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm.

Useful For: Evaluating patients suspected of having celiac disease, including patients with compatible symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disease, positivity for HLA-DQ2 and/or DQ8)

Interpretation: Immunoglobulin A: Total IgA levels below the age-specific reference range suggest either a selective IgA deficiency or a more generalized immunodeficiency. For individuals with a low or high IgA level, additional clinical and laboratory evaluation is recommended. Some individuals may have a partial IgA deficiency in which the IgA levels are detectable but fall below the age-adjusted reference range. For these individuals, both IgA and IgG isotypes for tissue transglutaminase (tTG) and deamidated gliadin antibodies are recommended for the evaluation of celiac disease; tTG IgA, tTG IgG, deamidated gliadin IgA, and deamidated gliadin IgG antibody assays are performed in this cascade. For individuals who have selective IgA deficiency or undetectable levels of IgA, only tTG IgG and deamidated gliadin IgG antibody assays are performed. tTG IgA/IgG Antibodies: Individuals positive for tTG antibodies of the IgA isotype likely have celiac disease and a small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for tTG antibodies of the IgG

isotype is performed. In these individuals, a positive tTG IgG antibody result suggests a diagnosis of celiac disease. However, just as with the tTG IgA antibody, a biopsy should be performed to confirm the diagnosis. Negative tTG IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Deamidated Gliadin IgA/IgG Antibodies: Positivity for deamidated gliadin antibodies of the IgA isotype is suggestive of celiac disease; small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for deamidated gliadin antibodies of the IgG isotype is performed. In these individuals, a positive deamidated gliadin IgG antibody result suggests a diagnosis of celiac disease. However, just as with the deamidated gliadin IgA antibody, a biopsy should be performed to confirm the diagnosis. Negative deamidated gliadin IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Endomysial IgA Antibodies: Positivity for endomysial antibodies (EMA) of the IgA isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, evaluation of EMA is not indicated. Negative EMA serology does not exclude a diagnosis of celiac disease as antibody levels decrease over time in patients who have been following a gluten-free diet.

Reference Values:

Immunoglobulin A (IgA)
0-<5 months: 7-37 mg/dL
5-<9 months: 16-50 mg/dL
9-<15 months: 27-66 mg/dL
15-<24 months: 36-79 mg/dL
2-3 years: 27-246 mg/dL
4-6 years: 29-256 mg/dL
7-9 years: 34-274 mg/dL
10-14 years: 42-295 mg/dL
13-15 years: 52-319 mg/dL
16-17 years: 60-337 mg/dL
> or =18 years: 61-356 mg/dL

Clinical References: 1. Rubin JE, Crowe SE. Celiac disease. Ann Int Med. 2020;172(1):ITC1-ITC16 2. Lebwohl B, Rubio-Tapia A. Epidemiology, presentation, and diagnosis of celiac disease. Gastroenterology. 2021;160(1):63-75 3. Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease. Am J Gastroenterol. 2023;118(1):59-76 4. Penny HA, Raju SA, Sanders DS. Progress in the serology-based diagnosis and management of adult celiac disease. Exp Rev Gastroenterol Hepatol. 2020;14(3):147-154 5. Penny HA, Raju SA, Lau MS, et.al. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. Gut. 2021;70(5):876-883. doi: 10.1136/gutjnl-2020-320913 6. Ylonen V, Lindfors K., Repo M, et al. Non-biopsy serology-based diagnosis of celiac disease in adults is accurate with different commercial kits and pre-test probabilities. Nutrients. 2020;12(9):2736. doi:10.3390/nu12092736 7. Werkstetter KJ, Korponay-Szabo IR, Popp A, et al. Accuracy in diagnosis of celiac disease without biopsies in clinical practice. Gastroenterology. 2017;153(4):924-935. doi:10.1053/j.gastro.2017.06.002 8. Wolf J, Petroff D, Richter T, et al. Validation of antibody-based strategies for diagnosis of pediatric celiac disease without biopsy. Gastroenterology. 2017;153(2):410-419.e417. doi:10.1053/j.gastro.2017.04.023 9. Ho SS, Keenan JI, Day AS. Role of serological tests in the diagnosis of coeliac disease in children in New Zealand. J Paediatr Child Health. 2020;56(12):1906-1911. doi:10.1111/jpc.15076

NCSPC 113338 Cell Concentration (Bill Only)

Reference Values:

This test is for billing purposes only.
This is not an orderable test.

BFCC
608873

Cell Count and Differential, Body Fluid

Clinical Information: Body fluids, other than the commonly analyzed urine and blood, include synovial, pleural, peritoneal, and pericardial fluids. These fluids may be present in increased volumes and may contain increased numbers of normal and abnormal cells in a variety of disease states.

Useful For: Aiding in the diagnosis of joint disease, systemic disease, inflammation, malignancy, infection, and trauma

Interpretation: Trauma and hemorrhage may result in increased red blood cells (RBC) and white blood cells (WBC); RBC predominate. WBC are increased in inflammatory and infectious processes: -Neutrophils predominate in bacterial infections -Lymphocytes predominate in viral infections -Macrophages may be increased in inflammatory and infectious processes -Eosinophils may be increased in parasitic or fungal infections

Reference Values:
TOTAL NUCLEATED CELLS
Synovial fluid: <150/mcL
Peritoneal/pleural/pericardial fluid: <500/mcL
NEUTROPHILS
Synovial Fluid: <25%
Peritoneal/pleural/pericardial fluid: <25%
LYMPHOCYTES
Synovial fluid: <75%
MONOCYTES/MACROPHAGES
Synovial fluid: <70%

Clinical References: 1. Kjeldsberg CR, Hussong, JW: Body Fluid Analysis. ASCP Press; 2015 2. Dyken PR, Shirley S, Trefz J, El Gammel T: Comparison of cyto-centrifugation and sedimentation techniques for CSF cyto-morphology. Acta Cytol. 1980 Mar-Apr;24(2):167-170 3. Sheth KV: Cerebrospinal and body fluid cell morphology through a hematologist's microscope, workshop presented at the ASCP-CAP Joint Spring Meeting, San Diego, March 1981 4. Schumacher AH, Reginato A: Atlas of Synovial Fluid Analysis and Crystal Identification. Lea and Febiger; 1991

BRAFB
65100

Cell-Free DNA BRAF V600, Blood

Clinical Information: This test uses DNA extracted from the peripheral blood to evaluate for the presence of BRAF V600E and V600K alterations. The BRAF gene is a member of the mitogen-activated protein/extracellular signal-regulated (MAP/ERK) kinase pathway, which plays a role in cell proliferation and differentiation. Dysregulation of this pathway is a key factor in tumor progression and BRAF alterations occur frequently in many different tumor types. BRAF variant analysis aids in the diagnosis of cancer types including anaplastic and papillary thyroid carcinoma, hairy cell leukemia, and papillary craniopharyngioma. BRAF V600E and V600K alterations are associated with response or resistance to specific targeted therapies in cancer. Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks.

Useful For: An alternative to invasive tissue biopsies for the determination of BRAF V600E and V600K alterations Identification of patients with cancer who are most likely to benefit from targeted therapies This test is not intended for serial monitoring of patients with cancer or as a screening test to

identify cancer.

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Sanmamed MJ, Fernandez-Landazuri S, Rodriguez C, et al: Quantitative cell-free circulating BRAFV600E mutation analysis by use of droplet digital PCR in the follow-up of patients with melanoma being treated with BRAF inhibitors. Clin Chem. 2015;61(1):297-304 2. Schwarzenbach H, Hoon DS, Pantel K: Cell-free nucleic acids as biomarkers in cancer patients. Nat Rev Cancer. 2011 Jun;11(6):426-437 3. Johnson DB, Sosman JA: Update on the targeted therapy of melanoma. Curr Treat Options Oncol. 2013 Jun 14;(2):280-292 4. McArthur GA, Chapman PB, Robert C, et al: Safety and efficacy of vemurafenib in BRAF (V600E) and BRAF (V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomized, open-label study. Lancet Oncol. 2014 Mar;15(3):323-332

T790M
113410

Cell-Free DNA EGFR T790M Mutation Analysis, Blood

Clinical Information: Epidermal growth factor receptor (EGFR)-targeted tyrosine kinase inhibitors (eg, gefitinib and erlotinib) have been approved by the US food and Drug Administration (FDA) for use in treating patients with non-small cell lung cancer (NSCLC) who previously failed to respond to traditional chemotherapy. However, the EGFR T790M mutation is associated with acquired resistance to tyrosine kinase inhibitor (TKI) therapy in about 60% of patients with disease progression after initial response to erlotinib, gefitinib, or afatinib. Recent data suggest that patients with metastatic NSCLC and the T790M mutation may benefit from osimertinib, an FDA-approved oral TKI that inhibits both EGFR-activating mutations and the T790M mutation.

Useful For: Determination of EGFR T790M mutation status in blood specimens as an alternative to invasive tissue biopsies Identification of patients with non-small cell lung cancer who harbor a T790M mutation and may benefit from specific EGFR-targeted therapies

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Schwarzenbach H, Hoon DSB, Pantel K: Cell-free nucleic acids as biomarkers in cancer patients. Nat Rev Cancer. 2011 Jun;11(6):426-437 2. Ettinger DS, Wood DE, Aisner DL, et al: Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017 Apr;15(4):504-535 3. Janne PA, Yang JCH, Kim DW, et al: AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med. 2015 Apr 30;372(18):1689-1699

KRASD
68003

Cell-Free DNA KRAS 12, 13, 61,146, Blood

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug

Administration for treatment of solid tumor malignancies. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. One of the most common somatic alterations in colorectal cancer (CRC) and non-small cell lung cancer (NSCLC) is the presence of activating variants in the protooncogene KRAS. KRAS is recruited by ligand-bound (active) epidermal growth factor receptor (EGFR) to initiate the signaling cascade induced by the RAS/MAPK pathway. Because altered KRAS constitutively activates the RAS/MAPK pathway downstream of EGFR, agents such as cetuximab and panitumumab, which prevent ligand-binding to EGFR, do not appear to have any meaningful inhibitor activity on cell proliferation in the presence of altered KRAS. Current data suggest that the efficacy of EGFR-targeted therapies in CRC and NSCLC is confined to patients with tumors lacking KRAS mutations. An exception is the KRAS G12C variant that is targetable with variant-specific inhibitors. This test uses DNA extracted from tumor tissue to evaluate for the presence of KRAS (G12A, G12C, G12D, G12R, G12S, G12V, G13D, Q61K, Q61L, Q61R, Q61H, and A146T) variants. A positive result indicates the presence of an activating KRAS mutation and can be useful for guiding the treatment of patients with CRC and NSCLC.

Useful For: An alternative to invasive tissue biopsies for the determination of KRAS 12, 13, 61,146 (G12A, G12C, G12D, G12R, G12S, G12V, G13D, Q61K, Q61L, Q61R, Q61H, and A146T) mutation status Detecting molecular markers associated with response or resistance to specific therapy This test is not intended as a screening test to identify cancer.

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Schwarzenbach H, Hoon DS, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. Nat Rev Cancer. 2011;11(6):426-437 2. Allegra CJ, Rumble BR, Hamilton SR, et al. Extended RAS gene mutation testing in metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J Clin Oncol. 2016;34(2):179-185. doi:10.1200/JCO.2015.63.967 3. Olmedillas Lopez S, Garcia-Olmo DC, Garcia-Arranz M, et al. KRAS G12V mutation detection by droplet digital PCR in circulating cell-free DNA of colorectal cancer patients. Int J Mol Sci. 2016;17(4):484 4.Lam DC. Clinical testing for molecular targets for personalized treatment in lung cancer. Respirology. 2013 Feb;18(2):233-237 5.Hong DS, Fakih MG, Strickler JH, et al. KRAS G12C inhibition with sotorasib in advanced solid tumors. N Engl J Med. 2020;383(13):1207-1217

PIK3B
614802

Cell-Free DNA PIK3CA Test, Blood

Clinical Information: More than 70% of breast cancers are hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER2) negative (HR+/HER2-). Approximately 40% of patients with HR+/HER2- advanced breast cancer have activating mutations in the gene PIK3CA, inducing hyperactivation of the alpha isoform (p110 alpha) of phosphatidylinositol 3-kinase, a key upstream component of the PI3K pathway. Mutations in PIK3CA are associated with tumor growth, resistance to endocrine therapy, and a poor overall prognosis. Patients with HR+/HER2- advanced breast cancer identified to have a PIK3CA mutation may be eligible for treatment with targeted kinase inhibitor therapy (eg, alpelisib). This test uses circulating tumor DNA extracted from blood to evaluate for the presence of 10 clinically actionable PIK3CA mutations: E542K (c.1624G>A) E542K (c.1633G>A) E545D (c.1635G>T) E545G (c.1634A>G) E545A (c.1634A>C) H1047Y (c.3139C>T) C420R (c.1285C>T) Q546E (c.1636C>G) H1047L (c.3140A>T) H1047R (c.3140A>G)

Useful For: Identification of hormone receptor positive and human epidermal growth factor receptor 2 negative (HR+/HER2-) advanced breast cancer tumors that may be eligible for treatment with targeted kinase inhibitor therapy (eg, alpelisib).

Interpretation: The interpretation of molecular biomarker results includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Bachman KE, Argani P, Samuels Y, et al: The PIK3CA gene is mutated with high frequency in human breast cancers. Cancer Biol Ther. 2004 Aug;3(8):772-775 2. Andre F, Ciruelos E, Rubovszky G, et al: Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med. 2019 May 16;380(20):1929-1940 3. Andre F, Ciruelos EM, Juric D, et al: Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. Ann Oncol. 2021 Feb;32(2):208-217

CNSA
70644

Central Nervous System Consultation, Autopsy, Varies

Clinical Information: Difficult neurological abnormalities, including congenital anomalies, sometimes require the assistance of a neuropathologist. This evaluation is offered to provide the careful dissection and diagnostic experience that may be needed for unusual or rare neuropathological cases.

Useful For:

Interpretation: This request will be processed as a consultation. Appropriate stains will be performed, and a diagnostic interpretation provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Collins KA, Powers JM: Autopsy procedures for the brain, spinal cord, and neuromuscular system. In: Collins KA, Hutchins GM, eds. Autopsy Performance and Reporting. 2nd ed. College of American Pathologists; 2003:chap 20 2. Crain BJ, Mirra SS: The autopsy in cases of Alzheimer's Disease and other dementias. In: Collins KA, Hutchins GM, eds. Autopsy Performance and Reporting. 2nd ed. College of American Pathologists; 2003:chap 21

CMA
9278

Centromere Antibodies, IgG, Serum

Clinical Information:

Useful For:

Interpretation:

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References: 1. Stochmal A, Czuwara J, Trojanowska M, et al. Antinuclear antibodies in systemic sclerosis: an update. Clin Rev Allergy Immunol 2020;58(1):40-51 2. Kajio N, Takeshita M, Suzuki K, et al. Anti-centromere antibodies target centromere-kinetochore macrocomplex: a comprehensive autoantigen profiling. Ann Rheum Dis. 2021;80(5):651-659 3. Earnshaw W, Bordwell B, Marino C, Rothfield N. Three human chromosomal autoantigens are recognized by sera from patients with anti-centromere antibodies. J Clin Invest. 1986;77(2):426-430 4. Takeshita M, Suzuki K, Kaneda Y, et al. Antigen-driven selection of antibodies against SSA, SSB and the centromere 'complex', including a novel antigen, MIS12 complex, in human salivary glands. Ann Rheum Dis. 2020;79(1):150-158 5. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of rheumatology/European League against rheumatism collaborative initiative. Ann Rheum Dis 2013;72(11):1747-1755 6. Kuramoto N, Ohmura K, Ikari K, et al. Anti-centromere antibody exhibits specific distribution levels among anti-nuclear antibodies and may characterize a distinct subset in rheumatoid arthritis. Sci Rep. 2017;7(1):6911 7. Cavazzana I, Vojinovic T, Airo P, et al. Systemic sclerosis-specific antibodies: novel and classical biomarkers. Clin Rev Allergy Immunol. 2023;64(3):412-430 8. Nihtyanova SI, Sari A, Harvey JC, et al. Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. Arthritis Rheumatol. 2020;72(3):465-476 9. Fritzler MJ, Rattner JB, Luft LM, et al. Historical perspectives on the discovery and elucidation of autoantibodies to centromere proteins (CENP) and the emerging importance of antibodies to CENP-F. Autoimmun Rev. 2011;10(4):194-200 10. Bossuyt X, De Langhe E, Borghi MO, Meroni PL. Understanding and interpreting antinuclear antibody tests in systemic rheumatic diseases. Nat Rev Rheumatol. 2020;16(12):715-726

CEAC
82387

Cephalosporium acremonium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Cephalosporium acremonium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CTSU
606147

Ceramide Trihexosides and Sulfatides, Random, Urine

Clinical Information: Urinary excretion of ceramide trihexosides (CT) can be suggestive of Fabry disease, while excretion of sulfatide with or without CT can be suggestive of metachromatic leukodystrophy, multiple sulfatase deficiency, mucolipidosis II (I-cell disease), or saposin B deficiency. Fabry disease is an X-linked recessive lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Affected individuals accumulate glycosphingolipids in the lysosomes throughout the body, particularly in the kidney, heart, and brain. Severity and onset of symptoms are dependent on the amount of residual enzyme activity. Symptoms may include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, corneal opacity, renal insufficiency leading to kidney failure, and cardiac and cerebrovascular disease. There are renal and cardiac variant forms of Fabry disease that may be underdiagnosed. Female patients who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected, and they may have alpha-Gal A activity in the normal range. Regardless of the severity of symptoms, individuals with Fabry disease may show an increased excretion of CT in urine. Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disorder most frequently caused by a deficiency of the arylsulfatase A enzyme. Various sulfatides accumulate in the brain, nervous system, and visceral organs, including the kidney and gallbladder and are excreted in the urine. Based on age of onset, the 3 clinical forms of MLD are late-infantile, juvenile, and adult, with late-infantile being the most common. All result in progressive neurologic changes and leukodystrophy demonstrated on magnetic resonance imaging. Symptoms may include hypotonia, clumsiness, diminished reflexes, slurred speech, behavioral problems, and personality changes. Individuals with MLD show an increased urinary excretion of sulfatides without CT. Saposin B deficiency is a rare condition with clinical features that mimic MLD; however, individuals with saposin B deficiency have normal arylsulfatase A activity. Individuals with saposin B deficiency typically have an increased urinary excretion of both sulfatides and CT. Low arylsulfatase A activity has been found in some clinically normal parents and other relatives of MLD patients. Individuals with this "pseudodeficiency" have been recognized with increasing frequency among patients with other apparently unrelated neurologic conditions as well as among the general population. This has been associated with a fairly common alteration in the arylsulfatase A gene (ARSA), which leads to low expression of the enzyme (5%-20% of normal). These individuals do not have metachromatic deposits in peripheral nerve tissues, and their urine sulfatides content is normal. Multiple sulfatase deficiency (MSD) is a rare autosomal recessive disorder caused by a defect in SUMF1, which is required

for post-translational activation of the family of 17 sulfatase enzymes, including arylsulfatase A and B. The clinical features of MSD include those of late-infantile MLD, dysmorphic features similar to the mucopolysaccharidoses, and ichthyosis as seen in steroid sulfatase deficiency. Individuals with MSD typically have an increased urinary excretion of sulfatides as well as increased urinary glycosaminoglycans (MPSQU / Mucopolysaccharides Quantitative, Random, Urine). Mucolipidosis II, also known as I-cell disease, is a rare autosomal recessive disorder with features of both mucopolysaccharidoses and sphingolipidoses. I-cell disease is a progressive disorder characterized by congenital or early infantile manifestations including coarse facial features, short stature, skeletal anomalies, cardio- and hepatomegaly, and developmental delays. Individuals with I-cell disease have abnormal oligosaccharide profiles (OLIGU / Oligosaccharide Screen, Random, Urine) and may show an increased urinary excretion of both CT and sulfatides.

Useful For: Identifying patients with Fabry disease Identifying patients with metachromatic leukodystrophy Identifying patients with saposin B deficiency Identifying patients with multiple sulfatase deficiency Identifying patients with mucolipidosis II (I-cell disease)

Interpretation: The pattern of ceramide trihexosides or sulfatide excretion will be described. A normal pattern of excretion suggests absence of these diseases (see Cautions). Evidence of ceramide trihexoside accumulation suggests decreased or deficient alpha-galactosidase activity, see Fabry Disease Testing Algorithm. Evidence of sulfatide accumulation suggests decreased or deficient arylsulfatase A activity. Follow-up with the specific enzyme assay is recommended: -ARSAW / Arylsulfatase A, Leukocytes -ARSU / Arylsulfatase A, 24 Hour, Urine To exclude multiple sulfatase deficiency (MSD), determination of iduronate-2-sulfatase activity is recommended. -I2SWB / Iduronate-2-Sulfatase, Leukocytes -I2SB / Iduronate-2-Sulfatase, Blood Spot Evidence of both ceramide trihexoside and sulfatide accumulation suggests a diagnosis of mucolipidosis II (I-cell disease) or saposin B deficiency. Follow-up testing to rule-out I-cell disease may include molecular analysis of the GNPTAB gene or measurement of serum hydrolases (NAGS / Hexosaminidase A and Total Hexosaminidase, Serum). Molecular genetic testing is required to confirm saposin B deficiency. For more information see Lysosomal Disorders Diagnostic Algorithm, Part 2

Reference Values:
An interpretive report will be provided.

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Accessed October 30, 2023. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Desnick RJ, Ioannou YA, Eng CM. Alpha-galactosidase A deficiency: Fabry disease. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed November 29, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546984 3. Kuchar L, Ledvinova J, Hrebicek M, et al. Prosaposin deficiency and saposin B deficiency (activator-deficient metachromatic leukodystrophy): report on two patients detected by analysis of urinary sphingolipids and carrying novel PSAP gene mutations. Am J Med Genet A. 2009;149A(4):613-621 4. Mehta A, Hughes DA. Fabry disease. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated March 9, 2023. Accessed November 29, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1292/ 5. Schlotawa L, Ennemann EC, Radhakrishnan K, et al. SUMF1 mutations affecting stability and activity of formylglycine generating enzyme predict clinical outcome in multiple sulfatase deficiency. Eur J Hum Genet. 2011;19(3):253-261 6. Gieselmann V, Ingeborg K. Metachromatic leukodystrophy. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed November 29, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546629 7. Leroy JG, Cathey SS, Friez MJ. GNPTAB-related disorders. In: Adam MP, Feldman J, Mirzaa GM, et al, eds.

GeneReviews [Internet]. University of Washington, Seattle; 2008. Updated August 29, 2019. Accessed November 29, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1828/

SFINC 2762 Cerebrospinal Fluid (CSF) IgG Index, Spinal Fluid

Clinical Information: Elevation of IgG in the cerebrospinal fluid (CSF) of patients with inflammatory diseases of the central nervous system (CNS), such as multiple sclerosis (MS), neurosyphilis, acute inflammatory polyradiculoneuropathy, and subacute sclerosing panencephalitis, may be due to local (intrathecal) synthesis of IgG. Elevations of CSF IgG or the CSF/serum IgG ratio may also occur as a result of permeability of the blood brain barrier, and hence, a correction using albumin measurements in CSF and serum is appropriate. The CSF index is the CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The CSF index is, therefore, an indicator of the relative amount of CSF IgG compared to serum. Any increase in the index reflects IgG production in the CNS. The IgG synthesis rate is a mathematical manipulation of the CSF index data and can also be used as a marker for CNS inflammatory diseases. The test is commonly ordered with oligoclonal banding or immunoglobulin kappa free light chains in CSF to aid in the diagnosis of demyelinating conditions.

Useful For: Aiding in the diagnosis of multiple sclerosis and other central nervous system inflammatory conditions using cerebrospinal fluid specimens

Interpretation: Cerebrospinal fluid (CSF) IgG synthesis rate indicates the rate of increase in the daily CSF production of IgG in milligrams per day. A result greater than 12 mg/24 hours is elevated. A CSF IgG index greater than 0.70 is elevated and indicative of increased synthesis of IgG.

Reference Values:
Only orderable as part of a profile. For more information see SFIG / Cerebrospinal Fluid IgG Index Profile, Serum and Spinal Fluid.

CSF index: 0.00-0.70
CSF IgG: 0.0-8.1 mg/dL
CSF albumin: 0.0-27.0 mg/dL
CSF IgG/albumin: 0.00-0.21
CSF IgG synthesis rate: 0-12 mg/24 hours

Clinical References: 1. Tourtellotte WW, Walsh MJ, Baumhefner RW, et al: The current status of multiple sclerosis intra-blood-brain-barrier IgG synthesis. Ann NY Acad Sci. 1984;436:52-67 2. Bloomer LC, Bray PF: Relative value of three laboratory methods in the diagnosis of multiple sclerosis. Clin Chem. 1981;27:2011-2013 3. Hische EA, van der Helm HJ: Rate of synthesis of IgG within the blood-brain barrier and the IgG index compared in the diagnosis of multiple sclerosis. Clin Chem. 1987;33:113-114 4. Thompson AJ, Banwell BL, Barkhof F, et al: Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018 Feb;17(2):162-73. doi: 10.1016/S1474-4422(17)30470-2 5. Gurtner KM, Shosha E, Bryant SC, et al: CSF free light chain identification of demyelinating disease: comparison with oligoclonal banding and other CSF indexes. Clin Chem Lab Med. 2018 Jun 27;56(7):1071-1080. doi: 10.1515/cclm-2017-0901 6. Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

SFIG 610783 Cerebrospinal Fluid IgG Index Profile, Serum and Spinal Fluid

Clinical Information: Elevation of IgG in the cerebrospinal fluid (CSF) of patients with inflammatory diseases of the central nervous system (CNS), such as multiple sclerosis, neurosyphilis, acute inflammatory polyradiculoneuropathy, and subacute sclerosing panencephalitis may be due to local (intrathecal) synthesis of IgG. The CSF index is the CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The CSF index is, therefore, an indicator of the relative amount of CSF IgG compared to serum. Any increase in the index reflects IgG production in the CNS. The IgG synthesis rate

is a mathematical manipulation of the CSF index data and can also be used as a marker for CNS inflammatory diseases. The test is commonly ordered with oligoclonal banding or immunoglobulin kappa free light chains in CSF to aid in the diagnosis of demyelinating conditions.

Useful For: Aiding in the diagnosis of multiple sclerosis and other central nervous system inflammatory conditions

Interpretation: Cerebrospinal fluid (CSF) IgG synthesis rate indicates the rate of increase in the daily CSF production of IgG in milligrams per day. A result greater than 12 mg/24 h is elevated. A CSF IgG index greater than 0.70 is elevated and indicative of increased synthesis of IgG.

Reference Values:
CSF index: 0.00-0.70
CSF IgG: 0.0-8.1 mg/dL
CSF albumin: 0.0-27.0 mg/dL

Serum IgG
0-4 months: 100-334 mg/dL
5-8 months: 164-588 mg/dL
9-14 months: 246-904 mg/dL
15-23 months: 313-1,170 mg/dL
2-3 years: 295-1,156 mg/dL
4-6 years: 386-1,470 mg/dL
7-9 years: 462-1,682 mg/dL
10-12 years: 503-1,719 mg/dL
13-15 years: 509-1,580 mg/dL
16-17 years: 487-1,327 mg/dL
> or =18 years: 767-1,590 mg/dL

Serum albumin
> or =12 months: 3,500-5,000 mg/dL
Reference values have not been established for patients who are younger than 12 months.

CSF IgG/albumin: 0.00-0.21
Serum IgG/albumin: 0.0-0.4
CSF IgG synthesis rate: 0-12 mg/24 h
Albumin quotient: <14

Clinical References: 1. Tourtellotte WW, Walsh MJ, Baumhefner RW, Staugaitis SM, Shapshak P. The current status of multiple sclerosis intra-blood-brain-barrier IgG synthesis. Ann NY Acad Sci. 1984;436:52-67 2. Bloomer LC, Bray PF: Relative value of three laboratory methods in the diagnosis of multiple sclerosis. Clin Chem. 1981 Dec;27(12):2011-2013 3. Hische EA, van der Helm HJ: Rate of synthesis of IgG within the blood-brain barrier and the IgG index compared in the diagnosis of multiple sclerosis. Clin Chem. 1987 Jan;33(1):113-114 4. Thompson AJ, Banwell BL, Barkhof F, et al: Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018 Feb;17(2):162-73. doi:10.1016/S1474-4422(17)30470-2 5. Gurtner KM, Shosha E, Bryant SC, et al: CSF free light chain identification of demyelinating disease: comparison with oligoclonal banding and other CSF indexes. Clin Chem Lab Med. 2018 Jun 27;56(7):1071-1080. doi:10.1515/cclm-2017-0901 6. Rifai N, Chiu, RWK, Burnham, CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 7. Saadeh RS, Ramos PA, Algeciras-Schimnich A, Flanagan EP, Pittock SJ, Willrich MA. An update on laboratory-based diagnostic biomarkers for multiple sclerosis and beyond. Clin Chem. 2022;68(9):1134-1150

CTXWB
113444

Cerebrotendinous Xanthomatosis, Blood

Clinical Information: Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disorder of bile acid synthesis resulting from the deficiency of the mitochondrial enzyme, sterol 27-hydrolase. Sterol 27-hydrolase is an important enzyme in both the alternative and classic bile acid synthesis pathways. Consequently, patients with CTX will experience increased storage of the sterol, cholestenol, and ketosterol bile acid precursors (7-alpha-hydroxy-4-cholesten-3-one [7aC4] and 7-alpha,12-alpha-dihydroxycholest-4-en-3-one [7a12aC4]) in multiple tissues throughout the body with a resulting deficiency of the bile acid, chenodeoxycholic acid (CDCA). CTX is caused by disease-causing variants in the CYP27A1 gene. Patients with CTX can present with a constellation of findings including infantile onset diarrhea, childhood onset cataracts, development of tendon/cerebral xanthomas in adolescence and early adulthood, early onset osteoporosis, as well as a broad array of neuropsychological manifestations, such as intellectual disability, dementia, psychiatric symptoms, ataxia, pyramidal signs, dystonia, and muscle weakness. Patients may occasionally present with cholestatic liver disease, which may present as jaundice, poor growth, and hepatosplenomegaly. Intrafamilial variability exists and can be substantial. Some heterozygous carriers may experience a higher incidence of cardiac disorders or gallstones; however, carriers are typically asymptomatic. Treatment with CDCA has been shown to improve both biochemical and clinical outcomes in patients with CTX. Supplementation with beta-hydroxy beta-methylglutaryl-CoA (HMG-CoA) reductase inhibitors can be used as alternative treatment alone or in combination with CDCA. Cholic acid treatment has been used in few patients showing a decrease in cholestanol levels and improvement in neurologic symptoms. The availability of effective therapy makes early diagnosis and treatment of patients with CTX essential. The diagnostic evaluation of patients with suspected CTX may reveal abnormalities on brain magnetic resonance imaging (eg, cerebellar atrophy, decrease in volume of grey and white matter, and abnormal white matter signal) in addition to the biochemical and clinical abnormalities. The biochemical diagnosis of CTX can be confirmed by molecular genetic analysis of the CYP27A1 gene (included in CHLGP / Cholestasis Gene Panel, Varies; or order CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies and indicate the gene to be assessed).

Useful For: Evaluating patients with a clinical suspicion of cerebrotendinous xanthomatosis (CTX) Monitoring of individuals with CTX on chenodeoxycholic acid (CDCA) therapy This test is not useful for the identification of carriers. This test is not useful for the evaluation of bile acid malabsorption.

Interpretation: An elevation of 7-alpha-hydroxy-4-cholesten-3-one (7a-C4) or 7-alpha,12-alpha-dihydroxycholest-4-en-3-one (7a12aC4) or both is strongly suggestive of cerebrotendinous xanthomatosis.

Reference Values:
7-Alpha-hydroxy-4-cholesten-3-one (7a-C4)
Cutoff: < or =0.750 nmol/mL

7-Alpha,12-alpha-dihydroxycholest-4-en-3-one (7a12aC4)
Cutoff: < or =0.250 nmol/mL

Clinical References: 1. Mignarri A, Magni A, Del Puppo M, et al. Evaluation of cholesterol metabolism in cerebrotendinous xanthomatosis. J Inherit Metab Dis. 2016;39(1):75-83 2. Nie S, Chen G, Cao X, Zhang Y. Cerebrotendinous xanthomatosis: a comprehensive review of pathogenesis, clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2014;9:179 3. DeBarber AE, Luo J, Star-Weinstock M, et al. A blood test for cerebrotendinous xanthomatosis with potential for disease detection in newborns. J Lipid Res. 2014;55(1):146-154 4. Federico A, Gallus GN. Cerebrotendinous xanthomatosis. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated November 14, 2024. Accessed December 2, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1409/ 5. Lutjohann D, Stellaard F, Bjorkhem I. Levels of 7alpha-hydroxycholesterol and/or 7alpha-hydroxy-4-cholest-3-one are the optimal biochemical markers for the

evaluation of treatment of cerebrotendinous xanthomatosis. J Neurol. 2020;267(2):572-573. doi:10.1007/s00415-019-09650-0 6. Mandia D, Chaussenot A, Besson G, et al. Cholic acid as a treatment for cerebrotendinous xanthomatosis in adults. J Neurol. 2019;266(8):2043-2050. doi:10.1007/s00415-019-09377-y 7. Nobrega PR, Bernardes AM, Ribeiro RM, et al. Cerebrotendinous xanthomatosis: A practice review of pathophysiology, diagnosis, and treatment. Front Neurol. 2022;13:1049850. Published 2022 Dec 23. doi:10.3389/fneur.2022.1049850

CTXBS 65630 Cerebrotendinous Xanthomatosis, Blood Spot

Clinical Information:

Useful For: Evaluating patients with a clinical suspicion of cerebrotendinous xanthomatosis (CTX) using dried blood spot specimens Monitoring individuals with CTX on chenodeoxycholic acid (CDCA) therapy This test is not useful for the identification of carriers. This test is not useful for the evaluation of bile acid malabsorption.

Interpretation: An elevation of 7-alpha-hydroxy-4-cholesten-3-one (7aC4) or 7-alpha,12 alpha-dihydroxycholest-4-en-3-one (7a12aC4) or both is strongly suggestive of cerebrotendinous xanthomatosis.

Reference Values:

7-Alpha-hydroxy-4-cholesten-3-one (7a-C4)
Cutoff: < or =0.750 nmol/mL

7-Alpha,12-alpha-dihydroxycholest-4-en-3-one (7a12aC4)
Cutoff: < or =0.250 nmol/mL

Clinical References: 1. Mignarri A, Magni A, Del Puppo M, et al. Evaluation of cholesterol metabolism in cerebrotendinous xanthomatosis. J Inherit Metab Dis. 2016;39(1):75-83 2. Nie S, Chen G, Cao X, Zhang Y. Cerebrotendinous xanthomatosis: a comprehensive review of pathogenesis, clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2014;9:179 3. DeBarber AE, Luo J, Star-Weinstock M, et al. A blood test for cerebrotendinous xanthomatosis with potential for disease detection in newborns. J Lipid Res. 2014;55(1):146-154 4. Federico A, Gallus GN. Cerebrotendinous xanthomatosis. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet].University of Washington, Seattle; 2003. Updated November 14, 2024. Accessed November 29, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1409/ 5. Lutjohann D, Stellaard F, Bjorkhem I. Levels of 7alpha-hydroxycholesterol and/or 7alpha-hydroxy-4-cholest-3-one are the optimal biochemical markers for the evaluation of treatment of cerebrotendinous xanthomatosis. J Neurol. 2020;267(2):572-573. doi:10.1007/s00415-019-09650-0 6. Mandia D, Chaussenot A, Besson G, et al. Cholic acid as a treatment for cerebrotendinous xanthomatosis in adults. J Neurol. 2019;266(8):2043-2050. doi:10.1007/s00415-019-09377-y 7. Nobrega PR, Bernardes AM, Ribeiro RM, et al. Cerebrotendinous xanthomatosis: A practice review of pathophysiology, diagnosis, and treatment. Front Neurol. 2022;13:1049850. Published 2022 Dec 23. doi:10.3389/fneur.2022.1049850

CTXP 65631 Cerebrotendinous Xanthomatosis, Plasma

Clinical Information:

Useful For: Evaluating patients with a clinical suspicion of cerebrotendinous xanthomatosis (CTX) using plasma specimens Monitoring of individuals with CTX on chenodeoxycholic acid (CDCA) therapy This test is not useful for the identification of carriers. This test is not useful for the evaluation

of bile acid malabsorption.

Interpretation: An elevation of 7-alpha-hydroxy-4-cholesten-3-one (7aC4) or 7-alpha,12-alpha-dihydroxycholest-4-en-3-one (7a12aC4) or both is strongly suggestive of cerebrotendinous xanthomatosis.

Reference Values:

7-Alpha-hydroxy-4-cholesten-3-one (7a-C4)
Cutoff: < or =0.300 nmol/mL

7-Alpha,12-alpha-dihydroxycholest-4-en-3-one (7a12aC4)
Cutoff: < or =0.100 nmol/mL

Clinical References: 1. Mignarri A, Magni A, Del Puppo M, et al. Evaluation of cholesterol metabolism in cerebrotendinous xanthomatosis. J Inherit Metab Dis. 2016;39(1):75-83 2. Nie S, Chen G, Cao X, Zhang Y. Cerebrotendinous xanthomatosis: a comprehensive review of pathogenesis, clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2014;9:179 3. DeBarber AE, Luo J, Star-Weinstock M, et al. A blood test for cerebrotendinous xanthomatosis with potential for disease detection in newborns. J Lipid Res. 2014;55(1):146-154 4. Federico A, Gallus GN. Cerebrotendinous xanthomatosis. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews[Internet]. University of Washington, Seattle; 2003. Updated November 14, 2024. Accessed December 2, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1409/ 5. Lutjohann D, Stellaard F, Bjorkhem I. Levels of 7alpha-hydroxycholesterol and/or 7alpha-hydroxy-4-cholest-3-one are the optimal biochemical markers for the evaluation of treatment of cerebrotendinous xanthomatosis. J Neurol. 2020;267(2):572-573. doi:10.1007/s00415-019-09650-0 6. Mandia D, Chaussenot A, Besson G, et al. Cholic acid as a treatment for cerebrotendinous xanthomatosis in adults. J Neurol. 2019;266(8):2043-2050. doi:10.1007/s00415-019-09377-y 7. Nobrega PR, Bernardes AM, Ribeiro RM, et al. Cerebrotendinous xanthomatosis: A practice review of pathophysiology, diagnosis, and treatment. Front Neurol. 2022;13:1049850. Published 2022 Dec 23. doi:10.3389/fneur.2022.1049850

FCZAC
75563

Certolizumab and Anti-Certolizumab Antibody, DoseASSURE CTZ

Useful For: Provides certolizumab drug concentration and anti-certolizumab antibodies in order to optimize treatment and facilitate clinical decision-making. This assay may be helpful in any patient on certolizumab therapy for Crohn's disease, psoriasis, or other autoimmune condition.

Reference Values:

Certolizumab:
Quantitation Limit: <1.0 ug/mL

Results of 1 ug/mL or higher indicate detection of certolizumab

Anti-Certolizumab Antibody:
Quantitation Limit: <40 ng/mL

Results of 40 ng/mL or higher indicate detection of anti-certolizumab pegol antibodies.

CERS
614504

Ceruloplasmin, Serum

Clinical Information: Ceruloplasmin is a positive acute-phase reactant and a copper-binding protein that accounts for over 95% of serum copper in normal adults. Ceruloplasmin is measured primarily to assist with a diagnosis of Wilson disease. Other indications include Menkes disease, dietary copper insufficiency, and risk of cardiovascular disease. Wilson disease is a rare inherited disorder of copper transport that results in low serum copper and ceruloplasmin and accumulation of copper in various tissues. The pathological accumulation of copper in the liver, brain, cornea, and kidney causes cirrhosis, neuropsychiatric symptoms, Kayser-Fleischer rings, and hematuria/proteinuria, respectively. See Wilson Disease Testing Algorithm for appropriate use of clinical findings, serum biomarkers, genetic tests, and tissue biopsies when working up suspected cases. Menkes disease is an X-linked disorder in which dietary copper is absorbed from the gastrointestinal tract but cannot be transported, so copper is not available to the liver for incorporation into ceruloplasmin. Dietary ceruloplasmin deficiency may be due to inadequate dietary copper intake, long-term parenteral nutrition without copper supplementation, malabsorption, penicillamine therapy, or a combination of these.

Useful For: Investigation of patients with possible Wilson disease

Interpretation: Low concentrations of ceruloplasmin are consistent with Wilson disease and warrant further investigation according to the recommended algorithm; see Wilson Disease Testing Algorithm. Ceruloplasmin is a positive acute-phase reactant. Increases in serum ceruloplasmin have been reported during pregnancy, in women taking oral contraceptives, in hepatitis, pneumonia, tuberculosis, rheumatoid arthritis, myocardial infarction, various forms of anemia, and many obscure neurological disorders.

Reference Values:

Males:
0-8 weeks: 7.4-23.7 mg/dL
9 weeks-5 months: 13.5-32.9 mg/dL
6-11 months: 13.7-38.9 mg/dL
12 months-7 years: 21.7-43.3 mg/dL
8-13 years: 20.5-40.2 mg/dL
14-17 years: 17.0-34.8 mg/dL
> or =18 years: 19.0-31.0 mg/dL

Females:
0-8 weeks: 7.4-23.7 mg/dL
9 weeks-5 months: 13.5-32.9 mg/dL
6-11 months: 13.7-38.9 mg/dL
12 months-7 years: 21.7-43.3 mg/dL
8-13 years: 20.5-40.2 mg/dL
14-17 years: 20.8-43.2 mg/dL
> or =18 years: 20.0-51.0 mg/dL

Clinical References: 1. Wilson Tang WH, Wu Y, Hartiala J, et al: Clinical and genetic association of serum ceruloplasmin with cardiovascular risk. Arterioscler Thromb Vasc Biol. 2012 Feb;32(2):516-522 2. Dadu RT, Dodge R, Nambi V, et al: Ceruloplasmin and heart failure in the Atherosclerosis Risk in Communities study. Circ Heart Fail. 2013 Sep 1;6(5):936-943 3. Cox DW, Tumer Z, Roberts EA: Copper transport disorders: Wilson's disease and Menkes disease. Inborn Metabolic Disease. Fernandes J, Sandubray JM, VandenBerghe F, eds. Springer-Verlag; 2000:385-391 4. Sontakke AN, More U: Changes in serum ceruloplasmin levels with commonly used methods of contraception. Indian J Clin Biochem. 2004 Jan:19(1):102-104 5. Schilsky ML: Wilson disease: Diagnosis, treatment, and follow-up. Clin Liver Dis. 2017 Nov;21(4):755-767 6. Hermann W: Classification and differential diagnosis of Wilson's disease. Ann Transl Med. 2019 Apr;7(Suppl 2):S63

G162
605195

CGO Custom Gene Panel (LPGD) (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

CHGL
82384

Chaetomium globosum, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to Chaetomium globosum Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FAMCE
57914

Cheese American IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

FCCGG
57573

Cheese Cheddar IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests

FSCE
57936

Cheese Swiss IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

CCHZ
82752

Cheese, Cheddar, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cheddar cheese Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MCHZ
82751

Cheese, Mold, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cheese mold Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of

allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CHER
82798

Cherry, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cherry Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon

identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CTRE
82607

Chestnut Tree, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to chestnut tree Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CNUT
82870

Chestnut, Sweet, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to sweet chestnut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with

the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CHXP
82494

Chick Pea, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to chick pea Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CDROP
82142

Chicken Droppings, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to chicken droppings Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CHCK
82713

Chicken Feathers, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to chicken feathers Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FCHXG
57625

Chicken IgG

Interpretation: These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

CSPR
82351

Chicken Serum Proteins, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to chicken serum proteins Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine

if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CHIC
82703

Chicken, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to chicken Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CHIKG
63868

Chikungunya IgG, Antibody, Serum

Clinical Information: Chikungunya virus (ChikV) is a single-stranded RNA alphavirus and a member of the Togaviridae family of viruses. The name Chikungunya is derived from the language of the Makonde ethnic groups in southeast Africa and means "that which bends" or "stooped walk." This is in reference to the hunched-over appearance of infected individuals due to the characteristically painful and incapacitating arthralgia caused by the virus. ChikV is endemic throughout Africa, India, and, more recently, the Caribbean islands. In 2014, the first case of autochthonous, or local transmission, in the US occurred in Florida. Humans are the primary reservoir for ChikV and Aedes species mosquitos are the primary vectors for transmission. Unlike other mosquito-borne viruses such as West Nile virus and Dengue, the majority of individuals who are exposed to ChikV become symptomatic, with the most severe manifestations observed at the extremes of age and in those with suppressed immunity. Once exposed to ChikV, individuals develop lasting immunity and protection from reinfection. Prior to development of symptoms, the incubation period ranges, on average, from 3 to 7 days. Infected patients typically present with sudden-onset high fever, incapacitating joint pain, and often a maculopapular rash lasting anywhere from 3 to 10 days. Notably, symptom relapse can occur in some individuals 2 to 3 months following resolution of initial symptoms. Currently, there are no licensed vaccines and treatment is strictly supportive care.

Useful For: Aiding in the diagnosis of recent infection with Chikungunya virus detecting IgG antibodies in patients with recent travel to endemic areas and a compatible clinical syndrome

Interpretation: IgM and IgG Negative: -No serologic evidence of exposure to Chikungunya virus. Repeat testing on a new specimen collected in 5 to 10 days is recommended if clinical suspicion persists. IgM and IgG Positive: -IgM and IgG antibodies to Chikungunya virus detected, suggesting

recent or past infection. IgM antibodies to Chikungunya virus may remain detectable for 3 to 4 months post-infection. IgM Positive, IgG Negative: -IgM antibodies to Chikungunya virus detected, suggesting recent infection. Repeat testing in 5 to 10 days is recommended to demonstrate anti-Chikungunya virus IgG seroconversion to confirm current infection. IgM Negative, IgG Positive: -IgG antibodies to Chikungunya virus detected, suggesting past infection. IgM and/or IgG Borderline: -Repeat testing in 10 to 14 days is recommended.

Reference Values:

Only orderable as part of a profile. For more information see CHIKV / Chikungunya IgM and IgG, Antibody, Serum.

Negative
Reference values apply to all ages.

Clinical References: Lwande OW, Obanda V, Bucht G, et al. Global emergence of Alphaviruses that cause arthritis in humans. Infect Ecol Epidemiol. 2015:29853. doi:10.3402/iee.v5.29853

CHIKV
64173

Chikungunya IgM and IgG, Antibody, Serum

Clinical Information: Chikungunya virus (ChikV) is a single-stranded RNA alphavirus and a member of the Togaviridae family of viruses. The name Chikungunya is derived from the language of the Makonde ethnic groups in southeast Africa and means "that which bends" or "stooped walk." This is in reference to the hunched-over appearance of infected individuals due to the characteristically painful and incapacitating arthralgia caused by the virus. ChikV is endemic throughout Africa, India, and, more recently, the Caribbean islands. In 2014, the first case of autochthonous, or local transmission, in the United States occurred in Florida. Humans are the primary reservoir for ChikV and Aedes species mosquitos are the primary vectors for transmission. Unlike other mosquito-borne viruses, such as West Nile virus and Dengue, the majority of individuals who are exposed to ChikV become symptomatic, with the most severe manifestations observed at the extremes of age and in those with suppressed immunity. Once exposed to ChikV, individuals develop lasting immunity and protection from reinfection. Prior to development of symptoms, the incubation period ranges, on average, from 3 to 7 days. Infected patients typically present with sudden-onset high fever, incapacitating joint pain, and often a maculopapular rash lasting anywhere from 3 to 10 days. Notably, symptom relapse can occur in some individuals 2 to 3 months following resolution of initial symptoms. Currently, there are no licensed vaccines and treatment is strictly supportive care.

Useful For: Aiding in the diagnosis of recent infection with Chikungunya virus in patients with recent travel to endemic areas and a compatible clinical syndrome

Interpretation: IgM and IgG Negative: -No serologic evidence of exposure to Chikungunya virus. Repeat testing on a new specimen collected in 5 to 10 days is recommended if clinical suspicion persists. IgM and IgG Positive: -IgM and IgG antibodies to Chikungunya virus detected, suggesting recent or past infection. IgM antibodies to Chikungunya virus may remain detectable for 3 to 4 months post-infection. IgM Positive, IgG Negative: -IgM antibodies to Chikungunya virus detected, suggesting recent infection. Repeat testing in 5 to 10 days is recommended to demonstrate anti-Chikungunya virus IgG seroconversion to confirm current infection. IgM Negative, IgG Positive: -IgG antibodies to Chikungunya virus detected, suggesting past infection. IgM and/or IgG Borderline: -Repeat testing in 10 to 14 days is recommended.

Reference Values:

IgM: Negative
IgG: Negative

Reference values apply to all ages.

Clinical References: Lwande OW, Obanda V, Bucht G, et al. Global emergence of Alphaviruses that cause arthritis in humans. Infect Ecol Epidemiol. 2015;5:29853. doi:10.3402/iee.v5.29853

CHIKM
63867

Chikungunya IgM, Antibody, Serum

Clinical Information: Chikungunya virus (ChikV) is a single-stranded RNA alphavirus and a member of the Togaviridae family of viruses. The name Chikungunya is derived from the language of the Makonde ethnic groups in southeast Africa and means "that which bends" or "stooped walk." This is in reference to the hunched-over appearance of infected individuals due to the characteristically painful and incapacitating arthralgia caused by the virus. ChikV is endemic throughout Africa, India, and, more recently, the Caribbean islands. In 2014, the first case of autochthonous, or local transmission, in the United States occurred in Florida. Humans are the primary reservoir for ChikV and Aedes species mosquitos are the primary vectors for transmission. Unlike other mosquito-borne viruses such as West Nile virus and Dengue, the majority of individuals who are exposed to ChikV become symptomatic, with the most severe manifestations observed at the extremes of age and in those with suppressed immunity. Once exposed to ChikV, individuals develop lasting immunity and protection from reinfection. Prior to development of symptoms, the incubation period ranges, on average, from 3 to 7 days. Infected patients typically present with sudden-onset high fever, incapacitating joint pain, and often a maculopapular rash lasting anywhere from 3 to 10 days. Notably, symptom relapse can occur in some individuals 2 to 3 months following resolution of initial symptoms. Currently, there are no licensed vaccines and treatment is strictly supportive care.

Useful For: Aiding in the diagnosis of recent infection with Chikungunya virus detecting IgM antibodies in patients with recent travel to endemic areas and a compatible clinical syndrome

Interpretation: IgM and IgG Negative: -No serologic evidence of exposure to Chikungunya virus. Repeat testing on a new specimen collected in 5 to 10 days is recommended if clinical suspicion persists. IgM and IgG Positive: -IgM and IgG antibodies to Chikungunya virus detected, suggesting recent or past infection. IgM antibodies to Chikungunya virus may remain detectable for 3 to 4 months post-infection. IgM Positive, IgG Negative: -IgM antibodies to Chikungunya virus detected, suggesting recent infection. Repeat testing in 5 to 10 days is recommended to demonstrate anti-Chikungunya virus IgG seroconversion to confirm current infection. IgM Negative, IgG Positive: -IgG antibodies to Chikungunya virus detected, suggesting past infection. IgM and/or IgG Borderline: -Repeat testing in 10 to 14 days is recommended.

Reference Values:
Only orderable as part of a profile. For more information see CHIKV / Chikungunya IgM and IgG, Antibody, Serum.

Negative
Reference values apply to all ages.

Clinical References: Lwande OW, Obanda V, Bucht G, et al. Global emergence of Alphaviruses that cause arthritis in humans. Infect Ecol Epidemiol. 2015;5:29853. doi:10.3402/iee.v5.29853

CHIKI
37102

Chikungunya Interpretation

Clinical Information: Chikungunya virus (ChikV) is a single-stranded RNA alphavirus and a member of the Togaviridae family of viruses. The name Chikungunya is derived from the language of

the Makonde ethnic groups in southeast Africa and means "that which bends" or "stooped walk." This is in reference to the hunched-over appearance of infected individuals due to the characteristically painful and incapacitating arthralgia caused by the virus. ChikV is endemic throughout Africa, India, and, more recently, the Caribbean islands. In 2014, the first case of autochthonous, or local transmission, in the United States occurred in Florida. Humans are the primary reservoir for ChikV and Aedes species mosquitos are the primary vectors for transmission. Unlike other mosquito-borne viruses, such as West Nile virus and Dengue, the majority of individuals who are exposed to ChikV become symptomatic, with the most severe manifestations observed at the extremes of age and in those with suppressed immunity. Once exposed to ChikV, individuals develop lasting immunity and protection from reinfection. Prior to development of symptoms, the incubation period ranges, on average, from 3 to 7 days. Infected patients typically present with sudden-onset high fever, incapacitating joint pain, and often a maculopapular rash lasting anywhere from 3 to 10 days. Notably, symptom relapse can occur in some individuals 2 to 3 months following resolution of initial symptoms. Currently, there are no licensed vaccines and treatment is strictly supportive care.

Useful For: Interpretation of testing that aids in the diagnosis of recent infection with Chikungunya virus in patients with recent travel to endemic areas and a compatible clinical syndrome

Interpretation: IgM and IgG Negative: -No serologic evidence of exposure to Chikungunya virus. Repeat testing on a new specimen collected in 5 to 10 days is recommended if clinical suspicion persists. IgM and IgG Positive: -IgM and IgG antibodies to Chikungunya virus detected, suggesting recent or past infection. IgM antibodies to Chikungunya virus may remain detectable for 3 to 4 months post-infection. IgM Positive, IgG Negative: -IgM antibodies to Chikungunya virus detected, suggesting recent infection. Repeat testing in 5 to 10 days is recommended to demonstrate anti-Chikungunya virus IgG seroconversion to confirm current infection. IgM Negative, IgG Positive: -IgG antibodies to Chikungunya virus detected, suggesting past infection. IgM and/or IgG Borderline: -Repeat testing in 10 to 14 days is recommended.

Reference Values:
Only orderable as part of a profile. For more information see CHIKV / Chikungunya IgM and IgG, Antibody, Serum.

An interpretive report will be provided.

Clinical References: Lwande OW, Obanda V, Bucht G, et al. Global emergence of Alphaviruses that cause arthritis in humans. Infect Ecol Epidemiol. 2015;5:29853. doi:10.3402/iee.v5.29853

CHIKS
603833

Chikungunya Virus, PCR, Molecular Detection, Serum

Clinical Information: Chikungunya virus (CHIK) is an RNA virus of the genus Alphavirus, family Togaviridae, transmitted mainly through the bite of infected mosquitoes in the genus Aedes (Aedes aegypti and Aedes albopictus). This is the same mosquito that transmits dengue, yellow fever, and Zika viruses. Most people infected with chikungunya virus will develop some symptoms, most commonly fever and joint pain. There is no specific antiviral treatment for chikungunya virus infection. Most cases of disease have occurred in Africa, Asia, Europe, and the Indian and Pacific Oceans, but transmission of CHIK has been identified in Caribbean countries and South American regions, as well as foci in the southern United States. Infection with chikungunya virus may be suspected based on symptoms (fever, joint pain, and headache) and recent history of travel. A diagnosis of CHIK infection can be confirmed through laboratory tests on serum or cerebrospinal fluid. This assay is designed to detect only species of clinical significance and is to be used for patients with a clinical history and symptoms consistent with chikungunya infection.

Useful For: Qualitative detection of chikungunya virus in serum after early symptom onset (ideally <7 days) This test is not recommended for screening healthy patients.

Interpretation: A positive test result indicates the presence of chikungunya virus RNA in the specimen. A negative test result with a positive internal control indicates that chikungunya virus RNA is not detectable in the specimen. A negative test result with a negative internal control is considered evidence of polymerase chain reaction inhibition or reagent failure. A new specimen should be collected for testing if clinically indicated.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Lanciotti RS, Kosoy OL, Laven JJ, et.al. Chikungunya virus in US travelers returning from India, 2006. Emerg Infect Dis. 2007;13(5):764-767 2. Johnson BW, Russell BJ, Goodman CH. Laboratory diagnosis of chikungunya virus infections and commercial sources for diagnostic assays. J Infect Dis. 2016;214(suppl 5):S471-S474. doi:10.1093/infdis/jiw274 3. Morrison TE. Reemergence of chikungunya virus. J Virol. 2014;88(20):11644-11647

CHIKC
603832

Chikungunya Virus, PCR, Molecular Detection, Spinal Fluid

Clinical Information: Chikungunya virus (CHIK) is an RNA virus of the genus Alphavirus, family Togaviridae transmitted mainly through the bite of infected mosquitoes in the genus Aedes (Aedes aegypti and Aedes albopictus). This is the same mosquito that transmits dengue, yellow fever, and Zika viruses. Most people infected with chikungunya virus will develop some symptoms, most commonly fever and joint pain. There is no specific antiviral treatment for chikungunya virus infection. Most cases of disease have occurred in Africa, Asia, Europe, and the Indian and Pacific Oceans, but transmission of CHIK has been identified in Caribbean countries and South American regions, as well as foci in the southern United States. Infection with chikungunya virus may be suspected based on symptoms (fever, joint pain, and headache) and recent history of travel. A diagnosis of CHIK infection can be confirmed through laboratory tests on serum or cerebrospinal fluid. This assay is designed to detect only species of clinical significance and is to be used for patients with a clinical history and symptoms consistent with chikungunya infection.

Useful For: Qualitative detection of chikungunya virus in cerebrospinal fluid after early symptom onset (ideally <7 days) This test is not recommended for screening healthy patients.

Interpretation: A positive test result indicates the presence of chikungunya virus RNA in the specimen. A negative test result with a positive internal control indicates that chikungunya virus RNA is not detectable in the specimen. A negative test result with a negative internal control is considered evidence of polymerase chain reaction inhibition or reagent failure. A new specimen should be collected for testing if clinically indicated.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Lanciotti RS, Kosoy OL, Laven JJ, et.al. Chikungunya virus in US travelers returning from India, 2006. Emerg Infect Dis. 2007;13(5):764-767 2. Johnson BW, Russell BJ, Goodman CH. Laboratory diagnosis of chikungunya virus infections and commercial sources for diagnostic assays. J Infect Dis. 2016;214(suppl 5):S471-S474. doi:10.1093/infdis/jiw274 3. Morrison TE. Reemergence of chikungunya virus. J Virol. 2014;88(20):11644-11647

CHIMU
62983

Chimerism Transplant No Cell Sort, Varies

Clinical Information: Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by identifying unique features of the donor's and the recipient's DNA prior to transplantation and then examining the recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STR are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people, and the STR lengths remain stable throughout life, making them useful as identity markers. Polymerase chain reaction is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can be evaluated again for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen.

Useful For: Determining the relative amounts of donor and recipient cells in a specimen An indicator of bone marrow transplant success

Interpretation: An interpretive report will be provided, which defines unique features of the donor's cells. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Antin JH, Childs R, Filipovich AH, et al: Establishment of complete and mixed donor chimerism after allogenic lymphohematopoietic transplantation: recommendations from a workshop at the 2001 Tandem Meetings of the International Bone Marrow Transplant Registry and the American Society of Blood and Bone Marrow Transplantation. Biol Blood Marrow Transplant. 2001;7(9):473-485 2. Tang X, Alatrash G, Ning J, et al: Increasing chimerism following allogeneic stem cell transplantation is associated with longer survival time. Biol Blood Marrow Transplant. 2014 Aug;20(8):1139-1144. doi: 10.1016/j.bbmt.2014.04.003 3. Ludeman MJ, Zhong C, Mulero JJ, et al: Developmental validation of GlobalFiler PCR amplification kit: a 6-dye multiplex assay designed for amplification of casework samples. Int J Legal Med. 2018 Nov;132(6):1555-1573. doi: 10.1007/s00414-018-1817-5 4. Tyler J, Kumer L, Fisher C, Casey H, Shike H: Personalized chimerism test that uses selection of short tandem repeat or quantitative PCR depending on patient's chimerism status. J Mol Diagn. 2019 May;21(3):483-490. doi: 10.1016/j.jmoldx.2019.01.007 5. Lion T, Watzinger F, Preuner S, et al: The EuroChimerism concept for a standardized approach to chimerism analysis after allogeneic stem cell transplantation. Leukemia. 2012 Aug;26(8):1821-1828. doi: 10.1038/leu.2012.66

CHIMS
62984

Chimerism Transplant Sorted Cells, Varies

Clinical Information: Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by identifying unique features of the donor's and the recipient's DNA prior to transplantation and then examining the recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STR are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among

people and the STR lengths remain stable throughout life, making them useful as identity markers. Polymerase chain reaction is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can be evaluated again for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen.

Useful For: Determining the relative amounts of donor and recipient cells in a specimen in sorted cell fractions An indicator of bone marrow transplant success

Interpretation: An interpretive report will be provided, which includes whether chimerism is detected and, if detected, the approximate percentage of donor and recipient cells. Sorted cell analysis permits more detailed evaluation of chimeric status in T-cell and myeloid cell fractions, which can be helpful in clinical management. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Antin JH, Childs R, Filipovich AH, et al: Establishment of complete and mixed donor chimerism after allogenic lymphohematopoietic transplantation: recommendations from a workshop at the 2001 Tandem Meetings of the International Bone Marrow Transplant Registry and the American Society of Blood and Bone Marrow Transplantation. Biol Blood Marrow Transplant. 2001;7(9):473-485 2. Tang X, Alatrash G, Ning J, et al: Increasing chimerism following allogeneic stem cell transplantation is associated with longer survival time. Biol Blood Marrow Transplant. 2014 Aug;20(8):1139-1144. doi: 10.1016/j.bbmt.2014.04.003 3. Ludeman MJ, Zhong C, Mulero JJ, et al: Developmental validation of GlobalFiler PCR amplification kit: a 6-dye multiplex assay designed for amplification of casework samples. Int J Legal Med. 2018 Nov;132(6):1555-1573. doi: 10.1007/s00414-018-1817-5 4. Tyler J, Kumer L, Fisher C, Casey H, Shike H: Personalized chimerism test that uses selection of short tandem repeat or quantitative PCR depending on patient's chimerism status. J Mol Diagn. 2019 May;21(3):483-490. doi: 10.1016/j.jmoldx.2019.01.007 5. Lion T, Watzinger F, Preuner S, et al: The EuroChimerism concept for a standardized approach to chimerism analysis after allogeneic stem cell transplantation. Leukemia. 2012 Aug;26(8):1821-1828. doi: 10.1038/leu.2012.66

CHIDB
83182

Chimerism-Donor, Varies

Clinical Information: Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by identifying unique features of the donor's and the recipient's DNA prior to transplantation and then examining the recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STR are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people, and the STR lengths remain stable throughout life, making them useful as identity markers. Polymerase chain reaction is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can be evaluated again for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen. This test evaluates the donor specimen prior to the recipient bone marrow transplant.

Useful For: Evaluating the donor cells prior to bone marrow transplant Determining the relative amounts of donor and recipient cells in a specimen An indicator of bone marrow transplant success

Interpretation: An interpretive report will be provided under CHIMU / Chimerism Transplant No Cell Sort, Varies or CHIMS / Chimerism Transplant Sorted Cells, Varies. This includes whether chimerism is detected and, if detected, the approximate percentage of donor and recipient cells. Sorted cell analysis permits more detailed evaluation of chimeric status in T-cell and myeloid cell fractions, which can be helpful in clinical management. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Antin JH, Childs R, Filipovich AH, et al: Establishment of complete and mixed donor chimerism after allogenic lymphohematopoietic transplantation: recommendations from a workshop at the 2001 Tandem Meetings of the International Bone Marrow Transplant Registry and the American Society of Blood and Bone Marrow Transplantation. Biol Blood Marrow Transplant. 2001;7(9):473-485 2. Tang X, Alatrash G, Ning J, et al: Increasing chimerism following allogeneic stem cell transplantation is associated with longer survival time. Biol Blood Marrow Transplant. 2014 Aug;20(8):1139-1144. doi: 10.1016/j.bbmt.2014.04.003 3. Ludeman MJ, Zhong C, Mulero JJ, et al: Developmental validation of GlobalFiler PCR amplification kit: a 6-dye multiplex assay designed for amplification of casework samples. Int J Legal Med. 2018 Nov;132(6):1555-1573. doi: 10.1007/s00414-018-1817-5 4. Tyler J, Kumer L, Fisher C, Casey H, Shike H: Personalized chimerism test that uses selection of short tandem repeat or quantitative PCR depending on patient's chimerism status. J Mol Diagn. 2019 May;21(3):483-490. doi: 10.1016/j.jmoldx.2019.01.007 5. Lion T, Watzinger F, Preuner S, et al: The EuroChimerism concept for a standardized approach to chimerism analysis after allogeneic stem cell transplantation. Leukemia. 2012 Aug;26(8):1821-1828. doi: 10.1038/leu.2012.66

CHRGB
83186

Chimerism-Recipient Germline (Pretransplant), Varies

Clinical Information: Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by identifying unique features of the donor's and the recipient's DNA prior to transplantation and then examining the recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STR are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people, and the STR lengths remain stable throughout life, making them useful as identity markers. Polymerase chain reaction is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can be evaluated again for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen. This test evaluates the recipient specimen prior to bone marrow transplant.

CHLG
619389

Chlamydia IgG, Immunofluorescence, Serum

Clinical Information: Members of the family Chlamydiaceae are small, nonmotile, gram-negative, obligate intracellular organisms that grow in the cytoplasm of host cells. While there are at least 9 species within the Chlamydia genus, 3 are clinically significant, including Chlamydia trachomatis, Chlamydia pneumoniae, and Chlamydia psittaci. The chlamydial life cycle can be divided into 2 distinct phases: an extracellular, nonreplicating, infectious stage and an obligate intracellular, replicating, noninfectious stage. The infectious form, or elementary body (EB), attaches to the target cell membrane and enters the cell via a phagosome. After cell entry, the EB reorganizes into reticulate particles (forming inclusion

bodies) and binary fission begins. After 18 to 24 hours, reticulate particles condense to form EBs. These new EBs are released, beginning another infection cycle. C psittaci is the causative agent of psittacosis, a disease characterized by pneumonia, headache, altered mentation, and hepatosplenomegaly. Psittacosis is acquired by airborne transmission from infected birds. C pneumoniae (formerly known as Taiwan acute respiratory agent and, more recently, as Chlamydophila pneumoniae) causes pneumonia in humans. It is unique because it is a primary pathogen of humans, is spread from human to human, and apparently has no animal or bird host. C pneumoniae is responsible for approximately 10% of pneumonia cases.

Useful For: Assessing IgG antibody levels to aid in the clinical diagnosis of Chlamydia pneumoniae or Chlamydia psittaci infections

Interpretation: Chlamydia pneumoniae > or =1:512 IgG endpoint titers of 1:512 or more are considered presumptive evidence of current infection. > or =1:64 and <1:512 A single specimen endpoint titer of 1:64 to 1:512 should be considered evidence of infection at an undetermined time. A second specimen collected 10 to 21 days after the original collection should be tested in parallel with the first. If the second specimen exhibits a titer 1:512 or more or a 4-fold increase over that of the initial specimen, current (acute) infection is indicated. Unchanging titers from 1:64 to 1:512 suggest past infection. <1:64 IgG endpoint titers below 1:64 suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels. C pneumoniae antibody is detectable in 25% to 45% of adults tested. Chlamydia psittaci > or =1:64 IgG endpoint titers of 1:64 or more are considered presumptive evidence of current infection. <1:64 IgG endpoint titers below 1:64 suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels.

Reference Values:
Chlamydia pneumoniae
<1:64

Chlamydia psittaci
<1:64

Clinical References: 1. Schlossberg D. Psittacosis (due to Chlamydia psittaci). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2320-2322 2. Hammerschlag MR, Kohlhoff SA, Gaydos CA. Chlamydia pneumoniae. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2323-2331

CHLAP
619387

Chlamydia IgM and IgG Panel, Immunofluorescence, Serum

Clinical Information: Members of the family Chlamydiaceae are small, nonmotile, gram-negative, obligate intracellular organisms that grow in the cytoplasm of host cells. While there are at least 9 species within the Chlamydia genus, 3 are clinically significant, including Chlamydia trachomatis, Chlamydia pneumoniae and Chlamydia psittaci. The chlamydial life cycle can be divided into 2 distinct phases: an extracellular, nonreplicating, infectious stage and an obligate intracellular, replicating, noninfectious stage. The infectious form, or elementary body (EB), attaches to the target cell membrane and enters the cell via a phagosome. After cell entry, the EB reorganizes into reticulate particles (forming inclusion bodies) and binary fission begins. After 18 to 24 hours, reticulate particles condense to form EBs. These new EBs are released, beginning another infection cycle. C psittaci is the causative agent of psittacosis, a disease characterized by pneumonia, headache, altered mentation, and

hepatosplenomegaly. Psittacosis is acquired by airborne transmission from infected birds. C pneumoniae (formerly known as Taiwan acute respiratory agent and, more recently, as Chlamydophila pneumoniae) causes pneumonia in humans. It is unique because it is a primary pathogen of humans, is spread from human to human, and apparently has no animal or bird host. C pneumoniae is responsible for approximately 10% of pneumonia cases.

Useful For: Aiding in the clinical diagnosis of Chlamydia pneumoniae or Chlamydia psittaci infection

Interpretation: IgM Chlamydia pneumoniae and Chlamydia psittaci > or =1:10 IgM endpoint titers of 1:10 or more are considered presumptive evidence of infection. <1:10 IgM endpoint titers below 1:10 suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels. IgG: C pneumoniae > or =1:512 IgG endpoint titers of 1:512 or more are considered presumptive evidence of current infection. > or =1:64 and <1:512 A single specimen endpoint titer of 1:64 to 1:512 should be considered evidence of infection at an undetermined time. A second specimen collected 10 to 21 days after the original collection should be tested in parallel with the first. If the second specimen exhibits a titer 1:512 or more or a 4-fold increase over that of the initial specimen, current (acute) infection is indicated. Unchanging titers from 1:64 to 1:512 suggest past infection. <1:64 IgG endpoint titers below 1:64 suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels. C pneumoniae antibody is detectable in 25% to 45% of adults tested. C psittaci > or =1:64 IgG endpoint titers of 1:64 or more are considered presumptive evidence of current infection. <1:64 IgG endpoint titers below 1:64 suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels.

Reference Values:
Chlamydia pneumoniae
IgM: <1:10
IgG: <1:64

Chlamydia psittaci
IgM: <1:10
IgG: <1:64

Clinical References: 1. Schlossberg D. Psittacosis (due to Chlamydia psittaci). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2320-2322 2. Hammerschlag MR, Kohlhoff SA, Gaydos CA. Chlamydia pneumoniae. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2323-2331

CHLM
619388

Chlamydia IgM, Immunofluorescence, Serum

Clinical Information: Members of the family Chlamydiaceae are small, nonmotile, gram-negative, obligate intracellular organisms that grow in the cytoplasm of host cells. While there are at least 9 species within the Chlamydia genus, 3 are clinically significant, including Chlamydia trachomatis, Chlamydia pneumoniae, and Chlamydia psittaci. The chlamydial life cycle can be divided into 2 distinct phases: an extracellular, nonreplicating, infectious stage and an obligate intracellular, replicating, noninfectious stage. The infectious form, or elementary body (EB), attaches to the target cell membrane and enters the cell via a phagosome. After cell entry, the EB reorganizes into reticulate particles (forming inclusion bodies) and binary fission begins. After 18 to 24 hours, reticulate particles condense to form EBs. These

new EBs are released, beginning another infection cycle. C psittaci is the causative agent of psittacosis, a disease characterized by pneumonia, headache, altered mentation, and hepatosplenomegaly. Psittacosis is acquired by airborne transmission from infected birds. C pneumoniae (formerly known as Taiwan acute respiratory agent and, more recently, as Chlamydophila pneumoniae) causes pneumonia in humans. It is unique because it is a primary pathogen of humans, is spread from human to human, and apparently has no animal or bird host. C pneumoniae is responsible for approximately 10% of pneumonia cases.

Useful For: Assessing IgM antibody levels to aid in the clinical diagnosis of Chlamydia pneumoniae or Chlamydia psittaci infections

Interpretation: Chlamydia pneumoniae, and Chlamydia psittaci > or =1:10 IgM endpoint titers of 1:10 or more are considered presumptive evidence of infection. <1:10 IgM endpoint titers below 1:10 suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels.

Reference Values:
Chlamydia pneumoniae
<1:10

Chlamydia psittaci
<1:10

Clinical References: 1. Schlossberg D. Psittacosis (due to Chlamydia psittaci). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2320-2322 2. Hammerschlag MR, Kohlhoff SA, Gaydos CA. Chlamydia pneumoniae. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2323-2331

MCTGC 43721 Chlamydia trachomatis and Neisseria gonorrhoeae, Miscellaneous Sites, Nucleic Acid Amplification, Varies

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted infection (STI) caused by bacteria in the United States. In 2020, over 1.5 million documented cases were reported to the Centers for Disease Control and Prevention (CDC). Given that 3 out of 4 infected women and 1 out of 2 infected men are initially asymptomatic, the actual prevalence of disease is thought to be much greater than reported. C trachomatis causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia in the newborn. Finally, C trachomatis may cause hepatitis and pharyngitis in adult. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women aged 25 years or younger and older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to

ensure therapeutic cure, although residual nucleic acid may remain in the absence of active infection. Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is a very common STI, with over 677,000 cases of gonorrhea reported to CDC in 2020. Like chlamydia, many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STIs, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence). The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. Culture was previously considered to be the gold standard test for diagnosis of C trachomatis and N gonorrhoeae infections. However, these organisms are labile in vitro, therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now considered the reference standard method for diagnosis in most cases. Immunoassays and nonamplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT. Improved screening rates and increased sensitivity of NAAT have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from improved performance characteristics of the assays and patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detecting Chlamydia trachomatis and Neisseria gonorrhoeae in non-US Food and Drug Administration-approved specimen types This test is not intended for use in medico-legal applications. This test is not useful for the detection of Chlamydia pneumoniae or other Chlamydia species.

Interpretation: A positive result indicates the presence of nucleic acid from Chlamydia trachomatis and/or Neisseria gonorrhoeae and strongly supports a diagnosis of chlamydial/gonorrheal infection. A negative result indicates the absence of nucleic acid from C trachomatis and/or N gonorrhoeae. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually transmitted infections, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal or chlamydial urogenital infection, positive results should be carefully assessed, and the patient retested by other methods (eg, culture for N gonorrhoeae) if appropriate. This test has not been shown to cross react with commensal (nonpathogenic) Neisseria species present in the oropharynx.

Reference Values:
Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic test for detecting Chlamydia trachomatis and Neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:101128/JCM.00211-21

CGRNA
61553

Chlamydia trachomatis and Neisseria gonorrhoeae, Nucleic Acid Amplification, Varies

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted infection (STI) caused by bacteria in the United States. In 2020, over 1.5 million documented cases were reported to the Centers for Disease Control and Prevention (CDC). Given that 3 out of 4 infected women and 1 out of 2 infected men are initially asymptomatic, the actual prevalence of disease is thought to be much greater than reported. C trachomatis causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia in the newborn. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women aged 25 years or younger and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure, although residual nucleic acid may remain in the absence of active infection. Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is also a very common STI, with over 677,000 cases of gonorrhea reported to CDC in 2020. Like chlamydia, many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STIs, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence). The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. Culture was previously considered to be the gold standard test for diagnosis of C trachomatis and N gonorrhoeae infections. However, these organisms are labile in vitro; therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now considered the reference standard method for diagnosis in most cases. Immunoassays and nonamplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT. Improved screening rates and increased sensitivity of NAAT have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from improved performance characteristics of the assays and patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detecting Chlamydia trachomatis and/or Neisseria gonorrhoeae This test is not intended for use in medico-legal applications. This test is not useful for the detection of other Chlamydia species.

SCCGR
621934

Chlamydia trachomatis and Neisseria gonorrhoeae, Self-

Collect, Amplified RNA, Rectal

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted infection (STI) caused by bacteria in the United States. In 2020, over 1.5 million documented cases were reported to the Centers for Disease Control and Prevention (CDC). Given that 3 out of 4 infected women and 1 out of 2 infected men are initially asymptomatic, the actual prevalence of disease is thought to be much greater than reported. C trachomatis causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia in the newborn. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women aged 25 years and younger and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure, although residual nucleic acid may remain in the absence of active infection. Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is also a very common STI with over 677,000 cases of gonorrhea reported to CDC in 2020. Like chlamydia, many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STIs, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence). The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. Culture was previously considered to be the gold standard test for diagnosis of C trachomatis and N gonorrhoeae infections. However, these organisms are labile in vitro; therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now considered the reference standard method for diagnosis in most cases. Immunoassays and nonamplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT. Improved screening rates and increased sensitivity of NAAT have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from improved performance characteristics of the assays and patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For:

Interpretation: A positive result indicates the presence of nucleic acid from Chlamydia trachomatis or Neisseria gonorrhoeae and strongly supports a diagnosis of chlamydial or gonorrheal infection. A negative result indicates that nucleic acid from C trachomatis or N gonorrhoeae was not detected in the specimen. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay

depends on the prevalence of the disease in any specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually transmitted infections, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal or chlamydial urogenital infection, positive results should be carefully assessed, and the patient retested by other methods (eg, culture for N gonorrhoeae) if appropriate.

Reference Values:
CHLAMYDIA TRACHOMATIS
Negative

NEISSERIA GONORRHOEAE
Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic test for detecting Chlamydia trachomatis and Neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:10.1128/JCM.00211-21

SCCGT 621931 Chlamydia trachomatis and Neisseria gonorrhoeae, Self-Collect, Amplified RNA, Throat

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted infection (STI) caused by bacteria in the United States. In 2020, over 1.5 million documented cases were reported to the Centers for Disease Control and Prevention (CDC). Given that 3 out of 4 infected women and 1 out of 2 infected men are initially asymptomatic, the actual prevalence of disease is thought to be much greater than reported. C trachomatis causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia in the newborn. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women aged 25 years and younger and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure, although residual nucleic acid may remain in the absence of active infection. Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is also a very common STI with over 677,000 cases of gonorrhea reported to CDC in 2020. Like chlamydia, many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STIs, inconsistent condom

use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence). The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. Culture was previously considered to be the gold standard test for diagnosis of C trachomatis and N gonorrhoeae infections. However, these organisms are labile in vitro; therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now considered the reference standard method for diagnosis in most cases. Immunoassays and nonamplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT. Improved screening rates and increased sensitivity of NAAT have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from improved performance characteristics of the assays and patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detecting Chlamydia trachomatis and Neisseria gonorrhoeae using a throat swab collected by the patient in a healthcare setting This test is not intended for use in medico-legal applications. This test is not useful for the detection of other Chlamydia species.

Interpretation: A positive result indicates the presence of nucleic acid from Chlamydia trachomatis or Neisseria gonorrhoeae and strongly supports a diagnosis of chlamydial or gonorrheal infection. A negative result indicates that nucleic acid from C trachomatis or N gonorrhoeae was not detected in the specimen. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually transmitted infections, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal or chlamydial urogenital infection, positive results should be carefully assessed, and the patient retested by other methods (eg, culture for N gonorrhoeae) if appropriate.

Reference Values:
CHLAMYDIA TRACHOMATIS
Negative

NEISSERIA GONORRHOEAE
Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic test for detecting Chlamydia trachomatis and Neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:10.1128/JCM.00211-21

SCCGV 621937 Chlamydia trachomatis and Neisseria gonorrhoeae, Self-Collect, Amplified RNA, Vaginal

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted infection (STI) caused by bacteria in the United States. In 2020, over 1.5 million documented cases were reported to the Centers for Disease Control and Prevention (CDC). Given that 3 out of 4 infected women and 1 out of 2 infected men are initially

asymptomatic, the actual prevalence of disease is thought to be much greater than reported. C trachomatis causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia in the newborn. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women aged 25 years and younger and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure, although residual nucleic acid may remain in the absence of active infection. Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is also a very common STI, with over 677,000 cases of gonorrhea reported to CDC in 2020. Like chlamydia, many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STIs, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence). The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. Culture was previously considered to be the gold standard test for diagnosis of C trachomatis and N gonorrhoeae infections. However, these organisms are labile in vitro; therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now considered the reference standard method for diagnosis in most cases. Immunoassays and nonamplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT. Improved screening rates and increased sensitivity of NAAT have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from improved performance characteristics of the assays and patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detecting Chlamydia trachomatis and Neisseria gonorrhoeae using self-collected vaginal swabs collected by the patient in a healthcare setting This test is not intended for use in medico-legal applications. This test is not useful for the detection of other Chlamydia species.

Interpretation: A positive result indicates the presence of nucleic acid from Chlamydia trachomatis or Neisseria gonorrhoeae and strongly supports a diagnosis of chlamydial or gonorrheal infection. A negative result indicates that nucleic acid from C trachomatis or N gonorrhoeae was not detected in the specimen. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually transmitted infections, or in any setting in

which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal or chlamydial urogenital infection, positive results should be carefully assessed, and the patient retested by other methods (eg, culture for N gonorrhoeae) if appropriate.

Reference Values:
CHLAMYDIA TRACHOMATIS
Negative

NEISSERIA GONORRHOEAE
Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic test for detecting Chlamydia trachomatis and Neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:10.1128/JCM.00211-21

MCRNA 61554 Chlamydia trachomatis, Miscellaneous Sites, Nucleic Acid Amplification, Varies

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted infection (STI) caused by bacteria in the United States. In 2020, over 1.5 million documented cases were reported to the Centers for Disease Control and Prevention (CDC). Given that 3 out of 4 infected women and 1 out of 2 infected men are initially asymptomatic, the actual prevalence of disease is thought to be much greater than reported. C trachomatis causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia in the newborn. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women aged 25 years or younger and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure, although residual nucleic acid may remain in the absence of active infection. Improved screening rates and increased sensitivity of nucleic acid amplification testing have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from improved performance characteristics of the assays and patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detecting Chlamydia trachomatis in non-US Food and Drug Administration-approved specimen types This test is not intended for use in medico-legal applications. This test is not useful for the detection of Chlamydia pneumoniae or other Chlamydia species.

Interpretation: A positive result indicates the presence of nucleic acid from Chlamydia trachomatis. A negative result indicates the absence of C trachomatis nucleic acid. A negative result does not exclude the

possibility of infection. If clinical indications strongly suggest chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually transmitted infections, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with chlamydial urogenital infection, positive results should be carefully assessed, and the patient retested by other methods if appropriate.

Reference Values:
Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic test for detecting Chlamydia trachomatis and Neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:10.1128/JCM.00211-21

CTRNA
61551

Chlamydia trachomatis, Nucleic Acid Amplification, Varies

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted infection (STI) caused by bacteria in the United States. In 2020, over 1.5 million documented cases were reported to the Centers for Disease Control and Prevention (CDC). Given that 3 out of 4 infected women and 1 out of 2 infected men are initially asymptomatic, the actual prevalence of disease is thought to be much greater than reported. C trachomatis causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia in the newborn. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women aged 25 years or younger and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure, although residual nucleic acid may remain in the absence of active infection. Improved screening rates and increased sensitivity of nucleic acid amplification testing have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from improved performance characteristics of the assays and patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detecting Chlamydia trachomatis This test is not intended for use in medico-legal applications. This test is not useful for the detection of other Chlamydia species.

Interpretation: A positive result indicates the presence of nucleic acid from Chlamydia trachomatis and strongly supports the diagnosis of chlamydial infection. A negative result indicates that nucleic acid from C trachomatis was not detected in the specimen. A negative result does not exclude the possibility

of infection. If clinical indications strongly suggest chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually transmitted infections, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with chlamydial urogenital infection, positive results should be carefully assessed, and the patient retested by other methods, if appropriate.

Reference Values:
Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic test for detecting chlamydia trachomatis and neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:10.1128/JCM.00211-21

SCCTV
621938

Chlamydia trachomatis, Self-Collect, Amplified RNA, Vaginal

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted infection (STI) caused by bacteria in the United States. In 2020, over 1.5 million documented cases were reported to the Centers for Disease Control and Prevention (CDC). Given that 3 out of 4 infected women and 1 out of 2 infected men are initially asymptomatic, the actual prevalence of disease is thought to be much greater than reported. C trachomatis causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia in the newborn. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women aged 25 years and younger and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure, although residual nucleic acid may remain in the absence of active infection.

Useful For: Detecting Chlamydia trachomatis using vaginal swabs collected by the patient in a healthcare setting This test is not intended for use in medico-legal applications. This test is not useful for the detection of other Chlamydia species.

Interpretation: A positive result indicates the presence of nucleic acid from Chlamydia trachomatis. A negative result indicates the absence of C trachomatis nucleic acid. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually transmitted

infections, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with chlamydial urogenital infection, positive results should be carefully assessed, and the patient retested by other methods if appropriate.

Reference Values:
Only orderable as part of a profile. For more information see SCCGV / Chlamydia trachomatis and Neisseria gonorrhoeae, Self-Collect, Amplified RNA, Vaginal.

Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic test for detecting Chlamydia trachomatis and Neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:10.1128/JCM.00211-21

SCCTR
621935

Chlamydia trachomatis, Self-Collect, Nucleic Acid Amplification, Rectal

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted infection (STI) caused by bacteria in the United States. In 2020, over 1.5 million documented cases were reported to the Centers for Disease Control and Prevention (CDC). Given that 3 out of 4 infected women and 1 out of 2 infected men are initially asymptomatic, the actual prevalence of disease is thought to be much greater than reported. C trachomatis causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia in the newborn. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women aged 25 years and younger and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure, although residual nucleic acid may remain in the absence of active infection.

Useful For: Detecting Chlamydia trachomatis using rectal swabs collected by the patient in a healthcare setting This test is not intended for use in medico-legal applications. This test is not useful for the detection of other Chlamydia species.

Interpretation: A positive result indicates the presence of nucleic acid from Chlamydia trachomatis. A negative result indicates the absence of C trachomatis nucleic acid. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually

transmitted infections, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with chlamydial urogenital infection, positive results should be carefully assessed, and the patient retested by other methods if appropriate.

Reference Values:
Only orderable as part of a profile. For more information see SCCGR / Chlamydia trachomatis and Neisseria gonorrhoeae, Self-Collect, Amplified RNA, Rectal

Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic test for detecting Chlamydia trachomatis and Neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:10.1128/JCM.00211-21

SCCTT 621932 Chlamydia trachomatis, Self-Collect, Nucleic Acid Amplification, Throat

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted infection (STI) caused by bacteria in the United States. In 2020, over 1.5 million documented cases were reported to the Centers for Disease Control and Prevention (CDC). Given that 3 out of 4 infected women and 1 out of 2 infected men are initially asymptomatic, the actual prevalence of disease is thought to be much greater than reported. C trachomatis causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or Throat discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia in the newborn. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women aged 25 years and younger and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure, although residual nucleic acid may remain in the absence of active infection.

Useful For: Detecting Chlamydia trachomatis using throat swabs collected by the patient in a healthcare setting This test is not intended for use in medico-legal applications. This test is not useful for the detection of other Chlamydia species.

Interpretation: A positive result indicates the presence of nucleic acid from Chlamydia trachomatis. A negative result indicates the absence of C trachomatis nucleic acid. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually transmitted infections, or in any setting in which a patient's clinical signs and symptoms or risk factors are

inconsistent with chlamydial urogenital infection, positive results should be carefully assessed, and the patient retested by other methods if appropriate.

Reference Values:
Only orderable as part of a profile. For more information see SCCGT / Chlamydia trachomatis and Neisseria gonorrhoeae, Self-Collect, Amplified RNA, Throat.

Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic test for detecting Chlamydia trachomatis and Neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:10.1128/JCM.00211-21

CDP
8610

Chlordiazepoxide and Metabolite, Serum

Clinical Information: Chlordiazepoxide (Librium) is a benzodiazepine widely used in the treatment of anxiety, alcohol withdrawal symptoms, and as a premedication for anesthesia. The mechanism of action of all benzodiazepines remains unclear. However, it is known that benzodiazepines facilitate gamma-amino butyric acid (GABA)-mediated neurotransmission in the brain. Benzodiazepines most likely facilitate the inhibitory presynaptic or postsynaptic reactions of GABA. Chlordiazepoxide is metabolized to long-acting metabolites in the liver to the active metabolite nordiazepam (desmethyldiazepam), and the clearance of the drug is reduced considerably in the elderly and in patients with hepatic disease. Therapeutic assessment should include measurement of both the parent drug (chlordiazepoxide) and the active metabolite (nordiazepam). Since chlordiazepoxide has a wide therapeutic index and toxicity is dose-dependent, routine drug monitoring is not indicated in all patients

Useful For: Monitoring chlordiazepoxide therapy Assessing toxicity

Interpretation: Chlordiazepoxide and nordiazepoxide combined concentrations above 5000 ng/mL have been associated with toxicity.

Reference Values:
Therapeutic concentration:
Chlordiazepoxide: 400-3,000 ng/mL
Nordiazepam: 100-500 ng/mL

Clinical References: 1. Langman, LJ, Bechtel L, Meier BM, Holstege CP. Clinical toxicology. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:832-887 2. Burtis CA, Ashwood ER, Bruns DE, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. WB Saunders Company; 2011:1109-1188 3. Hiemke C, Baumann P, Bergemann N, et al. AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry: Update 2011. Pharmacopsychiatry. 2011;44(6):195-235

CLU
614058

Chloride, 24 Hour, Urine

Clinical Information: Chloride is the major extracellular anion. Its precise function in the body is not well understood; however, it is involved in maintaining osmotic pressure, proper body hydration,

and electric neutrality. In the absence of acid-base disturbances, chloride concentrations in plasma will generally follow those of sodium. Since urine is the primary mode of elimination of ingested chloride, urinary chloride excretion during steady state conditions will reflect ingested chloride, which predominantly is in the form of sodium chloride. However, under certain clinical conditions, the renal excretion of chloride may not reflect intake. For instance, during states of extracellular volume depletion, urine chloride (and sodium) excretion is reduced.

Useful For: Indication of fluid balance and acid-base homeostasis using a 24-hour urine collection

Interpretation: Urine sodium and chloride excretion are similar, and, under steady-state conditions, both the urinary sodium and chloride excretion reflect the intake of sodium chloride. During states of extracellular volume depletion, low values indicate appropriate renal reabsorption of these ions, whereas elevated values indicate inappropriate excretion (renal wasting). Urinary sodium and chloride excretion may be dissociated during metabolic alkalosis with volume depletion where urine sodium excretion may be high (due to renal excretion of sodium bicarbonate), while urine chloride excretion remains appropriately low.

Reference Values:
> or =18 years: 34-286 mmol/24 hours
Reference values have not been stablished for patients who are less than 18 years of age.

Reference values apply to 24-hour collection.

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1308-1309 2. Kamel KS, Ethier JH, Richardson RM, Bear RA, Halperin ML: Urine electrolytes and osmolality: when and how to use them. Am J Nephrol. 1990;10(2):89-102

CL_F
606755

Chloride, Feces

Clinical Information: The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors: -Normal daily dietary intake of electrolytes -Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure -Electrolyte transport into fecal water due to exogenous substances and rare toxins (eg, cholera toxin) Fecal osmolality is normally in equilibrium with vascular osmolality, and sodium is the major effector of this equilibrium.(1) Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or drugs inducing secretions, such as phenolphthalein or bisacodyl. Chronic diarrhea with elevations in fecal chloride concentrations are caused by congenital chloridorrhea. This is a rare condition associated with a genetic defect in a protein responsible for transport of chloride ions across the mucosal membranes in the lower intestinal tract in exchange for bicarbonate ions. It plays an essential part in intestinal chloride absorption, therefore variants in this gene have been associated with congenital chloride diarrhea.(2. Acquired chloridorrhea is a rare condition that has been described as causing profuse, chloride-rich diarrhea and a surprising contraction metabolic alkalosis rather than metabolic acidosis often associated with typical diarrhea. Contributors to acquired chloridorrhea include chronic intestinal inflammation and reduction of chloride/bicarbonate transporter expression in genetically susceptible persons post-bowel resection and ostomy placement. Acquired chloridorrhea is rare but may be an under-recognized condition in post-bowel resection patients.(3)

Useful For: Workup of cases of chronic diarrhea Evaluation of suspected chloridorrhea

Interpretation: Fecal chloride may be low (<20 mmol/L) in sodium sulfate-induced diarrhea.(4)

Markedly elevated fecal chloride concentration in infants (>60 mmol/L) and adults (>100 mmol/L) is associated with congenital and secondary chloridorrhea.(5)

Reference Values:
An interpretive report will be provided

Clinical References: 1. Steffer KJ, Santa Ana CA, Cole JA, Fordtran JS: The practical value of comprehensive stool analysis in detecting the cause of idiopathic chronic diarrhea. Gastroenterol Clin North Am 2012;41:539-560 2. Makela S, Kere J, Holmberg C, Hoglund P: SLC26A3 mutations in congenital chloride diarrhea. Hum Mutat. 2002 Dec;20(6):425-438. doi: 10.1002/humu.10139/ 3. Ali OM, Shealy C, Saklayen M: Acute pre-renal failure: acquired chloride diarrhea after bowel resection. Clin Kidney J. 2012;5(4):356-358. doi: 10.1093/ckj/sfs082 4. Eherer AJ, Fordtran JS: Fecal osmotic gap and pH in experimental diarrhea of various causes. Gastroenterology. 1992;103:545-551 5. Casprary WF: Diarrhea associated with carbohydrate malabsorption. Clin Gastroenterol. 1986;15:631-655

RCHLU
610607

Chloride, Random, Urine

Clinical Information: Chloride is the major extracellular anion. Its precise function in the body is not well understood; however, it is involved in maintaining osmotic pressure, proper body hydration, and electric neutrality. In the absence of acid-base disturbances, chloride concentrations in plasma will generally follow those of sodium. Since urine is the primary mode of elimination of ingested chloride, urinary chloride excretion during steady state conditions will reflect ingested chloride, which predominantly is in the form of sodium chloride. However, under certain clinical conditions, the renal excretion of chloride may not reflect intake. For instance, during states of extracellular volume depletion, urine chloride (and sodium) excretion is reduced.

Useful For: An indicator of fluid balance and acid-base homeostasis

Interpretation: Urine sodium and chloride excretion are similar and, under steady state conditions, both the urinary sodium and chloride excretion reflect the intake of sodium chloride. During states of extracellular volume depletion, low values indicate appropriate renal reabsorption of these ions, whereas elevated values indicate inappropriate excretion (renal wasting). Urinary sodium and chloride excretion may be dissociated during metabolic alkalosis with volume depletion where urine sodium excretion may be high (due to renal excretion of sodium bicarbonate) while urine chloride excretion remains appropriately low.

Reference Values:
No established reference values
Random urine chloride may be interpreted in conjunction with serum chloride, using both values to calculate fractional excretion of chloride.

The calculation for fractional excretion (FE) of chloride (Cl) is
FE(Cl) =(Cl [urine] x Creat [serum])/(Cl [serum] x Creat [urine]) x100

Clinical References:

CL
8460

Chloride, Serum

Clinical Information: Chloride is the major anion in the extracellular water space; its physiological significance is in maintaining proper body water distribution, osmotic pressure, and normal anion-cation

balance in the extracellular fluid compartment. Chloride is increased in dehydration, renal tubular acidosis (hyperchloremia metabolic acidosis), acute renal failure, metabolic acidosis associated with prolonged diarrhea and loss of sodium bicarbonate, diabetes insipidus, adrenocortical hyperfunction, salicylate intoxication, and with excessive infusion of isotonic saline or extremely high dietary intake of salt. Hyperchloremia acidosis may be a sign of severe renal tubular pathology. Chloride is decreased in overhydration, chronic respiratory acidosis, salt-losing nephritis, metabolic alkalosis, congestive heart failure, Addisonian crisis, certain types of metabolic acidosis, persistent gastric secretion and prolonged vomiting, aldosteronism, bromide intoxication, syndrome of inappropriate antidiuretic hormone secretion, and conditions associated with expansion of extracellular fluid volume.

Useful For: Evaluation of water, electrolyte, and acid-base status

Interpretation: In normal individuals, serum chloride values vary little during the day, although there is a slight decrease after meals due to the diversion of chloride to the production of gastric juice.

Reference Values:
1-17 years: 102-112 mmol/L
> or =18 years: 98-107 mmol/L
Reference values have not been established for patients who are under 12 months of age.

Clinical References: Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. WB Saunders Company, Philadelphia, PA, 1994

FCHPZ 57719 Chlorpromazine (Thorazine)

Reference Values:
Reference Range: 30 – 300 ng/mL

FCHCG 57644 Chocolate/Cacao IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

FCCK1 75914 Cholecystokinin (CCK)

Reference Values:
<80 pg/mL

CHLGP 608018 Cholestasis Gene Panel, Varies

Clinical Information: Cholestasis is a decrease in or obstruction of bile flow that results in jaundice, pruritus, hepatomegaly, and splenomegaly. Cholestasis can be the primary clinical symptom due to progressive familial intrahepatic cholestasis (PFIC) or one of a number of symptoms due to a variety of genetic disorders that cause multisystem disease. Many forms of cholestasis are multifactorial in origin occurring due to the presence of both risk-associated alleles and environmental circumstances. This panel is not intended to diagnose multifactorial cholestasis and risk-associated alleles will not be reported unless requested. PFIC is a group of disorders caused by bile secretion or transport defects that result in intrahepatic cholestasis in infancy or childhood. There are 5 types of PFIC that are molecularly defined: FIC1 (ATP8B1 gene), PFIC2 (ABCB11 gene), PFIC3 (ABCB4 gene), PFIC4 (TJP2 gene), and PFIC5 (NR1H4 gene). PFICs 1, 2, and 4 have normal to mild elevations of gamma-glutamyltransferase (GGT). PFIC 3 results in significantly elevated serum GGT, whereas PFIC5 causes low to normal GGT levels. PFIC can present with cholestasis in neonates, but most commonly manifests around 3 months of age for those with PFIC2, the most common type. Studies of infants and children with cholestasis have shown that 12% to 13% have molecularly confirmed PFIC. Disease progression results in liver failure and hepatocellular carcinoma. Liver transplantation is an effective treatment, though less effective for multisystemic PFIC1 than for other types. However, there is significant mortality, as 87% of patients with untreated PFIC will not survive. A variety of other genetic disorders can also result in cholestasis, such as Alagille syndrome (JAG1 and NOTCH2 genes), alpha-1-antitrypsin deficiency (SERPINA1 gene), arthrogryposis, kidney dysfunction, and cholestasis syndrome (VPS33B and VIPAS39 genes), citrullinemia (SLC25A13 gene), congenital defects of bile acid synthesis (HSD3B7 and AKR1D1 genes), familial hypercholanemia (BAAT gene), neonatal ichthyosis-sclerosing cholangitis syndrome (CLDN1 gene), and Crigler-Najjar syndrome types I or II or Gilbert syndrome (UGT1A1). In addition, peroxisomal disorders (PEX genes) and mitochondrial disorders can include cholestatic liver disease among other features. This comprehensive gene panel is a rapid and reliable first-tier test to establish a diagnosis for patients with monogenic cholestasis.

Useful For: Establishing a molecular diagnosis for patients with monogenic cholestasis Identifying variants within genes known to be associated with primary, monogenic cholestasis, allowing for predictive testing of at-risk family members This panel is not intended to diagnose multifactorial cholestasis.

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Baker A, Kerkar N, Todorova L, et al: Systematic review of progressive familial intrahepatic cholestasis. Clin Res Hepatol Gastroenterol. 2019;43(1):20-36 3. Chowdhury J, Wolkoff AW, Chowdhury N, Arias IM: Hereditary jaundice and disorders of bilirubin metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 08, 2022. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225541453

CHLBF
606915

Cholesterol, Body Fluid

Clinical Information: Serum cholesterol is measured to determine the concentration of circulating

lipoprotein particles when screening for cardiovascular disease. The concentration is affected by genetic and lifestyle factors. Cholesterol concentrations in serous effusions increase due to exudative processes that cause cell lysis or increased vascular permeability. Measurement of cholesterol in body fluids is used for the diagnosis of a cholesterol effusion or cholesterol-rich pseudochylous effusion. Pseudochylous effusions contain low triglycerides and high cholesterol and occur from chronic pleural effusions such as rheumatic pleurisy and tuberculosis. Malignant effusions may become enriched with cholesterol due to increased synthesis and release from neoplastic cells or lymphatic obstruction.(1) Pleural fluid: Chylothorax is the name given to pleural effusions containing chylomicrons with accordingly high triglyceride and low cholesterol concentrations, which occurs when chyle accumulates from a disruption of the thoracic duct caused mainly by malignancy or trauma.(2) Pseudochylous effusions accumulate gradually through the breakdown of cellular lipids in long-standing effusions such as rheumatoid pleuritis, tuberculosis, or myxedema, and by definition the effluent contains high concentrations of cholesterol, while chylous effusions contain high concentrations of triglycerides in the form of chylomicrons.(3) Differentiation of pseudochylothorax from chylothorax is important as their milky or opalescent appearance is similar; however, therapeutic management strategies differ. Measurement of pleural fluid cholesterol has also been investigated in multiple studies for the purpose of differentiating exudates from transudates.(4) Most of these studies concluded that cholesterol performs as well as measurement of lactate dehydrogenase and total protein applying Light's criteria, but does not add much value beyond that. Peritoneal fluid: Ascites is the pathologic accumulation of excess fluid in the peritoneal cavity. Cholesterol analysis in peritoneal fluid may be a useful index to separate malignant ascites from nonmalignant, often cirrhotic ascites. Studies report concentrations ranging from greater than 32 to 70 mg/dL are greater than 88% sensitive and greater than 80% specific for malignant ascites, outperforming cytology.(4)

Useful For: Aiding in the diagnosis of a cholesterol effusion or cholesterol-rich pseudochylous effusion in body fluids Distinguishing between chylous and pseudochylous pleural effusions Distinguishing between malignant and nonmalignant ascites

Interpretation: Pleural fluid cholesterol concentrations between 46 to 65 mg/dL are consistent with exudative effusions. Cholesterol concentrations above 200 mg/dL suggest a pseudochylous effusion.(2) Peritoneal fluid cholesterol concentrations between 33 to 70 mg/dL suggest a malignant cause of ascites.(4)

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Gulyas M, Kaposi AD, Elek G, Szollar LG, Hjerpe A. Value of carcinoembryonic antigen (CEA) and cholesterol assays of ascitic fluid in cases of inconclusive cytology. J Clin Pathol. 2001;54(11):831-5. doi:10.1136/jcp.54.11.831 2. Hooper C, Lee YC, Maskell N. BTS Pleural Guideline Group. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii4-17. doi:10.1136/thx.2010.136978 3. Staats BA, Ellefson RD, Budahn LL, et al. The lipoprotein profile of chylous and nonchylous pleural effusions. Mayo Clin Proc. 1980;55(11):700-704 4. Block DR, Algeciras-Schimnich A. Body fluid analysis: clinical utility and applicability of published studies to guide interpretation of today's laboratory testing in serous fluids. Crit Rev Clin Lab Sci. 2013;50:107-124. doi:10.3109/10408363.2013.844679 5. Bhatnagar M, Fisher A, Ramsaroop S, Carter A, Pippard B. Chylothorax: pathophysiology, diagnosis, and management - a comprehensive review: J Thorac Dis. 2024;16(2):1645-1661. doi:10.21037/jtd-23-1636

HDCH
8429

Cholesterol, High-Density Lipoprotein (HDL), Serum

Clinical Information:

Useful For: Measurement of serum high-density lipoprotein concentrations for managing atherosclerotic cardiovascular disease risk

Interpretation: Low high-density lipoprotein cholesterol (HDL-C) is a risk factor for cardiovascular disease. HDL-C can be increased by the same lifestyle changes that reduce risk for cardiovascular disease: physical activity, smoking cessation, and eating healthier. However, medications that specifically increase HDL levels have failed to reduce cardiovascular disease. Extremely low HDL values (<20 mg/dL) may indicate liver disease or inherited dyslipidemia.

Reference Values:
The National Lipid Association and the National Cholesterol Education Program have set the following guidelines for lipids in a context of cardiovascular risk for adults 18 years old and older:
HDL CHOLESTEROL
Males
> or =40 mg/dL
Females
> or =50 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids in a context of cardiovascular risk for children 2-17 years of age:
HDL CHOLESTEROL
Low HDL: <40 mg/dL
Borderline Low: 40-45 mg/dL
Acceptable: >45 mg/dL
Reference values have not been established for patients who are younger than 24 months of age.

Clinical References: 1. Grundy SM, Stone NJ, Bailey AL, et al: AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Jun 18;139(25):e1082-e1143 2. Jacobson TA, Ito MK, Maki KC, et al: National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1-executive summary. J Clin Lipidol. 2014 Sep-Oct;8(5):473-488. doi: 10.1016/j.jacl.2014.07.007 3. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute: Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics. 2011 Dec;128 Suppl 5(Suppl 5):S213-S256. doi: 10.1542/peds.2009-2107C

CLDL1 617023 Cholesterol, Low-Density Lipoprotein (LDL), Calculated, Serum

Clinical Information: Lipoprotein cholesterol measurements are essential in managing risk for atherosclerotic cardiovascular disease (ASCVD). Atherosclerosis is defined by a buildup of plaque within arterial walls. ASCVD includes coronary heart disease, strokes, and peripheral artery disease. ASCVD develops over decades and is often asymptomatic until the patient experiences a life-threatening event such as a heart attack, stroke, or aneurysm. Low-density lipoprotein cholesterol (LDL-C) is the primary lipoprotein responsible for atherogenic plaque. Very low-density lipoprotein cholesterol (VLDL-C) is also atherogenic and the combination of LDL-C and VLDL-C is called non-high-density lipoprotein (HDL) cholesterol. Serum LDL-C and non-HDL cholesterol are directly associated with risk for ASCVD and often referred to as "bad" cholesterol. HDL-C is often referred to as "good" cholesterol because HDL-C concentrations are inversely related to ASCVD risk. Adjusted

LDL-C calculations, like the Sampson/NIH equation, are endorsed by multiple guidelines as being more accurate when triglycerides are greater than 150 mg/dL and/or LDL-C is less than 70 mg/dL.

Useful For: Calculation of low-density lipoprotein cholesterol using total cholesterol, non-high-density lipoprotein (HDL) cholesterol, HDL cholesterol, and triglyceride concentrations Managing atherosclerotic cardiovascular disease risk

Interpretation: Maintaining desirable concentrations of lipids lowers atherosclerotic cardiovascular disease risk. Establishing appropriate treatment strategies and lipid goals require that blood lipid values be considered in context with other risk factors including, age, sex, smoking status, and medical history of hypertension, diabetes, and cardiovascular disease. Low-density lipoprotein cholesterol results of 190 mg/dL or above in adults (> or =160 mg/dL in children) are severely elevated and may indicate familial hypercholesterolemia.

Reference Values:
Only orderable as part of a profile. For more information see LPSC1 / Lipid Panel, Serum

The National Lipid Association and the National Cholesterol Education Program have set the following guidelines for lipids in a context of cardiovascular risk for adults 18 years old and older:
LDL CHOLESTEROL
Desirable: <100 mg/dL
Above Desirable: 100-129 mg/dL
Borderline High: 130-159 mg/dL
High: 160-189 mg/dL
Very High: > or =190 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids in a context of cardiovascular risk for children 2 to 17 years old:

LDL CHOLESTEROL
Acceptable: <110 mg/dL
Borderline High: 110-129 mg/dL
High: > or =130 mg/dL
Reference values have not been established for patients who are younger than 24 months of age.

Clinical References: 1. Grundy SM, Stone NJ, Bailey AL, et al: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Jun 18;139(25):e1082-e1143 2. Jacobson TA, Ito MK, Maki KC, et al: National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1-executive summary. J Clin Lipidol. 2014;8(5):473-488. doi: 10.1016/j.jacl.2014.07.007 3. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011 Dec;128 Suppl 5(Suppl 5):S213-S256. doi: 10.1542/peds.2009-2107C 4. Sampson M, Ling C, Sun Q, et al: A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia. JAMA Cardiol. 2020 May 1;5(5):540-548

CHOL
8320

Cholesterol, Total, Serum

Clinical Information: Cholesterol is a lipid that is synthesized in most tissues and actively absorbed

from the diet. There is a strong association between serum cholesterol concentrations and cardiovascular disease. Cholesterol is carried in the blood by lipoproteins. Some lipoproteins carry a stronger risk of cardiovascular disease while others are associated with reduced cardiovascular risk. Total cholesterol concentration includes the sum of all "good" and "bad" cholesterol. Therefore, total cholesterol is recommended to be interpreted in context of a lipid panel that includes high-density lipoprotein cholesterol and triglyceride measures. Low levels of cholesterol can be seen in disorders that include hyperthyroidism, malabsorption, and deficiencies of apolipoproteins.

Useful For: Evaluation of cardiovascular risk

Interpretation: The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for total cholesterol: Desirable: <200 mg/dL Borderline High: 200 to 239 mg/dL High: > or =240 mg/dL The recommended clinical decision points of 200 mg/dL and 240 mg/dL total cholesterol correspond to the 50th percentile and 90th percentile of healthy U.S. adults, respectively. Values in hyperthyroidism usually are in the lower normal range; malabsorption values may be below 100 mg/dL, while apolipoprotein B deficiency values usually are below 80 mg/dL.

Reference Values:
The National Lipid Association and the National Cholesterol Education Program have set the following guidelines for lipids in a context of cardiovascular disease for adults 18 years old and older:

TOTAL CHOLESTEROL
Desirable: <200 mg/dL
Borderline High: 200-239 mg/dL
High: > or =240 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids in a context of cardiovascular disease for children 2 to 17 years of age:

TOTAL CHOLESTEROL
Acceptable: <170 mg/dL
Borderline High: 170-199 mg/dL
High: > or =200 mg/dL

Reference values have not been established for patients who younger than 24 months of age.

Clinical References: 1. Grundy SM, Stone NJ, Bailey AL, et al: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. circulation. 2019 Jun 18;139(25):e1082-e1143. doi: 10.1161/CIR.0000000000000625 2. Jacobson TA, Ito MK, Maki KC, et al: National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1-executive summary. J Clin Lipidol. 2014;8(5):473-488. doi: 10.1016/j.jacl.2014.07.007 3. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary report. Pediatrics. 2011 Dec;128 Suppl 5(Suppl 5):S213-S256. doi: 10.1542/peds.2009-2107C

CHLE
606888

Cholesteryl Esters, Serum

Clinical Information: Cholesterol in the blood serum is normally 60% to 80% esterified with fatty acids, largely as a result of the action of the enzyme lecithin-cholesterol acyltransferase (LCAT), which circulates in the blood in association with the high-density lipoproteins. Familial deficiency of LCAT is

uncommon, usually occurring in individuals of northern European descent, and is associated with erythrocyte abnormalities (target cells) and decreased (20% or less) esterification of serum cholesterol. LCAT deficiency is associated with early atherosclerosis, corneal opacification, hyperlipidemia, and mild hemolytic anemia. In persons who are deficient in LCAT, a much smaller percentage of the serum cholesterol is esterified. Persons who have a familial deficiency of LCAT have only 20% or less of serum cholesterol esterified. In association with a deficiency of LCAT, the concentration of unesterified cholesterol in the serum may increase 2 to 5 times the normal value and the concentration of lecithin may also increase. Persons with liver disease may have impaired formation of LCAT and, therefore an acquired LCAT deficiency and reduced cholesterol ester.

Useful For: Establishing a diagnosis of lecithin-cholesterol acyltransferase deficiency Evaluating the extent of metabolic disturbance by bile stasis or liver disease

Interpretation: Persons who have a familial deficiency of lecithin-cholesterol acyltransferase have only 20% or less of serum cholesterol esterified.

Reference Values:
> or =18 years: 60-80% of total cholesterol
Reference values have not been established for patients who are less than 18 years of age.

Clinical References: 1. Meikle PJ, Mundra PA, Wong G, et al. Circulating lipids are associated with alcoholic liver cirrhosis and represent potential biomarkers for risk assessment. PLoS One. 2015;10(6):e0130346. doi:10.1371/journal.pone.0130346 2. Leach NV, Dronca E, Vesa SC, et al. Serum homocysteine levels, oxidative stress and cardiovascular risk in non-alcoholic steatohepatitis. Eur J Intern Med. 2014;25(8):762-767. doi:10.1016/j.ejim.2014.09.007 3. Santamarina-Fojo S, Hoeg JM, Assmann G, Brewer B. Lecithin cholesterol acyltransferase deficiency and fish eye disease. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed June 8, 2021. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225539713&bookid=2709

FCNAB 57737 Chromatin (Nucleosomal) Antibody

Reference Values:
<1.0 Negative AI

CRCOF 606424 Chromium and Cobalt, Synovial Fluid

Clinical Information: Per US Food and Drug Administration recommendations, orthopedic surgeons should consider measuring and following serial chromium and cobalt concentrations in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal hip implants as part of their overall clinical evaluation. However, a recent publication(1) has shown synovial fluid measurements were superior to whole blood and serum chromium and cobalt concentrations in predicting local tissue destruction in failed hip arthroplasty constructs. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside are typically made of chromium, cobalt, and molybdenum. This list of products is incomplete, and the products' compositions change occasionally; see each prostheses' product information for composition details. Chromium: Chromium (Cr) is a naturally occurring element widely distributed in the environment. It exists in several valence states with the 3 main forms being Cr(0), Cr(III), and Cr(VI). Cr(III) is an essential trace element that enhances the action of insulin. Deficiency leads to impaired growth, reduced life span, corneal lesions, and alterations in carbohydrates, lipid, and protein metabolism. Chromium is widely used in manufacturing processes to make various metal alloys, such as stainless steel. It is also

used in many consumer products, including wood treated with copper dichromate, leather tanned with chromic sulfate, and metal-on-metal hip replacements. The general population is most likely to be exposed to trace levels of chromium, as Cr(III) is naturally occurring in foods, such as fruits, vegetables, nuts, beverages, and meats. The highest potential occupational exposure occurs in the metallurgy and tanning industries, where workers may be exposed to high air concentrations. Cobalt: Cobalt is a naturally occurring, hard, gray element widely distributed in the environment. It is used to produce alloys in the manufacturing of aircraft engines, cutting tools, and some artificial hip and knee joint prosthesis devices. Cobalt is an essential cofactor in vitamin B12, which is necessary for neurological function, brain function, and the formation of blood. For most people, food is the largest source of cobalt intake. However, more than a million workers are potentially exposed to cobalt and its compounds, with the greatest exposure in mining processes, cemented tungsten-carbide industry, cobalt powder industry, and alloy production industry. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms include pulmonary edema, allergy, nausea, vomiting, hemorrhage, and kidney failure. Chronic exposure to cobalt-containing hard metal (dust or fume) can result in a serious lung disease called hard metal lung disease, which is a type of pneumoconiosis (lung fibrosis). Furthermore, inhalation of cobalt particles can cause respiratory sensitization, asthma, shortness of breath, and decreased pulmonary function. Even though the primary route of occupational exposure to cobalt is the respiratory tract, skin contact is also important because dermal exposures to hard metal and cobalt salts can result in significant systemic uptake. Sustained exposures can cause skin sensitization, which may result in eruptions of contact dermatitis. In cases of suspected toxicity, blood, serum, or urine concentrations of cobalt can be checked. Vitamin B12 should be used to assess nutritional status.

Useful For: Monitoring metallic prosthetic implant wear and local tissue destruction in failed hip arthroplasty constructs This test is not useful for assessment of vitamin B12 activity.

Interpretation: Chromium: Based on an internal study, synovial fluid chromium concentrations of 16.9 ng/mL or above were more likely due to a metal reaction (eg, adverse local tissue reaction [ALTR]/adverse reaction to metal debris [ARMD]) versus a nonmetal reaction in patients undergoing metal-on-metal revision (sensitivity of 92.3% and specificity of 92.6%). Cobalt: Based on an internal study, synovial fluid cobalt concentrations of 19.8 ng/mL or above were more likely due to a metal reaction (eg, ALTR/ ARMD) versus a nonmetal reaction in patients undergoing metal-on-metal revision (sensitivity of 92.3% and specificity of 96.3%).

Reference Values:

CHROMIUM:
0-17 years: Not established
> or =18 years: <16.9 ng/mL

COBALT:
0-17 years: Not established
> or =18 years: <19.8 ng/mL

Clinical References: 1. Houdek MT, Taunton MJ, Wyles CC, Jannetto PJ, Lewallen DG, Berry DJ. Synovial fluid metal ion levels are superior to blood metal ion levels in predicting an adverse local tissue reaction in failed total hip arthroplasty. J Arthroplasty. 2021;36(9):3312-3317.e1. doi:10.1016/j.arth.2021.04.034 2. Eltit F, Assiri A, Garbuz D, et al. Adverse reactions to metal on polyethylene implants: Highly destructive lesions related to elevated concentration of cobalt and chromium in synovial fluid. J Biomed Mater Res A. 2017;105(7):1876-1886. doi:10.1002/jbm.a.36057 3. Lass R, Grubl A, Kolb A, et al. Comparison of synovial fluid, urine, and serum ion levels in metal-on-metal total hip arthroplasty at minimum follow-up of 18 years. J Orthop Res. 2014;32(9):1234-1240. doi:10.1002/jor.22652 4. De Pasquale D, Stea S, Squarzoni S, et al. Metal-on-metal hip prostheses: Correlation between debris in the synovial fluid and levels of cobalt and chromium ions in the bloodstream. Int Orthop. 2014;38(3):469-475. doi:10.1007/s00264-013-2137-5

CRUO
65719

Chromium Occupational Exposure, Random, Urine

Clinical Information: Chromium (Cr) has an atomic mass of 51.996, atomic number 24, and valences ranging from 2 to 6(+). Hexavalent chromium, Cr(6+), and trivalent chromium, Cr(3+), are the 2 most prevalent forms. Cr(3+) is the only oxidation state present under normal physiologic conditions. Cr(6+) is widely used in industry to make chromium alloys including stainless steel pigments and electroplated coatings. Cr(6+), a known carcinogen, is rapidly metabolized to Cr(3+). Cr(3+) is the only form present in human urine.

Useful For: Screening for occupational exposure

Interpretation: The National Institute for Occupational Safety and Health draft document on occupational exposure reviews the data supporting use of urine to assess chromium exposure.(1) They recommend a Biological Exposure Index of 10 mcg/g creatinine and 30 mcg/g creatinine for the increase in urinary chromium concentrations during a work shift and at the end of shift at the end of the workweek, respectively (Section 3.3.1).

Reference Values:
0-17 years: Not established
> or =18 years: The American Conference of Governmental Industrial Hygienists (ACGIH) Biological Exposure Index (BEI) for daily occupational exposure to hexavalent chromium in urine is an increase of 10.0 mcg/L between pre-shift and post-shift urine collections. The ACGIH BEI for long- and short-term hexavalent chromium in urine is an end-of-shift concentration above 24.9 mcg/L at the end of the work week.

Clinical References: 1. Centers for Disease Control and Prevention; National Institute for Occupational Safety and Health (NIOSH). Criteria for a recommended standard occupational exposure to hexavalent chromium. CDC; September 2013. Accessed November 06, 2020. Available at www.cdc.gov/niosh/docs/2013-128/pdfs/2013_128.pdf 2. Sodi R. Vitamins and trace elements. In: Rifai N, Chiu RWK, Young I, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 39

CRU
8593

Chromium, 24 Hour, Urine

Clinical Information: Chromium (Cr) exists in valence states. Hexavalent chromium (Cr[6+]) and trivalent chromium (Cr[3+]) are the 2 most prevalent forms. Cr(6+) is used in industry to make chromium alloys including stainless steel, pigments, and electroplated coatings. Cr(6+), a known carcinogen, is immediately converted to Cr(3+) upon exposure to biological tissues. Cr(3+) is the only chromium species found in biological specimens. Urine chromium concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by DePuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Screening for occupational exposure to chromium Monitoring metallic prosthetic implant wear

Interpretation: Chromium is principally excreted in the urine. Urine levels correlate with exposure. Results greater than the reference range indicate either recent exposure to chromium or specimen contamination during collection. Prosthesis wear is known to result in increased circulating concentration of metal ions. Modest increase (8-16 mcg/24 hour) in urine chromium concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations greater than 20 mcg/24 hours in a patient with chromium-based implant suggest significant prosthesis wear. Increased urine trace

element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. The National Institute for Occupational Safety and Health draft document on occupational exposure reviews the data supporting use of urine to assess chromium exposure. They recommend a Biological Exposure Index of 10 mcg/g creatinine and 30 mcg/g creatinine for the increase in urinary chromium concentrations during a work shift and at the end of shift at the end of the workweek, respectively. A test for this specific purpose (CRUO / Chromium Occupational Exposure, Random, Urine) is available.

Reference Values:

0-17 years: Not established
> or =18 years: 0.1-1.2 mcg/24 hours

Clinical References: 1. Vincent JB. Elucidating a biological role for chromium at a molecular level. Acc Chem Res. 2000;33(7):503-510 2. Centers for Disease Control and Prevention, The National Institute for Occupational Safety and Health (NIOSH): Criteria for a Recommended Standard for an Occupational Exposure to Hexavalent Chromium. September 2013. Accessed July 22, 2022. CDC; Available at www.cdc.gov/niosh/docs/2013-128/pdfs/2013_128.pdf 3. Keegan GM, Learmonth ID, Case CP. A systematic comparison of the actual, potential, and theoretical health effects of cobalt and chromium exposures from industry and surgical implants. Crit Rev Toxicol. 2008;38:645-674 4. Sodi R. Vitamins and trace elements. In: Rifai N, Chiu RWK, Young I, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 39 5. Eliaz N. Corrosion of metallic biomaterials: A review. Materials (Basel). 2019;12(3):407. doi: 10.3390/ma12030407 6. US Food and Drug Administration. Information about Soft Tissue Imaging and Metal Ion Testing. FDA; Updated March 15, 2019. Accessed March 2, 2021. Available at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/MetalonMetalHipImplants/ucm331971.htm

CRWB
65601

Chromium, Blood

Clinical Information: Chromium (Cr) is a naturally occurring element widely distributed in the environment. Chromium exists in several valence states with the 3 main forms being Cr, Cr(3+), and Cr(6+). Cr(3+) is an essential trace element that enhances the action of insulin. Deficiency leads to impaired growth, reduced life span, corneal lesions, and alterations in carbohydrates, lipid, and protein metabolism. Chromium is widely used in manufacturing processes to make various metal alloys such as stainless steel. It is also used in many consumer products including wood treated with copper dichromate, leather tanned with chromic sulfate, and metal-on-metal hip replacements. The general population is most likely to be exposed to trace levels of chromium in the food that is eaten. Low levels of Cr(3+) occur naturally in a variety of foods, such as fruits, vegetables, nuts, beverages, and meats. The highest potential occupational exposure occurs in the metallurgy and tanning industries, where workers may be exposed to high air concentrations. Per US Food and Drug Administration recommendations, orthopedic surgeons should consider measuring and following serial chromium concentrations in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal hip implants as part of their overall clinical evaluation. Blood Cr concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by DePuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Monitoring exposure to chromium using whole blood specimens Monitoring metallic prosthetic implant wear

Interpretation: Results greater than the reference range indicate exposure to chromium (see

Cautions about specimen collection). Prosthesis wear is known to result in increased circulating concentration of metal ions. Increased blood trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

Reference Values:
0-17 years: Not established
> or =18 years: <1.0 ng/mL

Clinical References: 1. Vincent JB. Elucidating a biological role for chromium at a molecular level. Acc Chem Res. 2000;33(7):503-510 2. Centers for Disease Control and Prevention; National Institute for Occupational Safety and Health (NIOSH): Criteria for a recommended standard occupational exposure to hexavalent chromium. CDC; September 2013. Accessed December 3, 2024. Available at www.cdc.gov/niosh/docs/2013-128/pdfs/2013_128.pdf 3. Keegan GM, Learmonth ID, Case CP. A systematic comparison of the actual, potential, and theoretical health effects of cobalt and chromium exposures from industry and surgical implants. Crit Rev Toxicol. 2008;38:645-674 4. Tower SS. Arthroprosthetic cobaltism: Neurological and cardiac manifestations in two patients with metal-on-metal arthroplasty: A case report. J Bone Joint Surg Am. 2010;92(17):2847-2851 5. US Food and Drug Administration: Information about Soft Tissue Imaging and Metal Ion Testing. FDA; Updated March 15, 2019. Accessed December 3, 2024. Available at: www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/MetalonMetalHipImplants/ucm331971.htm 6. US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry: Toxicology profile for chromium. HHS; September 2012. Accessed December 3, 2024. Available at www.atsdr.cdc.gov/ToxProfiles/tp7.pdf 7. Sodi R. Vitamins and trace elements. In: Rifai N, Chiu RWK, Young I, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 39. 8. Eliaz N. Corrosion of metallic biomaterials: A review. Materials (Basel). 2019;12(3):407. doi:10.3390/ma12030407

CRS
8638

Chromium, Serum

Clinical Information: Chromium (Cr) exists in valence states. Hexavalent chromium (Cr[+6]) and trivalent chromium (Cr[+3]) are the 2 most prevalent forms. Cr(+6) is used in industry to make chromium alloys including stainless steel, pigments, and electroplated coatings. Cr(+6), a known carcinogen, is immediately converted to Cr(+3) upon exposure to biological tissues. Cr(+3) is the only chromium species found in biological specimens. Serum Cr concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by DePuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Screening for occupational exposure Monitoring metallic prosthetic implant wear

Interpretation: Results greater than the flagged value indicate clinically significant exposure to chromium (Cr) (see Cautions about specimen collection). The reported units of measurement for chromium of ng/mL is equivalent to mcg/L. Prosthesis wear is known to result in an increased circulating concentration of metal ions. A modest increase (0.3-0.6 ng/mL) in serum Cr concentration is likely to be associated with a prosthetic device in good condition. Serum concentrations above 1 ng/mL in a patient with a Cr-based implant suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. However, the US Food and Drug Administration recommends testing chromium in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal implants.

Reference Values:

<0.3 ng/mL

When collected by a phlebotomist experienced in ultra-clean collection technique and handled according to the instructions in Metals Analysis Specimen Collection and Transport, we have observed the concentration of chromium in serum to be below 0.3 ng/mL. However, the majority of specimens submitted for analysis from unexposed individuals contain 0.3 ng/mL to 0.9 ng/mL of chromium. Commercial evacuated blood collection tubes not designed for trace-metal specimen collection yield serum containing 2.0 ng/mL to 5.0 ng/mL chromium derived from the collection tube.

Clinical References: 1. Vincent JB. Elucidating a biological role for chromium at a molecular level. Acc Chem Res. 2000;33(7):503-510 2. Centers for Disease Control and Prevention, The National Institute for Occupational Safety and Health (NIOSH): Criteria for a Recommended Standard for an Occupational Exposure to Hexavalent Chromium. September 2013. Accessed October 22, 2023. CDC; Available at www.cdc.gov/niosh/docs/2013-128/pdfs/2013_128.pdf 3. Keegan GM, Learmonth ID, Case CP. A systematic comparison of the actual, potential, and theoretical health effects of cobalt and chromium exposures from industry and surgical implants. Crit Rev Toxicol. 2008;38:645-674 4. Tower SS. Arthroprosthetic cobaltism: Neurological and cardiac manifestations in two patients with metal-on-metal arthroplasty: A case report. J Bone Joint Surg Am. 2010;92:1-5 5 Eliaz N. Corrosion of metallic biomaterials: A Review. Materials (Basel). 2019;12(3):407. doi:10.3390/ma12030407 6. US Food and Drug Administration: Information about Soft Tissue Imaging and Metal Ion Testing. FDA; Updated March 15, 2019. Accessed October 17, 2023. Available at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/MetalonMetalHipImplants/ucm331971.htm 7. Sodi R. Vitamins and trace elements. Rifai N, Chiu RWK, Young I, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 39

CRSY
606353

Chromium, Synovial Fluid

Clinical Information: Chromium (Cr) is a naturally-occurring element widely distributed in the environment. It exists in several valence states with the 3 main forms being Cr(0), Cr(III), and Cr(VI). Cr(III) is an essential trace element that enhances the action of insulin. Deficiency leads to impaired growth, reduced life span, corneal lesions, and alterations in carbohydrates, lipid, and protein metabolism. Chromium is widely used in manufacturing processes to make various metal alloys, such as stainless steel. It is also used in many consumer products, including wood treated with copper dichromate, leather tanned with chromic sulfate, and metal-on-metal hip replacements. Per US Food and Drug Administration recommendations, orthopedic surgeons should consider measuring and following serial chromium concentrations in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal hip implants as part of their overall clinical evaluation. However, a recent publication(1) has shown synovial fluid measurements were superior to whole blood and serum chromium concentrations in predicting local tissue destruction in failed hip arthroplasty constructs. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside are typically made of chromium, cobalt, and molybdenum. This list of products is incomplete, and the products' compositions change occasionally; see each prostheses' product information for composition details. The general population is most likely to be exposed to trace levels of chromium, as Cr(III) is naturally occurring in foods, such as fruits, vegetables, nuts, beverages, and meats. The highest potential occupational exposure occurs in the metallurgy and tanning industries, where workers may be exposed to high air concentrations. In cases of suspected toxicity, blood, serum, or urine concentrations of chromium can be checked.

Useful For: Monitoring metallic prosthetic implant wear and local tissue destruction in failed hip arthroplasty constructs This test is not useful for assessment of potential chromium toxicity.

Interpretation: Based on an internal study, synovial fluid chromium concentrations of 16.9 ng/mL

or above were more likely due to a metal reaction (eg, adverse local tissue reaction [ALTR]/adverse reaction to metal debris [ARMD]) versus a nonmetal reaction in patients undergoing metal-on-metal revision (sensitivity of 92.3% and specificity of 92.6%).

Reference Values:
0-17 years: Not established
> or =18 years: <16.9 ng/mL

Clinical References: 1. Houdek MT, Taunton MJ, Wyles CC, Jannetto PJ, Lewallen DG, Berry DJ. Synovial fluid metal ion levels are superior to blood metal ion levels in predicting an adverse local tissue reaction in failed total hip arthroplasty. J Arthroplasty. 2021;36(9):3312-3317.e1. doi:10.1016/j.arth.2021.04.034 2. Eltit F, Assiri A, Garbuz D, et al. Adverse reactions to metal on polyethylene implants: Highly destructive lesions related to elevated concentration of cobalt and chromium in synovial fluid. J Biomed Mater Res A. 2017;105(7):1876-1886. doi:10.1002/jbm.a.36057 3. Lass R, Grubl A, Kolb A, et al. Comparison of synovial fluid, urine, and serum ion levels in metal-on-metal total hip arthroplasty at minimum follow-up of 18 years. J Orthop Res. 2014;32(9):1234-1240. doi:10.1002/jor.22652 4. De Pasquale D, Stea S, Squarzoni S, et al. Metal-on-metal hip prostheses: Correlation between debris in the synovial fluid and levels of cobalt and chromium ions in the bloodstream. Int Orthop. 2014;38(3):469-475. doi:10.1007/s00264-013-2137-5

CRCRU
607758

Chromium/Creatinine Ratio, Random, Urine

Clinical Information: Chromium (Cr) has an atomic mass of 51.996, atomic number 24, and valences ranging from 2to 6(+). Hexavalent chromium, Cr(6+), and trivalent chromium, Cr(3+), are the 2 most prevalent forms. Cr(3+) is the only oxidation state present under normal physiologic conditions. Cr(6+) is widely used in industry to make chromium alloys including stainless steel pigments and electroplated coatings. Cr(6+), a known carcinogen, is rapidly metabolized to Cr(3+). Cr(3+) is the only form present in human urine.

Useful For: Detecting chromium exposure

Interpretation: Chromium is principally excreted in the urine. Results greater than the reference range indicate either recent exposure to chromium or specimen contamination during collection. The National Institute for Occupational Safety and Health document on occupational exposure reviews the data supporting use of urine to assess chromium exposure. The biological exposure index (BEI) for total chromium in urine measured at the end of the shift at the end of the workweek is 25 mcg/L. The BEI for the increase in total chromium during a shift is 10 mcg/L. A test for this specific purpose (CRUO / Chromium Occupational Exposure, Random, Urine) is available.

Reference Values:
0-17 years: Not established
>17 years: <0.8 mcg/g Creatinine

Clinical References: 1. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. Toxicology profile for chromium. HHS; September 2012. Accessed 11/06/2020. Available at www.atsdr.cdc.gov/ToxProfiles/tp7.pdf 2. Sodi R. Vitamins and trace elements. In: Rifai N, Chiu RWK, Young I, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 39 3. Centers for Disease Control and Prevention. National Institute for Occupational Safety and Health (NIOSH): Criteria for a recommended standard occupational exposure to hexavalent chromium. CDC; September 2013. Accessed 11/06/2020. Available at www.cdc.gov/niosh/docs/2013-128/pdfs/2013_128.pdf 4. Gianello G, Masci O, Carelli G, Vinci F, Castellino N. Occupational exposure to chromium-an assessment of environmental pollution levels and

biological monitoring of exposed workers. Ind Health. 1998;36(1):74-77. doi: 10.2486/indhealth.36.74 5. Eliaz N. Corrosion of metallic biomaterials: A review. Materials (Basel). 2019;12(3):407. doi: 10.3390/ma12030407 6. US Food and Drug Administration. Information about Soft Tissue Imaging and Metal Ion Testing. FDA; Updated March 15, 2019. Accessed March 2, 2021. Available at: www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/MetalonMetalHipImplants/ucm331971.htm

CH9
65029

Chromogenic Factor IX Activity Assay, Plasma

Clinical Information: Factor IX (FIX) is a vitamin K-dependent serine protease synthesized in the liver and participates in the intrinsic coagulation pathway. Its biological half-life is 18 to 24 hours. Congenital FIX deficiency is inherited as an X-linked recessive bleeding disorder (hemophilia B). Severe deficiency (<1%) characterized by hemarthroses, deep tissue bleeding, excessive bleeding with trauma, and ecchymoses. Typically, these patients are tested using a 1-stage clotting assay. However, new treatment options using long-acting glycoPEGylated replacement products are being approved for clinical use. Pharmacokinetic studies for these products indicate ideal monitoring of patients should be performed by the 2-stage chromogenic assay.

Useful For: Monitoring coagulation factor replacement therapy of selected extended half-life coagulation factor replacements Aiding in the diagnosis of hemophilia B using a 2-stage assay, especially when a 1-stage assay was normal

Interpretation: Factor IX deficiency may be acquired (eg, vitamin K deficiency, warfarin anticoagulation effect, liver disease, or a consumptive coagulopathy) or congenital (hemophilia B). Optimal laboratory monitoring of selected extended half-life factor IX replacement therapy (eg, glycoPEGylated factor FIX) may be achieved with the chromogenic factor IX assay. Elevated factor IX levels may be associated with acute or chronic inflammation, excess factor IX replacement therapy, or as a result of a rare genetic variant, factor IX Padua.

Reference Values:
65-140%

Chromogenic factor IX activity generally correlates with the one-stage FIX activity. In full term/premature neonates, infants, children, and adolescents the one-stage FIX activity* is similar to adults. However, no similar data for chromogenic FIX activity are available.(Appel IM, Grimminck B, Geerts J, Stigter R, Cnossen MH, Beishuizen A. Age dependency of coagulation parameters during childhood and puberty. J Thromb Haemost. 2012;10(11):2254-2263)

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing

Clinical References: 1. Bowyer AE, Hillarp A, Ezban M, Persson P, Kitchen S. Measuring factor IX activity of noacog beta pegol with commercially available one-stage clotting and chromogenic assay kits: a two-center study. J Thromb Haemost. 2016;14(7 1428-1435. doi:10.1111/jth.13348 2. Kitchen S, Signer-Romero K, Key NS. Current laboratory practices in the diagnosis and management of haemophilia: a global assessment. Haemophilia. 2015;21(4)550-557 3. Sorensen MH, Anderson S, Ezban M. Factor IX-deficient plasma spiked with N9-GP behaves similarly to N9-GP post-administration clinical samples in N9-GP ELISA and FIX activity assays. Haemophilia. 2015;21(6):832-836 4. Dodt J, Hubbard AR, Wicks SJ, et al. Potency determination of factor VIII and factor IX for new product labelling and postinfusion testing: challenges for caregivers and regulators. Haemophilia. 2015;21(4):543-549 5. Wilmot HV, Hogwood J, Gray E. Recombinant factor IX: discrepancies between one-stage clotting and chromogenic assays. Haemophilia. 2014;20(6):891-897

CHF8
610419

Chromogenic Factor VIII Activity Assay, Plasma

Clinical Information: Factor VIII (FVIII) is synthesized in the endothelial cells of the liver and, perhaps, in other tissues. It is a coagulation cofactor that circulates bound to von Willebrand factor and is part of the intrinsic coagulation pathway. The biological half-life is 9 to 18 hours (average is 12 hours). Congenital FVIII deficiency is inherited in a recessive X-linked manner and results in hemophilia A, which has an incidence of 1 in 10,000 live male births. Patients with severe deficiency (<1%) experience spontaneous bleeding episodes (eg, hemarthrosis, deep-tissue bleeding), whereas patients with moderate or mild deficiency (>1%) typically experience post-trauma or surgical bleeding. FVIII activity assays (FVIII:C) are performed to diagnose hemophilia A and to monitor FVIII replacement therapy. FVIII:C assays are typically 1-stage clotting assays. However, there is a subset of patients with mild hemophilia A who have shown discrepantly low results when measured with the 2-stage (chromogenic) assay, indicating that testing patients with a mild bleeding history with both a 1- and 2-stage assay would aid in diagnosis. In addition, there are new treatment options using long-acting glycoPEGylated products. Pharmacokinetic studies are showing that ideal monitoring of patients should be performed by the 2-stage chromogenic assay.

Useful For: Monitoring coagulation factor replacement therapy of selected extended half-life coagulation factor replacements Aiding in the diagnosis of hemophilia A using a 2-stage assay, especially when the 1-stage assay result was normal

Interpretation: Factor VIII deficiency may be seen in congenital hemophilia A, acquired (autoimmune) hemophilia A, or von Willebrand disease (congenital and acquired). Laboratory artifacts that may result in artificially reduced factor VIII include specimens collected in EDTA, instead of citrate, or heparin contamination of the plasma specimen. Elevated factor VIII may be seen in acute or chronic inflammatory states or excess factor VIII replacement therapy.

Reference Values:
55.0-200.0%

Chromogenic factor VIII activity generally correlates with the one-stage FVIII activity. In full term/premature neonates, infants, children, and adolescents the one-stage FVIII activity* is similar to adults. However, no similar data for chromogenic FVIII activity are available.(Appel IM, Grimminck B, Geerts J, Stigter R, Cnossen MH, Beishuizen A. Age dependency of coagulation parameters during childhood and puberty. J Thromb Haemost. 2012;10(11):2254-63)

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing

Clinical References: 1. Rodgers SE, Duncan EM, Sobieraj-Teague M, Lloyd JV. Evaluation of three automated chromogenic FVIII kits for the diagnosis of mild discrepant haemophilia A. Int J Lab Hematol. 2009;31(2):180-188 2. Kitchen S, Beckman H, Katterle Y, et al. BAY 81-8973, a full-length recombinant factor VIII: results from an International comparative laboratory field study. Haemophilia. 2016;22(3):e192-199. doi:10.1111/hae.12925 3. Peyvandi F, Oldenburg J, Friedman KD. A critical appraisal of one-stage and chromogenic assays of factor VIII activity. J Thromb Haemost. 2016;14(2):248-261 4. Dodt J, Hubbard AR, Wicks SJ, et al. Potency determination of factor VIII and factor IX for new product labelling and postinfusion testing: challenges for caregivers and regulators. Haemophilia. 2015;21(4):543-549

CH8BI
606844

Chromogenic Factor VIII Inhibitor Bethesda Profile Interpretation

Clinical Information: Factor VIII (FVIII) inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may be alloimmune: developing in patients with congenital FVIII deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate or autoimmune: occurring in patients without hemophilia (not previously factor VIII deficient) either spontaneously or during pregnancy or in association with autoimmune diseases.

Useful For: Interpretation of CHF8P / Chromogenic Factor VIII Inhibitor Bethesda Profile, Plasma Detecting the presence and titer of a specific factor inhibitor directed against coagulation factor VIII This test is not useful for detecting the presence of inhibitors directed against other clotting factors and will not detect the presence of lupus anticoagulants.

Interpretation: The interpretive report will include assay information, background information, and conclusions based on the test results.

Reference Values:
Only orderable as part of a profile. For more information see CHF8P / Chromogenic Factor VIII Inhibitor Bethesda Profile, Plasma.

An interpretive report will be provided.

Clinical References: 1. Peyvandi F, Oldenburg J, Friedman KD. A critical appraisal of one-stage and chromogenic assays of factor VIII activity. J Thromb Haemost. 2016;14(2):248-261 2. Verbruggen B, van Heerde WL, Laros-van Gorkom BA. Improvements in factor VIII inhibitor detection: From Bethesda to Nijmegen. Semin Thromb Hemost. 2009;35(8):752-759 3. Miller C, Platt S, Rice A, Kelly F, Soucie JM, Hemophilia Inhibitor Research Study Investigators. Validation of Nijmegen-Bethesda assay modifications to allow inhibitor measurement during replacement therapy and facilitate inhibitor surveillance. J Thromb Haemost. 2012;10:1055-1061

CHF8P
610420

Chromogenic Factor VIII Inhibitor Bethesda Profile, Plasma

Clinical Information: Factor VIII (FVIII) inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may be alloimmune: developing in patients with congenital FVIII deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate or autoimmune: occurring in patients without hemophilia (not previously factor VIII deficient) either spontaneously, during pregnancy, or in association with autoimmune diseases.

Useful For: Detecting the presence and titer of a specific factor inhibitor directed against coagulation factor VIII for patients on emicizumab (Hemlibra) Detecting the presence and titer of an inhibitor directed against factor VIII This test is not useful for detecting the presence of inhibitors directed against other clotting factors and will not detect the presence of lupus anticoagulants.

Interpretation: An interpretive report will be provided when testing is completed, noting a presence or absence of a chromogenic factor VIII inhibitor.

Reference Values:
CHROMOGENIC Factor VIII Activity Assay
Adults: 55.0-200.0%
Normal, full-term newborn infants or healthy premature infants usually have normal or elevated factor VIII.*
*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and

Processing.

BETHESDA TITER
< or =0.5 Bethesda Units

Clinical References: 1. Peyvandi F, Oldenburg J, Friedman KD. A critical appraisal of one-stage and chromogenic assays of factor VIII activity. J Thromb Haemost. 2016;14(2):248-261 2. Verbruggen B, van Heerde WL, Laros-van Gorkom BA. Improvements in factor VIII inhibitor detection: From Bethesda to Nijmegen. Semin Thromb Hemost. 2009;35(8):752-759 3. Miller CH, Platt SJ, Rice AS, Kelly F, Soucie JM: Hemophilia Inhibitor Research Study Investigators. Validation of Nijmegen-Bethesda assay modifications to allow inhibitor measurement during replacement therapy and facilitate inhibitor surveillance. J Thromb Haemost. 2012;10(6):1055-1061

CH8B
606843

Chromogenic Factor VIII Inhibitor Bethesda Titer, Plasma

Clinical Information: Factor VIII (FVIII) inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may be alloimmune: developing in patients with congenital FVIII deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate or autoimmune: occurring in patients without hemophilia (not previously factor VIII deficient) either spontaneously, during pregnancy, or in association with autoimmune diseases.

Useful For: Detecting the presence and titer of a specific factor inhibitor directed against coagulation factor VIII This test is not useful for detecting the presence of inhibitors directed against other clotting factors and will not detect the presence of lupus anticoagulants.

Interpretation: The interpretive report will include assay information, background information, and conclusions based on the test results.

Reference Values:
Only orderable as part of a profile. For more information see CHF8P / Chromogenic Factor VIII Inhibitor Bethesda Profile, Plasma.

< or =0.5 Bethesda Units

Clinical References: Favaloro EJ and Lippi G. Eds. Hemostasis and Thrombosis, Methods and Protocols. Humana Press 2017.

CGAK
34641

Chromogranin A, Serum

Clinical Information: Chromogranin A (CgA) is a 439-amino acid protein with a molecular weight of 48 to 60 kDa, depending on glycosylation and phosphorylation status. It is a member of the granin family of proteins and polypeptides. Granins are widespread in endocrine, neuroendocrine, peripheral, and central nervous tissues, where they are found in secretory granules alongside the tissue-specific secretion products. The role of granins within the granules is to maintain the regulated secretion of these signaling molecules. This includes: -Facilitating the formation of secretory granules -Calcium- and pH-mediated sequestration and re-solubilization of hormones or neurotransmitters -Regulation of neuropeptide and peptide hormone processing through modulation of prohormone convertase activity In addition, granins contain multiple protease and peptidase cleavage sites and, upon intra- or extracellular cleavage, give rise to a series of peptides with distinct extracellular functions. Some of these have defined functions, such as pancreastatin, vasostatin, and catestatin, while others are less well characterized.(1) Because of its

ubiquitous distribution within neuroendocrine tissues, CgA can be a useful diagnostic marker for neuroendocrine neoplasms, including carcinoids, pheochromocytomas, neuroblastomas, medullary thyroid carcinomas, some pituitary tumors, functioning and nonfunctioning islet cell tumors, and other amine precursor uptake and decarboxylation tumors. It can also serve as a sensitive means for detecting residual or recurrent disease in treated patients.(2-4) Carcinoid tumors in particular almost always secrete CgA along with a variety of specific modified amines, chiefly serotonin (5-hydroxytryptamine) and peptides.(1-4) Carcinoid tumors are subdivided into foregut carcinoids, arising from respiratory tract, stomach, pancreas or duodenum (approximately 15% of cases); midgut carcinoids, occurring within jejunum, ileum, or appendix (approximately 70% of cases); and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases). Serum CgA and urine 5-hydroxyindolacetic acid (5-HIAA) are considered the most useful biochemical markers and are first-line tests in disease surveillance of most patients with carcinoid tumors.(2-4) Serum CgA measurements have been used in conjunction with, or alternative to, measurements of serum or whole blood serotonin, urine serotonin and 5-HIAA, and imaging studies in the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular, flushing. A number of tumors that are not derived from classical endocrine or neuroendocrine tissues but contain cells with partial neuroendocrine differentiation, such as small-cell carcinoma of the lung or prostate carcinoma, may also display elevated CgA levels. However, the role of CgA measurement is not well defined in these tumors.

Useful For: Aiding in monitoring disease progression during the course of disease and treatment in patients with gastroenteropancreatic neuroendocrine tumors (grade 1 and grade 2) when used in conjunction with other clinical methods This test is not indicated for use as a stand-alone monitoring assay.

Interpretation: Follow-up/Surveillance: In patients diagnosed with gastroenteropancreatic neuroendocrine tumors (GEP-NET) grade 1 and grade 2, when used in combination with clinical symptoms and/or other laboratory parameters, the change of chromogranin A (CgA) concentration over time provides diagnostic information whether a tumor progression has occurred. The change of CgA is calculated from measurements at consecutive routine monitoring visits within a typical interval of 3 to 6 months and is considered test-positive if the serum CgA concentration increases by more than 50% to an absolute value greater than 100 ng/mL. A positive CgA-change test was shown to be significantly associated with tumor progression ($p < 0.001$). Calculation and Interpretation of delta CgA in G1/G2 GEP-NET: Delta CgA = ([CgA concentration of current visit-CgA concentration of previous visit]/CgA concentration of previous visit) x 100% For delta CgA Above 50% and CgA Concentrations Above 100 ng/mL: An increase of CgA serum concentrations of more than 50% to a value of greater than 100 ng/mL between consecutive monitoring visits defines a positive test result representing a higher probability that tumor progression has occurred with an observed sensitivity of 34%. For delta CgA Less Than or Equal to 50% or CgA Concentrations Less than or Equal to 100 ng/mL: A change of CgA serum concentrations of a less than or equal to 50% increase between monitoring visits or to a value of 100 ng/ml or less defines a negative test result representing a lower probability that tumor progression has occurred with an observed specificity of 93%. CgA in Other Tumors: Urine 5-hydroxyindolacetic acid (5-HIAA) and serum CgA levels increase in proportion to carcinoid tumor burden. Because of the linear relationship of CgA to tumor burden, its measurement also may provide prognostic information. Most mid- and hindgut tumors secrete CgA even if they do not produce significant amounts of serotonin or serotonin metabolites (eg, 5-HIAA). Guidelines recommend 3 to 12 monthly measurements of CgA or 5-HIAA in follow-up of midgut carcinoids.(2,3) Patients with foregut tumors can also be monitored with CgA or 5-HIAA measurements if they were positive for these markers at initial diagnosis. Hindgut tumors usually do not secrete serotonin and consequently, only CgA monitoring is recommended.(1-4) As is typical for tumor marker use in follow-up and surveillance, a 50% change in serum CgA concentrations should be considered potentially clinically significant in the absence of confounding factors (see Cautions). Much smaller changes in CgA concentrations might be considered significant if they occur over several serial measurements and are all in the same direction. Adjunct in Diagnosis of Carcinoid Tumors: CgA is elevated in most patients (approximately 90%) with symptomatic or advanced carcinoids (carcinoid syndrome), usually to levels several times the upper limit of the

reference interval. Serum CgA measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though serotonin and 5-HIAA are often normal. CgA is also elevated in 80% to 90% of patients with symptomatic foregut and midgut tumors. To achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, serum CgA, serotonin in serum or blood, and 5-HIAA in urine should all be measured. In most cases, if none of these analytes are elevated, carcinoids can usually be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests, such as urine serotonin measurement, will be required. An example would be a foregut tumor that does not secrete CgA and only produces 5-hydroxytryptophan (5-HTP) rather than serotonin. In this case, circulating chromogranin, serotonin, and urine 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to serotonin, leading to high urine serotonin levels. Adjunct in the Diagnosis of Other Neuroendocrine Tumors: In patients with suspected neuroendocrine tumors other than carcinoids, CgA is often elevated alongside any specific amine and peptide hormones or neurotransmitters that may be produced. The CgA elevations are less pronounced than in carcinoid tumors, and measurement of specific tumor secretion products is considered of greater utility. However, CgA measurements can occasionally aid in diagnosis of these tumors if specific hormone measurements are inconclusive. This is the case with pheochromocytoma and neuroblastoma, where CgA levels may be substantially elevated and can, therefore, provide supplementary and confirmatory information to measurements of specific hormones. In particular, CgA measurements might provide useful diagnostic information in patients with mild elevations in catecholamines and metanephrines;(5) such mild elevations often represent false-positive test results. Possible Adjunct in Outcome Prediction and Follow-up of Prostate Cancer: Prostate cancers often contain cells with partial neuroendocrine differentiation. These cells secrete CGA. The amounts secreted are insufficient in most cases to make this a useful marker for prostate cancer diagnosis. However, if patients with advanced prostate cancer are found to have elevated CGA levels, this indicates the tumor contains a significant neuroendocrine cell subpopulation. Such tumors are often resistant to antiandrogen therapy and have a worse prognosis. These patients should be monitored particularly closely.(6)

Reference Values:

<93 ng/mL

Reference values apply to all ages.

Clinical References: 1. Bartolomucci A, Possenti R, Mahata SK, Fischer-Colbrie R, Loh YP, Salton SRJ. The extended granin family: structure, function, and biomedical implications. Endocr Rev. 2011;32(6):755-797 2. Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. Pancreas. 2010;39(6):753-766 3. Anthony LB, Stosberg JR, Klimstra DS, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors (nets): well-differentiated nets of the distal colon and rectum. Pancreas. 2010;39(6):767-774 4. Kullke MH, Benson AB, Bergsland E, et al. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines): NCCN Guidelines Version 1. Neuroendocrine Tumors. 2012:1-94 5. Algeciras-Schimnich A, Preissner CM, Young WF Jr, Singh RJ, Grebe SK. Plasma chromogranin A or urine fractionated metanephrines follow-up testing improves the diagnostic accuracy of plasma fractionated metanephrines for pheochromocytomas. J Clin Endocrinol Metab. 2008;93(1):91-95 6. Ploussard G, Rozet F, Roubaud G, Stanbury T, Sargos P, Roupret M. Chromogranin A: a useful biomarker in castration-resistant prostate cancer. World J Urol. 2023;41(2):361-369. doi:10.1007/s00345-022-04248-0 7. Korse CM, Muller M, Taal BG. Discontinuation of proton pump inhibitors during assessment of chromogranin A levels in patients with neuroendocrine tumors. Br J Cancer. 2011;105(8):1173-1175 8. Bech PR, Ramachandran R, Dhillo WS, Martin NM, Bloom SR. Quantifying the effects of renal impairment on plasma concentrations of the neuroendocrine neoplasia biomarkers chromogranin A, chromogranin B, and cocaine- and amphetamine-regulated transcript. Clin Chem. 2012;58(5):941-943 9. B R A H M S CgAII KRYPTOR. Instruction for Use. V1.1us. Thermo Fisher Scientific Inc; 2023 10. Wang YH, Yang QC, Lin Y, Xue L, Chen MH, Chen J. Chromogranin A as a marker for diagnosis, treatment, and survival in patients with gastroenteropancreatic neuroendocrine neoplasm. Medicine (Baltimore). 2014;93(27):e247.

doi:10.1097/MD.0000000000000247 11. Ciobanu OA, Martin S, Fica S. Perspectives on the diagnostic, predictive and prognostic markers of neuroendocrine neoplasms (Review). Exp Ther Med. 2021;22(6):1479. doi:10.3892/etm.2021.10914

CHRO
70402

Chromogranin Immunostain, Technical Component Only

Clinical Information: Chromogranin A is widely expressed in neuronal tissues and in secretory granules of human endocrine cells such as parathyroid gland, adrenal medulla, anterior pituitary gland, Langerhans islets of the pancreas, and C-cells of the thyroid. It is useful for the identification of tumors with neuroendocrine differentiation such as pituitary adenomas, islet cell tumors, pheochromocytomas, medullary thyroid carcinomas, Merkel cell tumors, and carcinoids.

Useful For: Aiding in the identification of tumors with neuroendocrine differentiation

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Zhang D, Xie C, Wang R, et al. Effective preparation of a monoclonal antibody against human chromogranin A for immunohistochemical diagnosis. BMC Biotechnology. 2018;18(1):25 2. Kyriakopoulos G, Mavroeidi V, Chatzellis E, Kaltsas GA, Alexandraki,KI. Histopathological, immunohistochemical, genetic and molecular markers of neuroendocrine neoplasms. Ann Transl Med. 2018;6(12):252 3. Gkolfinopoulos S, Tsapakidis K, Papadimitriou K, Papamichael D, Kountourakis P. Chromogranin A as a valid marker in oncology: Clinical application or false hopes? World J Methodol. 2017;7(1):9-15 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CMAFF
35263

Chromosomal Microarray (CMA) Familial Testing, FISH

Clinical Information: Chromosomal microarray (CMA) is a method for detecting copy number changes (gains or losses) across the entire genome. When copy number changes are identified in a patient, parental studies are sometimes necessary to assess their clinical significance. Changes that are inherited from clinically normal parents are less likely to be clinically significant in the patient and de novo changes are more likely to be pathogenic. To identify familial copy number changes in parents of previously tested patients, fluorescence in situ hybridization testing is utilized. the parental results will provide the context for interpretation of the patient's CMA results.

Useful For: Determining the inheritance pattern of copy number changes previously identified by chromosomal microarray analysis in a patient and aiding in the clinical interpretation of the pathogenicity of the copy number change

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Shaffer LG, Kashork CD, Saleki R, et al: Targeted genomic microarray

analysis for identification of chromosome abnormalities in 1500 consecutive clinical cases. J Pediatr. 2006 Jul;149(1):98-102 2. Baldwin EL, Lee JY, Blake DM, et al: Enhanced detection of clinically relevant genomic imbalances using a targeted plus whole genome oligonucleotide microarray. Genet Med. 2008 May;10:415-429

CMAPC 63042 Chromosomal Microarray, Autopsy, Products of Conception, or Stillbirth

Clinical Information: Chromosomal abnormalities may result in malformed fetuses, spontaneous abortions, or neonatal deaths. Estimates of the frequency of chromosome abnormalities in spontaneously aborted fetuses range from 15% to 60%. Chromosomal microarray (CMA) studies of products of conception, a stillborn infant, or neonate (autopsy) may provide useful information concerning the cause of fetal loss. In addition, CMA may provide information regarding the recurrence risk for future pregnancy loss and risk of having subsequent children with chromosome anomalies. This is particularly useful information if there is a family history of 2 or more miscarriages or when fetal malformations are evident. Chromosomal microarray is a high-resolution method for detecting copy number changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. This CMA test utilizes greater than 2 million copy number probes and approximately 750,000 single nucleotide polymorphism probes for the detection of copy number changes and regions with absence of heterozygosity. Identification of regions of excess homozygosity on a single chromosome could suggest uniparental disomy that may warrant further clinical investigation when observed on chromosomes with known imprinting disorders. In addition, the detection of excess homozygosity on multiple chromosomes may suggest consanguinity.

Useful For: Prenatal diagnosis of copy number changes (gains or losses) across the entire genome Diagnosing chromosomal causes for fetal death Determining recurrence risk of future pregnancy losses Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods, such as conventional chromosome and fluorescence in situ hybridization studies Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, as a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray Assessing regions of homozygosity related to uniparental disomy or identical by descent

Interpretation: Copy number variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. While many copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories, making interpretation of these variants challenging. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, as well as whether the change is a deletion or duplication. Parental testing may also be necessary to further assess the potential pathogenicity of a copy number change. In such situations, the inheritance pattern and clinical and developmental history of the transmitting parent will be taken into consideration. All copy number variants within the limit of detection classified as pathogenic or likely pathogenic will be reported regardless of size. This includes but is not limited to incidental findings currently recommended for reporting by the American College of Medical Genetics and Genomics.(1) Copy number changes with unknown significance will be reported when at least one protein-coding gene is involved in a deletion greater than 1 megabase (Mb) or a duplication greater than 2 Mb. The detection of excessive homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy (UPD) or to test for variants in genes associated with autosomal recessive disorders consistent with the patient's clinical presentation that are present in regions of homozygosity. Regions with absence of heterozygosity (AOH) of unknown significance will be reported when greater

than 5 Mb (terminal) and 10 Mb (interstitial) on UPD-associated chromosomes. Whole genome AOH will be reported when greater than 5% of the genome. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Kalia S, Adelman K, Bale S, et al: Recommendations for reporting of secondary findings in clinical exome and genome sequencing. 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19(2):249-255. doi:10.1038/gim.2016.190 2. Shao L, Akkari Y, Cooley LD, et al. Chromosomal microarray analysis, including constitutional and neoplastic disease applications, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(10):1818-1829. doi:10.1038/s41436-021-01214-w 3. Society for Maternal-Fetal Medicine (SMFM), Dugoff L, Norton ME, Kuller JA: The use of chromosomal microarray for prenatal diagnosis. Am J Obstet Gynecol. 2016;215(4):B2-B9. doi:10.1016/j.ajog.2016.07.016 4. Sahoo T, Dzidic N, Strecker MN, et al: Comprehensive genetic analysis of pregnancy loss by chromosomal microarrays: Outcomes, benefits, and challenges. Genet Med. 2017;19(1):83-89. doi:10.1038/gim.2016.69 5. Rosenfeld JA, Tucker ME, Escobar LF, et al: Diagnostic utility of microarray testing in pregnancy loss. Ultrasound Obstet Gynecol. 2015;46(4):478-486. doi:10.1002/uog.14866

CMAMT
62667

Chromosomal Microarray, Autopsy/Products of Conception/Stillbirth, Tissue

Clinical Information: Chromosomal abnormalities may result in malformed fetuses, spontaneous abortions, or neonatal deaths. Estimates of the frequency of chromosome abnormalities in spontaneously aborted fetuses range from 15% to 60%. Chromosomal microarray (CMA) studies of products of conception, a stillborn infant, or a neonate (autopsy) may provide useful information concerning the cause of miscarriage or fetal loss. In addition, CMA may provide information regarding the recurrence risk for future pregnancy loss and risk of having subsequent children with chromosome anomalies. This is particularly useful information if there is a family history of 2 or more miscarriages or when fetal malformations are evident. Chromosomal microarray is a high-resolution method for detecting copy number changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. This CMA test utilizes over 220,000 markers for the detection of copy number changes and regions with absence of heterozygosity. The detection of excess homozygosity on multiple chromosomes may suggest consanguinity. Homozygosity involving the entire genome is indicative of a complete molar pregnancy.

Useful For: Diagnosis of congenital copy number changes in products of conception, including aneuploidy (ie, trisomy or monosomy) and structural abnormalities Diagnosing chromosomal causes for fetal death Determining recurrence risk of future pregnancy losses Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected previously by other methods such as conventional chromosome and fluorescence in situ hybridization studies Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray

Interpretation: Copy number variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. While many copy number changes observed by chromosomal microarray testing can readily be

characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories, making interpretation of these variants challenging. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, as well as whether the change is a deletion or duplication. Parental testing may also be necessary to further assess the potential pathogenicity of a copy number change. In such situations, the inheritance pattern and clinical and developmental history of the transmitting parent will be taken into consideration. All copy number variants within the limit of detection classified as pathogenic or likely pathogenic will be reported regardless of size. This includes, but is not limited to, incidental findings currently recommended for reporting by the American College of Medical Genetics and Genomics.(1) Copy number changes with unknown significance will be reported when at least one protein-coding gene is involved in a deletion greater than 1 megabase (Mb) or a duplication greater than 2 Mb. The detection of excessive homozygosity may suggest the need to test for variants in genes associated with autosomal recessive disorders consistent with the patient's clinical presentation that are present in regions of homozygosity. Homozygosity will be reported when involving greater than 20% of the genome. Homozygosity involving the entire genome is indicative of a complete molar pregnancy. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Kalia S, Adelman K, Bale S, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing. 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19:249-255 2. American College of Obstetricians and Gynecologists Committee on Genetics: Committee opinion No. 581: the use of chromosomal microarray analysis in prenatal diagnosis. Obstet Gynecol. 2013;122:1374-1377 3. Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. N Engl J Med. 2012;367:2175-2184 4. Armengol L, Nevado J, Serra-Juhe C, et al. Clinical utility of chromosomal microarray analysis in invasive prenatal diagnosis. Hum Genet. 2012;131:513-523 5. Laurino MY, Bennett RL, Saraiya DS, et al. Genetic evaluation and counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2005;14:165-181 6. Reddy UM, Page GP, Saade GR, et al. Karyotype versus microarray testing for genetic abnormalities after stillbirth. N Engl J Med. 2012;367:2185-2193

CMACB
35247

Chromosomal Microarray, Congenital, Blood

Clinical Information: Aneuploidy or unbalanced chromosome rearrangements are often found in patients with intellectual disability, developmental delay, autism, dysmorphic features, or congenital anomalies. Some chromosomal abnormalities are large enough to be detected with conventional chromosome analysis. However, many pathogenic rearrangements are below the resolution limits of chromosome analysis (approximately 5 megabases). Chromosomal microarray (CMA) is a high-resolution method for detecting copy number changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. This CMA test utilizes greater than 2 million copy number probes and approximately 750,000 single nucleotide polymorphism probes for the detection of copy number changes and regions of excessive homozygosity. Identification of regions of excessive homozygosity on a single chromosome could suggest uniparental disomy (UPD), which may warrant further clinical investigation when observed on chromosomes with known imprinting disorders associated with UPD. In addition, the detection of excessive homozygosity on multiple chromosomes may suggest consanguinity and, therefore, could be useful in determining candidate genes for further testing for autosomal recessive disorders. An online research opportunity called GenomeConnect (genomeconnect.org) is available for the recipients of genetic test results. This patient registry collects deidentified genetic and health information to advance knowledge of genetic variants. For more information see GenomeConnect Patient Portal.

Useful For: First-tier, postnatal testing for individuals with multiple anomalies that are not specific to well-delineated genetic syndromes, apparently nonsyndromic developmental delay or intellectual disability, or autism spectrum disorders as recommended by the American College of Medical Genetics and Genomics Follow-up testing for individuals with unexplained developmental delay or intellectual disability, autism spectrum disorders, or congenital anomalies with a previously normal conventional chromosome study Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods such as conventional chromosome and fluorescence in situ hybridization studies Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray Assessing regions of homozygosity related to uniparental disomy or identity by descent

Interpretation: When interpreting results, the following factors need to be considered: Copy number variation is found in all individuals, including patients with abnormal phenotypes and normal populations. Therefore, determining the clinical significance of a rare or novel copy number change can be challenging. Parental testing may be necessary to further assess the potential pathogenicity of a copy number change. While most copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, whether the change is a deletion or duplication, the inheritance pattern, and the clinical and/or developmental history of a transmitting parent. All copy number variants within the limit of detection classified as pathogenic or likely pathogenic will be reported regardless of size. This includes but is not limited to incidental findings currently recommended for reporting by the American College of Medical Genetics and Genomics.(1) Copy number changes with unknown significance will be reported when at least one protein-coding gene is involved in a deletion greater than 200 kilobases or a duplication greater than 1 megabase (Mb). The detection of excessive homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy (UPD) or to test for variants in genes associated with autosomal recessive disorders consistent with the patient's clinical presentation that are present in regions of homozygosity. Interstitial regions with absence of heterozygosity (AOH) of unknown significance will be reported when greater than 10 Mb on UPD-associated chromosomes, and greater than 15 Mb on non-imprinted chromosomes. Terminal AOH will be reported when greater than 5 Mb. Whole genome AOH will be reported when greater than 2% of the genome. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Families benefit from hearing genetic information multiple times and in multiple ways. A referral to a clinical genetics professional is appropriate for individuals and families to discuss the results of chromosomal microarray testing.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing. 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19(2):249-255. doi:10.1038/gim.2016.190 2. Manning M, Hudgins L, Professional Practice and Guidelines Committee. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. Genet Med. 2010;12(11):742-745. doi:10.1097/GIM.0b013e3181f8baad 3. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010;86(5):749-764. doi:10.1016/j.ajhg.2010.04.006 4. Kearney HM, Thorland EC, Brown KK, et al. American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional

copy number variants. Genet Med. 2011;13(7)680-685. doi:10.1097/GIM.0b013e3182217a3a 5. Kearney HM, Kearney JB, Conlin LK. Diagnostic implications of excessive homozygosity detected by SNP-based microarrays: consanguinity, uniparental disomy, and recessive single-gene mutations. Clin Lab Med. 2011;31(4):595-613. doi:10.1016/j.cll.2011.08.003 6. Marcou CA, Pitel B, Hagen CE, et al. Limited diagnostic impact of duplications <1 Mb of uncertain clinical significance: a 10-year retrospective analysis of reporting practices at the Mayo Clinic. Genet Med. 2020;22(12):2120-2124. doi:10.1038/s41436-020-0932-0

CMAH
35899

Chromosomal Microarray, Hematologic Disorders, Varies

Clinical Information: The importance of identifying chromosome abnormalities in hematologic disorders is well established and often provides important diagnostic, prognostic, and therapeutic information critical to proper patient management. Although many chromosomal abnormalities are large enough to be detected with conventional chromosome analysis, many others are below its limits of resolution, and conventional chromosome analysis does not detect copy-neutral loss of heterozygosity. Chromosomal microarray (CMA) improves the diagnostic yield to identify genetic changes that are not detected by conventional chromosome analysis or fluorescence in situ hybridization (FISH) studies. CMA utilizes greater than 2 million copy number probes and approximately 750,000 single nucleotide polymorphism probes to detect copy number changes and regions of copy-neutral loss of heterozygosity. Chromosomal microarray analysis is appropriate to identify gain or loss of chromosome material throughout the genome at a resolution of 30 to 60 kilobases. CMA can do the following: -Define the size, precise breakpoints, and gene content of copy number changes to demonstrate the complexity of abnormalities -Characterize unidentified chromosome material, marker chromosomes, and DNA amplification detected by conventional chromosome and FISH studies -Determine if apparently balanced chromosome rearrangements identified by conventional chromosome studies have cryptic imbalances -Assess regions of copy-neutral loss of heterozygosity, which is common in neoplasia and often masks homozygous mutations involving tumor suppressor genes The limit of detection is dependent on size of the abnormality, type of abnormality (deletion or duplication) and DNA quality. When a deletion or duplication exceeds the reporting limits, mosaicism can confidently be detected as low as 25% and may be lower if the abnormality is large and DNA quality is good.

Useful For: Detection and characterization of clonal copy number imbalance and loss of heterozygosity associated with hematologic neoplasms Assisting in the diagnosis and classification of certain hematologic neoplasms Evaluating the prognosis for patients with certain hematologic neoplasms

Interpretation: The interpretive report describes copy number changes and any loss of heterozygosity that may be associated with the neoplastic process. Abnormal clones with subclonal cytogenetic evolution will be discussed if identified. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Although the presence of a clonal abnormality usually indicates a neoplasia, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly pathogenic (eg, XYY), consultation with a Clinical Geneticist may be suggested. The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the disorder is caused by a point mutation that is not detectable by chromosomal microarray. Chromosomal microarray, fluorescence in situ hybridization (FISH), and conventional cytogenetics are to some extent complementary methods. In some instances, additional FISH or conventional cytogenetic studies will be recommended to clarify interpretive uncertainties.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Shao L, Akkari Y, Cooley LD, et al. ACMG Laboratory Quality Assurance Committee. Chromosomal microarray analysis, including constitutional and neoplastic disease applications, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(10):1818-1829. doi:10.1038/s41436-021-01214-w 2. Peterson JF, Aggarwal N, Smith CA, et al. Integration of microarray analysis into the clinical diagnosis of hematological malignancies: How much can we improve cytogenetic testing?. Oncotarget. 2015;6(22):18845-18862 3. Mikhail FM, Biegel JA, Cooley LD, et al. Technical laboratory standards for interpretation and reporting of acquired copy-number abnormalities and copy-neutral loss of heterozygosity in neoplastic disorders: a joint consensus recommendation from the American College of Medical Genetics and Genomics (ACMG) and the Cancer Genomics Consortium (CGC). Genet Med. 2019;21(9):1903-1916

CMAP 35898 Chromosomal Microarray, Prenatal, Amniotic Fluid/Chorionic Villus Sampling

Clinical Information: Chromosomal abnormalities cause a wide range of disorders associated with birth defects and intellectual disability. Many of these disorders can be diagnosed prenatally by analysis of chorionic villi or amniocytes. The most common reasons for performing cytogenetic studies for prenatal diagnosis include advanced maternal age, abnormal prenatal screen, a previous child with a chromosome abnormality, abnormal fetal ultrasound, or a family history of a chromosome abnormality. Chromosomal microarray (CMA) is a high-resolution method for detecting copy number changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend the chromosomal microarray as a replacement for the fetal karyotype in patients with a pregnancy demonstrating one or more major structural abnormalities on ultrasound when undergoing invasive prenatal diagnosis.(1) This CMA test utilizes greater than 2 million copy number probes and approximately 750,000 single nucleotide polymorphism probes for the detection of copy number changes and regions with absence of heterozygosity. Identification of regions of excessive homozygosity on a single chromosome could suggest uniparental disomy, which may warrant further clinical investigation when observed on chromosomes with known imprinting disorders. In addition, the detection of excessive homozygosity on multiple chromosomes may suggest consanguinity.

Useful For: Prenatal diagnosis of copy number changes (gains or losses) across the entire genome Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods, such as conventional chromosome and fluorescence in situ hybridization studies Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, as a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray Assessing regions of homozygosity related to uniparental disomy or identity by descent

Interpretation: Copy number variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. When interpreting results, it is important to realize that copy number variation is found in all individuals, including patients with abnormal phenotypes and normal populations. Therefore, determining the clinical significance of a rare or novel copy number change can be challenging. Parental testing may be necessary to further assess the potential pathogenicity of a copy number change. While most copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, whether the change is a deletion or duplication, the inheritance pattern, and the clinical and developmental history of a transmitting

parent. All copy number variants within the limit of detection classified as pathogenic or likely pathogenic will be reported regardless of size. This includes but is not limited to incidental findings currently recommended for reporting by the American College of Medical Genetics and Genomics.(2) Copy number changes with unknown significance will be reported when at least one protein-coding gene is involved in a deletion greater than 1 megabase (Mb) or a duplication greater than 2 Mb. The detection of excessive homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy (UPD) or to test for variants in genes associated with autosomal recessive disorders consistent with the patient's clinical presentation that are present in regions of homozygosity. Regions with absence of heterozygosity (AOH) of unknown significance will be reported when greater than 5 Mb (terminal) and 10 Mb (interstitial) on UPD-associated chromosomes. Whole genome AOH will be reported when greater than 5% of the genome. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Shao L, Akkari Y, Cooley LD, et al. Chromosomal microarray analysis, including constitutional and neoplastic disease applications, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(10):1818-1829. doi:10.1038/s41436-021-01214-w 2. Kalia S, Adelman K, Bale S, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing. 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19(2):249-255. doi:10.1038/gim.2016.190 3. Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. N Engl J Med. 2012;367(23):2175-2184. doi:10.1056/NEJMoa1203382 4. Armengol L, Nevado J, Serra-Juhe C, et al. Clinical utility of chromosomal microarray analysis in invasive prenatal diagnosis. Hum Genet. 2012;131(3):513-523. doi:10.1007/s00439-011-1095-5 5. Breman A, Pursley AN, Hixson P, et al. Prenatal chromosomal microarray analysis in a diagnostic laboratory; experience with >1000 cases and review of the literature. Prenat Diagn. 2012;32(4):351-361. doi:10.1002/pd.3861 6. South ST, Lee C, Lamb AN, et al. ACMG Standards and Guidelines for constitutional cytogenomic microarray analysis, including postnatal and prenatal applications: Revision 2013. Genet Med. 2013;15(11):903-909. doi:10.1038/gim.2013.129

CMAPT 35901 Chromosomal Microarray, Tumor, Formalin-Fixed Paraffin-Embedded

Clinical Information: The importance of identifying chromosome abnormalities in malignant neoplasms is well established, and often provides important diagnostic, prognostic, and therapeutic information critical to proper patient management. Although many chromosomal abnormalities are large enough to be detected with conventional chromosome analysis, many others are below its limits of resolution, and conventional chromosome analysis does not detect copy-neutral loss of heterozygosity. Chromosomal microarray (CMA) improves the diagnostic yield to identify genetic changes that are not detected by conventional chromosome analysis or fluorescence in situ hybridization (FISH) studies. CMA utilizes copy number probes and single nucleotide polymorphism probes to detect copy number changes and regions of copy-neutral loss of heterozygosity. Chromosomal microarray analysis is appropriate to identify gain or loss of chromosome material throughout the genome at a resolution of 50 to 100 kilobases. CMA can: -Define the size, precise breakpoints, and gene content of copy number changes to demonstrate the complexity of abnormalities -Characterize unidentified chromosome material, marker chromosomes, and DNA amplification detected by conventional chromosome and FISH studies -Determine if apparently balanced chromosome rearrangements identified by conventional chromosome studies have cryptic imbalances -Assess regions of copy-neutral loss of heterozygosity, which is common in neoplasia and often masks homozygous mutations involving tumor suppressor genes The limit of

detection is dependent on size of the abnormality, type of abnormality (deletion or duplication) and DNA quality. When a deletion or duplication exceeds the reporting limits, mosaicism can confidently be detected as low as 25% and may be lower if the abnormality is large and DNA quality is good.

Useful For: Genomic characterization of tumor for copy number imbalances and loss of heterozygosity Assisting in the diagnosis and classification of malignant neoplasms Evaluating the prognosis for patients with malignant tumors

Interpretation: The interpretive report describes copy number changes and any loss of heterozygosity that may be associated with the neoplastic process. Abnormal clones with subclonal cytogenetic evolution will be discussed if identified. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Although the presence of a clonal abnormality usually indicates a neoplasia, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly disease-associated (eg, XYY), follow-up with a medical genetic consultation may be suggested. The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the disorder is caused by a point mutation that is not detectable by chromosomal microarray. Chromosomal microarray, fluorescence in situ hybridization (FISH), and conventional cytogenetics are to some extent complementary methods. In some instances, additional FISH or conventional cytogenetic studies will be recommended to clarify interpretive uncertainties. For more information and frequently asked questions, see Clarity on Reason for and Benefits of Chromosomal Microarray.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Mikhail FM, Biegel JA, Cooley LD, et al. Technical laboratory standards for interpretation and reporting of acquired copy-number abnormalities and copy-neutral loss of heterozygosity in neoplastic disorders: a joint consensus recommendation from the American College of Medical Genetics and Genomics (ACMG) and the Cancer Genomics Consortium (CGC). Genet Med. 2019;21(9):1903-1916 2. Chun K, Wenger GD, Chaubey A, et al. Assessing copy number aberrations and copy-neutral loss-of-heterozygosity across the genome as best practice: An evidence-based review from the Cancer Genomics Consortium (CGC) working group for chronic lymphocytic leukemia. Cancer Genet. 2018;228-229:236-250 3. Shao L, Akkari Y, Cooley LD, et al. Chromosomal microarray analysis, including constitutional and neoplastic disease applications, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(10):1818-1829 4. Wang Y, Cottman M, Schiffman JD. Molecular inversion probes: a novel microarray technology and its application in cancer research. Cancer Genet. 2012;205(7-8):341-355

CMAT
35900

Chromosomal Microarray, Tumor, Fresh or Frozen

Clinical Information: The importance of identifying chromosome abnormalities in malignant neoplasms is well established, and often provides important diagnostic, prognostic, and therapeutic information critical to proper patient management. Although many chromosomal abnormalities are large enough to be detected with conventional chromosome analysis, many others are below its limits of resolution, and conventional chromosome analysis does not detect copy-neutral loss of heterozygosity. Chromosomal microarray (CMA) improves the diagnostic yield to identify genetic changes that are not detected by conventional chromosome analysis or fluorescence in situ hybridization (FISH) studies. CMA utilizes greater than 2 million copy number probes and approximately 750,000 single nucleotide polymorphism probes to detect copy number changes and regions of copy-neutral loss of heterozygosity. Chromosomal microarray analysis is appropriate to identify gain or loss of chromosome material throughout the genome at a resolution of 30 to 60 kilobases. CMA can: -Define the size,

breakpoints, and gene content of copy number changes to demonstrate the complexity of abnormalities -Characterize unidentified chromosome material, marker chromosomes, and DNA amplification detected by conventional chromosome and FISH studies -Determine if apparently balanced chromosome rearrangements identified by conventional chromosome studies have cryptic imbalances -Assess regions of copy-neutral loss of heterozygosity, which is common in neoplasia and often masks homozygous mutations involving tumor suppressor genes The limit of detection is dependent on size of the abnormality, type of abnormality (deletion or duplication) and DNA quality. When a deletion or duplication exceeds the reporting limits, mosaicism can confidently be detected as low as 25% and may be lower if the abnormality is large and DNA quality is good.

Useful For: Genomic characterization of tumor for copy number imbalances and loss of heterozygosity Assisting in the diagnosis and classification of malignant neoplasms, including hematolymphoid malignancies Evaluating the prognosis for patients with malignant tumors

Interpretation: The interpretive report describes copy number changes and loss of heterozygosity that may be associated with the neoplastic process being evaluated. Abnormal clones with subclonal abnormalities will be discussed if identified. The continual discovery and publication of novel copy number abnormalities and losses of heterozygosity associated with neoplastic processes means that the interpretation of any given detected abnormality may change with increased scientific understanding. Although the presence of a clonal abnormality is usually associated with neoplasia, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly pathogenic or likely pathogenic and/or related to the clinical reason for referral, this will be included in the report and follow-up with a medical genetic consultation may be suggested. The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the disorder is caused by a point mutation that is not detectable by chromosomal microarray. Chromosomal microarray, fluorescence in situ hybridization (FISH), and conventional cytogenetics are to some extent complementary methods. In some instances, additional FISH or conventional cytogenetic studies will be recommended to clarify interpretive uncertainties.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Mikhail FM, Biegel JA, Cooley LD, et al. Technical laboratory standards for interpretation and reporting of acquired copy-number abnormalities and copy-neutral loss of heterozygosity in neoplastic disorders: a joint consensus recommendation from the American College of Medical Genetics and Genomics (ACMG) and the Cancer Genomics Consortium (CGC). Genet Med. 2019;21(9):1903-1916. doi:10.1038/s41436-019-0545-7 2. Chun K, Wenger GD, Chaubey A, et al. Assessing copy number aberrations and copy-neutral loss-of-heterozygosity across the genome as best practice: An evidence-based review from the Cancer Genomics Consortium (CGC) working group for chronic lymphocytic leukemia. Cancer Genet. 2018;228-229:236-250. doi:10.1016/j.cancergen.2018.07.004 3. Shao L, Akkari Y, Cooley LD, et al. Chromosomal microarray analysis, including constitutional and neoplastic disease applications, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(10):1818-1829. doi:10.1038/s41436-021-01214-w

CHRAF 35243 Chromosome Analysis, Amniotic Fluid

Clinical Information: Chromosome analysis for prenatal diagnosis is appropriate in pregnancies with abnormal maternal screening or advanced maternal age and with clinical features suggestive of, or concerns for, aneuploidy syndromes, including Down syndrome, Turner syndrome, Klinefelter syndrome, trisomy 13 syndrome, and trisomy 18 syndrome. Chromosomal abnormalities are the cause of a wide range of disorders associated with birth defects and congenital diseases. Many of these disorders can be

diagnosed prenatally by analysis of amniocytes. This method permits diagnosis of chromosome abnormalities during the second trimester of pregnancy or later. A chromosomal microarray (CMAP / Chromosomal Microarray, Prenatal, Amniotic Fluid/Chorionic Villus Sampling) is recommended, rather than chromosomal analysis, to detect clinically relevant gains or losses of chromosomal material in pregnancies with one or more major structural abnormalities. Chromosomal microarray can also be considered, rather than chromosome analysis, for patients undergoing invasive prenatal diagnostic testing with a structurally normal fetus.

Useful For: Prenatal diagnosis of chromosome abnormalities, including aneuploidy (ie, trisomy or monosomy) and balanced rearrangements

Interpretation: Cytogenetic studies on amniotic fluid are considered nearly 100% accurate for the detection of large fetal chromosome abnormalities. However, subtle or cryptic abnormalities involving microdeletions/duplications usually can be detected only with the use of targeted fluorescence in situ hybridization testing or chromosomal microarray. Approximately 3% of amniotic fluid specimens analyzed are found to have chromosome abnormalities. Some of these chromosome abnormalities are balanced and may not be associated with birth defects. A normal karyotype does not rule out the possibility of birth defects, such as those caused by submicroscopic cytogenetic abnormalities, pathogenic molecular variants, and other environmental factors (ie, teratogen exposure). For these reasons, clinicians should inform their patients of the technical limitations of chromosome analysis prior to performing the amniocentesis. Limitations: -Abnormal results from amniotic fluid analysis may not represent fetal karyotype in all tissues. -Only large abnormalities visible by manual inspection are detectable; subtle structural chromosome abnormalities may be missed -Artifacts of cell culture may very rarely be misinterpreted as mosaicism in the sample. It is recommended that a qualified professional in Medical Genetics communicate all results to the patient.

Reference Values:
An interpretative report will be provided.

Clinical References: 1. American College of Obstetricians and Gynecologists Committee on Genetics. Committee Opinion No. 581: the use of chromosomal microarray analysis in prenatal diagnosis. Obstet Gynecol. 2013;122(6):1374-1377 2. Society for Maternal-Fetal Medicine (SMFM). The use of chromosomal microarray for prenatal diagnosis. Am J Obstet Gynecol. 2016;215(4):B2-B9 3. Committee Opinion, 640. Cell-free DNA screening for fetal aneuploidy. Obstet Gynecol. 2015;126(3):e31-e37 4. Wilson KL, Czerwinski JL, Hoskovec JM, et al. NSGC practice guideline: prenatal screening and diagnostic testing options for chromosome aneuploidy. J Genet Couns. 2013;22(1):4-15

CHRCV
35251

Chromosome Analysis, Chorionic Villus Sampling

Clinical Information: Although not used as widely as amniocentesis, the use of chorionic villus sampling (CVS) for chromosome analysis is an important procedure for the prenatal diagnosis of chromosome abnormalities. CVS can be collected by either transcervical or transabdominal techniques. The medical indications for performing chromosome studies on CVS are similar to those for amniocentesis, and may include advanced maternal age, abnormal prenatal screen, and family history of a chromosome abnormality. A chromosomal microarray (CMAP / Chromosomal Microarray, Prenatal, Amniotic Fluid/Chorionic Villus Sampling) is recommended, rather than chromosomal analysis, to detect clinically relevant gains or losses of chromosomal material in pregnancies with one or more major structural abnormalities. Chromosomal microarray can also be considered, rather than chromosome analysis, for patients undergoing invasive prenatal diagnostic testing with a structurally normal fetus.

Useful For: Prenatal diagnosis of chromosome abnormalities, including aneuploidy (ie, trisomy or monosomy) and balanced rearrangements This test is not appropriate as a first-tier test for detecting gains or losses of chromosomal material in pregnancies with 1 or more major structural abnormalities.

Interpretation: Cytogenetic studies on chorionic villus specimens (CVS) are considered nearly 100% accurate for the detection of non-mosaic whole chromosome abnormalities. Most sub-chromosomal abnormalities greater than 5-20Mb are also easily detectable dependent on size, location, and quality of the metaphase chromosomes. Very subtle or cryptic abnormalities involving microdeletions/duplication can typically only be detected by chromosomal microarray or targeted fluorescence in situ hybridization testing. Approximately 3% of CVS samples analyzed are found to have chromosome abnormalities. Some of these chromosome abnormalities are balanced and may not be associated with birth defects. A normal karyotype does not rule out the possibility of birth defects, such as those caused by submicroscopic cytogenetic abnormalities, pathogenic molecular variants, and environmental factors (ie, teratogen exposure). For these reasons, clinicians should inform their patients of the technical limitations of chromosome analysis before the procedure is performed, so that patients may make an informed decision about pursuing the procedure. Limitations: -Abnormal results from CVS analysis may represent confined placental mosaicism and may not reflect the fetal karyotype. -Only large abnormalities visible by manual inspection are detectable; subtle structural chromosome abnormalities may be missed -Artifacts of cell culture may very rarely be misinterpreted as mosaicism in the sample. It is recommended that a qualified professional in Medical Genetics communicate all results to the patient.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. American College of Obstetricians and Gynecologists Committee on Genetics. Committee Opinion No. 581: the use of chromosomal microarray analysis in prenatal diagnosis. Obstet Gynecol. 2013;122:1374-1377 2. Society for Maternal-Fetal Medicine (SMFM). The use of chromosomal microarray for prenatal diagnosis. Am J Obstet Gynecol. 2016;215:B2-B9 3. Committee Opinion, 640. Cell-free DNA screening for fetal aneuploidy. American College of Obstetricians and Gynecologists Committee on Genetics. Obstet Gynecol. 2015;123:e31-e37 4. Wilson KL, Czerwinski JL, Hoskovec JM, et al. NSGC practice guideline: prenatal screening and diagnostic testing options for chromosome aneuploidy. J Genet Couns. 2013;22:4-15

CHRCB
35248

Chromosome Analysis, Congenital Disorders, Blood

Clinical Information: Chromosome analysis is appropriate for individuals with clinical features including infertility, multiple miscarriages, delayed puberty, ambiguous genitalia, amenorrhea, or individuals with clinical features suggestive of an aneuploidy syndrome, including Down syndrome, Turner syndrome, Klinefelter syndrome, Trisomy 13 syndrome, and Trisomy 18 syndrome. A chromosomal microarray study (CMACB / Chromosomal Microarray, Congenital, Blood) is recommended as the first-tier test (rather than a congenital chromosome study) to detect clinically relevant gains or losses of chromosomal material for individuals with multiple anomalies not specific to well-delineated genetic syndromes, individuals with apparently nonsyndromic developmental delay or intellectual disability, and individuals with autism spectrum disorders. Chromosome analysis may be appropriate for this patient population if microarray has been performed with normal results. Some chromosome rearrangements are balanced (no gain or loss of material) and, therefore, not detectable by chromosomal microarray. In rare situations these rearrangements may interrupt gene functioning and have the potential to cause abnormal clinical features. Limitations: A normal karyotype (46,XX or 46,XY with no apparent chromosome abnormality) does not eliminate the possibility of abnormal clinical features such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). Chromosomal mosaicism may be missed due to statistical sampling error (rare) and subtle structural chromosome abnormalities can occasionally be missed.

Useful For: Diagnosis of congenital chromosome abnormalities, including aneuploidy, structural abnormalities, and balanced rearrangements

Interpretation: When interpreting results, the following factors need to be considered: -Some chromosome abnormalities are balanced (no apparent gain or loss of genetic material) and may not be associated with birth defects. However, balanced abnormalities often cause infertility and, when inherited in an unbalanced fashion, may result in birth defects in the offspring. -A normal karyotype (46,XX or 46,XY with no apparent chromosome abnormality) does not eliminate the possibility of birth defects such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). It is recommended that a qualified professional in Medical Genetics communicate all abnormal results to the patient.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. McKinlay Gardner RJ, Amor DJ, eds. Amor, Gardner and Sutherland's Chromosome Abnormalities and Genetic Counseling, 5th ed. Oxford Monographs on Medical Genetics, 2018 2. Manning M, Hudgins L. Professional Practice and Guidelines Committee: Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. Genet Med. 2010;12(11):742-745 3. Sheets KB, Crissman BG, Feist CD, et al. Practice guidelines for communicating a prenatal or postnatal diagnosis of Down syndrome: recommendations of the national society of genetic counselors. J Genet Couns. 2011;20(5):432-441 4. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012;98(5):1103-1111 5. Committee opinion no. 605: primary ovarian insufficiency in adolescents and young women. Obstet Gynecol. 2014;124(1):193-197

CHRHB
35308

Chromosome Analysis, Hematologic Disorders, Blood

Clinical Information: Chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and monitoring of treatment of many hematologic disorders. Whenever possible, it is best to do chromosome studies for neoplastic hematologic disorders on bone marrow. Bone marrow studies are more sensitive and the chances of finding metaphases are about 95%, compared with only a 60% chance for blood studies. When it is not possible to collect bone marrow, chromosome studies on blood may be useful. When blood cells are cultured in a medium without mitogens, the observation of any chromosomally abnormal clone may be consistent with a neoplastic process. Conventional chromosome studies of B-cell disorders are not always successful because B lymphocytes do not proliferate well in cell culture. The agent CpG 7909 (CpG) is a synthetic oligodeoxynucleotide that binds to the Toll-like receptor 9 (TLR9) present on B cells, causing B-cell activation. In the laboratory setting, CpG may be used as a mitogen to stimulate B cells in patient specimens, thus allowing identification of chromosome abnormalities. CpG stimulation reveals an abnormal karyotype in approximately 80% of patients with of chronic lymphocytic leukemia, and the karyotype is complex in 20% to 25% of cases. Several studies have reported that increased genetic complexity revealed by CpG-stimulated chromosome studies confers a less favorable time to first treatment, treatment response, and overall survival. For more information see Multiple Myeloma: Laboratory Screening.

Useful For: Assisting in the classification and follow-up of certain malignant hematological disorders when bone marrow is not available This test is not useful for congenital disorders.

Interpretation: The presence of an abnormal clone usually indicates a malignant neoplastic process. The absence of an apparent abnormal clone in blood may result from a lack of circulating abnormal cells and not from an absence of disease. On rare occasions, the presence of an abnormality may be

associated with a congenital abnormality and thus, not related to a malignant process. When this situation is suspected, consultation with a Clinical Geneticist is recommended.

Reference Values:
An interpretative report will be provided.

Clinical References: 1. Swerdlow et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press:Lyon, 2017 2. Dewald GW, Ketterling RP, Wyatt WA, Stupca PJ. Cytogenetic studies in neoplastic hematologic disorders. In: McClatchey KD, ed. Clinical Laboratory Medicine. 2nd ed. Williams and Wilkens; 2002:658-685 2. Rigolin GM, Cibien F, Martinelli S, et al. Chromosome aberrations detected by conventional karyotyping using novel mitogens in chronic lymphocytic leukemia with "normal" FISH: correlations with clinicobiological parameters. Blood. 2012;119(10):2310-2313

CHRBM 35245 Chromosome Analysis, Hematologic Disorders, Bone Marrow

Clinical Information: Chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and treatment monitoring of many hematologic disorders. Cytogenetic studies on bone marrow may be helpful in many malignant hematologic disorders as the observation of a chromosomally abnormal clone may be consistent with a neoplastic process. Certain chromosome abnormalities may help classify a malignancy. As examples, the Philadelphia (Ph) chromosome, also referred to as der(22)t(9;22)(q34;q11.2), is usually indicative of chronic myeloid leukemia (CML) or acute leukemia; t(8;21)(q22;q22) defines a specific subset of patients with acute myeloid leukemia; and t(8;14)(q24.1;q32) is associated with Burkitt lymphoma. Cytogenetic studies are also used to monitor patients with hematologic neoplasia and may identify disease progression, such as the onset of blast crisis in CML, which is often characterized by trisomy 8, isochromosome 17q, and multiple Ph chromosomes. Conventional chromosome studies of B-cell disorders are not always successful because B lymphocytes do not proliferate well in cell culture. The agent CpG 7909 (CpG) is a synthetic oligodeoxynucleotide that binds to the Toll-like receptor 9 (present on B cells, causing B-cell activation. In the laboratory setting, CpG may be used as a mitogen to stimulate B cells in patient specimens, thus allowing identification of chromosome abnormalities. CpG stimulation reveals an abnormal karyotype in approximately 80% of patients with chronic lymphocytic leukemia, and the karyotype is complex in 20% to 25% of cases. Several studies have reported that increased genetic complexity revealed by CpG-stimulated chromosome studies confers a less favorable time to first treatment, treatment response, and overall survival.

Useful For: Assisting in the diagnosis and classification of certain malignant hematological disorders in bone marrow specimens Evaluating the prognosis in patients with certain malignant hematologic disorders Monitoring effects of treatment Monitoring patients in remission

Interpretation: To ensure the best interpretation, it is important to provide some clinical information to verify the appropriate type of cytogenetic study is performed. The following factors are important when interpreting the results: -Although the presence of an abnormal clone usually indicates a malignant neoplastic process, in rare situations, the clone may reflect a benign condition. -The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the disorder is caused by submicroscopic abnormalities that cannot be identified by chromosome analysis. -On rare occasions, the presence of an abnormality may be associated with a constitutional abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended. -On occasion, bone marrow chromosome studies are unsuccessful. If clinical information has been provided, there may be a fluorescence in situ hybridization study option that could be performed.

Reference Values:

An interpretative report will be provided.

Clinical References: 1. Mellors PW, Binder M, Ketterling RH, et al. Metaphase cytogenetics and plasma cell proliferation index for risk stratification in newly diagnosed multiple myeloma. Blood Adv. 2020;4(10):2236-2244 2. Dewald GW, Ketterling RP, Wyatt WA, Stupca PJ. Cytogenetic studies in neoplastic hematologic disorders. In: McClatchey KD, ed. Clinical Laboratory Medicine. 2nd ed. Williams and Wilkens; 2002:658-685 3. Rigolin GM, Cibien F, Martinelli S, et al. Chromosome aberrations detected by conventional karyotyping using novel mitogens in chronic lymphocytic leukemia with "normal" FISH: correlations with clinicobiological parameters. Blood. 2012;119(10):2310-2313 4. Swerdlow et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press:Lyon, 2017

COGBL 113532 Chromosome Analysis, Hematologic Disorders, Children's Oncology Group Enrollment Testing, Blood

Clinical Information: Clonal chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and treatment monitoring of pediatric hematologic malignancies. Whenever possible, it is best to do chromosome studies for neoplastic hematologic disorders on bone marrow. Bone marrow studies are more sensitive and the chances of finding metaphases are about 95%, compared with only a 60% chance for blood studies. When it is not possible to collect bone marrow, chromosome studies on blood may be useful. When blood cells are cultured in a medium without mitogens, the observation of any chromosomally abnormal clone may be consistent with a neoplastic process. Characteristic chromosome rearrangements and copy number patterns may help classify a pediatric hematologic malignancy. For example, t(1;19)(q23;p13.3) is typically observed in B-cell acute lymphoblastic leukemia/lymphoma and t(8;21)(q22;q22) defines a specific subset of patients with acute myeloid leukemia; while t(7;14)(q35;q11.2) is associated with T-lymphoblastic leukemia/lymphoma. Confirmation of classic gene fusions associated with the above translocations together with evaluation for other recurrent abnormalities are available within the appropriate Children's Oncology Group (COG) fluorescence in situ hybridization (FISH) panels; COGBF / B-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Children's Oncology Group Enrollment Testing, FISH, Varies; COGTF / T-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Children's Oncology Group Enrollment Testing, FISH, Varies; and COGMF / Acute Myeloid Leukemia (AML), Children's Oncology Group Enrollment Testing, FISH, Varies. Some rearrangements identified by chromosomal analysis may be extremely rare but are known, recurrent entities for which the Mayo Clinic Genomics Laboratory has the most extensive catalogue of FISH testing to confirm the corollary gene fusions. Metaphase FISH confirmation of classic translocations which are cryptic and not visually detectable by chromosome analysis [ie, t(12;21)] associated with ETV6/RUNX1 fusion) is performed as required by COG and is included as part of the electronic case submission by the Mayo Clinic Genomics Laboratory to COG for central review. Additional cytogenetic techniques such as chromosomal microarray (CMAH / Chromosomal Microarray, Hematologic Disorders, Varies) may be helpful to resolve questions related to ploidy (hyperdiploid clone vs doubled hypodiploid clone) or to resolve certain clonal structural rearrangements such as the presence or absence of intrachromosomal amplification of chromosome 21 (iAMP21).

Useful For: Evaluation of pediatric blood specimens for chromosomal abnormalities associated with hematologic malignancies for diagnostic and prognostic purposes in patients being considered for enrollment in Children's Oncology Group clinical trials and research protocols This test is not useful for congenital disorders.

Interpretation: The presence of an abnormal clone usually indicates a malignant neoplastic process. The absence of an apparent abnormal clone in blood may result from a lack of circulating abnormal cells and not from an absence of disease. On rare occasions, the presence of an abnormality may be

associated with a congenital abnormality and, thus, not related to a malignant process. When this situation is suspected, follow-up with a medical genetics consultation is recommended.

Reference Values:
An interpretative report will be provided.

Clinical References: 1. Dewald GW, Ketterling RP, Wyatt WA, Stupca PJ. Cytogenetic studies in neoplastic hematologic disorders. In: McClatchey KD, ed. Clinical Laboratory Medicine. 2nd ed. Williams and Wilkens; 2002: 658-685 2. Rigolin GM, Cibien F, Martinelli S, et al. Chromosome aberrations detected by conventional karyotyping using novel mitogens in chronic lymphocytic leukemia with "normal" FISH: correlations with clinicobiological parameters. Blood. 2012;119(10):2310-2313 3. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press; 2017 4. Arber DA, Borowitz MJ, Cessna M, et al. Initial Diagnostic Workup of Acute Leukemia: Guideline from the College of American Pathologists and the American Society of Hematology. Arch Pathol Lab Med. 2017;141(10):1342-1393

COGBM 113531 Chromosome Analysis, Hematologic Disorders, Children's Oncology Group Enrollment Testing, Bone Marrow

Clinical Information: Clonal chromosome abnormalities in bone marrow (or peripheral blood or tissue if bone marrow is not available) play a central role in the pathogenesis, diagnosis, and treatment monitoring of pediatric hematologic malignancies. Characteristic chromosome rearrangements and copy number patterns may help classify a pediatric hematologic malignancy. For example, t(1;19)(q23;p13.3) is typically observed in B-cell acute lymphoblastic leukemia/lymphoma and t(8;21)(q22;q22) defines a specific subset of patients with acute myeloid leukemia; while t(7;14)(q35;q11.2) is associated with T-lymphoblastic leukemia/lymphoma. Confirmation of classic gene fusions associated with the above translocations together with evaluation for other recurrent abnormalities are available within the appropriate Children's Oncology Group (COG) fluorescence in situ hybridization (FISH) panels; COGBF / B-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Children's Oncology Group Enrollment Testing, FISH, Varies; COGTF / T-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Children's Oncology Group Enrollment Testing, FISH, Varies; and COGMF / Acute Myeloid Leukemia (AML), Children's Oncology Group Enrollment Testing, FISH, Varies. Some rearrangements identified by chromosomal analysis may be extremely rare but are known recurrent entities for which the Mayo Clinic Genomics Laboratory has the most extensive catalogue of FISH testing to confirm the corollary gene fusions. Metaphase FISH confirmation of classic translocations that are cryptic and not visually detectable by chromosome analysis [ie, t(12;21) associated with ETV6/RUNX1 fusion] is performed as required by COG and is included as part of the electronic case submission by the Mayo Clinic Genomics Laboratory to COG for central review. Additional cytogenetic techniques such as chromosomal microarray (CMAH / Chromosomal Microarray, Hematologic Disorders, Varies) may be helpful to resolve questions related to ploidy (hyperdiploid clone vs doubled hypodiploid clone) or to resolve certain clonal structural rearrangements such as the presence or absence of intra-chromosomal amplification of chromosome 21 (iAMP21). If the expert cytogeneticist at Mayo Clinic reviewing this test's case feels microarray assay may be of benefit, the client will be contacted. For children in whom disease relapse or a secondary myeloid neoplasm is a concern and enrollment in a new COG protocol is being considered; this test is appropriate for bone marrow chromosome analysis.

Useful For: Evaluation of pediatric bone marrow specimens for chromosomal abnormalities associated with hematologic malignancies for diagnostic and prognostic purposes in patients being considered for enrollment in Children's Oncology Group clinical trials and research protocols using bone marrow specimens

Interpretation: The following factors are important when interpreting the results: -Although the

presence of an abnormal clone usually indicates a malignant neoplastic process, in rare situations, the clone may reflect a benign condition. -The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the disorder is caused by submicroscopic abnormalities that cannot be identified by chromosome analysis. -On rare occasions, the presence of an abnormality may be associated with a constitutional abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended. -On occasion, bone marrow chromosome studies are unsuccessful. If clinical information has been provided, we may have a fluorescence in situ hybridization study option that could be performed.

Reference Values:
An interpretative report will be provided.

Clinical References: 1. Dewald GW, Ketterling RP, Wyatt WA, Stupca PJ. Cytogenetic studies in neoplastic hematologic disorders. In: McClatchey KD, ed. Clinical Laboratory Medicine. 2nd ed. Williams and Wilkens; 2002:658-685 2. De Haas V, Ismaila N, Advani A, et al. Initial diagnostic work-up of acute leukemia: ASCO Clinical Practice Guideline Endorsement of the College of American Pathologists and American Society of Hematology Guideline. J Clin Oncol. 2019;37(3):239-253 3. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press; 2017 4. Arber DA, Borowitz MJ, Cessna M, et al. Initial diagnostic workup of acute leukemia: Guideline from the College of American Pathologists and the American Society of Hematology. Arch Pathol Lab Med. 2017;141(10):1342-1393

CHFXH
64922

Chromosome Analysis, Hematologic Disorders, Fixed Cells

Clinical Information: Chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and treatment monitoring of many hematologic disorders. Cytogenetic studies on bone marrow may be helpful in many malignant hematologic disorders as the observation of a chromosomally abnormal clone may be consistent with a neoplastic process. Certain chromosome abnormalities may help classify a malignancy. As examples, the Philadelphia (Ph) chromosome, also referred to as der(22)t(9;22)(q34;q11.2), is usually indicative of chronic myeloid leukemia (CML) or acute leukemia, t(8;21)(q22;q22) defines a specific subset of patients with acute myeloid leukemia, and t(8;14)(q24.1;q32) is associated with Burkitt lymphoma. Cytogenetic studies are also used to monitor patients with hematologic neoplasia and may identify disease progression, such as the onset of blast crisis in CML, which is often characterized by trisomy 8, isochromosome 17q, and multiple Ph chromosomes.

Useful For: Assisting in the diagnosis and classification of certain malignant hematological disorders in fixed cells Evaluating the prognosis of patients with certain malignant hematologic disorders Monitoring effects of treatment Monitoring patients in remission

Interpretation: To ensure the best interpretation, it is important to provide some clinical information to verify the appropriate type of cytogenetic study is performed. The following factors are important when interpreting the results: -Although the presence of an abnormal clone usually indicates a malignant neoplastic process, in rare situations, the clone may reflect a benign condition. -The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the disorder is caused by submicroscopic abnormalities that cannot be identified by chromosome analysis. -On rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended. -On occasion, bone marrow chromosome studies are unsuccessful. If clinical information has been provided, we may have a FISH study option that could be performed.

Reference Values:
An interpretative report will be provided.

Clinical References: 1. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press; 2017. WHO Classification of Tumours Vol 2 2. Dewald GW, Ketterling RP, Wyatt WA, Stupca PJ. Cytogenetic studies in neoplastic hematologic disorders. In: McClatchey KD, ed. Clinical Laboratory Medicine. 2nd edition. Williams and Wilkens; 2002:658-685 3. Rigolin GM, Cibien F, Martinelli S, et al. Chromosome aberrations detected by conventional karyotyping using novel mitogens in chronic lymphocytic leukemia with "normal" FISH: correlations with clinicobiological parameters. Blood 2012;119(10):2310-2313

CHRTI
35250

Chromosome Analysis, Skin Biopsy

Clinical Information: Chromosomal abnormalities cause a wide range of disorders associated with birth defects and congenital diseases. Usually, the abnormalities can be demonstrated in peripheral blood, which is readily available. Chromosome analysis on skin fibroblasts may be indicated when the results from peripheral blood are inconclusive or in clinical circumstances such as suspected cases of chromosome mosaicism, confirmation of new chromosome disorders, or some dermatological disorders. Subtle structural chromosomal anomalies can occasionally be missed. Chromosomal mosaicism may be missed due to statistical sampling error (rare).

Useful For: Diagnosis of mosaic congenital chromosome abnormalities, including mosaic aneuploidy and mosaic structural abnormalities Subsequent chromosome analysis when results from peripheral blood are inconclusive

Interpretation: When interpreting results, the following factors need to be considered: -Some chromosome abnormalities are balanced (no apparent gain or loss of genetic material) and may not be associated with birth defects. However, balanced abnormalities often cause infertility and, when inherited in an unbalanced fashion, may result in birth defects in the offspring. -A normal karyotype (46,XX or 46,XY with no apparent chromosome abnormality) does not eliminate the possibility of birth defects such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). It is recommended that a qualified professional in Medical Genetics communicate all results to the patient.

Reference Values:
An interpretative report will be provided.

Clinical References: 1. McKinlay Gardner RJ, Amor DJ, eds. Gardner and Sutherland's Chromosome Abnormalities and Genetic Counseling, 5th ed. Oxford Monographs on Medical Genetics, 2018 2. Gersen S, Keagle M. The Principles of Clinical Cytogenetics. Springer; 2013 3. Azcona C, Bareille P, Stanhop R. Lesson of the week: Turner's syndrome mosaicisim in patients with a normal blood lymphocyte karyotype. BMJ. 1999;318:856-857 4. Woods CG, Bankier A, Curry J, et al. Asymmetry and skin pigmentary anomalies in chromosome mosaicism. J Med Genet. 1994;31(9):694-701 5. Ribeiro Noce T, de Pina-Neto JM, Happle R. Phylloid pattern of pigmentary disturbance in a case of complex mosaicism. Am J Med Genet. 2001;98(2):145-147

EOSDF
609587

Chronic Eosinophilia, Diagnostic FISH, Varies

Clinical Information: The myeloid/lymphoid neoplasms with eosinophilia and rearrangements of PDGFRA, PDGFRB, FGFR1 and JAK2 represent a significantly diverse group of hematologic malignancies. Despite the disparate clinical presentations, which include chronic myeloid neoplasms

(chronic myelomonocytic leukemia, chronic myeloproliferative neoplasms, chronic eosinophilic leukemia) versus more acute myeloid and lymphoid neoplasms (acute myeloid leukemia, B- and T-lymphoblastic leukemia/lymphoma and mixed phenotypic acute leukemias), this diagnostic subgroup shares rearrangements involving 4 specific gene regions: PDGFRA, PDGFRB, FGFR1, and JAK2. While conventional chromosome studies may detect many of the rearrangements associated with these gene rearrangements, several are cytogenetically "cryptic," including the most common abnormality involving PDGFRA activation. This one megabase submicroscopic, intrachromosomal deletion results in loss of the CHIC2 gene region with subsequent fusion of neighboring genes FIP1L1 and PDGFRA. In addition to this more common, cryptic deletion, the PDGFRA gene has many translocation partners described (at least 15) that similarly result in PDGFRA upregulation. The PDGFRB, FGFR1, and JAK2 gene regions similarly have numerous translocation/inversion partners described, at least 50 for PDGFRB, 10 for FGFR1, and 40 for JAK2. Despite the significant heterogeneity in gene partners, the identification of PDGFRA, PDGFRB, FGFR1, and JAK2 rearrangements is critical for disease categorization and potential therapeutic intervention. Both PDGFRA and PDGFRB have the potential for response to targeted tyrosine kinase inhibitor therapies such as imatinib mesylate. Similarly, JAK2 rearrangements have the potential for response to targeted inhibitor therapy. Rearrangements of FGFR1 are typically more aggressive and less responsive to targeted inhibitors. While not formally included in the World Health Organization categorization of myeloid/lymphoid neoplasms with PDGFRA, PDGFRB, FGFR1, or JAK2 rearrangements, rearrangements of the ABL1 gene other than with the BCR locus, can result in similar clinical phenotypes. Thus, the ABL1 gene region has been included in this fluorescence in situ hybridization panel evaluation to appropriately interrogate this gene region, particularly since these patients may not be identified by conventional karyotype analysis and may significantly benefit from targeted tyrosine kinase therapies.

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement (including PDGFRA, PDGFRB, FGFR1, JAK2, and ABL1). Supporting the diagnosis of malignancy if a clone is present An adjunct to conventional chromosome studies.

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References:

EOSMF
614254

Chronic Eosinophilia, Specified FISH, Varies

Clinical Information: The myeloid/lymphoid neoplasms with eosinophilia and rearrangements of PDGFRA, PDGFRB, FGFR1, and JAK2 represent a significantly diverse group of hematologic malignancies. Despite the disparate clinical presentations, which include chronic myeloid neoplasms (chronic myelomonocytic leukemia, chronic myeloproliferative neoplasms, chronic eosinophilic leukemia) versus more acute myeloid and lymphoid neoplasms (acute myeloid leukemia, B- and T-lymphoblastic leukemia/lymphoma and mixed phenotypic acute leukemias), this diagnostic subgroup shares rearrangements involving 4 specific gene regions: PDGFRA, PDGFRB, FGFR1, and JAK2. While conventional chromosome studies may detect many of the rearrangements associated with these gene rearrangements, several are cytogenetically "cryptic", including the most common abnormality involving PDGFRA activation. This one megabase submicroscopic, intrachromosomal deletion results in loss of the CHIC2 gene region with subsequent fusion of neighboring genes FIP1L1 and PDGFRA. In addition to this more common, cryptic deletion, the PDGFRA gene has many translocation partners

described (at least 15) that similarly result in PDGFRA upregulation. The PDGFRB, FGFR1, and JAK2 gene regions similarly have numerous translocation/inversion partners described, at least 50 for PDGFRB, 10 for FGFR1, and 40 for JAK2. Despite the significant heterogeneity in gene partners, the identification of PDGFRA, PDGFRB, FGFR1, and JAK2 rearrangements is critical for disease categorization and potential therapeutic intervention. Both PDGFRA and PDGFRB have the potential for response to targeted tyrosine kinase inhibitor therapies such as imatinib mesylate. Similarly, JAK2 rearrangements have the potential for response to targeted inhibitor therapy. Rearrangements of FGFR1 are typically more aggressive and less responsive to targeted inhibitors. While not formally included in the World Health Organization categorization of myeloid/lymphoid neoplasms with PDGFRA, PDGFRB, FGFR1, or JAK2 rearrangements, rearrangements of the ABL1 gene, other than with the BCR locus, can result in similar clinical phenotypes. Thus, the ABL1 gene region has been included in this fluorescence in situ hybridization panel evaluation to appropriately interrogate this gene region, particularly since these patients may not be identified by conventional karyotype analysis and may significantly benefit from targeted tyrosine kinase therapies.

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement (including PDGFRA, PDGFRB, FGFR1, JAK2, and ABL1) using specified probes set Supporting a diagnosis of malignancy when a clone is present An adjunct to conventional chromosome studies

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement. In: Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours. Vol 2. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017:71-80

CHSBP
9023

Chronic Hepatitis B Monitoring Profile, Serum

Clinical Information:

Useful For: Evaluating and monitoring individuals with known chronic hepatitis B Monitoring hepatitis B viral infectivity after resolution of acute hepatitis B

Interpretation: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 8 weeks following hepatitis B virus (HBV) infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either chronic carrier state or chronic liver disease. HBs antibody appears with the resolution of acute hepatitis B after the disappearance of HBsAg. Anti-HBs also appears as the immune response following a course of inoculation with the hepatitis B vaccine. Hepatitis B core (HBc) IgM and total antibodies appears shortly after the onset of symptoms of HBV infection, and HBc total antibodies may be the only serologic marker remaining years after exposure to hepatitis B. The presence of hepatitis B e antigen correlates with infectivity, the number of viral Dane particles, the presence of core antigen in the nucleus of the hepatocyte, and the presence of viral DNA polymerase in serum. HBe antibody-positivity in a carrier is often associated with chronic asymptomatic infection. If the patient has a sudden exacerbation of disease, testing for anti-hepatitis C and anti-hepatitis D virus (HDV) total is recommended. If HBsAg converts to negative and patient's condition warrants, consider testing for HBs antibody. If HBsAg is confirmed positive, testing for anti-HDV total is recommended. For more

information see: -Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management -Viral Hepatitis Serologic Profiles

Reference Values:
HEPATITIS B SURFACE ANTIGEN:
Negative

HEPATITIS Be ANTIGEN:
Negative

HEPATITIS Be ANTIBODY:
Negative

Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles.

Clinical References: 1. LeFevre ML, U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 2. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis. 2018;12(1):5-11. doi:10.1002/cld.729 3. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019;156(2):355-368. doi:10.1053/j.gastro.2018.11.037 4. WHO guidelines on hepatitis B and C testing. World Health Organization; 2017. Accessed December 19, 2023. Available at www.who.int/publications/i/item/9789241549981 5. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

CHBVS
615268

Chronic Hepatitis B Screen, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles among injection drug users). The virus is also found in various human body fluids and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 8 weeks following exposure to HBV. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months in duration indicates development of either a chronic carrier state or chronic HBV infection. Serum levels of both hepatitis B e antigen (HBeAg) and HBsAg rise rapidly during the period of viral replication. The presence of HBeAg in serum correlates with viral infectivity, the number of infectious virions, and the presence of HBV core antigen in the infected hepatocytes. During recovery from acute hepatitis B, HBeAg level declines and becomes undetectable in the serum, while HBe antibody (anti-HBe) appears and becomes detectable in the serum. Anti-HBe usually remains detectable for many years after recovery from acute HBV infection. In HBV carriers and patients with chronic hepatitis B, positive HBeAg results usually indicate presence of active HBV replication and high infectivity, while a negative HBeAg result indicates very minimal or no HBV replication. Positive anti-HBe results usually indicate inactivity of the virus and low infectivity, and such positive results in the presence of detectable HBV DNA in serum also indicate active viral replication in these patients. The following algorithms are available: -Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profiles

Useful For: Diagnosis and evaluation of patients at risk for or suspected of having chronic hepatitis

B This test is not offered as a screening or confirmatory test for blood donor specimens. This test is not useful during the "window period" of acute hepatitis B virus infection (ie, after disappearance of hepatitis B surface antigen [HBsAg] and prior to appearance of hepatitis B surface antibody). This test is not useful as a stand-alone prenatal screening test of HBsAg status in pregnant women.

Interpretation: A reactive screen result (cutoff index value of 1.00 or above) confirmed as positive by hepatitis B surface antigen (HBsAg) confirmatory test (see Method Description) is indicative of acute or chronic hepatitis B or chronic hepatitis B virus (HBV) carrier state. Specimens with reactive screen results but negative (ie, not confirmed) HBsAg confirmatory test results are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. Repeat testing at a later date is recommended if clinically indicated. Confirmed presence of HBsAg is frequently associated with HBV replication and infectivity, especially when accompanied by the presence of HBe antigen or detectable HBV DNA. The following algorithms are available: -Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profiles

Reference Values:
Negative
See Viral Hepatitis Serologic Profiles

Clinical References: 1. LeFevre ML, U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014; 161(1):58-66. doi:10.7326/M14-1018 2. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: standard of care and investigational. Clin Liver Dis. 2018; 12(1):5-11. doi:10.1002/cld.729 3. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019; 156(2):355-368. doi:10.1053/j.gastro.2018.11.037 4. WHO guidelines on hepatitis B and C testing. World Health Organization; 2017. Accessed December 19, 2023. Available at www.who.int/publications/i/item/9789241549981 5. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

CIDP
616443

Chronic Inflammatory Demyelinating Polyradiculoneuropathy/Nodopathy Evaluation, Serum

Clinical Information:

Useful For: Evaluating for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and related demyelinating peripheral neuropathies

Interpretation: Seropositivity for contactin-1 IgG is consistent with an immune-mediated demyelinating polyradiculoneuropathy/polyradiculopathy. Seropositivity for neurofascin-155 IgG4 is consistent with an immune-mediated demyelinating polyradiculoneuropathy.

Reference Values:
CONTACTIN-1 IgG:
Negative

NEUROFASCIN 155 IgG4:
Negative

Clinical References: 1. Dubey D, Honorat JA, Shelly S, et al. Contactin-1 autoimmunity: Serologic, neurologic, and pathologic correlates. Neurol Neuroimmunol Neuroinflamm. 2020;7(4):e771 2. Cortese A, Lombardi R, Briani C, et al. Antibodies to neurofascin, contactin-1, and contactin-associated protein 1 in CIDP: Clinical relevance of IgG isotype. Neurol Neuroimmunol Neuroinflamm. 2019;7(1):e639 3. Manso C, Querol L, Mekaouche M, Illa I, Devaux JJ. Contactin-1 IgG4 antibodies cause paranode dismantling and conduction defects. Brain. 2016;139(Pt 6):1700-1712 4. Le Quintrec M, Teisseyre M, Bec N, et al: Contactin-1 is a novel target antigen in membranous nephropathy associated with chronic inflammatory demyelinating polyneuropathy. Kidney Int. 2021 Dec;100(6):1240-1249 5. Ogata H, Yamasaki R, Hiwatashi A, et al: Characterization of IgG4 anti-neurofascin 155 antibody-positive polyneuropathy. Ann Clin Transl Neurol. 2015(10):960-971 6. Cortese A, Lombardi R, Briani C, et al. Antibodies to neurofascin, contactin-1, and contactin-associated protein 1 in CIDP: Clinical relevance of IgG isotype. Neurol Neuroimmunol Neuroinflamm. 2020;7(1):e639 7. Querol L, Nogales-Gadea G, Rojas-Garcia R, et al. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. Neurology. 2014;82(10):879-886 8. Shelly S, Klein CJ, Dyck PJB, et al. Neurofascin-155 immunoglobulin subtypes: Clinicopathologic associations and neurologic outcomes. Neurology. 2021;97(24):e2392-e2403

CIDPI
616444

Chronic Inflammatory Demyelinating Polyradiculoneuropathy/Nodopathy Interpretation, Serum

Clinical Information: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired, immune-mediated condition effecting peripheral nerves and nerve roots and is characterized by electrodiagnostic features of demyelination with a chronic onset that leads to significant disability. The prevalence of CIDP is estimated at approximately 2 to 4 cases per 100,000 persons. Although a rarer cause of polyneuropathy, it is important to recognize as it is treatable with the appropriate use of immunomodulating therapies. Although the exact immunological trigger of CIDP remains unclear, a subset of patients with suspected CIDP have been identified with autoantibodies targeting nodal-paranodal proteins. These patients share common immunopathological mechanisms of disease, clinical features, and treatment responses that are distinct from classic CIDP. A common target of these autoantibodies is the neurofascin-155 (NF155): contactin-1 (CNTN1) complex. NF155 is expressed at the paranodal loops of Schwann cells where it interacts with CNTN1 expressed on adjacent axons. This interaction stabilizes and allows the proper organization of the paranodal axoglial junction. Antibody-mediated disruption of this interaction in animal models recapitulates the pathophysiology observed in humans. NF155 IgG antibodies are present in approximately 5% to 10% of patients with CIDP like presentations and, more rarely, in those with more acute forms of demyelinating polyradiculoneuropathy. NF155 IgG positive cases are more likely to present with distal weakness, gait disturbance, tremor, and dysarthria as compared to classic CIDP. Most patients who are seropositive for NF155 IgG have been reported to be refractory to intravenous immune globulin (IVIG) therapy and often require second line treatment that includes B-cell depleting therapies such as rituximab. Studies in animal models, as well as the disease pathology indicate NF155 IgG4 antibodies directly disrupt the paranodal axoglial junction ultimately leading to demyelination. IgG4 is the predominant antibody subclass found in these patients and associates with poorer treatment responses to IVIG. The detection of NF155 IgG4 is a highly specific finding and has not been reported in other disease mimics such as hereditary neuropathies, distal acquired demyelinating symmetric neuropathy, and motor neuron disease. CNTN1 IgG antibodies are present in approximately 2% of patients with CIDP like presentations. CNTN1 IgG positive cases are more likely to present with neuropathic pain, sensory ataxia, and subacute progressive demyelinating polyradiculoneuropathy or polyradiculopathy. The majority of seropositive patients have been reported to be refractory to treatment with IVIG. However, some of these patients respond well to B-cell depleting therapies such as rituximab. Up to half of CNTN1 IgG positive patients with CIDP or CIDP-like presentations have been reported to develop membranous nephropathy and, thus, screening for proteinuria may be warranted.

Useful For:

Interpretation: Seropositivity for contactin-1 IgG is consistent with an immune-mediated demyelinating polyradiculoneuropathy/polyradiculopathy. Seropositivity for neurofascin-155 IgG4 is consistent with an immune-mediated demyelinating polyradiculoneuropathy.

Reference Values:
Only orderable as part of a profile. For more information see CIDP / Chronic Inflammatory Demyelinating Polyradiculoneuropathy/Nodopathy Evaluation, Serum.

Clinical References: 1. Dubey D, Honorat JA, Shelly S, et al: Contactin-1 autoimmunity: Serologic, neurologic, and pathologic correlates. Neurol Neuroimmunol Neuroinflamm. 2020 May 27;7(4):e771 2. Cortese A, Lombardi R, Briani C, et al: Antibodies to neurofascin, contactin-1, and contactin-associated protein 1 in CIDP: Clinical relevance of IgG isotype. Neurol Neuroimmunol Neuroinflamm. 2020 Nov 21;7(1):e639 3. Manso C, Querol L, Mekaouche M, Illa I, Devaux JJ: Contactin-1 IgG4 antibodies cause paranode dismantling and conduction defects. Brain. 2016 Jun;139(Pt 6):1700-1712 4. Le Quintrec M, Teisseyre M, Bec N, et al: Contactin-1 is a novel target antigen in membranous nephropathy associated with chronic inflammatory demyelinating polyneuropathy. Kidney Int. 2021 Dec;100(6):1240-1249 5. Ogata H, Yamasaki R, Hiwatashi A, et al: Characterization of IgG4 anti-neurofascin 155 antibody-positive polyneuropathy. Ann Clin Transl Neurol. 2015 Oct;2(10):960-971 6. Cortese A, Lombardi R, Briani C, et al: Antibodies to neurofascin, contactin-1, and contactin-associated protein 1 in CIDP: Clinical relevance of IgG isotype. Neurol Neuroimmunol Neuroinflamm. 2020 Nov 21;7(1):e639 7. Querol L, Nogales-Gadea G, Rojas-Garcia R, et al: Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. Neurology. 2014 Mar 11;82(10):879-886 8. Shelly S, Klein CJ, Dyck PJB, et al: Neurofascin-155 immunoglobulin subtypes: Clinicopathologic associations and neurologic outcomes. Neurology. 2021;97(24):e2392-e2403

CLLMD
608972

Chronic Lymphocytic Leukemia (CLL) Monitoring Minimal Residual Disease Detection, Flow Cytometry, Varies

Clinical Information: Chronic lymphocytic leukemia (CLL) is a low-grade, B-cell neoplasm and is the most common leukemia detected in the western world. It is primarily associated with adult patients and may present as a lymphocytosis, be detected as part of a lymphadenopathy evaluation, or be found incidentally in an otherwise asymptomatic patient. The diagnosis of CLL is based on a combination of morphologic features showing primarily small lymphoid cells with coarse chromatin and scant cytoplasm and an immunophenotype of clonal B cells with dim immunoglobulin, dim CD20, and coexpression of CD5, CD22, CD43, and CD200. New therapeutic approaches in CLL have been increasingly successful with some patients showing no or only very minimal residual disease (MRD) in their peripheral blood or bone marrow specimens following a therapeutic course. Immunophenotyping studies are necessary as morphologic features are not sufficient to detect MRD. The absence of MRD is an important prognostic indicator in these patients.

Useful For: Confirming the presence or absence of minimal residual disease in patients with known chronic lymphocytic leukemia who are either post-chemoimmunotherapy or post-bone marrow transplant

CLLDF
610713

Chronic Lymphocytic Leukemia, Diagnostic FISH, Varies

Clinical Information: Chronic lymphocytic leukemia (CLL) is one of the most common leukemias in adults. The most frequently seen cytogenetic abnormalities in CLL involve chromosomes 6, 11, 12, 13 and 17. These are detected and quantified using the CLL fluorescence in situ hybridization (FISH) panel. Use of CpG-oligonucleotide mitogen will identify an abnormal CLL karyotype in at least 80% of cases. This mitogen is added to cultures when chromosome analysis is ordered and the reason for testing is B-cell lymphoproliferative disorders (CHRBM / Chromosome Analysis, Hematologic Disorders, Bone Marrow and CHRHB / Chromosome Analysis, Hematologic Disorders, Blood). This FISH test detects an

abnormal clone in approximately 70% of patients with indolent disease and in greater than 80% of patients who require treatment. At least 5% of patients referred for CLL FISH testing have translocations involving the IGH locus. Fusion of IGH with CCND1 is associated with t(11;14)(q13;q32), and fusion of IGH with BCL3 is associated with t(14;19)(q32;q13.3). Patients with t(11;14) usually have the leukemic phase of mantle cell lymphoma. Patients with t(14;19) may have an atypical form of B-CLL or the leukemic phase of a lymphoma. The prognostic associations for chromosome abnormalities detected by this FISH assay are, from best to worst: 13q-, normal, +12, 6q-, 11q- and 17p-.

Useful For: Detecting recurrent common chromosome abnormalities in patients with chronic lymphocytic leukemia (CLL) Distinguishing patients with 11;14 translocations who have the leukemic phase of mantle cell lymphoma from patients who have CLL Detecting patients with atypical CLL with translocations between IGH and BCL3 Evaluating specimens in which chromosome studies are unsuccessful

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. The absence of an abnormal clone does not rule out the presence of a CLL clone or another neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Dewald GW, Brockman SR, Paternoster SF, et al: Chromosome anomalies detected by interphase FISH: correlation with significant biological features of B-cell chronic lymphocytic leukemia. Br J Haematol. 2003;121:287-295 2. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343(26):1910-1916 3. Van Dyke DL, Shanafelt TD, Call TG, et al. A comprehensive evaluation of the prognostic significance of 13q deletions in patients with B-chronic lymphocytic leukaemia. Br J Haematol. 2010;148:544-550 4. Shanafelt TD: Predicting clinical outcome in CLL: how and why. Hematology Am Soc Hematol Educ Program. 2009;421-429 5. Van Dyke DL, Werner L, Rassenti LZ, et al. The Dohner fluorescence in situ hybridization prognostic classification of chronic lymphocytic leukaemia (CLL): the CLL Research Consortium experience. Br J Haematol. 2016;173(1):105-113 6. Fang H, Reichard KK, Rabe KG, et al. IGH translocations in chronic lymphocytic leukemia: Clinicopathologic features and clinical outcomes. Am J Hematol. 2019;94(3):338-345 7. Huh YO, Schweighofer CD, Ketterling RP, et al. Chronic lymphocytic leukemia with t(14;19)(q32;q13) is characterized by atypical morphologic and immunophenotypic features and distinctive genetic features. Am J Clin Pathol. 2011;135(5):686-696

CLLMF
610724

Chronic Lymphocytic Leukemia, Specified FISH, Varies

Clinical Information: Chronic lymphocytic leukemia (CLL) is one of the most common leukemias in adults. The most frequently seen cytogenetic abnormalities in CLL involve chromosomes 6, 11, 12, 13, and 17. These are detected and quantified using the CLL fluorescence in situ hybridization (FISH) panel. Use of CpG-oligonucleotide mitogen will identify an abnormal CLL karyotype in at least 80% of cases. This mitogen is added to cultures when chromosome analysis is ordered and the reason for testing is B-cell lymphoproliferative disorders (CHRBM / Chromosome Analysis, Hematologic Disorders, Bone Marrow and CHRHB / Chromosome Analysis, Hematologic Disorders, Blood). This FISH test detects an abnormal clone in approximately 70% of patients with indolent disease and greater than 80% of patients who require treatment. At least 5% of patients referred for CLL FISH testing have translocations involving the IGH locus. Fusion of IGH with CCND1 is associated with t(11;14)(q13;q32), and fusion of IGH with BCL3 is associated with t(14;19)(q32;q13.3). Patients with t(11;14) usually have the leukemic phase of mantle cell lymphoma. Patients with t(14;19) may have an

atypical form of B-CLL or the leukemic phase of a lymphoma. The prognostic associations for chromosome abnormalities detected by this FISH assay are, from best to worst: 13q-, normal, +12, 6q-, 11q-, and 17p-.

Useful For: Detecting recurrent common chromosome abnormalities in patients with chronic lymphocytic leukemia (CLL) Distinguishing patients with 11;14 translocations who have the leukemic phase of mantle cell lymphoma from patients who have CLL Detecting patients with atypical CLL with translocations between IGH and BCL3 Evaluating specimens in which chromosome studies are unsuccessful

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. The absence of an abnormal clone does not rule out the presence of a chronic lymphocytic leukemia clone or another neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References:

CRHEP 113119 Chronic Viral Hepatitis (Unknown Type), Serum

Clinical Information: Hepatitis B: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles among injection drug users). The virus is found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some of these carriers are asymptomatic while others develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. Individuals who have recovered from acute hepatitis B (defined as being negative for hepatitis B virus surface [HBs] antigen positive for hepatitis B virus core [HBc] total antibodies, negative or positive for HBs antibody) are lower risk (up to 20%) of HBV reactivation than those with inactive chronic hepatitis B during immunosuppressive therapy or organ transplantation. For individuals born in regions of the world where HBV prevalence is moderate to high, universal HBV serologic screening before initiation of immunosuppressive therapy is recommended. In the absence of systematic, risk-based testing, universal HBV serologic screening is an option to reduce the risk of missing persons with HBV infection prior to initiation of immunosuppressive treatment. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus recognized as the cause of most cases of posttransfusion hepatitis and is a significant cause of morbidity and mortality worldwide. HCV is transmitted through contaminated blood or blood products or close, personal contact. HCV shows a high rate of progression (~75%) to chronic disease. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Cirrhosis and hepatocellular carcinoma are sequelae of chronic HCV. Laboratory testing for HCV infection usually begins by screening for the presence of HCV-specific antibodies in serum, using an US Food and Drug Administration-approved screening test. Specimens that are repeatedly reactive by screening tests should be confirmed with HCV tests with higher specificity, such as direct detection of HCV RNA by reverse transcription polymerase chain reaction or HCV-specific antibody confirmatory tests. HCV antibodies are usually not detectable during the first 2 months following infection, but they are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies do not neutralize the virus and they do not provide immunity against this viral infection. The following algorithms are available: -Chronic Hepatitis C Treatment and Monitoring Algorithm: Direct Antiviral Antigen (DAA) Combination -Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management -Hepatitis C: Testing Algorithm for Screening and Diagnosis

Useful For: Diagnosis and evaluation of patients with symptoms of hepatitis lasting more than 6 months Distinguishing between chronic hepatitis B and C

Interpretation: Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles Chronic hepatitis B: Hepatitis B surface antigen (HBsAg is the first serologic marker appearing in the serum 6 to 8 weeks following hepatitis B viral (HBV) infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either a chronic carrier state or chronic HBV infection. Hepatitis B virus core IgM and total antibodies (anti-HBc IgM and total) appear shortly after the onset of symptoms of HBV infection and soon after the appearance of HBsAg. The anti-HBc IgM usually falls to undetectable levels within 6 months and anti-HBc total remains detectable for many years. Anti-HBs usually appears with the resolution of hepatitis B after the disappearance of HBsAg. If HBsAg and anti-HBc total antibody are positive, testing for HBeAg, anti-HBe, HBV-DNA, and anti-HDV total is recommended. Chronic hepatitis C: HCV antibodies (anti-HCV) are almost always detectable by the late convalescent and chronic stage of infection. Reactive anti-HCV results with cutoff index (COI) values less than or equal to 20.0 with this assay are not predictive of the true HCV antibody status. Additional testing is available to confirm HCV antibody status. Reactive results with COI values of greater than 20.0 with this assay are highly predictive (95% or greater probability) of the true HCV antibody status, but additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to low antibody levels that are below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with acute or recent HCV infections (<2 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks). Testing for HCV RNA using HCVQN / Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR, Serum is necessary for detection of HCV infection in such patients.

Reference Values:

HEPATITIS B SURFACE ANTIGEN:
Negative

HEPATITIS B SURFACE ANTIBODY, QUALITATIVE/QUANTITATIVE
Hepatitis B Surface Antibody
Unvaccinated: Negative
Vaccinated: Positive

HEPATITIS B SURFACE ANTIBODY, QUANTITATIVE
Unvaccinated: <8.5 mIU/mL
Vaccinated: > or =11.5 mIU/mL

HEPATITIS B CORE TOTAL ANTIBODIES:
Negative

HEPATITIS C ANTIBODY:
Negative

Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles.

Clinical References: 1. LeFevre MLL. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 2. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis. 2018;12(1):5-11. doi:10.1002/cld.729 3. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and

management of chronic hepatitis B virus infection. Gastroenterology. 2019;156(2):355-368.e3. doi:10.1053/j.gastro.2018.11.037 4. World Health Organization. Guidelines on hepatitis B and C testing. World Health Organization; 2017. Accessed October 8, 2024. Available at www.who.int/publications/i/item/9789241549981 5 Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. Published 2023 Mar 10. doi:10.15585/mmwr.rr7201a1 6. American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA): HCV guidance: Recommendations for testing, managing, and treating hepatitis C. AASLD, IDSA; Updated December 19, 2023. Accessed October 8, 2024. Available at www.hcvguidelines.org/contents

CHUB
82822

Chub Mackerel, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to chub mackerel Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive

6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CSU
606921

Chyluria Screen, Random, Urine

Clinical Information: Chyluria is a medical condition in which chyle is present in the urine. Chyle is a milky substance composed of lymphatic fluid and chylomicrons formed in the small intestine during the digestion of fatty foods. Chyluria is most prevalent in tropical areas where it is caused by parasitic (Wuchereria bancrofti) infections spread by mosquitoes. Parasitic chyluria is so rare as to be nonexistent in the continental United States. Nonparasitic chyluria causes include traumatic lesions, tumors, lymphangioma, pregnancy, and granulomatous infections.

Useful For: Aiding in the diagnosis of chyluria (galacturia)

Interpretation: This assay provides information regarding the fat content in urine fluid. Urinary cholesterol and triglyceride values are normally less than 10 mg/dL. High triglyceride levels in urine may indicate chyluria.

Reference Values:
No lipoproteins present

Clinical References: 1. Diamond E, Schapira HE. Chyluria-a review of the literature. Urology. 1985;26(5):427-431 2. Mendu DR, Sternlicht H, Ramanathan LV, et al. Two cases of spontaneous remission of non-parasitic chyluria. Clin Biochem. 2017;50(15):886-888. doi:10.1016/j.clinbiochem.2017.05.002

FCHYS
57806

Chymotrypsin, Stool

Reference Values:
2.3 – 51.4 U/g

FCING
57676

Cinnamon IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

CINN
82624

Cinnamon, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cinnamon Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CINPC
618275

CINtec IHC Multiplex, PC (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

FCICP
75925

Circulating Immune Complex Panel

Interpretation: Circulating Immune Complex, C1q Binding: Less than or equal to 3.9 ug Eq/mL is considered negative for circulating complement binding immune complexes. Circulating immune complexes may be found without any evident pathology and positive results do not necessarily implicate the immune complex in a disease process. Circulating Immune Complex, C3 fragments: Many autoimmune disorders, chronic infections and malignancies are associated with circulating immune complexes. Quantitation of immune complexes assists in staging immunologic disorders. Detection of circulating immune complexes is not essential to any specific diagnosis. Circulating immune complexes may be found without any evident pathology and positive results do not necessarily implicate immune complex-related disease process. Values between 15 and 20 ug Eq/mL are considered equivocal for Circulating Immune Complex, C3 fragments assay. Repeat- testing using a new specimen is recommended, if clinically indicated.

Reference Values:
Circulating Immune Complex, C1q Binding: 0.0-3.9 ug Eq/mL
Circulating Immune Complex, C3 fragments: Less than or equal to 15 ug Eq/mL

FCQBA
57301

Circulating Immune Complex, C1q Binding

Interpretation: Less than or equal to 3.9 ug Eq/mL is considered negative for circulating complement binding immune complexes. Circulating immune complexes may be found without any evident pathology and positive results do not necessarily implicate the immune complex in a disease process.

Reference Values:
0.0-3.9 ug Eq/mL

FCIC3
75772

Circulating Immune Complex, C3 fragments

Interpretation: Many autoimmune disorders, chronic infections and malignancies are associated with circulating immune complexes. Quantitation of immune complexes assists in staging immunologic disorders. Detection of circulating immune complexes is not essential to any specific diagnosis. Circulating immune complexes may be found without any evident pathology and positive results do not necessarily implicate immune complex-related disease process. Values between 15 and 20 ug Eq/mL are considered equivocal for the Circulating Immune Complex, C3 fragments assay. Repeat testing using a new specimen is recommended, if clinically indicated.

Reference Values:
Less than or equal to 15 ug Eq/mL

FCIC
91497

Circulating Immune Complexes (CIC)

Interpretation: Circulating immune complexes (CICs) are detectable in a variety of systemic

disorders such as rheumatological, autoimmune, allergic diseases; viral, bacterial infections and malignancies. Although detection of CICs is neither essential nor specific for any disease, anti-C1q assay is likely to provide information regarding disease activity in lupus nephritis.

Reference Values:

Negative	<20 EU/mL
Borderline/Equivocal	20 – 25 EU/mL
Positive	>25 EU/mL

CITR2
606637

Citrate Concentration, Random, Urine

Clinical Information: Urinary citrate is a major inhibitor of kidney stone formation due in part to binding of calcium in urine. Low urine citrate levels are considered a risk for kidney stone formation. Several metabolic disorders are associated with low urine citrate. Any condition that lowers renal tubular pH or intracellular pH may decrease citrate (eg, metabolic acidosis, increased acid ingestion, hypokalemia, or hypomagnesemia). Low urinary citrate is subject to therapy by correcting acidosis, hypokalemia, or hypomagnesemia by altering diet or using drugs such as citrate and potassium.

Useful For: Diagnosing risk factors for patients with calcium kidney stones Monitoring results of therapy in patients with calcium stones or renal tubular acidosis

Interpretation: A low citrate value represents a potential risk for kidney stone formation/growth. Patients with low urinary citrate and new or growing stone formation may benefit from adjustments in therapy known to increase urinary citrate excretion. Very low citrate levels suggest investigation for the possible diagnosis of metabolic acidosis (eg, renal tubular acidosis). For children ages 5 to 18, a ratio of less than 0.176 mg citrate/ mg creatinine is below the 5% reference range and considered low.(1)

Reference Values:
Only orderable as part of a profile. For more information see CITRA / Citrate Excretion, Random, Urine.

No established reference values

Clinical References: 1. Srivastava T, Winston MJ, Auron A et al: Urine calcium/citrate ratio in children with hypercalciuric stones. Pediatr Res. 2009;66:85-90 2. Hosking DH, Wilson JW, Liedtke RR, et al: The urinary excretion of citrate in normal persons and patients with idiopathic calcium urolithiasis (abstract). Urol Res. 1984;12:26 3. Lieske JC, Wang X: Heritable traits that contribute to nephrolithiasis. Urolithiasis. 2019 Feb;47(1):5-10 4. Lieske JC, Turner ST, Edeh SN, Smith JA, Kardia SLR: Heritability of urinary traits that contribute to nephrolithiasis. Clin J Am Soc Nephrol. 2014 May;9(5):943-950. doi: 10.2215/CJN.08210813

CITR
606710

Citrate Excretion, 24 Hour, Urine

Clinical Information: Urinary citrate is a major inhibitor of kidney stone formation due in part to binding of calcium in urine. Low urine citrate levels are considered a risk for kidney stone formation. Several metabolic disorders are associated with low urine citrate. Any condition that lowers renal tubular pH or intracellular pH may decrease citrate (eg, metabolic acidosis, increased acid ingestion, hypokalemia, or hypomagnesemia). Low urinary citrate promotes kidney stone formation and growth, and is subject to therapy by correcting acidosis, hypokalemia, or hypomagnesemia by altering diet or using drugs such as citrate and potassium.

Useful For: Diagnosing risk factors for patients with calcium kidney stones Monitoring results of therapy in patients with calcium stones or renal tubular acidosis

Interpretation: Any value less than the mean for 24 hours represents a potential risk for kidney stone formation and growth. Patients with low urinary citrate and new or growing stone formation, may benefit from adjustments in therapy known to increase urinary citrate excretion. (See Clinical Information) Very low levels (<150 mg/24 hours) suggest investigation is needed for the possible diagnosis of metabolic acidosis (eg, renal tubular acidosis).

Reference Values:

0-19 years: not established
20 years: 150-1,191 mg/24 hours
21 years: 157-1,191 mg/24 hours
22 years: 164-1,191 mg/24 hours
23 years: 171-1,191 mg/24 hours
24 years: 178-1,191 mg/24 hours
25 years: 186-1,191 mg/24 hours
26 years: 193-1,191 mg/24 hours
27 years: 200-1,191 mg/24 hours
28 years: 207-1,191 mg/24 hours
29 years: 214-1,191 mg/24 hours
30 years: 221-1,191 mg/24 hours
31 years: 228-1,191 mg/24 hours
32 years: 235-1,191 mg/24 hours
33 years: 242-1,191 mg/24 hours
34 years: 250-1,191 mg/24 hours
35 years: 257-1,191 mg/24 hours
36 years: 264-1,191 mg/24 hours
37 years: 271-1,191 mg/24 hours
38 years: 278-1,191 mg/24 hours
39 years: 285-1,191 mg/24 hours
40 years: 292-1,191 mg/24 hours
41 years: 299-1,191 mg/24 hours
42 years: 306-1,191 mg/24 hours
43 years: 314-1,191 mg/24 hours
44 years: 321-1,191 mg/24 hours
45 years: 328-1,191 mg/24 hours
46 years: 335-1,191 mg/24 hours
47 years: 342-1,191 mg/24 hours
48 years: 349-1,191 mg/24 hours
49 years: 356-1,191 mg/24 hours
50 years: 363-1,191 mg/24 hours
51 years: 370-1,191 mg/24 hours
52 years: 378-1,191 mg/24 hours
53 years: 385-1,191 mg/24 hours
54 years: 392-1,191 mg/24 hours
55 years: 399-1,191 mg/24 hours
56 years: 406-1,191 mg/24 hours
57 years: 413-1,191 mg/24 hours
58 years: 420-1,191 mg/24 hours
59 years: 427-1,191 mg/24 hours
60 years: 434-1,191 mg/24 hours
>60 years: not established

Clinical References: 1. Hosking DH, Wilson JW, Liedtke RR, Smith LH, Wilson DM: The urinary excretion of citrate in normal persons and patients with idiopathic calcium urolithiasis. Lab Clin Med. 1985 Dec;106(6):682-689. 2. Lieske JC, Wang X: Heritable traits that contribute to nephrolithiasis. Urolithiasis. 2019 February; 47(1): 5-10 3. Lieske JC, Turner ST, Edeh SN, Smith JA, Kardia SLR: Heritability of urinary traits that contribute to nephrolithiasis. Clin J Am Soc Nephrol. 2014 May;9(5):943-950

CITRA
606715

Citrate Excretion, Random, Urine

Clinical Information: Urinary citrate is a major inhibitor of kidney stone formation due in part to binding of calcium in urine. Low urine citrate levels are considered a risk for kidney stone formation. Several metabolic disorders are associated with low urine citrate. Any condition that lowers renal tubular pH or intracellular pH may decrease citrate (eg, metabolic acidosis, increased acid ingestion, hypokalemia, or hypomagnesemia). Low urinary citrate is subject to therapy by correcting acidosis, hypokalemia, or hypomagnesemia by altering diet or using drugs such as citrate and potassium.

Useful For: Diagnosing risk factors for patients with calcium kidney stones using random urine specimens Monitoring results of therapy in patients with calcium stones or renal tubular acidosis

Interpretation: A low value represents a potential risk for kidney stone formation/growth. Patients with low urinary citrate and new or growing stone formation may benefit from adjustments in therapy known to increase urinary citrate excretion. Very low citrate levels suggest investigation for the possible diagnosis of metabolic acidosis (eg, renal tubular acidosis). For children ages 5 to 18, a ratio of less than 0.176 mg citrate/ mg creatinine is below the 5% reference range and considered low.(1)

Reference Values:
No established reference values.

Clinical References: 1. Srivastava T, Winston MJ, Auron A, Alon US: Urine calcium/citrate ratio in children with hypercalciuric stones. Pediatr Res. 2009 Jul;66(1):85-90. doi: 10.1203/PDR.0b013e3181a2939e 2. Hosking DH, Wilson JW, Liedtke RR, Smith LH, Wilson DM: The urinary excretion of citrate in normal persons and patients with idiopathic calcium urolithiasis. J Lab Clin Med. 1985 Dec;106(6):682-689 3. Lieske JC, Wang X: Heritable traits that contribute to nephrolithiasis. Urolithiasis. 2019 Feb;47(1):5-10. doi: 10.1007/s00240-018-1095-1 4. Lieske JC, Turner ST, Edeh SN, Smith JA, Kardia SL: Heritability of urinary traits that contribute to nephrolithiasis. Clin J Am Soc Nephrol. 2014 May;9(5):943-950

RAT10
606642

Citrate/Creatinine Ratio, Urine

Clinical Information: Urinary citrate is a major inhibitor of kidney stone formation due in part to binding of calcium in urine. Low urine citrate levels are considered a risk for kidney stone formation. Several metabolic disorders are associated with low urine citrate. Any condition that lowers renal tubular pH or intracellular pH may decrease citrate (eg, metabolic acidosis, increased acid ingestion, hypokalemia, or hypomagnesemia). Low urinary citrate is subject to therapy by correcting acidosis, hypokalemia, or hypomagnesemia by altering diet or using drugs such as citrate and potassium.

Useful For: Calculating the citrate concentration per creatinine Diagnosing risk factors for patients with calcium kidney stones Monitoring results of therapy in patients with calcium stones or renal tubular acidosis

Interpretation: A low citrate value represents a potential risk for kidney stone formation/growth. Patients with low urinary citrate and new or growing stone formation may benefit from adjustments in therapy known to increase urinary citrate excretion. Very low citrate levels suggest investigation for the possible diagnosis of metabolic acidosis (eg, renal tubular acidosis). For children ages 5 to 18, a ratio of less than 0.176 mg citrate/ mg creatinine is below the 5% reference range and considered low.(1)

Reference Values:

Only orderable as part of a profile. For more information see CITRA / Citrate Excretion, Random, Urine.

No established reference values

Clinical References: 1. Srivastava T, Winston MJ, Auron A et al: Urine calcium/citrate ratio in children with hypercalciuric stones. Pediatr Res. 2009;66:85-90 2. Hosking DH, Wilson JW, Liedtke RR, et al: The urinary excretion of citrate in normal persons and patients with idiopathic calcium urolithiasis (abstract). Urol Res. 1984;12:26 3. Lieske JC, Wang X: Heritable traits that contribute to nephrolithiasis. Urolithiasis. 2019 Feb;47(1):5-10 4. Lieske JC, Turner ST, Edeh SN, Smith JA, Kardia SLR: Heritability of urinary traits that contribute to nephrolithiasis. Clin J Am Soc Nephrol. 2014 May;9(5):943-950. doi: 10.2215/CJN.08210813

CLAD
82912

Cladosporium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Cladosporium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CLAM
82884

Clam, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to clam Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CLD18 620665 Claudin 18 (CLDN18) (43-14A), Semi-Quantitative Immunohistochemistry, Manual

Clinical Information: Claudin 18 (CLDN18) is a member of the claudin protein family that regulates cell adhesion. A qualitative immunohistochemistry assessment using mouse monoclonal anti-claudin 18, clone 43-14A, serves as a biomarker in gastric and gastroesophageal junction cancer and may aid in identifying patients eligible for VYLOY (zolbetuximab) treatment.

Useful For: Identification of tumor cells expressing claudin 18 As an aid in screening patients who may be eligible for VYLOY (zolbetuximab) treatment

Interpretation: Claudin 18.2 is a biomarker for gastric and gastroesophageal junction cancer. When positive (defined as at least moderate membranous staining in greater than or equal to 75% of viable tumor cells), it predicts response to zolbetuximab which has been approved for the treatment of gastric and gastroesophageal adenocarcinoma.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Kubota Y, Kawazoe A, Mishima S, et al. Comprehensive clinical and molecular characterization of claudin 18.2 expression in advanced gastric or gastroesophageal junction cancer. ESMO Open. 2023;8(1):100762 2. Cao W, Xing H, Li Y, et Al. Claudin18.2 is a novel molecular biomarker for tumor-targeted immunotherapy. Biomark Res. 2022;10(1):38 3. Pellino A, Brignola S, Riello E, et al. Association of CLDN18 protein expression with clinicopathological features and prognosis in advanced gastric and gastroesophageal junction adenocarcinomas. J Pers Med. 2021;11(11):1095 4. Arnold A, Daum S, von Winterfeld M, et al. Prognostic impact of Claudin 18.2 in gastric and esophageal adenocarcinomas. Clin Transl Oncol. 2020;22(12):2357-2363

CLAUD 70403 Claudin-1 Immunostain, Technical Component Only

Clinical Information: Claudin proteins are a family of tight junction-associated proteins that prevent leakage of ions, water, etc between cells. Differential expression of claudin proteins is seen in various epithelial cell types. Strong expression of claudin-1 is seen on squamous epithelial cells of the skin. Claudin-1 may have reduced expression in invasive versus benign breast lesions. In the diagnostic setting, 30% to 50% of soft tissue and intramucosal intestinal perineuriomas are positive for claudin-1. Gastric intestinal-type adenocarcinoma shows more frequent claudin-1 expression than diffuse gastric carcinomas.

Useful For: Identification of a number of different soft tissue and epithelial neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Katzka DA, Tadi R, Smyrk TC, et al. Effects of topical steroids on tight junction proteins and spongiosis in esophageal epithelia of patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2014;12(11):1824-9.e1. doi:10.1016/j.cgh.2014.02.039 2. Bhat AA, Syed N, Therachiyil L, et al. Claudin-1, a double-edged sword in cancer. Int J Mol Sci. 2020;21(2):569. doi:10.3390/ijms21020569 3. Moldvay J, Fabian K, Jackel M, et al. Claudin-1 protein expression Is a good prognostic factor in non-small cell lung cancer, but only in squamous cell carcinoma cases. Pathol Oncol Res. 2017;23(1):151-156. doi:10.1007/s12253-016-0115-0 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CLDN4
607334

Claudin-4 Immunostain, Technical Component Only

Clinical Information: Claudin-4 is a component of tight junction strands and is expressed on the membrane of cells of epithelial origin. Claudin-4 has been shown to distinguish carcinoma from mesothelioma and carcinoma from sarcoma.

Useful For: Distinguishing carcinoma from mesothelioma and sarcoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Jo VY, Cibas ES, Pinkus GS. Claudin-4 immunohistochemistry is highly effective in distinguishing adenocarcinoma from malignant mesothelioma in effusion cytology. Cancer Cytopathol. 2014;122(4):299-306 2. Ohta Y, Sasaki Y, Saito M, et al. Claudin-4 as a marker for distinguishing malignant mesothelioma from lung carcinoma and serous adenocarcinoma. Int J Surg Pathol. 2013;21(5):493-501 3. Ordonez NG. Value of claudin-4 immunostaining in the diagnosis of mesothelioma. Am J Clin Pathol. 2013;139(5):611-619 4. Schaefer IM, Agaimy A, Fletcher CD, Hornick JL. Claudin-4 expression distinguishes SWI/SNF complex-deficient undifferentiated carcinomas from sarcomas. Mod Pathol. 2017;30(4):539-548 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FCLCN
75262

CLCN1 DNA Sequencing Test

Reference Values:
A final report will be attached in MayoAccess.

CLOBZ
65483

Clobazam and Metabolite, Serum

Clinical Information: Clobazam is a broad spectrum, antiepileptic drug used for various types of seizures, Lennox-Gastaut syndrome (a type of childhood onset epilepsy), and migraine prophylaxis. Clobazam blocks voltage-dependent sodium channels, potentiates gamma-aminobutyric acid (GABA) activity at some of the GABA receptors, and inhibits potentiation of the glutamate receptor and carbonic anhydrase enzyme, all of which contribute to its antiepileptic and antimigraine efficacy. In general, clobazam shows favorable pharmacokinetics with good absorption (1-4 hours for the immediate-release formulation), low protein binding, and minimal hepatic metabolism. Elimination is predominantly renal, and it is excreted unchanged in the urine with an elimination half-life of approximately 21 hours. As with other anticonvulsant drugs eliminated by the renal system, patients with impaired kidney function exhibit decreased clobazam clearance and a prolonged elimination half-life. Serum concentrations of other anticonvulsant drugs are not significantly affected by the concurrent administration of clobazam, with the exception of patients on phenytoin whose serum concentrations can increase after the addition of clobazam. Other drug-drug interactions include the coadministration of phenobarbital, phenytoin, or carbamazepine, which can result in decreased clobazam concentrations. In addition, concurrent use of posaconazole and clobazam may result in the elevation of clobazam serum concentrations. Therefore, changes in cotherapy with these medications (phenytoin, carbamazepine, posaconazole, or phenobarbital) may require dose adjustment of clobazam, and therapeutic drug monitoring can be helpful. The most common adverse drug effects associated with clobazam include weight loss, loss of appetite, somnolence, dizziness, coordination problems, memory impairment, and paresthesia.

Useful For: Monitoring clobazam therapy

Interpretation: The results of this test should be interpreted in conjunction with the patient's physical signs, symptoms, and other laboratory test results. Most individuals display optimal response to clobazam when serum levels of clobazam are between 30 and 300 ng/mL and N-desmethylclobazam are between 300 and 3000 ng/mL. Risk of toxicity is increased when clobazam levels are above 500 ng/mL or N-desmethlyclobazam levels are above 5000 ng/mL. Some individuals may respond well outside of these ranges or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation.

Reference Values:
Clobazam
Therapeutic Range: 30-300 ng/mL

N-desmethylclobazam (Norclobazam)
Therapeutic Range: 300-3,000 ng/mL

Clinical References: 1. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62 2. Patsalos PN, Berry DJ, Bourgeois BF, et al: Antiepileptic drugs-best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239-1276 3. Johannessen SI, Tomsom T. Pharmacokinetic variability of newer antiepileptic drugs: when is monitoring needed?. Clin Pharmacokinet. 2006;45(11):1061-1075

CLOM
80902

Clomipramine, Serum

Clinical Information: Clomipramine (chlorimipramine, Anafranil) is a tricyclic antidepressant drug used primarily to treat obsessive-compulsive disorder. Clomipramine is also used to treat panic disorder and treatment-resistant depression. Clomipramine preferentially blocks synaptic reuptake of serotonin; its pharmacologically active metabolite, norclomipramine (desmethylclomipramine) preferentially blocks synaptic reuptake of norepinephrine. Clomipramine undergoes significant first-pass hepatic metabolism (up to 50%), which probably explains the high degree of interindividual variability observed between administered dose and steady-state serum concentrations of the drug and its metabolite. The serum ratio of clomipramine to norclomipramine is typically 1:2 to 1:2.5. The elimination half-lives of clomipramine and norclomipramine are 19 to 37 hours and 54 to 77 hours, respectively. When a patient is started on clomipramine or following an alteration in the dose, 1 to 2 weeks are required to achieve a steady-state condition. Anticholinergic side effects (ie, dry mouth, excessive sweating, blurred vision, urinary retention, constipation) frequently accompany treatment. Other side effects may include tremor, nausea, orthostatic hypotension, dizziness, sexual dysfunction, and sleep disturbances. Signs and symptoms following overdose are similar to other tricyclic antidepressant drugs with cardiac toxicity (eg, tachycardia, arrhythmia, impaired conduction, congestive heart failure) the major concern.

Useful For: Determining whether a poor therapeutic response is attributable to noncompliance
Monitoring serum concentration of clomipramine and norclomipramine to assist in optimizing the administered dose

Interpretation: Studies investigating the relationship between serum concentrations of clomipramine and norclomipramine and therapeutic response have yielded conflicting results. However, the probability of therapeutic failure seems to increase if the sum of the clomipramine and norclomipramine serum concentrations is less than 230 ng/mL. Summed serum concentrations of clomipramine and norclomipramine that exceed 450 ng/mL seem to result in no additional enhancement in therapeutic response and may predispose the patient to greater risk of adverse side effects. A toxic range has not been well established at this time.

Reference Values:
Clomipramine and norclomipramine
Therapeutic concentration: 230-450 ng/mL

Note: Therapeutic ranges are for specimens collected at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

Clinical References: 1. Wille SM, Cooreman SG, Neels HM, Lambert WE. Relevant issues in the monitoring and the toxicology of antidepressants. Crit Rev Clin Lab Sci. 2008;45(1):25-89 2. Thanacoody HK, Thomas SHL. Antidepressant poisoning. Clin Med (Lond). 2003;3(2):114-118 3. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51:9-62 4. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

CZPS
65044

Clonazepam and 7-Aminoclonazepam, Serum

Clinical Information: Clonazepam (5 [2-chlorophenyl]-2, 3-dihydro-7-nitro-1, 4-benzodiazepin-2-one), a benzodiazepine is useful alone or as an adjunct in the treatment of certain seizures. In addition, it may be useful in patients with panic disorder and restless legs syndrome. Clonazepam has no definite antiseizure and antipanic mechanism of action, although it is believed to be related to its capacity to enhance gamma-aminobutyric acid (GABA) activity, which is the major

inhibitory neurotransmitter in the central nervous system. It is able to suppress the spike and wave discharges in absence seizures and decreases the frequency, duration, amplitude, and spread of discharge in minor motor seizures. Clonazepam is highly protein bound (approximately 85%). It is extensively metabolized by hepatic cytochrome P450, family 3, subfamily A (CYP3A) to inactive metabolites and has a half-life of 30 to 40 hours.

Useful For: Assessing patient compliance Monitoring for appropriate therapeutic level Assessing clonazepam toxicity

Interpretation: The therapeutic range varies depending on the indication. Some individuals may respond well outside of these ranges or may display toxicity within the therapeutic range, and thus, interpretation should include clinical evaluation. The possibility of toxicity is increased when levels exceed 100 ng/mL.

Reference Values:
Clonazepam
Anticonvulsant: 20-70 ng/mL
Anxiolytic: 4-80 ng/mL
Some individuals may show therapeutic response outside of these ranges or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation.
Note: Therapeutic ranges are for specimens collected at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

Clinical References: Hiemke C, Baumann P, Bergemann N, et al: AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry: Update 2011. Pharmacopsychiatry. 2011;44(6):195-235

FCLMS 75524 Clonazepam and Metabolite, Serum

Interpretation: Clonazepam: Therapeutic range: 10-75 ng/mL Toxic: greater than 100 ng/mL
7-Amino Clonazepam: Plasma concentrations following chronic therapy with 6 mg/day of Clonazepam: 20 to 140 ng/mL

Reference Values:
Reporting limit(s) determined each analysis.
Clonazepam: None Detected ng/mL
7-Amino Clonazepam: None Detected ng/mL

FCLON 91107 Clonidine (Catapres)

Reference Values:
Reference Range: 1.00 - 2.00 ng/mL

Sedation has been associated with serum clonidine concentrations greater than 1.5 ng/mL

Toxic concentration has not been established.

CDIFS 603416 Clostridioides difficile Culture with Antimicrobial Susceptibilities, Varies

Clinical Information: Clostridioides difficile can cause diarrhea and may cause pseudomembranous colitis. Overgrowth of toxin-producing C difficile in the colon leads to the production of toxins A and/or B by the organism, and subsequent diarrhea. C difficile infection should be suspected in patients with symptoms of diarrhea with risk factors such as current or recent use of antibiotics, history of C difficile infection, current or recent hospitalization or placement in a nursing home or long-term care facility, over 65 years of age, and gastric acid suppression. C difficile infection is the most common cause of diarrhea in hospitalized patients and may lead to serious complications, including sepsis, bowel perforation, and increased overall mortality (especially in elderly patients). The incidence of C difficile infection has risen in the community and in healthcare settings. While culture is not the preferred means to diagnose C difficile-associated diarrhea, culture for C difficile provides an isolate suitable for antimicrobial susceptibility testing. Susceptibility testing routinely includes metronidazole and vancomycin. Routine antimicrobial susceptibility testing of C difficile isolates associated with intestinal infection is not suggested.(4,5) Recent Infectious Diseases Society of America and Society for Healthcare Epidemiology of America guidelines provide treatment guidance for C difficile infection based on clinical course and history rather than measured minimal inhibitory concentrations of isolates.(6) Susceptibility testing of C difficile isolates may be warranted in cases of treatment failure, or when used to guide therapy of extraluminal infections. Note that this test does not differentiate between toxin-producing and nontoxigenic strains of C difficile.

Useful For: Providing an isolate suitable for antimicrobial susceptibility testing to direct antimicrobial therapy of extraluminal infections and in cases of treatment failure

Interpretation: A positive result indicates the presence of viable Clostridioides difficile in stool. A positive culture may be found with asymptomatic C difficile colonization with a toxin-producing or non-toxin-producing strain, or with C difficile-associated diarrhea. A negative result indicates the absence of C difficile growth in culture. Isolation of C difficile does not differentiate between toxin-producing and non-toxin-producing strains. Refer to the Reference Values section for interpretation of various antimicrobial categories.

Reference Values:
No growth of Clostridioides difficile.

Susceptibility results are reported as minimal inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as clinical breakpoints) are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, or nonsusceptible according to breakpoint setting organizations, either the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST), as applicable.

In some instances, an interpretive category cannot be provided based on available data; therefore, the following comment will be included on the report: There are no established interpretive guidelines for agents reported without interpretations.

For information regarding CLSI and EUCAST susceptibility interpretations, see Susceptibility Interpretative Category Definitions.

Clinical References: 1. Lawson PA, Citron DM, Tyrrell KL, Finegold SM. Reclassification of clostridium difficile as clostridioides difficile (Hall and O'Toole 1935) Prevot 1938. Anaerobe. 2016;40;95-99. doi:10.1016/j.anaerobe.2016.06.008 2. Oren A, Garrity GM. List of new names and new combinations previously effectively, but not validly, published. Int J Syst Evol Microbiol, 2016;66(7):2463-2466. doi:10.1099/ijsem.0.001149 3. CLSI: Performance Standards for Antimicrobial Susceptibility Testing. 32nd edition. CLSI Supplement M100. Wayne, PA. Clinical and Laboratory Standards Institute. 2023 4. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for clostridium difficile Infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis.

2018;66(7):987-994) 5. Schuetz AN, Carpenter DE: Susceptibility test methods: anaerobic bacteria. In: Carroll KC, Pfaller MA, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:1377-1397 6. Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of clostridioides difficile infection in adults. Clin Infect Dis. 2021;73(5):e1029-e1044 7. Snydman DR, McDermott LA, Jacobus NV, et al. U.S.-Based National Sentinel Surveillance Study for the epidemiology of clostridium difficile-associated diarrheal isolates and their susceptibility to fidaxomicin. Antimicrob Agents Chemother. 2015;59(10):6437-6443. doi:10.1128/AAC.00845-15 8. Goldstein EJ, Citron DM, Tyrrell KL, Merriam CV. Comparative in vitro activities of SMT19969, a new antimicrobial agent, against clostridium difficile and 350 gram-positive and gram-negative aerobic and anaerobic intestinal flora isolates. Antimicrob Agents Chemother. 2013;57(10):4872-4876. doi:10.1128/AAC.01136-13 6. Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of clostridioides difficile infection in adults. Clin Infect Dis. 2021;73(5):e1029-e1044

CDIF
64354

Clostridioides difficile Culture, Varies

Clinical Information: Clostridioides difficile (formerly Clostridium difficile) can cause diarrhea and may cause pseudomembranous colitis. Overgrowth of toxin-producing C difficile in the colon leads to the production of toxins A and/or B by the organism and consequent diarrhea. C difficile infection should be suspected in patients with symptoms of diarrhea with risk factors such as current or recent use of antibiotics, a history of C difficile infection, current or recent hospitalization or placement in a nursing home or long-term care facility, age older than 65 years, gastric acid suppression, etc. C difficile infection is the most common cause of diarrhea in hospitalized patients and may lead to serious complications, including sepsis, bowel perforation, and increased overall mortality (especially in older patients). The incidence of C difficile infection has risen in the community and in healthcare settings. While culture is not the preferred means to diagnose C difficile-associated diarrhea, culture for C difficile provides an isolate suitable for antimicrobial susceptibility testing. Note that this test does not differentiate between toxin-producing and nontoxigenic strains of C difficile.

Useful For: Providing an isolate suitable for antimicrobial susceptibility testing

Interpretation: A positive result indicates the presence of viable Clostridioides difficile in feces. A positive culture may be found with asymptomatic C difficile colonization with a toxin-producing or non-toxin-producing strain or with C difficile-associated diarrhea. A negative result indicates the absence of C difficile growth in culture.

Reference Values:
No growth of Clostridioides difficile.

Clinical References: 1. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431-455 2. Lawson PA, Citron DM, Tyrrell KL, Finegold SM. Reclassification of Clostridium difficile as Clostridioides difficile (Hall and O'Toole 1935) Prevot 1938. Anaerobe. 2016;40:95-99. doi:10.1016/j.anaerobe.2016.06.008 3. Oren A, Garrity GM. List of new names and new combinations previously effectively, but not validly, published. Int J Syst Evol Microbiol. 2016;66(11):4299-4305. doi:10.1099/ijsem.0.001585

EIACD
622780

Clostridioides difficile Toxin, EIA, Feces

Clinical Information: In the United States, toxigenic Clostridioides difficile (TCD) accounts for 15% to 25% of all episodes of antibiotic-associated diarrhea. TCD is also associated with a spectrum of disease states, ranging from asymptomatic colonization to pseudomembranous colitis, toxic megacolon, sepsis, and death. Pathogenic C difficile produces one or both of 2 toxins, toxin A and toxin B. While toxin A is produced by most disease-causing strains of C difficile, it has been shown that some disease-causing strains of C difficile produce only toxin B. C difficile strains that do not produce toxins A or B are thought to be avirulent. Toxin A and B enzyme immunoassays (EIA) have low sensitivity and moderate specificity for C difficile infection. The suboptimal performance of EIA sparked the development of molecular tests (eg, polymerase chain reaction) that have high sensitivity. EIA may be useful as part of a multi-step algorithm if patients do not meet preanalytic criteria for stool submission (unexplained and new onset diarrhea with at least 3 unformed stools/day and no recent laxative use).

Useful For: Diagnosing the presence of toxigenic Clostridioides difficile

Interpretation:

Reference Values:
Negative

Clinical References: 1. Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clin Infect Dis. 2021;73(5):e1029-e1044. doi:10.1093/cid/ciab549 2. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66(7):987-994 3. Miller R, Morillas JA, Brizendine KD, Fraser TG. Predictors of Clostridioides difficile infection -related complications and treatment patterns among nucleic acid amplification test -positive/toxin enzyme immunoassay-negative patients. J Clin Microbiol. 2020;58(3):e01764-19

CDPCR
618554

Clostridioides difficile Toxin, PCR, Feces

Clinical Information: Clostridioides difficile (formerly Clostridium difficile) is the cause of C difficile-associated diarrhea (CDAD), an antibiotic-associated diarrhea, and pseudomembranous colitis (PMC). In these disorders bacterial overgrowth of C difficile develops in the colon, typically as a consequence of antibiotic usage. Clindamycin and broad-spectrum cephalosporins have most frequently been associated with CDAD and PMC, but almost all antimicrobials may be responsible. Disease is related to production of toxin A and B. Treatment typically involves withdrawal of the associated antimicrobials and, if symptoms persist, orally administered and intraluminally active metronidazole, vancomycin, or fidaxomicin. Intravenous metronidazole may be used if an oral agent cannot be administered. In recent years, a more severe form of CDAD with increased morbidity and mortality has been recognized as being caused by an epidemic toxin-hyperproducing strain of C difficile (NAP1 strain). Many toxin-hyperproducing isolates also contain the binary toxin gene and are resistant to quinolones. This test does not differentiate between toxin-hyperproducing and non-toxin-hyperproducing strains. Traditionally, diagnosis relied upon: 1. Clinical and epidemiologic features 2. Culture, which is labor intensive and time consuming 3. Cytotoxicity assays, which are labor intensive and time consuming 4. Toxin detection immunoassays, which are insensitive This test uses a polymerase chain reaction assay that detects the regulatory gene (tcdC) responsible for production of toxins A and B. This test is used for rapid diagnosis of CDAD and PMC, enabling prompt treatment that may reduce hospital stays for inpatients with CDAD.

Useful For: Sensitive, specific, and rapid diagnosis of Clostridioides (Clostridium) difficile-associated

diarrhea and pseudomembranous colitis The test is not recommended as a test of cure.

Interpretation: Positive: Toxin producing Clostridioides (Clostridium) difficile target nucleic acid is detected. Negative: Clostridium difficile target nucleic acid is not detected.

Reference Values:
Negative

Clinical References: 1. Aichinger E, Schleck CD, Harmsen WS, Nyre LM, Patel R. Nonutility of repeat laboratory testing for detection of Clostridium difficile by use of PCR or enzyme immunoassay. J Clin Microbiol. 2008;46(11):3795-3797 2. Sloan LM, Duresko BJ, Gustafson DR, Rosenblatt JE. Comparison of real-time PCR for detection of the tcdC gene with four toxin immunoassays and culture in diagnosis of Clostridium difficile infection. J Clin Microbiol. 2008;46(6):1996-2001 3. Verdoorn BP, Orenstein R, Rosenblatt JE, et al. High prevalence of tcdC deletion-carrying Clostridium difficile and lack of association with disease severity. Diagn Microbiol Infect Dis. 2010;66(1):24-28 4. Karre T, Sloan L, Patel R, Mandrekar J, Rosenblatt J. Comparison of two commercial molecular assays to a laboratory-developed molecular assay for diagnosis of Clostridium difficile infection. J Clin Microbiol. 2011;49(2):725-727 5. Lawson PA, Citron DM, Tyrrell KL, Finegold SM. Reclassification of Clostridium difficile as Clostridioides difficile (Hall and O'Toole 1935) Prevot 1938. Anaerobe. 2016;40:95-99. doi:10.1016/j.anaerobe.2016.06.008

CLOV
82490

Clove, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to clove Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CLZ
42366

Clozapine, Serum

Clinical Information: Clozapine (Clozaril), a tricyclic dibenzodiazepine, is used for the symptomatic management of psychotic disorders and is considered an atypical antipsychotic drug. It is currently used primarily for the treatment of patients with schizophrenia or schizoaffective disorders who are at risk for recurrent suicidal behavior and who have encountered nonresponse or adverse, intolerable extrapyramidal side effects with more classical antipsychotics (chlorpromazine, haloperidol). Although clozapine was developed about 30 years ago and the initial results were promising, the development of several fatal cases of agranulocytosis resulted in the discontinued use of this agent. Seizures, orthostatic hypotension, and an increased risk of fatal myocarditis have also been associated with the use of clozapine. The use of clozapine has regained interest for several reasons. Patients who did not respond to treatment with other antipsychotics improved when clozapine was administered. Also, agranulocytosis, which occurs in approximately 1% to 2% of patients, can be controlled with close hematologic monitoring. However, because of the significant risk of agranulocytosis and seizure associated with its use, clozapine should only be used in patients who have failed to respond adequately to treatment with appropriate courses of standard drug treatments, either because of insufficient effectiveness or the inability to achieve an effective dose because of intolerable adverse reactions from those drugs. Treatment is usually started with dosages of 25 to 75 mg/day with a gradual increase to reach a final dose of 300 to 450 mg/day within approximately 2 weeks of the initiation of treatment. Once the desired effect is achieved, the dose may be gradually decreased to keep the patient on the lowest possible effective dose. Patients being treated with clozapine should be closely monitored during treatment for adverse reactions. Treatment must include monitoring of white blood cell count and absolute neutrophil count. Clozapine treatment should be discontinued in patients failing to show an acceptable clinical response. In addition, the need for continuing treatment should be periodically reevaluated in patients exhibiting beneficial clinical responses. Clozapine is metabolized to desmethylated and N-oxide derivatives. The desmethyl metabolite (norclozapine) has only limited activity, and N-oxide metabolite is inactive.

Useful For: Monitoring patient compliance of clozapine treatment An aid to achieving desired serum levels

Interpretation: The effectiveness of clozapine treatment should be based on clinical response and treatment should be discontinued in patients failing to show an acceptable clinical response.

Reference Values:
Clozapine
Therapeutic range: 350-600 ng/mL

Norclozapine
Therapeutic range: Not well established

Clozapine + Norclozapine
Therapeutic range: Not well established

Clinical References: 1. Volpicelli SA, Centorrino F, Puopolo PR, et a,: Determination of clozapine, norclozapine, and clozapine-N-oxide in serum by liquid chromatography. ClinChem. 1993;39(8):1656-1659 2. Chung MC, Lin SK, Chang WH, Jann MW. Determination of clozapine and desmethylclozapine in human plasma by high-performance liquid chromatography with ultraviolet detection. J Chromatogr. 1993;613(1):168-173. doi:10.1016/0378-4347(93)80212-m 3. Perry PJ, Miller DD, Arndt SV, Cadoret RJ. Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenia patients. Am J Psychiatry. 1991;148(2):231-235. doi:10.1176/ajp.148.2.231 4. Physicians' Desk Reference (PDR). 61st ed. Thomson PDR; 2007 5. Fitton A, Heel RC. Clozapine. A review of its pharmacological properties, and therapeutic use in schizophrenia. Drugs. 1990;40(5);722-747. doi:10.2165/00003495-199040050-00007 6. Clozaril. Package insert: Novartis Pharmaceuticals; 05/2005 7. Mitchell PB. Therapeutic drug monitoring of psychotropic medications. Br J Clin Pharmacol. 2001;52(Suppl 1):45S-54S. doi:10.1046/j.1365-2125.2001.0520s1045.x 8. Hiemke C, Bergemann N, Clement HW, et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62. doi:10.1055/s-0043-116492 9. Milone MC, Shaw LM: Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

CLUS
70404

Clusterin Immunostain, Technical Component Only

Clinical Information: In lymph nodes, tonsils, and spleen, clusterin stains the follicular dendritic cell meshworks. B cells, T cells, and histiocytes are negative. Clusterin is often positive in the tumor cells of systemic anaplastic large-cell lymphoma and is usually negative in Reed Sternberg cells in classical Hodgkin lymphoma. It is a sensitive marker for follicular dendritic cell sarcomas.

Useful For: A marker of follicular dendritic cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Zhang J, Miao C, Xu A. Prognostic role of secretory clusterin in multiple human malignant neoplasms: A meta-analysis of 26 immunohistochemistry studies. PLoS One. 2016;11(8):e0161150. doi:10.1371/journal.pone.0161150 2. Tang L, Zhou J, Jiang ZM, Zhang HZ, Liu L, Chen J. Value of clusterin expression in pathologic diagnosis and histogenesis of giant cell tumor of tendon sheath. Zhonghua Bing Li Xue Za Zhi. 2012;41(3):161-167. doi:10.3760/cma.j.issn.0529-5807.2012.03.004 3. Fu Y, Lai Y, Wang Q, et al. Overexpression of clusterin promotes angiogenesis via the vascular endothelial growth factor in primary ovarian cancer. Mol Med Rep. 2013;7(6):1726-1732. doi:10.3892/mmr.2013.1436 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol.

2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CMET
70405

cMET Immunostain, Technical Component Only

Clinical Information: c-Met, a cell surface receptor tyrosine kinase, regulates cellular proliferation, migration, and differentiation during development. Increased expression of c-Met has been shown to correlate with poor prognosis in nonsmall cell carcinomas of the lung.

Useful For: Identification of normal and neoplastic c-Met expressing cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Wang M, Liang L, Lei X, et al. Evaluation of cMET aberration by immunohistochemistry and fluorescence in situ hybridization (FISH) in triple negative breast cancers. Ann Diagn Pathol. 2018;35:69-76. doi:10.1016/j.anndiagpath.2018.04.004. 2. Rossi G, Ragazzi M, Tamagnini I, et al. Does immunohistochemistry represent a robust alternative technique in determining drugable predictive gene alterations in non-small cell lung cancer? Curr Drug Targets. 2017;18(1):13-26. doi:10.2174/1389450116666150330114441 3. Pyo JS, Kang G, Cho WJ, Choi SB. Clinicopathological significance and concordance analysis of c-MET immunohistochemistry in non-small cell lung cancers: A meta-analysis. Pathol Res Pract. 2016;212(8):710-6. doi:10.1016/j.prp.2016.05.006. 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FCMVQ
91734

CMV by PCR

Reference Values:

FCMVR
75857

CMV Resistance: Ganciclovir, Foscarnet, Cidofovir

Clinical Information: For the most up to date information, see www.eurofins-viracor.com.

Useful For: For the most up to date information, see www.eurofins-viracor.com.

Interpretation: If a mutation has been detected in a Gene Target, the mutation site is indicated. A result of "None Detected" indicates that no mutations were detected for that gene target. A twofold impact of the mutation in the IC50 value must be indicated to assign a result of resistance. A complete list of mutations that have been reported in the literature can be found on our website. Maribavir resistance is not evaluated in this panel. See test code 33126.

Reference Values:
None Detected

Clinical References: For the most up to date information, see www.eurofins-viracor.com.

FDMZ
57859

CNBP DNA Test (DM2)

Clinical Information: Detects CCTG repeat expansions in the Zinc Finger Protein 9 (ZNF9) gene. Typical Presentation: Individuals with a range of symptoms from cataracts to significant muscle wasting, cardiac complications, ptosis and myotonia.

Reference Values:
A final report will be attached in MayoAccess.

CDS1
65565

CNS Demyelinating Disease Evaluation, Serum

Clinical Information:

Useful For: Diagnosis of inflammatory demyelinating diseases (IDDs) with similar phenotype to neuromyelitis optica spectrum disorder (NMOSD), including optic neuritis (single or bilateral) and transverse myelitis Diagnosis of autoimmune myelin oligodendrocyte glycoprotein-opathy Diagnosis of neuromyelitis optica Distinguishing NMOSD, acute disseminated encephalomyelitis (ADEM), optic neuritis, and transverse myelitis from multiple sclerosis early in the course of disease Diagnosis of ADEM Prediction of a relapsing disease course

Interpretation:

Reference Values:
MYELIN OLIGODENDROCYTE GLYCOPROTEIN FLORESCENCE-ACTIVATED CELL SORTING(FACS)
Negative
Reference values apply to all ages.

NEUROMYELITIS OPTICA/AQUAPORIN-4-IgG FACS
Negative
Reference values apply to all ages.

Clinical References:

F_2
9121

Coagulation Factor II Activity Assay, Plasma

Clinical Information: Factor II (prothrombin) is a vitamin K-dependent serine protease synthesized in liver. It participates in the final common pathway of coagulation, as the substrate for the prothrombinase enzyme complex. Prothrombin is the precursor of thrombin (IIa), which converts fibrinogen to fibrin. Plasma biological half-life is about 3 days. Deficiency of factor II may cause prolonged prothrombin time and activated partial thromboplastin time. Deficiency may result in a bleeding diathesis.

Useful For: Diagnosing a congenital deficiency (rare) of coagulation factor II Evaluating acquired deficiencies associated with liver disease or vitamin K deficiency, oral anticoagulant therapy, and antibody-induced deficiencies (eg, in association with lupus-like anticoagulant) Determining warfarin treatment stabilization in patients with nonspecific inhibitors (ie, lupus anticoagulant) Determining degree of anticoagulation with warfarin to correlate with level of protein S Investigation of prolonged prothrombin time or activated partial thromboplastin time

Interpretation: Liver disease, vitamin K deficiency, or warfarin anticoagulation can cause decreased factor II activity. Normal newborn infants may have levels of 25% to 50%.

Reference Values:

Adults: 75-145%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =25%) which may remain below adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing

Clinical References: 1. Lancellotti S, De Cristofaro R. Congenital prothrombin deficiency. Semin Thromb Hemost. 2009;35(4):367-381. doi:10.1055/s-0029-1225759 2. Peyvandi F, Bolton-Maggs PH, Batorova A, De Moerloose P. Rare bleeding disorders. Haemophilia. 2012;18 Suppl 4:148-153. doi:10.1111/j.1365-2516.2012.02841.x 3. Girolami A, Scandellari R, Scapin M, Vettore S. Congenital bleeding disorders of the vitamin K-dependent clotting factors. Vitam Horm. 2008;78:281-374. doi:10.1016/S0083-6729(07)00014-3 4. Brenner B, Kuperman AA, Watzka M, Oldenburg J. Vitamin K-dependent coagulation factors deficiency. Semin Thromb Hemost. 2009;35(4):439-446. doi:10.1055/s-0029-1225766 5. Favaloro EJ and Lippi G. eds. Hemostasis and Thrombosis, Methods and Protocols. Humana Press 2017

F_9
9065

Coagulation Factor IX Activity Assay, Plasma

Clinical Information: Factor IX is a vitamin K-dependent serine protease synthesized in the liver and participates in the intrinsic coagulation pathway. Its biological half-life is 18 to 24 hours. Congenital deficiency is inherited as an X-linked recessive bleeding disorder (hemophilia B). Severe deficiency (<1%) is characterized by hemarthroses, deep tissue bleeding, excessive bleeding with trauma, and ecchymoses. Acquired deficiency is associated with liver disease, vitamin K deficiency, warfarin therapy, and inhibitors (rare).

Useful For: Diagnosing deficiencies, particularly hemophilia B (Christmas disease) Assessing the impact of liver disease on hemostasis Investigation of a prolonged activated partial thromboplastin time

Interpretation: Acquired deficiency is more common than congenital. Mild hemophilia B: 5% to 50% activity Moderate hemophilia B: 1% to 5% activity Severe hemophilia B: <1% activity

Reference Values:

< or =6 months: Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%), which may not reach adult levels for 180 or more days postnatal.* (Literature derived)

>6 months: 65-140%

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing.

Clinical References: 1. Barrowcliffe TW, Raut S, Sands D, Hubbard AR. Coagulation and chromogenic assays of factor VIII activity: general aspects, standardization, and recommendations. Semin Thromb Hemost. 2002;28(3):247-256 2. Franchini M, Lippi G, Favaloro EJ. Acquired inhibitors of coagulation factors: part II. Semin Thromb Hemost. 2012;38(5):447-453 3. Carcao MD. The diagnosis and management of congenital hemophilia. Semin Thromb Hemost. 2012;38(7):727-734 4. Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. Humana Press; 2017

FACTV
9054

Coagulation Factor V Activity Assay, Plasma

Clinical Information: Factor V is a vitamin K-independent protein synthesized in the liver and in other tissues (endothelium, megakaryocytes/platelets). In its thrombin-activated form (factor Va), it serves as an essential cofactor in the prothrombinase enzyme complex, which converts prothrombin to thrombin (the prothrombinase complex consists of the enzyme, activated factor X, factor Va cofactor, a phospholipid surface, and calcium). Deficiency of factor V may cause prolonged prothrombin time and activated partial thromboplastin time and may result in a bleeding diathesis. Plasma biological half-life varies from 12 to 36 hours. Platelets contain 20% to 25% of the factor V in blood. Factor V (also known as labile factor) is highly susceptible to proteolytic inactivation, with the potential for spuriously decreased assay results.

Useful For: Diagnosing congenital deficiencies (rare) of coagulation factor V Evaluating acquired deficiencies associated with liver disease, factor V inhibitors, myeloproliferative disorders, and intravascular coagulation and fibrinolysis Investigation of prolonged prothrombin time or activated partial thromboplastin time

Interpretation: Acquired deficiencies are much more common than congenital. Patients that are congenitally deficient homozygous generally have activity levels less than or equal to10% to 20%. Patients that are congenitally deficient heterozygous generally have activity levels less than or equal to 50%. Congenital deficiency may occur in combined association with factor VIII deficiency.

Reference Values:
>1 month: 70%-165%
<1 month: Normal, full-term and premature newborn infants may have mildly decreased levels (> or =30% to 35%) which reach adult levels within 21 days postnatal.

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing

Clinical References: 1. Girolami A, Scandellari R, Scapin M, Vettore S. Congenital bleeding disorders of the vitamin K-dependent clotting factors. Vitam Horm. 2008;78:281-374 2. Brenner B, Kuperman AA, Watzka M, Oldenburg J. Vitamin K-dependent coagulation factors deficiency. Semin Thromb Hemost. 200935(4):439-446 3. Asselta R, Peyvandi F. Factor V deficiency. Semin Thromb Hemost. 200935(4):382-389 4. Lippi G, Favaloro EJ, Montagnana M, et al: Inherited and acquired factor V deficiency. Blood Coagul Fibrinolysis. 2011 Apr;22(3):160-166 5. Spreafico M, Peyvandi F. Combined FV and FVIII deficiency. Haemophilia. 2008;14(6):1201-1208 6. Kottke-Marchant K, ed: Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012 7. Favaloro EJ and Lippi G. eds. Hemostasis and Thrombosis, Methods and Protocols. Humana Press 2017

F_7
9055

Coagulation Factor VII Activity Assay, Plasma

Clinical Information: Factor VII is a vitamin K-dependent serine protease synthesized in the liver. It is a component of the extrinsic coagulation scheme, measured by the prothrombin time. Plasma biological half-life is about 3 to 6 hours. Deficiency may result in a bleeding diathesis.

Useful For: Diagnosing congenital deficiency of coagulation factor VII Evaluating acquired deficiencies associated with liver disease, oral anticoagulant therapy, and vitamin K deficiency Determining degree of anticoagulation with warfarin to correlate with level of protein C Investigation of a prolonged prothrombin time

Interpretation: Liver disease, vitamin K deficiency, or warfarin anticoagulation can cause decreased

factor VII activity. Newborn infants usually have levels 25% or more.

Reference Values:
Adults: 65-180%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%) which increase within the first postnatal week but may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing

Clinical References: 1. Girolami A, Scandellari R, Scapin M, Vettore S. Congenital bleeding disorders of the vitamin K-dependent clotting factors. Vitam Horm. 2008;78:281-374. doi:10.1016/S0083-6729(07)00014-3 2. Brenner B, Kuperman AA, Watzka M, Oldenburg J. Vitamin K-dependent coagulation factors deficiency. Semin Thromb Hemost. 2009;35(4):439-446. doi:10.1055/s-0029-1225766 3. Mariani G, Bernardi F. Factor VII deficiency. Semin Thromb Hemost. 2009;35(4):400-406. doi:10.1055/s-0029-1225762 4. Franchini M, Marano G, Pupells S, et al. Rare congenital bleeding disorders. Ann Transl Med. 2018;6(17):331. doi:10.21037/atm.2018.08.34

F8A
9070

Coagulation Factor VIII Activity Assay, Plasma

Clinical Information: Factor VIII is synthesized in the liver and, perhaps, in other tissues. It is a coagulation cofactor that circulates bound to von Willebrand factor and is part of the intrinsic coagulation pathway. The biological half-life is 9 to 18 hours (average is 12 hours). Congenital factor VIII deficiency is the cause of hemophilia A, which has an incidence of 1 in 10,000 and is inherited in a recessive sex-linked manner on the X chromosome. Severe deficiency (<1%) characteristically demonstrates as hemarthrosis, deep-tissue bleeding, excessive bleeding with trauma, and ecchymoses. Factor VIII may be decreased in von Willebrand disease. Acquired deficiency states also occur. Antibodies specific for factor VIII are the most commonly occurring specific inhibitors of coagulation factors and can produce serious bleeding disorders (acquired hemophilia). Spuriously decreased results may occur, as factor VIII is highly susceptible to proteolytic inactivation.

Useful For: Diagnosing hemophilia A Diagnosing von Willebrand disease when measured with the von Willebrand factor (VWF) antigen and VWF activity Diagnosing acquired deficiency states Investigation of prolonged activated partial thromboplastin time Monitoring infusions of factor VIII replacement during interventional procedures and prophylactic infusions This test is not useful for inferring carrier status in suspected female carriers of hemophilia A, unless it is 50% of normal (<28% activity in adults).

Interpretation: Mild hemophilia A: 5% to 50% activity Moderate hemophilia A: 1% to 5% activity Severe hemophilia A: <1% activity Congenital deficiency may also occur in combined association with factor V deficiency. Liver disease usually causes an increase of factor VIII activity. Acquired deficiencies of factor VIII have been associated with myeloproliferative or lymphoproliferative disorders (acquired von Willebrand disease: VWD), inhibitors of factor VIII (autoantibodies, postpartum conditions, etc), and intravascular coagulation and fibrinolysis. Levels may be decreased with von Willebrand factor in VWD.

Reference Values:
Adults: 55-200%

Normal, full-term newborn infants or healthy premature infants typically have levels greater than or equal to 40%.*

*See Pediatric Hemostasis References in Coagulation Guidelines for Specimen Handling and Processing.

Clinical References: 1. Spreafico M, Peyvandi F. Combined FV and FVIII deficiency. Haemophilia. 2008;14(6):1201-1208 2. Barrowcliffe TW, Raut S, Sands D, Hubbard AR. Coagulation and chromogenic assays of factor VIII activity: general aspects, standardization, and recommendations. Semin Thromb Hemost. 2002;28(3):247-256 3. Franchini M, Lippi G, Favaloro EJ. Acquired inhibitors of coagulation factors: part II. Semin Thromb Hemost. 2012;38(5):447-453 4. Carcao MD. The diagnosis and management of congenital hemophilia. Semin Thromb Hemost. 2012;38(7):727-734 5. Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. Humana Press; 2017

F8IS
7289

Coagulation Factor VIII Inhibitor Screen, Plasma

Clinical Information: Specific factor inhibitors are antibodies that are found most often in response to the use of factor VIII concentrate by patients congenitally deficient in factor VIII (hemophilia A). Factor VIII inhibitors can also develop in non-hemophiliac patients (not previously factor VIII deficient), most commonly in the following: the elderly, postpartum patients, and patients with autoimmune disease. Testing will include coagulation factor VIII activity assay with dilutions to evaluate assay inhibition, and if the factor VIII assay activity is decreased, an inhibitor screen to look for specific factor VIII inhibition. If specific inhibition is apparent, it will be titered.

Useful For: Detecting the presence of a specific factor inhibitor directed against coagulation factor VIII

Interpretation: When testing is complete, if factor activity results fall within clinically normal ranges, an interpretive comment will be provided noting that inhibitor testing was not indicated and, therefore, not performed. If factor activity indicates the performance of inhibitor screen testing, an interpretive comment will be provided noting the presence or absence of a factor VIII inhibitor.

Reference Values:
Only orderable as a reflex. For more information see:
8INHE / Factor VIII Inhibitor Evaluation, Plasma
ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
APROL / Prolonged Clot Time Profile, Plasma
AVWPR / von Willebrand Disease Profile, Plasma

Negative

Clinical References: 1. Bowie EJW, Thompson JH Jr, Didisheim P, Owen CA Jr. Mayo Clinic Laboratory Manual of Hemostasis. WB Saunders Company; 1971:111-115 2. Kasper CK. Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86 3. Peerschke EI, Castellone DD, Ledford-Kraemer M, et al. Laboratory assessment of FVIII inhibitor titer. Am J Clin Pathol. 2009;131(4):552-558 4. Pruthi RK, Nichols WL. Autoimmune factor VIII inhibitors. Curr Opin Hematol. 1999;6(5):314-322 5. Laboratory Hematology Practice. In: Kottke-Marchant K, ed. Wiley Blackwell Publishing; 2012 6. Hematology: Basic Principles and Practice. In: Hoffman R, Benz EJ Jr, Silberstein LE, ed. 7th ed. Elsevier; 2018

F_10
9066

Coagulation Factor X Activity Assay, Plasma

Clinical Information: Factor X is a vitamin K-dependent serine protease that is synthesized in the liver. Its biological half-life is 24 to 48 hours. Factor X participates in both intrinsic and extrinsic pathways of coagulation (final common pathway) by serving as the enzyme (factor Xa) in the prothrombinase complex. Congenital factor X deficiency is rare. Acquired deficiency is associated with

liver disease, warfarin therapy, vitamin K deficiency, systemic amyloidosis, and inhibitors (rare). Deficiency may cause prolonged prothrombin time and activated partial thromboplastin time.

Useful For: Diagnosing deficiency of coagulation factor X, congenital or acquired Evaluating hemostatic function in liver disease Investigation of prolonged prothrombin time or activated partial thromboplastin time

Interpretation: Acquired deficiency is more common than congenital deficiency. Homozygous individuals: <25% activity Heterozygous individuals: 25% to 50% activity

Reference Values:

Clinical References: 1. Girolami A, Scandellari R, Scapin M, Vettore S. Congenital bleeding disorders of the vitamin K-dependent clotting factors. Vitam Horm 2008;78:281-374 2. Brenner B, Kuperman AA, Watzka M, Oldenburg J: Vitamin K-dependent coagulation factors deficiency. Semin Thromb Hemost. 2009;35(4):439-446 3. Menegatti M, Peyvandi F: Factor X deficiency. Semin Thromb Hemost. 2009;35(4):407-415 4. Girolami A, Ruzzon E, Tezza F, et al. Congenital FX deficiency combined with other clotting defects or with other abnormalities: a critical evaluation of the literature. Haemophilia 2008;14(2):323-328 5. Girolami A, Scarparo P, Scandellari R, Allemand E: Congenital factor X deficiencies with a defect only or predominantly in the extrinsic or in the intrinsic system: a critical evaluation. Am J Hematol 2008;83(8):668-671 6. Favaloro EJ and Lippi G. eds. Hemostasis and Thrombosis, Methods and Protocols. Humana Press 2017

FXCH
89042

Coagulation Factor X Chromogenic Activity Assay, Plasma

Clinical Information: The antithrombotic effect of oral vitamin K antagonists (eg, warfarin) is mediated by reduction in the plasma activity of vitamin K-dependent procoagulant factors II (prothrombin) and X. The intensity of oral anticoagulation therapy with vitamin K antagonists must be monitored and adjusted to a narrow therapeutic range; under medicating increases the risk of thrombosis, while overmedicating increases the risk of bleeding. Such therapy typically is monitored with the prothrombin time/international normalized ratio (INR) system. Lupus anticoagulants (LAC) are autoantibodies that interfere with phospholipid-dependent clotting tests and most commonly cause prolongation of the activated partial thromboplastin time (APTT). LAC can be associated with a prothrombotic disorder termed the antiphospholipid syndrome. LAC occasionally may cause prolongation of the baseline prothrombin time, rendering the INR system inaccurate for monitoring the intensity of oral anticoagulant therapy. LAC-induced prolongation of the prothrombin time is most commonly seen with recombinant human tissue factor thromboplastins (ie, prothrombin time reagents) with a low international sensitivity index (ISI) such as Innovin or RecombiPlasTin 2G (ISI = 1.0). The chromogenic factor X activity is an alternative assay for monitoring oral anticoagulant therapy. This assay is unaffected by LAC because the assay end point is not a phospholipid-dependent clotting time. Argatroban is a parenteral direct thrombin inhibitor that is approved for treatment of heparin-induced thrombocytopenia (HIT), an antibody-mediated prothrombotic disorder. Argatroban therapy prolongs the prothrombin time, which also renders the INR inaccurate for monitoring the warfarin effect while transitioning from Argatroban to oral anticoagulant therapy. The chromogenic coagulation factor X activity assay may be used as an alternative to the INR for monitoring and adjusting the warfarin dose during this transition.

Useful For: Monitoring warfarin anticoagulant therapy, especially in patients whose plasma contains lupus anticoagulants that interfere with baseline prothrombin time/international normalized ratio and in patients receiving the drug Argatroban who are being transitioned to warfarin This assay should not be used for monitoring heparin, or oral direct factor Xa inhibitors such as rivaroxaban (Xarelto), apixaban (Eliquis), or edoxaban (Savaysa).

Interpretation: A chromogenic factor X activity of approximately 20% to 40% corresponds to the usual warfarin international normalized ratio range (ie, 2.0-3.0).

Reference Values:

> or =18 years of age: 60%-140%

Chromogenic Factor X activity generally correlates with the one-stage factor X activity. In full term or premature neonates, infants, and children, the one-stage factor X activity* is lower than adult reference range and progressively rises to the adult reference range by adolescence. However, no similar data for the chromogenic factor X activity have been published.

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing.

Clinical References: 1. Austin JH, Stearns CR, Winkler AM, et al. Use of the chromogenic factor X assay in patients transitioning from Argatroban to warfarin therapy. Pharmacotherapy. 2012;32(6):493-501 2. McGlasson DL, Romick BG, Rubal BJ. Comparison of a chromogenic factor x assay with international normalized ratio for monitoring oral anticoagulation therapy. Blood Coagul Fibrinolysis. 2008;19:513-517 3. Moll S, Ortel TL. Monitoring warfarin therapy in patients with lupus anticoagulants. Ann Intern Med. 1997;127:177-185 4. Robert A, Le Querrec A, Delahousse B, et al. Control of oral anticoagulation in patients with antiphospholipid syndrome--influence of the lupus anticoagulant on International Normalized Ratio. Thromb Haemost. 1998;80:99-103

F_11
9067

Coagulation Factor XI Activity Assay, Plasma

Clinical Information: Factor XI is synthesized in the liver. Its biological half-life is 60 to 80 hours. Factor XI is a component of intrinsic coagulation pathway and, when activated, activates factor IX to IXa. Factor XI deficiency may cause prolonged partial thromboplastin time. Deficiency is associated with mild bleeding diathesis, but there is poor correlation between activity level and clinical bleeding. A relatively high incidence of congenital deficiency occurs among individuals of Ashkenazi Jewish descent (hemophilia C).

Useful For: Diagnosing deficiency of coagulation factor XI Investigating prolonged activated partial thromboplastin time

Interpretation: Acquired deficiency is associated with liver disease and rarely inhibitors. Patients who are homozygous: <20% activity Patients who are heterozygous: 20% to 60% activity

Reference Values:

Adults: 55-150%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =10%), which may not reach adult levels for 180 or more days postnatal.*

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing.

Clinical References: 1. He R, Chen D, He S. Factor XI: hemostasis, thrombosis, and antithrombosis. Thromb Res. 2012;129(5):541-550 2. Martin-Salces M, Jimenez-Yuste V, Alvarez MT, Quintana M, Hernandez-Navarro F. Review: Factor XI deficiency: review and management in pregnant women. Clin Appl Thromb Hemost. 2010;16(2):209-213 3. Seligsohn U. Factor XI in haemostasis and thrombosis: past, present and future. Thromb Haemost. 2007;98(1):84-89 4. Santoro R, Prejano S, Iannaccaro P. Factor XI deficiency: a description of 34 cases and literature review. Blood Coagul Fibrinolysis. 2011;22(5):431-435 5. Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. Humana Press; 2017

F_12
9069

Coagulation Factor XII Activity Assay, Plasma

Clinical Information: Factor XII is synthesized in the liver. Its biological half-life is 40 to 50 hours. Factor XII is a component of the contact activation system and is involved in both intrinsic pathway and fibrinolytic system. Factor XII deficiency is often discovered when activated partial thromboplastin time is found to be unexpectedly long. The deficiency does not cause a known bleeding disorder. An association between severe factor XII deficiency and thrombosis risk has been proposed but not proven.

Useful For: Diagnosing deficiency of coagulation factor XII Determining cause of prolonged activated partial thromboplastin time

Interpretation: Acquired deficiency is associated with liver disease, nephritic syndrome, and chronic granulocytic leukemia. Congenital homozygous deficiency: 20% activity Congenital heterozygous deficiency: 20% to 50% activity

Reference Values:
Adults: 55-180%
Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =15% to 20%), which may not reach adult levels for 180 or more days postnatal.*
*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing.

Clinical References: 1. Renne T, Schmaier AH, Nickel KF, Blomback M, Maas C. In vivo roles of factor XII. Blood. 2012;120(22):4296-4303 2. Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. Humana Press; 2017

CMMPP
606103

Cobalamin, Methionine, and Methylmalonic Acid Pathways, Plasma

Clinical Information: Homocysteine, methylmalonic acid (MMA), methylcitric acid, methionine, cysteine, and cystathionine can be used to evaluate patients for inborn errors of methionine, cobalamin, and propionate metabolism. Homocysteine is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinemia or homocystinuria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine remethylation. Homocystinuria is an autosomal recessive disorder caused by a deficiency of the enzyme cystathionine beta-synthase. The incidence of homocystinuria is approximately 1 in 200,000 to 335,000 live births. Classical homocystinuria is characterized by a normal presentation at birth followed by failure to thrive and developmental delay. Untreated homocystinuria can lead to ophthalmological problems, developmental delay, seizures, thromboembolic episodes, and skeletal abnormalities. The biochemical phenotype is characterized by increased plasma concentrations of methionine and homocysteine along with decreased concentrations of cystine. Elevated levels of MMA result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12. Enzymatic deficiencies of propionyl-CoA carboxylase and methylmalonyl-CoA mutase are associated with propionic academia (PA) and methylmalonic acidemia mut(0/-) type (MMAmut), respectively. The clinical phenotype includes vomiting, hypotonia, lethargy, apnea, hypothermia, and coma. The biochemical phenotype for MMAmut includes elevations of propionyl carnitine, methylmalonic acid, and methylcitric acid. Patients with PA will have elevations of propionyl carnitine and methylcitric acid with normal MMA concentrations as the enzymatic defect is upstream of methylmalonic-CoA mutase. Inherited conditions of cobalamin (Cbl) absorption and transport are caused by variants in several genes encoding Cbl binding factors and transmembrane transporters and receptors. In addition, inside the cell, Cbl undergoes several steps of modification until it reaches a divergent point beyond which 2 separate paths lead to the formation of the 2 active components of this cofactor:

adenosylcobalamin (AdoCbl), a cofactor for methylmalonyl-CoA mutase; and methylcobalamin (MeCbl), a cofactor for methionine synthase, remethylating homocysteine to methionine. Defects of AdoCbl and MeCbl metabolism after the point where the synthetic pathways separate lead to isolated deficiencies of methylmalonyl-CoA mutase (elevations of propionyl carnitine, MMA, and methylcitric acid) or methionine synthase (elevated homocysteine with low/low normal methionine) respectively. Defects prior to this point are associated with deficiencies of both enzymes and lead to elevation of all markers (propionyl carnitine, MMA, methylcitric acid, and homocysteine). Acquired cobalamin (vitamin B12) deficiency can be a result of pernicious anemia, vegan diet, malabsorption, and decreased intrinsic factor excretion (secondary to gastrectomy) and can be distinguished from most inherited defects (particularly intracellular deficiencies) with the identification of decreased levels of vitamin B12. Older adult patients with acquired cobalamin deficiency may present with megaloblastic anemia, peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as kidney insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. Additional testing with homocysteine and MMA determinations may help distinguish between vitamin B12 and folate deficiency states.

Useful For: Screening and monitoring patients suspected of or confirmed with an inherited disorder of methionine, cobalamin, or propionate metabolism using plasma specimens Evaluating individuals with suspected deficiency of vitamin B12

Interpretation: An interpretive report will be provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (complementation studies, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, complementation studies) or molecular genetic analyses are required.

Reference Values:

Age	Total homocysteine (nmol/mL)	Methylmalonic acid (nmol/mL)	2-Methylcitric acid (nmol/mL)	Total cysteine (nmol/mL)
Female	Male	Female	Male	
0-11 months	3.1-8.3	3.2-9.7	0.08-0.32	0.02-0.35
12-23 months	3.2-8.3	3.3-9.6	0.08-0.31	0.02-0.35
24-35 months	3.2-8.2	3.3-9.6	0.08-0.31	0.02-0.35
3 years	3.2-8.2	3.3-9.6	0.08-0.31	0.02-0.35
4 years	3.3-8.2	3.4-9.5	0.08-0.30	0.02-0.35
5 years	3.4-8.1	3.5-9.4	0.08-0.30	0.02-0.35
6 years	3.5-8.1	3.6-9.4	0.08-0.29	0.02-0.35
7 years	3.5-8.1	3.7-9.4	0.08-0.29	0.02-0.35
8 years	3.6-8.2	3.8-9.3	0.08-0.28	0.02-0.35
9 years	3.7-8.2	3.9-9.4	0.09-0.28	0.02-0.35
10 years	3.8-8.3	4.1-9.4	0.09-0.28	0.02-0.35
11 years	3.9-8.4	4.3-9.4	0.09-0.28	0.02-0.35

12 years	3.9-8.6	4.4-9.5	0.09-0.27	0.02-0.35
13 years	4.0-8.7	4.6-9.6	0.09-0.27	0.02-0.35
14 years	4.1-8.8	4.8-9.7	0.09-0.27	0.02-0.35
15 years	4.2-8.9	5.0-9.8	0.09-0.27	0.02-0.35
16 years	4.2-9.1	5.2-9.9	0.09-0.27	0.02-0.35
17 years	4.3-9.2	5.4-10.0	0.09-0.27	0.02-0.35
18 years	4.3-9.3	5.6-10.1	0.08-0.27	0.02-0.35
19 years	4.4-9.5	5.7-10.3	0.08-0.26	0.02-0.35
20 years	4.4-9.6	5.9-10.5	0.08-0.26	0.02-0.35
21 years	4.4-9.8	6.0-10.6	0.08-0.26	0.02-0.35
22 years	4.4-9.9	6.1-10.8	0.08-0.27	0.02-0.35
23 years	4.4-10.1	6.2-11.0	0.08-0.27	0.02-0.35
24 years	4.4-10.3	6.2-11.1	0.08-0.27	0.02-0.35
25 years	4.4-10.4	6.3-11.3	0.08-0.28	0.02-0.35
26 years	4.4-10.6	6.3-11.4	0.08-0.28	0.02-0.35
27 years	4.3-10.8	6.4-11.6	0.08-0.28	0.02-0.35
28 years	4.3-11.0	6.4-11.7	0.08-0.29	0.02-0.35
29 years	4.3-11.2	6.4-11.8	0.08-0.29	0.02-0.35
30 years	4.3-11.4	6.4-11.9	0.08-0.30	0.02-0.35
31 years	4.4-11.6	6.4-12.1	0.08-0.30	0.02-0.35
32 years	4.4-11.8	6.4-12.2	0.08-0.31	0.02-0.35
33 years	4.4-11.9	6.4-12.3	0.08-0.31	0.02-0.35
34 years	4.5-12.1	6.4-12.4	0.08-0.31	0.02-0.35
35 years	4.5-12.2	6.4-12.6	0.08-0.32	0.02-0.35
36 years	4.6-12.4	6.4-12.8	0.08-0.32	0.02-0.35
37 years	4.6-12.5	6.4-12.9	0.08-0.33	0.02-0.35
38 years	4.7-12.7	6.4-13.1	0.08-0.33	0.02-0.35
39 years	4.7-12.8	6.4-13.2	0.08-0.34	0.02-0.35
40 years	4.8-13.0	6.5-13.4	0.08-0.34	0.02-0.35
41 years	4.8-13.2	6.5-13.5	0.08-0.35	0.02-0.35
42 years	4.8-13.4	6.5-13.7	0.08-0.36	0.02-0.35
43 years	4.9-13.5	6.6-13.9	0.08-0.36	0.02-0.35
44 years	4.9-13.7	6.6-14.0	0.08-0.37	0.02-0.35
45 years	4.9-13.9	6.6-14.2	0.08-0.38	0.02-0.35
46 years	4.9-14.0	6.7-14.4	0.08-0.38	0.02-0.35
47 years	4.9-14.2	6.7-14.5	0.08-0.39	0.02-0.35
48 years	5.0-14.3	6.8-14.7	0.08-0.39	0.02-0.35

49 years	5.0-14.4	6.8-14.9	0.08-0.40	0.02-0.35
50 years	5.0-14.5	6.8-15.0	0.08-0.40	0.02-0.35
51 years	5.1-14.6	6.8-15.2	0.08-0.41	0.02-0.35
52 years	5.1-14.7	6.9-15.4	0.08-0.41	0.02-0.35
53 years	5.1-14.8	6.9-15.5	0.08-0.42	0.02-0.35
54 years	5.2-14.9	6.9-15.6	0.08-0.42	0.02-0.35
55 years	5.2-15.0	6.9-15.7	0.08-0.43	0.02-0.35
56 years	5.3-15.0	6.9-15.8	0.08-0.43	0.02-0.35
57 years	5.3-15.1	6.9-15.9	0.08-0.44	0.02-0.35
58 years	5.3-15.2	6.9-16.0	0.08-0.44	0.02-0.35
59 years	5.4-15.2	6.9-16.0	0.08-0.44	0.02-0.35
60 years	5.4-15.3	6.9-16.1	0.08-0.45	0.02-0.35
61 years	5.4-15.4	7.0-16.2	0.09-0.45	0.02-0.35
62 years	5.5-15.4	7.0-16.2	0.09-0.46	0.02-0.35
63 years	5.5-15.5	7.0-16.3	0.09-0.46	0.02-0.35
64 years	5.6-15.5	7.1-16.3	0.09-0.46	0.02-0.35
65 years	5.6-15.6	7.1-16.3	0.09-0.47	0.02-0.35
66 years	5.7-15.6	7.1-16.3	0.09-0.47	0.02-0.35
67 years	5.7-15.7	7.2-16.3	0.09-0.47	0.02-0.35
68 years	5.8-15.7	7.2-16.3	0.09-0.47	0.02-0.35
69 years	5.9-15.7	7.2-16.3	0.09-0.47	0.02-0.35
70 years	6.0-15.8	7.3-16.3	0.09-0.48	0.02-0.35
71 years	6.1-15.8	7.3-16.3	0.09-0.48	0.02-0.35
72 years	6.2-15.8	7.3-16.3	0.09-0.48	0.02-0.35
73 years	6.3-15.9	7.3-16.3	0.09-0.48	0.02-0.35
74 years	6.4-15.9	7.3-16.3	0.09-0.48	0.02-0.35
75 years	6.5-15.9	7.3-16.3	0.09-0.48	0.02-0.35
76 years	6.6-15.9	7.3-16.3	0.09-0.48	0.02-0.35
77 years	6.7-16.0	7.4-16.3	0.10-0.48	0.02-0.35
78 years	6.8-16.0	7.4-16.3	0.10-0.48	0.02-0.35
79 years	6.9-16.0	7.5-16.3	0.10-0.48	0.02-0.35
80 years	7.0-16.0	7.5-16.3	0.10-0.48	0.02-0.35
81 years	7.1-16.0	7.7-16.2	0.10-0.48	0.02-0.35
82 years	7.2-16.0	7.8-16.2	0.10-0.48	0.02-0.35
83 years	7.2-16.0	7.9-16.2	0.10-0.48	0.02-0.35
84 years	7.3-16.0	8.0-16.2	0.10-0.48	0.02-0.35
85 years	7.3-16.0	8.2-16.2	0.10-0.48	0.02-0.35

>85 years	7.4-16.0	8.3-16.2	0.10-0.48	0.02-0.35

Clinical References: 1. Turgeon CT, Magera MJ, Cuthbert CD, et al. Determination of total homocysteine, methylmalonic acid, and 2-methylcitric acid in dried blood spots by tandem mass spectrometry. Clin Chem. 2010;56(11):1686-1695 2. Tortorelli S, Turgeon CT, Lim JS, et al. Two-tier approach to the newborn screening of methylenetetrahydrofolate reductase deficiency and other remethylation disorders with tandem mass spectrometry. J Pediatr. 2010;157(2):271-275 3. Huemer M, Diodato D, Schwahn B, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. J Inherit Metab Dis. 2017;40(1):21-48 4. Baric I, Staufner C, Augoustides-Savvopoulou P, Chien YH, Dobbelaere D, Grunert SC. Consensus recommendations for the diagnosis, treatment and follow-up of inherited methylation disorders. J Inherit Metab Dis. 2017;40(1):5-20 5. Morris AA, Kozich V, Santra S, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. J Inherit Metab Dis. 2017;40(1):49-74 6. Sloan JS, Carrillo N, Adams D, Venditti CP. Disorders of intracellular cobalamin metabolism. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2008. Updated December 16, 2021. Accessed November 29, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1328/ 7. Langan RC, Goodbred AJ. Vitamin B12 deficiency: Recognition and management. Am Fam Physician. 2017;96(6):384-389

CMMPS 606111 Cobalamin, Methionine, and Methylmalonic Acid Pathways, Serum

Clinical Information: Homocysteine, methylmalonic acid (MMA), methylcitric acid, methionine, cysteine, and cystathionine can be used to evaluate patients for inborn errors of methionine, cobalamin, and propionate metabolism. Homocysteine is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinemia or homocystinuria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine remethylation. Homocystinuria is an autosomal recessive disorder caused by a deficiency of the enzyme cystathionine beta-synthase. The incidence of homocystinuria is approximately 1 in 200,000 to 335,000 live births. Classical homocystinuria is characterized by a normal presentation at birth followed by failure to thrive and developmental delay. Untreated homocystinuria can lead to ophthalmological problems, developmental delay, seizures, thromboembolic episodes, and skeletal abnormalities. The biochemical phenotype is characterized by increased plasma concentrations of methionine and homocysteine along with decreased concentrations of cystine. Elevated levels of MMA result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12. Enzymatic deficiencies of propionyl-CoA carboxylase and methylmalonyl-CoA mutase are associated with propionic acidemia (PA) and methylmalonic acidemia mut(0/-) type (MMAmut), respectively. The clinical phenotype includes vomiting, hypotonia, lethargy, apnea, hypothermia, and coma. The biochemical phenotype for MMAmut includes elevations of propionyl carnitine, methylmalonic acid, and methylcitric acid. Patients with PA will have elevations of propionyl carnitine and methylcitric acid with normal MMA concentrations as the enzymatic defect is upstream of methylmalonic-CoA mutase. Inherited conditions of cobalamin (Cbl) absorption and transport are caused by variants in several genes encoding Cbl binding factors and transmembrane transporters and receptors. In addition, inside the cell, Cbl undergoes several steps of modification until it reaches a divergent point beyond which 2 separate paths lead to the formation of the 2 active components of this cofactor: adenosylcobalamin (AdoCbl), a cofactor for methylmalonyl-CoA mutase; and methylcobalamin (MeCbl), a cofactor for methionine synthase, remethylating homocysteine to methionine. Defects of AdoCbl and MeCbl metabolism after the point where the synthetic pathways separate lead to isolated deficiencies of methylmalonyl-CoA mutase (elevations of propionyl carnitine, MMA, and methylcitric acid) or methionine synthase (elevated homocysteine, with low/low normal methionine) respectively. Defects prior to this point are associated with deficiencies of both enzymes and lead to elevation of all markers

(propionyl carnitine, MMA, methylcitric acid, and homocysteine). Acquired cobalamin (vitamin B12) deficiency can be a result of pernicious anemia, vegan diet, malabsorption, and decreased intrinsic factor excretion (secondary to gastrectomy) and can be distinguished from most inherited defects (particularly intracellular deficiencies) with the identification of decreased levels of vitamin B12. Older adult patients with acquired cobalamin deficiency may present with megaloblastic anemia, peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as kidney insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. Additional testing with homocysteine and MMA determinations may help distinguish between vitamin B12 and folate deficiency states.

Useful For: Screening and monitoring patients suspected of or confirmed with an inherited disorder of methionine, cobalamin, or propionate metabolism using serum specimens Evaluating individuals with suspected deficiency of vitamin B12

Interpretation: An interpretive report will be provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (complementation studies, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, complementation studies) or molecular genetic analyses are required.

Reference Values:

Age	Total homocysteine (nmol/mL)	Methylmalonic acid (nmol/mL)	2-Methylcitric acid (nmol/mL)	Total cysteine (nmol/mL)
Female	Male	Female	Male	
0-11 months	3.1-8.3	3.2-9.7	0.08-0.32	0.02-0.35
12-23 months	3.2-8.3	3.3-9.6	0.08-0.31	0.02-0.35
24-35 months	3.2-8.2	3.3-9.6	0.08-0.31	0.02-0.35
3 years	3.2-8.2	3.3-9.6	0.08-0.31	0.02-0.35
4 years	3.3-8.2	3.4-9.5	0.08-0.30	0.02-0.35
5 years	3.4-8.1	3.5-9.4	0.08-0.30	0.02-0.35
6 years	3.5-8.1	3.6-9.4	0.08-0.29	0.02-0.35
7 years	3.5-8.1	3.7-9.4	0.08-0.29	0.02-0.35
8 years	3.6-8.2	3.8-9.3	0.08-0.28	0.02-0.35
9 years	3.7-8.2	3.9-9.4	0.09-0.28	0.02-0.35
10 years	3.8-8.3	4.1-9.4	0.09-0.28	0.02-0.35
11 years	3.9-8.4	4.3-9.4	0.09-0.28	0.02-0.35
12 years	3.9-8.6	4.4-9.5	0.09-0.27	0.02-0.35
13 years	4.0-8.7	4.6-9.6	0.09-0.27	0.02-0.35
14 years	4.1-8.8	4.8-9.7	0.09-0.27	0.02-0.35

15 years	4.2-8.9	5.0-9.8	0.09-0.27	0.02-0.35
16 years	4.2-9.1	5.2-9.9	0.09-0.27	0.02-0.35
17 years	4.3-9.2	5.4-10.0	0.09-0.27	0.02-0.35
18 years	4.3-9.3	5.6-10.1	0.08-0.27	0.02-0.35
19 years	4.4-9.5	5.7-10.3	0.08-0.26	0.02-0.35
20 years	4.4-9.6	5.9-10.5	0.08-0.26	0.02-0.35
21 years	4.4-9.8	6.0-10.6	0.08-0.26	0.02-0.35
22 years	4.4-9.9	6.1-10.8	0.08-0.27	0.02-0.35
23 years	4.4-10.1	6.2-11.0	0.08-0.27	0.02-0.35
24 years	4.4-10.3	6.2-11.1	0.08-0.27	0.02-0.35
25 years	4.4-10.4	6.3-11.3	0.08-0.28	0.02-0.35
26 years	4.4-10.6	6.3-11.4	0.08-0.28	0.02-0.35
27 years	4.3-10.8	6.4-11.6	0.08-0.28	0.02-0.35
28 years	4.3-11.0	6.4-11.7	0.08-0.29	0.02-0.35
29 years	4.3-11.2	6.4-11.8	0.08-0.29	0.02-0.35
30 years	4.3-11.4	6.4-11.9	0.08-0.30	0.02-0.35
31 years	4.4-11.6	6.4-12.1	0.08-0.30	0.02-0.35
32 years	4.4-11.8	6.4-12.2	0.08-0.31	0.02-0.35
33 years	4.4-11.9	6.4-12.3	0.08-0.31	0.02-0.35
34 years	4.5-12.1	6.4-12.4	0.08-0.31	0.02-0.35
35 years	4.5-12.2	6.4-12.6	0.08-0.32	0.02-0.35
36 years	4.6-12.4	6.4-12.8	0.08-0.32	0.02-0.35
37 years	4.6-12.5	6.4-12.9	0.08-0.33	0.02-0.35
38 years	4.7-12.7	6.4-13.1	0.08-0.33	0.02-0.35
39 years	4.7-12.8	6.4-13.2	0.08-0.34	0.02-0.35
40 years	4.8-13.0	6.5-13.4	0.08-0.34	0.02-0.35
41 years	4.8-13.2	6.5-13.5	0.08-0.35	0.02-0.35
42 years	4.8-13.4	6.5-13.7	0.08-0.36	0.02-0.35
43 years	4.9-13.5	6.6-13.9	0.08-0.36	0.02-0.35
44 years	4.9-13.7	6.6-14.0	0.08-0.37	0.02-0.35
45 years	4.9-13.9	6.6-14.2	0.08-0.38	0.02-0.35
46 years	4.9-14.0	6.7-14.4	0.08-0.38	0.02-0.35
47 years	4.9-14.2	6.7-14.5	0.08-0.39	0.02-0.35
48 years	5.0-14.3	6.8-14.7	0.08-0.39	0.02-0.35
49 years	5.0-14.4	6.8-14.9	0.08-0.40	0.02-0.35
50 years	5.0-14.5	6.8-15.0	0.08-0.40	0.02-0.35
51 years	5.1-14.6	6.8-15.2	0.08-0.41	0.02-0.35

52 years	5.1-14.7	6.9-15.4	0.08-0.41	0.02-0.35
53 years	5.1-14.8	6.9-15.5	0.08-0.42	0.02-0.35
54 years	5.2-14.9	6.9-15.6	0.08-0.42	0.02-0.35
55 years	5.2-15.0	6.9-15.7	0.08-0.43	0.02-0.35
56 years	5.3-15.0	6.9-15.8	0.08-0.43	0.02-0.35
57 years	5.3-15.1	6.9-15.9	0.08-0.44	0.02-0.35
58 years	5.3-15.2	6.9-16.0	0.08-0.44	0.02-0.35
59 years	5.4-15.2	6.9-16.0	0.08-0.44	0.02-0.35
60 years	5.4-15.3	6.9-16.1	0.08-0.45	0.02-0.35
61 years	5.4-15.4	7.0-16.2	0.09-0.45	0.02-0.35
62 years	5.5-15.4	7.0-16.2	0.09-0.46	0.02-0.35
63 years	5.5-15.5	7.0-16.3	0.09-0.46	0.02-0.35
64 years	5.6-15.5	7.1-16.3	0.09-0.46	0.02-0.35
65 years	5.6-15.6	7.1-16.3	0.09-0.47	0.02-0.35
66 years	5.7-15.6	7.1-16.3	0.09-0.47	0.02-0.35
67 years	5.7-15.7	7.2-16.3	0.09-0.47	0.02-0.35
68 years	5.8-15.7	7.2-16.3	0.09-0.47	0.02-0.35
69 years	5.9-15.7	7.2-16.3	0.09-0.47	0.02-0.35
70 years	6.0-15.8	7.3-16.3	0.09-0.48	0.02-0.35
71 years	6.1-15.8	7.3-16.3	0.09-0.48	0.02-0.35
72 years	6.2-15.8	7.3-16.3	0.09-0.48	0.02-0.35
73 years	6.3-15.9	7.3-16.3	0.09-0.48	0.02-0.35
74 years	6.4-15.9	7.3-16.3	0.09-0.48	0.02-0.35
75 years	6.5-15.9	7.3-16.3	0.09-0.48	0.02-0.35
76 years	6.6-15.9	7.3-16.3	0.09-0.48	0.02-0.35
77 years	6.7-16.0	7.4-16.3	0.10-0.48	0.02-0.35
78 years	6.8-16.0	7.4-16.3	0.10-0.48	0.02-0.35
79 years	6.9-16.0	7.5-16.3	0.10-0.48	0.02-0.35
80 years	7.0-16.0	7.5-16.3	0.10-0.48	0.02-0.35
81 years	7.1-16.0	7.7-16.2	0.10-0.48	0.02-0.35
82 years	7.2-16.0	7.8-16.2	0.10-0.48	0.02-0.35
83 years	7.2-16.0	7.9-16.2	0.10-0.48	0.02-0.35
84 years	7.3-16.0	8.0-16.2	0.10-0.48	0.02-0.35
85 years	7.3-16.0	8.2-16.2	0.10-0.48	0.02-0.35
>85 years	7.4-16.0	8.3-16.2	0.10-0.48	0.02-0.35

Clinical References: 1. Turgeon CT, Magera MJ, Cuthbert CD, et al. Determination of total homocysteine, methylmalonic acid, and 2-methylcitric acid in dried blood spots by tandem mass spectrometry. Clin Chem. 2010;56(11):1686-1695 2. Tortorelli S, Turgeon CT, Lim JS, et al. Two-tier approach to the newborn screening of methylenetetrahydrofolate reductase deficiency and other remethylation disorders with tandem mass spectrometry. J Pediatr. 2010;157(2):271-275 3. Huemer M, Diodato D, Schwahn B, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. J Inherit Metab Dis. 2017;40(1):21-48 4. Baric I, Staufner C, Augoustides-Savvopoulou P, Chien YH, Dobbelaere D, Grunert SC. Consensus recommendations for the diagnosis, treatment and follow-up of inherited methylation disorders. J Inherit Metab Dis. 2017;40(1):5-20 5. Morris AA, Kozich V, Santra S, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. J Inherit Metab Dis. 2017;40(1):49-74 6. Sloan JS, Carrillo N, Adams D, Venditti CP. Disorders of intracellular cobalamin metabolism. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2008. Updated December 16, 2021. Accessed October 7, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1328/ 7. Langan RC, Goodbred AJ. Vitamin B12 deficiency: Recognition and management. Am Fam Physician. 2017;96(6):384-389

COUO
607762

Cobalt Occupational Exposure, Random, Urine

Clinical Information: Cobalt is rare but widely distributed in the environment. It is an essential cofactor in vitamin B12. While cobalt is an essential element, cobalt deficiency has not been reported in humans. Cobalt is used in the manufacture of hard alloys with high melting points and resistance to oxidation. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and kidney failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Improperly handled (60)Co can cause radiation poisoning from exposure to gamma radiation.

Useful For: Screening for occupational exposure to cobalt

Interpretation: For occupational exposure, the sampling time is at the end of the shift at the end of the work week. The American Conference of Governmental Industrial Hygienists Biological Exposure Index for cobalt is a concentration of 15.0 mcg/L or above at the end of the work week.

Reference Values:
COBALT:
0-17 years: Not established
> or =18 years: The American Conference of Governmental Industrial Hygienists Biological Exposure Index for cobalt in urine is an end-of-shift concentration above14.9 mcg/L at the end of the work week.

CREATININE:
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists (ACGIH); 2010 2. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. Toxicology profile for cobalt. HHS; April 2004. Accessed October 17, 2023. Available at

www.atsdr.cdc.gov/ToxProfiles/tp33.pdf 3. Lison D, De Boeck M, Verougstraete V, Kirsch-Volders M. Update on the genotoxicity and carcinogenicity of cobalt compounds. Occup Environ Med. 2001;58(10):619-625 4. Sodi R. Vitamins and trace elements. Rifai N, Chiu RWK, Young I, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 39. 5. Crutsen JRW, Koper MC, Jelsma J, et al. Prosthetic hip-associated cobalt toxicity: a systematic review of case series and case reports. EFORT Open Rev. 2022;7(3):188-199 6. Leyssens L, Vinck B, Van Der Straeten C, Wuyts F, Maes L. Cobalt toxicity in humans-A review of the potential sources and systemic health effects. Toxicology. 2017;387:43-56. doi:10.1016/j.tox.2017.05.015

COU
80083

Cobalt, 24 Hour, Urine

Clinical Information: Cobalt is rare but widely distributed in the environment. It is an essential cofactor in vitamin B12. While cobalt is an essential element, cobalt deficiency has not been reported in humans. Cobalt is used in the manufacture of hard alloys with high melting points and resistance to oxidation. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and kidney failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Improperly handled (60)Co can cause radiation poisoning from exposure to gamma radiation. Urine cobalt concentrations are likely to be increased above the reference value in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by DePuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Detecting cobalt exposure Monitoring metallic prosthetic implant wear This test is not useful to assess vitamin B12 activity.

Interpretation: Concentrations of 2.0 mcg/specimen or more indicate excess exposure. There are no Occupational Safety and Health Administration blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal ions. In a patient with a cobalt-based implant, modest increase (2-4 mcg/specimen) in urine cobalt concentration is likely to be associated with a prosthetic device in good condition. Excessive exposure is indicated when urine cobalt concentration is above 5 mcg/specimen, consistent with prosthesis wear. Urine concentrations above 20 mcg/specimen in a patient with a cobalt-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

Reference Values:
0-17 years: Not established
> or =18 years: 0.2-3.5 mcg/24 hours

Clinical References: 1. Keegan GM, Learmonth ID, Case CP. A systematic comparison of the actual, potential, and theoretical health effects of cobalt and chromium from industry and surgical implants. Crit Rev Toxicol. 2008;38(8):645-674 2. Lhotka C, Szekes T, Stefan I, Zhuber K, Zweymuller K. Four-year study of cobalt and chromium blood levels in patients managed with two different metal-on-metal total hip replacements. J Orthop Res. 2003;21(2):189-195 3. Lison D, De Boeck M,

Verougstraete V, Kirsch-Volders M. Update on the genotoxicity and carcinogenicity of cobalt compounds. Occup Environ Med. 2001;58(10):619-625 4. Crutsen JRW, Koper MC, Jelsma J, et al: Prosthetic hip-associated cobalt toxicity: a systematic review of case series and case reports. EFORT Open Rev. 2022;7(3):188-199 5. Leyssens L, Vinck B, Van Der Straeten C, Wuyts F, Maes L. Cobalt toxicity in humans-A review of the potential sources and systemic health effects. Toxicology. 2017;387:43-56. doi:10.1016/j.tox.2017.05.015 6. Sodi R. Vitamins and trace elements. Rifai N, Chiu RWK, Young I, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 39

COWB
60355

Cobalt, Blood

Clinical Information: Cobalt (Co) is a naturally occurring, hard, grey element widely distributed in the environment. It is used to produce alloys in the manufacturing of aircraft engines, cutting tools, and some artificial hip and knee joint prosthesis devices. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. One of the radioactive isotopes of cobalt, (60)Co, is used to sterilize medical equipment, in radiation therapy for cancer patients, and to irradiate food. Cobalt is an essential cofactor in vitamin B12, which is necessary for neurological function, brain function, and the formation of blood. For most people, food is the largest source of cobalt intake. However, more than a million workers are potentially exposed to cobalt and its compounds, with the greatest exposure in mining processes, cemented tungsten-carbide industry, cobalt powder industry, and alloy production industry. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms include pulmonary edema, allergy, nausea, vomiting, hemorrhage, and kidney failure. Chronic exposure to cobalt-containing hard metal (dust or fume) can result in a serious lung disease called hard metal lung disease, which is a type of pneumoconiosis (lung fibrosis). Furthermore, inhalation of cobalt particles can cause respiratory sensitization, asthma, shortness of breath, and decreased pulmonary function. Even though the primary route of occupational exposure to cobalt is the respiratory tract, skin contact is also important because dermal exposures to hard metal and cobalt salts can result in significant systemic uptake. Sustained exposures can cause skin sensitization, which may result in eruptions of contact dermatitis. Per US Food and Drug Administration recommendations, orthopedic surgeons should consider measuring and following serial cobalt concentrations in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal hip implants as part of their overall clinical evaluation. Blood cobalt concentrations are likely to be increased above the reference range in patients with joint prosthesis containing cobalt. Prosthetic devices produced by DePuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside are typically made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Monitoring exposure to cobalt using whole blood specimens Monitoring metallic prosthetic implant wear This test is not useful for assessment of vitamin B12 activity.

Interpretation: Concentrations of 1.0 ng/mL and above indicate possible environmental or occupational exposure. Cobalt concentrations associated with toxicity must be interpreted in the context of the source of exposure. In the context of failed metal-on-metal prosthetics, elevated cobalt in serum or blood is rarely the initial finding and is often preceded by physical symptoms including reduced range of motion, swelling, inflammation around the joints, and general discomfort or pain. The American Conference of Governmental Industrial Hygienists (ACGIH) Biological Exposure Index (BEI) for cobalt in blood is 1 mcg/L (1 ng/mL), which should be collected at the end of shift at the end of the work week.

Reference Values:
0-17 years: Not established
> or =18 years: <1.0 ng/mL

Clinical References: 1. Tower SS. Arthroprosthetic cobaltism: neurological and cardiac manifestations in two patients with metal-on-metal arthroplasty: a case report. J Bone Joint Surg Am. 2010;92(17):2847-2851 2. Keegan GM, Learmonth ID, Case CP. A systematic comparison of the actual, potential, and theoretical health effects of cobalt and chromium from industry and surgical implants. Crit Rev Toxicol. 2008;38(8):645-674 3. De Smet K, De Hann R, Calistri A, et al. Metal ion measurement as a diagnostic tool to identify problems with metal-on-metal hip resurfacing. J Bone Joint Surg Am. 2008;90 Sppl 4:202-208 4. Lison D, De Boeck M, Verougstraete V, Kirsch-Volders M. Update on the genotoxicity and carcinogenicity of cobalt compounds. Occup Environ Med. 2001;58(10):619-625 5. US Food and Drug Administration: Information about Soft Tissue Imaging and Metal Ion Testing. FDA; Updated March 15, 2019. Accessed October 17, 2023. Available at: www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/MetalonMetalHipImplants/ucm331971.htm 6. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. Toxicology profile for cobalt. HHS; April 2004. Accessed October 17, 2023. Available at www.atsdr.cdc.gov/ToxProfiles/tp33.pdf 7. Sodi R. Vitamins and trace elements. Rifai N, Chiu RWK, Young I, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 39. 8. Crutsen JRW, Koper MC, Jelsma J, et al. Prosthetic hip-associated cobalt toxicity: a systematic review of case series and case reports. EFORT Open Rev. 2022;7(3):188-199 9. Leyssens L, Vinck B, Van Der Straeten C, Wuyts F, Maes L. Cobalt toxicity in humans-A review of the potential sources and systemic health effects. Toxicology. 2017;387:43-56. doi:10.1016/j.tox.2017.05.015

COS
80084

Cobalt, Serum

Clinical Information: Cobalt is rare but widely distributed in the environment, used in the manufacture of hard alloys with high melting points and resistance to oxidation; cobalt alloys are used in manufacture of some artificial joint prosthesis devices. Cobalt salts are used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is an essential cofactor in vitamin B12 metabolism. Cobalt deficiency has not been reported in humans. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and kidney failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Serum cobalt concentrations are likely to be increased above the reference range in patients with joint prosthesis containing cobalt. Prosthetic devices produced by DePuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside are typically made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Detecting cobalt toxicity Monitoring metallic prosthetic implant wear This test is not useful for assessment of vitamin B12 activity.

Interpretation: Concentrations greater than or equal to 1.0 ng/mL indicate possible environmental or occupational exposure. Cobalt concentrations associated with toxicity must be interpreted in the context of the source of exposure. If cobalt is ingested, concentrations greater than 5 ng/mL suggest major exposure and likely toxicity. If cobalt exposure is due to orthopedic implant wear, there are no large case number reports associating high circulating serum cobalt with toxicity. There are no Occupational Health and Safety Administration blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal ions. Modest increase (4-10 ng/mL) in serum cobalt concentration is likely to be associated with a prosthetic device in good condition. Serum concentrations above 10 ng/mL in a patient with cobalt-based implant suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. However, the

US Food and Drug Administration recommends testing cobalt in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal implants.

Reference Values:

<1.0 ng/mL
<10.0 ng/mL (Metal-on-metal implant)
Reference values apply to all ages.

The reported unit of measurement for cobalt of ng/mL is equivalent to mcg/L.

Clinical References: 1. Tower SS. Arthroprosthetic cobaltism: neurological and cardiac manifestations in two patients with metal-on-metal arthroplasty: a case report. J Bone Joint Surg Am. 2010;92(17):2847-2851 2. Keegan GM, Learmonth ID, Case CP. A systematic comparison of the actual, potential, and theoretical health effects of cobalt and chromium from industry and surgical implants. Crit Rev Toxicol. 2008;38(8):645-674 3. De Smet K, De Hann R, Calistri A, et al. Metal ion measurement as a diagnostic tool to identify problems with metal-on-metal hip resurfacing. J Bone Joint Surg Am. 2008;90 Sppl 4:202-208 4. Lison D, De Boeck M, Verougstraete V, Kirsch-Volders M. Update on the genotoxicity and carcinogenicity of cobalt compounds. Occup Environ Med. 2001;58(10):619-625 5. Crutsen JRW, Koper MC, Jelsma J, et al. Prosthetic hip-associated cobalt toxicity: a systematic review of case series and case reports. EFORT Open Rev. 2022;7(3):188-199 6. Leyssens L, Vinck B, Van Der Straeten C, Wuyts F, Maes L. Cobalt toxicity in humans-A review of the potential sources and systemic health effects. Toxicology. 2017;387:43-56. doi:10.1016/j.tox.2017.05.015 7. Sodi R. Vitamins and trace elements. Rifai N, Chiu RWK, Young I, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 39

COSY
606352

Cobalt, Synovial Fluid

Clinical Information: Per US Food and Drug Administration recommendations, orthopedic surgeons should consider measuring and following serial cobalt concentrations in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal hip implants as part of their overall clinical evaluation. However, a recent publication(1) has shown synovial fluid measurements were superior to whole blood and serum Cobalt concentrations in predicting local tissue destruction in failed hip arthroplasty constructs. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside are typically made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products' compositions change occasionally; see each prostheses' product information for composition details. Cobalt is a naturally occurring, hard, gray element widely distributed in the environment. It is used to produce alloys in the manufacturing of aircraft engines, cutting tools, and some artificial hip and knee joint prosthesis devices. Cobalt is an essential cofactor for vitamin B12, which is necessary for neurological function, brain function, and the formation of blood. For most people, food is the largest source of cobalt intake. The greatest environmental exposure occurs in mining processes, cemented tungsten-carbide industry, cobalt powder industry, and alloy production industry. Cobalt is not highly toxic; however large doses may produce adverse clinical manifestations. Acute symptoms include pulmonary edema, allergy, nausea, vomiting, hemorrhage, and kidney failure. Chronic exposure to cobalt-containing hard metal (dust or fume) can result in a serious lung disease called hard metal lung disease, which is a type of pneumoconiosis (lung fibrosis). Furthermore, inhalation of cobalt particles can cause respiratory sensitization, asthma, shortness of breath, and decreased pulmonary function. Even though the primary route of occupational exposure to cobalt is the respiratory tract, skin contact is also important because dermal exposures to hard metal and cobalt salts can result in significant systemic uptake. Sustained exposures can cause skin sensitization, which may result in eruptions of contact dermatitis. In cases of suspected toxicity, blood, serum, or urine concentrations of cobalt can be checked. Vitamin B12 should be used to assess nutritional status.

Useful For: Monitoring metallic prosthetic implant wear and local tissue destruction in failed hip arthroplasty constructs This test is not useful for assessment of nutritional status or potential cobalt toxicity.

Interpretation: Based on an internal study, synovial fluid cobalt concentrations of 19.8 ng/mL or above were more likely due to a metal reaction (eg, adverse local tissue reaction [ALTR]/adverse reaction to metal debris [ARMD]) versus a nonmetal reaction in patients undergoing metal-on-metal revision (sensitivity of 92.3% and specificity of 96.3%).

Reference Values:
0-17 years: Not established
> or =18 years: <19.8 ng/mL

Clinical References: 1. Houdek MT, Taunton MJ, Wyles CC, Jannetto PJ, Lewallen DG, Berry DJ. Synovial fluid metal ion levels are superior to blood metal ion levels in predicting an adverse local tissue reaction in failed total hip arthroplasty. J Arthroplasty. 2021;36(9):3312-3317.e1. doi:10.1016/j.arth.2021.04.034 2. Eltit F, Assiri A, Garbuz D, et al. Adverse reactions to metal on polyethylene implants: Highly destructive lesions related to elevated concentration of cobalt and chromium in synovial fluid. J Biomed Mater Res A. 2017;105(7):1876-1886. doi:10.1002/jbm.a.36057 3. Lass R, Grubl A, Kolb A, et al. Comparison of synovial fluid, urine, and serum ion levels in metal-on-metal total hip arthroplasty at minimum follow-up of 18 years. J Orthop Res. 2014;32(9):1234-1240. doi:10.1002/jor.22652 4. De Pasquale D, Stea S, Squarzoni S, et al. Metal-on-metal hip prostheses: Correlation between debris in the synovial fluid and levels of cobalt and chromium ions in the bloodstream. Int Orthop. 2014;38(3):469-475. doi:10.1007/s00264-013-2137-5

COBRU 607760 Cobalt/Creatinine Ratio, Random, Urine

Clinical Information: Cobalt (Co) is rare but widely distributed in the environment. It is an essential cofactor in vitamin B12. While cobalt is an essential element, cobalt deficiency has not been reported in humans. Cobalt is used in the manufacture of hard alloys with high melting points and resistance to oxidation. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and kidney failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Improperly handled (60)Co can cause radiation poisoning from exposure to gamma radiation. Urine cobalt concentrations are likely to be increased above the reference value in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by DePuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Detecting cobalt exposure in a random urine collection Monitoring metallic prosthetic implant wear This test is not useful for assessment of vitamin B12 activity.

Interpretation: Concentrations greater or equal to 2.0 mcg/g creatinine indicate excess exposure. There are no Occupational Safety and Health Administration blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal

ions. In a patient with a cobalt-based implant, modest increase (2-4 mcg/g creatinine) in urine cobalt concentration is likely to be associated with a prosthetic device in good condition. Excessive exposure is indicated when urine cobalt concentration is greater than 5 mcg/g creatinine, consistent with prosthesis wear. Urine concentrations greater than 20 mcg/g creatinine in a patient with a cobalt-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

Reference Values:

COBALT:
0-17 years: Not established
>17 years: <1.7 mcg/g Cr

CREATININE:
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Keegan GM, Learmonth ID, Case CP. A systematic comparison of the actual, potential, and theoretical health effects of cobalt and chromium from industry and surgical implants. Crit Rev Toxicol. 2008;38(8):645-674 2. Lhotka C, Szekes T, Stefan I, Zhuber K, Zweymuller K: Four-year study of cobalt and chromium blood levels in patients managed with two different metal-on-metal total hip replacements. J Orthop Res. 2003;21(2):189-195 3. Lison D, De Boeck M, Verougstraete V, Kirsch-Volders M. Update on the genotoxicity and carcinogenicity of cobalt compounds. Occup Environ Med. 2001;58(10):619-625 4. Sodi R. Vitamins and trace elements. Rifai N, Chiu RWK, Young I, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 39. 5. Crutsen JRW, Koper MC, Jelsma J, et al. Prosthetic hip-associated cobalt toxicity: a systematic review of case series and case reports. EFORT Open Rev. 2022;7(3):188-199 6. Leyssens L, Vinck B, Van Der Straeten C, Wuyts F, Maes L. Cobalt toxicity in humans-A review of the potential sources and systemic health effects. Toxicology. 2017;387:43-56. doi:10.1016/j.tox.2017.05.015

FCOKE 75174 Cocaine Analysis - Whole Blood

Reference Values:

Cocaine Screen:
Cocaine and Metabolite, UA – Negative; Cutoff: 25 ng/mL

Cocaine Confirmation: Cocaine
Benzoylecgonine
Confirmation threshold: 10 ng/mL

COKMX 62720 Cocaine and Metabolite Confirmation, Chain of Custody, Meconium

Clinical Information: Cocaine is an alkaloid found in Erythroxylon coca, which grows principally in the northern South American Andes and, to a lesser extent, in India, Africa, and Java.(1) Cocaine is a powerfully addictive stimulant drug. Cocaine abuse has a long history, is rooted in the drug culture in the United States,(2) and is one of the most common illicit drugs of abuse.(3,4) Cocaine is rapidly metabolized primarily to benzoylecgonine, which is further metabolized to m-hydroxybenzoylecgonine (m-HOBE).(1,5) Cocaine is frequently used with other drugs, most commonly alcohol, and the simultaneous use of both can be determined by the presence of the unique metabolite cocaethylene.(4) Intrauterine drug exposure to cocaine has been associated with placental abruption, premature labor, small for gestational age status, microcephaly, and congenital anomalies (eg, cardiac and genitourinary

abnormalities, necrotizing enterocolitis, and central nervous system stroke or hemorrhage).(6) The disposition of drug in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid.(7) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(8) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(7) Chain of custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting in utero drug exposure up to 5 months before birth Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

Interpretation: The presence of any of the following: cocaine, benzoylecgonine, cocaethylene, or m-hydroxybenzoylecgonine, at 20 ng/g or more is indicative of in utero drug exposure up to 5 months before birth.

Reference Values:
Negative

Positive results are reported with a quantitative liquid chromatography tandem mass spectrometry (LC-MS/MS) result.

Cutoff concentrations for LC-MS/MS testing:
Cocaine: 20ng/g
Benzoylecgonine: 20 ng/g
Cocaethylene: 20 ng/g
m-Hydroxybenzoylecgonine: 20ng/g

Clinical References: 1. Isenschmid DS. Cocaine. In: Levine B, ed. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:207-228 2. US Drug Enforcement Administration: Cocaine. DEA; 2020. Accessed June 2, 2025. Available at https://www.dea.gov/factsheets/cocaine 3. National Institute on Drug Abuse: Cocaine DrugFacts. NIDA; 2021. Accessed June 2, 2025. Available at www.drugabuse.gov/publications/drugfacts/cocaine 4. Isenschmid DS. Cocaine-effects on human performance and behavior. Forensic Sci Rev. 2002;14(1-2):61-100 5. Kolbrich EA, Barnes AJ, Gorelick DA, Boyd SJ, Cone EJ, Huestis MA. Major and minor metabolites of cocaine in human plasma following controlled subcutaneous cocaine administration. J Anal Toxicol. 2006;30(8):501-510 6. Kwong TC, Ryan RM. Detection of intrauterine illicit drug exposure by newborn drug testing. National Academy of Clinical Biochemistry. Clin Chem. 1997;43(1):235-242 7. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989;115(3):474-477 8. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero: mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-74 9. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020. 10. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. St Louis, MO: Elsevier; 2023:chap 43

COKEX
62719

Cocaine and Metabolite Confirmation, Chain of Custody, Random, Urine

Clinical Information: Cocaine is a drug of current health concern because of its proliferation among recreational drug abusers. Freebase and crack increase the potential for major cocaine toxicity. Cocaine use is declining across the nation according to the National Institute of Drug Abuse. Increasingly, laboratory results are disputed or there are medical/legal overtones. Therefore, physicians are finding an increased need to confirm positive results before informing or confronting the patients. Chain of custody is a record of the disposition of a specimen to document all personnel who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting and confirming drug abuse involving cocaine Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited. This test is not intended for use in employment-related testing.

Interpretation: Reports will specifically indicate the presence or absence of cocaine and benzoylecgonine. The presence of cocaine, or its major metabolite, benzoylecgonine, indicates use within the past 4 days. Cocaine has a 6-hour half-life, so it will be present in urine for 1 day after last use. Benzoylecgonine has a half-life of 12 hours, so it will be detected in urine up to 72 hours after last use. There is no correlation between concentration and pharmacologic or toxic effects.

Reference Values:
Negative
Positive results are reported with a quantitative result.

Cutoff concentrations:

Immunoassay screen: 150 ng/mL

Gas chromatography mass spectrometry:
Cocaine: 50 ng/mL
Benzoylecgonine: 50 ng/mL

Clinical References: 1. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020 2. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 3. Isenschmid DS. Cocaine. In: Levine BS, Kerrigan S, eds. Principles of Forensic Toxicology. 5th ed. Springer Nature; 2020:371-388

COKEU
9286

Cocaine and Metabolite Confirmation, Random, Urine

Clinical Information: Cocaine is a drug of current health concern because of its proliferation among recreational drug abusers. Freebase and crack increase the potential for major cocaine toxicity. Cocaine use is declining across the nation according to the National Institute of Drug Abuse. Increasingly, laboratory results are disputed or there are medical/legal overtones. Therefore, physicians are finding an increased need to confirm positive results before informing or confronting the patients.

Useful For: Detecting and confirming drug abuse involving cocaine This test is not intended for

employment-related testing.

Interpretation: Reports will specifically indicate the presence or absence of cocaine and benzoylecgonine. The presence of cocaine, or its major metabolite, benzoylecgonine, indicates use within the past 4 days. Cocaine has a 6-hour half-life, so it will be present in urine for 1 day after last use. Benzoylecgonine has a half-life of 12 hours, so it will be detected in urine up to 4 days after last use. There is no correlation between concentration and pharmacologic or toxic effects.

Reference Values:
Negative (Positive results are reported with a quantitative result.)

Cutoff concentrations by gas chromatography mass spectrometry:
Cocaine: 50 ng/mL
Benzoylecgonine: 50 ng/mL

Clinical References: 1. Baselt RC, ed. Disposition of Toxic Drugs and Chemicals in Man. 10th ed. In: Biomedical Publications; 2014 2. Langman LJ, Bechtel LK, Holstege C. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

COKEM
84140

Cocaine and Metabolites Confirmation, Meconium

Clinical Information: Cocaine is an alkaloid found in Erythroxylon coca, which grows principally in the northern South American Andes and, to a lesser extent, in India, Africa, and Java.(1) Cocaine is a powerfully addictive stimulant drug. Cocaine abuse has a long history, is rooted in the drug culture in the United States,(2) and is 1 of the most common illicit drugs of abuse.(3,4) Cocaine is rapidly metabolized primarily to benzoylecgonine, which is further metabolized to m-hydroxybenzoylecgonine (m-HOBE).(1,5) Cocaine is frequently used with other drugs, most commonly alcohol, and the simultaneous use of both can be determined by the presence of the unique metabolite cocaethylene.(4) Intrauterine drug exposure to cocaine has been associated with placental abruption, premature labor, small for gestational age status, microcephaly, and congenital anomalies (eg, cardiac and genitourinary abnormalities, necrotizing enterocolitis, and central nervous system stroke or hemorrhage).(6) The disposition of drug in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid.(7) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation and slowly moves into the colon by the 16th week of gestation.(8) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(7)

Useful For: Detecting in utero drug exposure up to 5 months before birth

Interpretation: The presence of any of the following: cocaine, benzoylecgonine, cocaethylene, or m-hydroxybenzoylecgonine, at 20 ng/g or more, is indicative of in utero drug exposure up to 5 months before birth.

Reference Values:
Negative

Positive results are reported with a quantitative liquid chromatography tandem mass spectrometry (LC-MS/MS) result.

Cutoff concentrations for LC-MS/MS testing:
Cocaine: 20 ng/g
Benzoylecgonine: 20 ng/g
Cocaethylene: 20 ng/g
m-Hydroxybenzoylecgonine: 20 ng/g

Clinical References: 1. Isenschmid DS. Cocaine. In: Levine B, ed. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:207-228 2. US Drug Enforcement Administration: Cocaine. DEA; 2020. Accessed June 2, 2025. Available at https://www.dea.gov/factsheets/cocaine 3. National Institute on Drug Abuse: Cocaine DrugFacts. NIDA; 2021. Accessed June 2, 2025. Available at www.drugabuse.gov/publications/drugfacts/cocaine 4. Isenschmid DS. Cocaine-effects on human performance and behavior. Forensic Sci Rev. 2002;14(1-2):61-100 5. Kolbrich EA, Barnes AJ, Gorelick DA, Boyd SJ, Cone EJ, Huestis MA. Major and minor metabolites of cocaine in human plasma following controlled subcutaneous cocaine administration. J Anal Toxicol. 2006;30(8):501-510 6. Kwong TC, Ryan RM. Detection of intrauterine illicit drug exposure by newborn drug testing. National Academy of Clinical Biochemistry. Clin Chem. 1997;43(1):235-242 7. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989;115(3):474-477 8. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero: mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-74 9. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020. 10. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. St Louis, MO: Elsevier; 2023:chap 43

FCDU6 75781 Cocaine and Metabolites, Umbilical Cord Tissue

Reference Values:
Reporting limit determined each analysis.

Units: ng/g

Only orderable as part of a profile-see FCDSU.

RSCOC 35928 Coccidioides Antibody Reflex, Complement Fixation and Immunodiffusion, Serum

Clinical Information: Coccidioidomycosis (valley fever, San Joaquin Valley fever) is a fungal infection found in the Southwestern US, Central America, and South America. It is acquired by inhalation of arthroconidia of Coccidioides immitis/posadasii. Usually, it is a mild, self-limiting pulmonary infection. Less commonly, chronic pneumonia may occur, progressing to fibronodular, cavitary disease. A rash often develops within a day or 2, followed by erythema nodosum or multiforme and accompanying arthralgias. About 2 weeks after exposure, symptomatic patients develop fever, cough, malaise, and anorexia; chest pain is often severe. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs, including the meninges. IgG antibody is detected by the complement-fixation tests. Precipitating antibodies (IgM and IgG) are detected by immunodiffusion. They are rarely found in cerebrospinal fluid; however, their presence is associated with meningitis. Chronic coccidioidal pulmonary cavities are often accompanied by IgG and IgM precipitating antibodies. Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of pulmonary or meningeal infection and have lived or traveled in areas where Coccidioides immitis/posadasii is endemic. Any history of exposure to the organism or travel cannot be overemphasized when a diagnosis of coccidioidomycosis is being considered.

Useful For: Detection of antibodies to Coccidioides species

Interpretation: Complement Fixation: Titer results of 1:2 or higher may suggest active disease; however, titers may persist for months after infection has resolved. Increasing complement fixation (CF) titer results in serial specimens are considered diagnostic of active disease. Immunodiffusion: The presence of IgM antibody may be detectable within 2 weeks after the onset of symptoms; however, antibody may be detected longer than 6 months after infection. The presence of IgG antibody parallels the CF antibody and may suggest an active or a recent asymptomatic infection with Coccidioides immitis/posadasii; however, antibodies may persist after the infection has resolved. An equivocal result (a band of nonidentity) cannot be interpreted as significant for a specific diagnosis. However, this may be an indication that a patient should be followed serologically. Over 90% of primary symptomatic cases will be detected by combined immunodiffusion (ID) and CF testing.

Reference Values:
Only orderable as a reflex. For more information see COXIS / Coccidioides Antibody Screen with Reflex, Serum.

Complement Fixation: Negative
If positive, results are titered.

Immunodiffusion: Negative
Results are reported as positive, negative, or equivocal.

Clinical References: 1. McHardy IH, Barker B, Thompson GR 3rd. Review of clinical and laboratory diagnostics for coccidioidomycosis. J Clin Microbiol. 2023;61(5):e0158122. doi:10.1128/jcm.01581-22 2. Ramanan P, Wengenack NL, Theel ES. Laboratory diagnosis for fungal infections. A review of current and future diagnostic assays. Clin Chest Med. 2017;38(3):535-554. doi:10.1016/j.ccm.2017.04.013

COXIS
62079

Coccidioides Antibody Screen with Reflex, Serum

Clinical Information: Coccidioidomycosis (valley fever, San Joaquin Valley fever, desert rheumatism) is caused by the dimorphic fungus Coccidioides immitis/posadasii, which is found in the Southwestern US, regions in the Northwestern US, and in Central and South America. It is acquired by inhalation of airborne Coccidioides arthroconidia. The majority of infections are subclinical. Among symptomatic patients, the majority will present acute flulike, pulmonary symptoms approximately 7 to 28 days post exposure. Symptoms may include chest pain, cough, fever, malaise, and lymphadenopathy.(1) A rash often develops within a couple of days, followed by erythema nodosum or multiforme with accompanying arthralgia. A pulmonary lesion or nodule may develop months following infection and may be a source of infection if the patient becomes immunosuppressed in the future. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs including the meninges. Individuals at greater risk for dissemination include African Americans, patients of Filipino descent, pregnant women, and immunocompromised patients.(2) Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of pulmonary or meningeal infection and have lived or traveled in areas where C immitis/posadasii is endemic. Any history of exposure to the organism or travel cannot be overemphasized when a diagnosis of coccidioidomycosis is being considered.

Useful For: Detecting antibodies to Coccidioides immitis/posadasii This assay should not be used for monitoring response to therapy.

Interpretation: Enzyme immunoassay (EIA) results greater than or equal to 0.75 will be reported as

Reactive: Confirmatory testing by complement fixation and immunodiffusion has been ordered. A reactive result is presumptive evidence that the patient was previously or is currently infected with Coccidioides immitis/posadasii. EIA results less than 0.75 will be reported as Negative: Repeat testing on a new sample in 2 to 3 weeks if clinically indicated. A negative result indicates the absence of antibodies to C immitis/posadasii. It is presumptive evidence that the patient has not been previously exposed to, and is not infected with, Coccidioides. However, a negative result does not preclude the diagnosis of coccidioidomycosis as the specimen may have been collected before antibody levels were detectable, due to early acute infection or immunosuppression. This test is designed for the qualitative detection of both IgM- and IgG-class antibodies against antigens from Coccidioides. The report will not indicate which class of antibody is present.

Reference Values:
Negative

Reference value applies to all ages

Clinical References: 1. Thompson GR 3rd: Pulmonary coccidioidomycosis. Semin Respir Crit Care Med. 2011;32(6):754-763 2. Ruddy BE, Mayer AP, Ko MG, et al. Coccidioidomycosis in African Americans. Mayo Clin Proc. 2011;86(1):63-69 3. Crum NF. Coccidioidomycosis: a contemporary review. Infect Dis Ther. 2022;11(2):713-742. doi:10.1007/s40121-022-00606-y

SCOC
8295

Coccidioides Antibody, Complement Fixation and Immunodiffusion, Serum

Clinical Information: Coccidioidomycosis (valley fever, San Joaquin Valley fever) is a fungal infection found in the Southwestern US, Central America, and South America. It is acquired by inhalation of arthroconidia of Coccidioides immitis/posadasii. Usually, it is a mild, self-limiting pulmonary infection. Less commonly, chronic pneumonia may occur, progressing to fibronodular, cavitary disease. A rash often develops within a day or 2, followed by erythema nodosum or multiforme and accompanying arthralgias. About 2 weeks after exposure, symptomatic patients develop fever, cough, malaise, and anorexia; chest pain is often severe. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs, including the meninges. IgG antibody is detected by the complement-fixation tests. Precipitating antibodies (IgM and IgG) are detected by immunodiffusion. They are rarely found in cerebrospinal fluid; however, their presence is associated with meningitis. Chronic coccidioidal pulmonary cavities are often accompanied by IgG and IgM precipitating antibodies. Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of pulmonary or meningeal infection and have lived or traveled in areas where C immitis/posadasii is endemic. Any history of exposure to the organism or travel cannot be overemphasized when a diagnosis of coccidioidomycosis is being considered.

Useful For: Diagnosis of coccidioidomycosis using serum specimens

Interpretation: Complement Fixation: Titer results of 1:2 or higher may suggest active disease; however, titers may persist for months after infection has resolved. Increasing complement fixation (CF) titer results in serial specimens are considered diagnostic of active disease. Immunodiffusion: The presence of IgM antibodies may be detectable within 2 weeks after the onset of symptoms; however, the antibody may be detected longer than 6 months after infection. The presence of IgG antibodies parallels the CF antibodies and may suggest an active or a recent asymptomatic infection with Coccidioides immitis/posadasii; however, antibodies may persist after the infection has resolved. An equivocal result (a band of nonidentity) cannot be interpreted as significant for a specific diagnosis. However, this may be an indication that a patient should be followed serologically. Over 90% of primary symptomatic cases will be detected by combined immunodiffusion and CF testing.

Reference Values:
Complement Fixation: Negative
If positive, results are titered.

Immunodiffusion: Negative
Results are reported as positive, negative, or equivocal.

Clinical References: 1. McHardy IH, Barker B, Thompson GR 3rd. Review of clinical and laboratory diagnostics for coccidioidomycosis. J Clin Microbiol. 2023;61(5):e0158122. doi:10.1128/jcm.01581-22 2. Ramanan P, Wengenack NL, Theel ES. Laboratory diagnosis for fungal infections: a review of current and future diagnostic assays. Clin Chest Med. 2017;38(3):535-554. doi:10.1016/j.ccm.2017.04.013

CCOC
81542

Coccidioides Antibody, Complement Fixation and Immunodiffusion, Spinal Fluid

Clinical Information: Coccidioidomycosis (valley fever, San Joaquin Valley fever) is a fungal infection found in the Southwestern US, Central America, and South America. It is acquired by inhalation of arthroconidia of Coccidioides immitis/posadasii. Usually, it is a mild, self-limiting pulmonary infection. Less commonly, chronic pneumonia may occur, progressing to fibronodular cavitary disease. A rash often develops within 1 to 2 days, followed by erythema nodosum or multiforme and accompanying arthralgias. About 2 weeks after exposure, symptomatic patients develop fever, cough, malaise, and anorexia; chest pain is often severe. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs, including the meninges. IgG antibody is detected by the complement-fixation tests. Precipitating antibodies (IgM and IgG) are detected by immunodiffusion. They are rarely found in cerebrospinal fluid; however, their presence is associated with meningitis. Chronic coccidioidal pulmonary cavities are often accompanied by IgG and IgM precipitating antibodies. Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of meningeal infection and have lived in or traveled to areas where Coccidioides immitis/posadasii is endemic. Any history of exposure to the organism or travel cannot be overemphasized when coccidioidomycosis serologic tests are being considered.

Useful For: Diagnosing coccidioidomycosis using spinal fluid specimens

Interpretation: Complement Fixation: IgG antibody is detected by complement fixation (CF) testing. Any CF titer in cerebrospinal fluid (CSF) should be considered significant. A positive complement fixation test in unconcentrated CSF is diagnostic of meningitis. Immunodiffusion: IgM and IgG precipitins are rarely found in CSF. However, when present, they are diagnostic of meningitis (100% specific). Since the immunodiffusion test is 100% specific, it is helpful in interpreting CF results.

CIMT
62204

Coccidioides immitis/posadasii, Molecular Detection, PCR, Paraffin, Tissue

Clinical Information: Coccidioidomycosis is caused by the dimorphic fungi, Coccidioides immitis and Coccidioides posadasii. These organisms are endemic to the southwestern regions of the United States, northern Mexico, and areas of Central and South America, with recent literature suggests the geographic area of endemicity may be expanding over time. The gold standard for the diagnosis of coccidioidomycosis is culture of the organism from clinical specimens due to its high sensitivity. However, growth in culture may take up to several weeks, which can delay diagnosis and treatment. In addition, the propagation of Coccidioides species in the clinical laboratory is a significant safety hazard

to laboratory personnel. This polymerase chain reaction method can identify Coccidioides species directly from clinical specimens, allowing for a rapid diagnosis, and should be used in conjunction with culture. For specimen types such as formalin-fixed, paraffin-embedded tissue, culture is not possible, but the molecular test may provide useful information.

Useful For: Rapid detection of Coccidioides DNA Aiding in the diagnosis of coccidioidomycosis using paraffin-embedded tissue specimens

Interpretation: A positive result indicates presence of Coccidioides DNA. A negative result indicates absence of detectable Coccidioides DNA. An inhibition result indicates that the detection of Coccidioides DNA is inhibited in this specimen. A new specimen can be resubmitted under a new order, if desired.

Reference Values:
Not applicable

Clinical References: 1. Vucicevic D, Blair JE, Binnicker MJ, et al: The utility of Coccidioides polymerase chain reaction testing in the clinical setting. Mycopathologia. 2010 Nov;170(5):345-351 2. Hartmann CA, Aye WT, Blair JE: Treatment considerations in pulmonary coccidioidomycosis. 2016 Oct;10(10):1079-1091

CIMRP 88804 Coccidioides immitis/posadasii, Molecular Detection, PCR, Varies

Clinical Information: Coccidioidomycosis is caused by the dimorphic fungi, Coccidioides immitis and Coccidioides posadasii. These organisms are endemic to the southwestern regions of the United States, northern Mexico, and areas of Central and South America, with recent literature suggests the geographic area of endemicity may be expanding over time. The gold standard for the diagnosis of coccidioidomycosis is culture of the organism from clinical specimens due to its high sensitivity. However, growth in culture may take up to several weeks, which can delay diagnosis and treatment. In addition, the propagation of Coccidioides species in the clinical laboratory is a significant safety hazard to laboratory personnel. This polymerase chain reaction method can identify Coccidioides species directly from clinical specimens, allowing for a rapid diagnosis. Fungal culture should also always be performed since it may enhance detection, and the isolate may be needed for antifungal susceptibility testing.

Useful For: Rapid detection of Coccidioides DNA, preferred method An aid in diagnosing coccidioidomycosis

Interpretation: A positive result indicates presence of Coccidioides DNA. A negative result indicates absence of detectable Coccidioides DNA.

Reference Values:
Not applicable

Clinical References: 1. Williams SL, Chiller T: Update on the epidemiology, diagnosis, and treatment of coccidioidomycosis. J Fungi (Basel). 2022 Jun 25;8(7):666. doi: 10.3390/jof8070666 2. Thompson GR, Ampel NM, Blair JE, et al: Controversies in the management of central nervous system coccidioidomycosis. Clin Infect Dis. 2022 Sep 10;75(4):555-559. doi: 10.1093/cid/ciac478 3. Boro R, Iyer PC, Walczak MA: Current landscape of coccidioidomycosis. J Fungi (Basel). 2022 Apr 17;8(4):413. doi: 10.3390/jof8040413

FCKTF
57966

Cockatiel Feathers IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

CBUR
82802

Cocklebur, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cocklebur Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FCAIG
75561

Cockroach American (Periplaneta americana) IgE

Clinical Information:

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

COCR
82693

Cockroach, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cockroach Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal

2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FCOCN
57668

Coconut IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

CCNT
82739

Coconut, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to coconut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with

the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

COD
82889

Codfish, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to codfish Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

Q10
87853

Coenzyme Q10, Reduced and Total, Plasma

Clinical Information: Coenzyme Q10 (CoQ10) is an essential cofactor in the mitochondrial respiratory chain responsible for oxidative phosphorylation where it functions as an electron carrier and acts as an antioxidant. It is found in all cell membranes and is carried by lipoproteins in the circulation. Approximately 60% of CoQ10 is associated with low-density lipoprotein (LDL), 25% with high-density lipoprotein, and 15% with other lipoproteins. CoQ10 is present in the body in both the reduced and oxidized forms, with the antioxidant activity of CoQ10 dependent on both its concentration and its reduction-oxidation (redox) status. CoQ10 deficiencies, which are clinically and genetically diverse, can occur due to defects in genes involved in the biosynthesis of ubiquinone (primary CoQ10 deficiency) or due to other causes, such as mitochondrial disorders (secondary or CoQ10 deficiency). Five major clinical phenotypes of CoQ10 deficiency have been described: -Encephalomyopathy (elevated serum creatine kinase [CK], recurrent myoglobinuria, lactic acidosis) -Cerebellar ataxia and atrophy (neuropathy, hypogonadism) -Severe multisystemic infant form (nystagmus, optic atrophy, sensorineural hearing loss, dystonia, rapidly progressing nephropathy) -Nephropathy, steroid resistant nephrotic syndrome leading to end stage kidney disease -Isolated myopathy (exercise intolerance, fatigue, elevated serum CK) Treatment with CoQ10 in patients with mitochondrial cytopathies can improve mitochondrial respiration in both brain and skeletal muscle. CoQ10 has been implicated in other disease processes, including diabetes, neurodegenerative conditions such as Parkinson and Alzheimer diseases, as well as in aging and oxidative stress. CoQ10 may also play a role in hydroxymethylglutaryl-CoA reductase inhibitor (statin) therapy and may be relevant to statin-induced myalgia. Additionally, the redox status of CoQ10 may be a useful early marker for the detection of oxidative LDL modification.

Useful For: Diagnosis of primary coenzyme Q10 (CoQ10) deficiencies in some patients who are not supplemented with CoQ10 Diagnosis of CoQ10 deficiency in mitochondrial disorders Monitoring CoQ10 status during treatment of various degenerative conditions, including Parkinson and Alzheimer diseases This test is not useful for distinguishing primary CoQ10 deficiencies from acquired CoQ10 deficiencies.

Interpretation: Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:

COENZYME Q10 (CoQ10) REDUCED
<18 years: 320-1376 mcg/L
> or =18 years: 415-1480 mcg/L

CoQ10 TOTAL
<18 years: 320-1558 mcg/L
> or =18 years: 433-1532 mcg/L

CoQ10 % REDUCED
<18 years: 93-100%
> or =18 years: 92-98%

Miles MV, Horn PS, Tang PH, et al. Age-related changes in plasma coenzyme Q10 concentrations and redox state in apparently healthy children and adults. Clin Chim Acta. 2004;34:139-144

Clinical References: 1. Salviati L, Trevisson E, Agosto C, Doimo M, Navas P. Primary coenzyme Q10 deficiency overview. In: Adam MP, Mirzaa GM, Pagon RA, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2017. Updated June 8, 2023. Accessed November 1, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK410087/ 2. Desbats MA, Lunardi G, Doimo M, Trevisson E, Salviati L. Genetic bases and clinical manifestations of coenzyme Q10 (CoQ 10) deficiency. J Inherit Metab Dis. 2015;38(1):145-56. doi:10.1007/s10545-014-9749-9 3. Littarru GP, Tiano L. Clinical aspects of coenzyme Q10: An update. Nutrition. 2010;26:250-254 4. Hargreaves I, Heaton RA, Mantle D. Disorders of human coenzyme Q10 metabolism: An overview. Int J Mol Sci. 2020;21(18):6695. doi:10.3390/ijms21186695 5. Banach M, Serban C, Ursoniu S, et al. Statin therapy and plasma coenzyme Q10 concentrations-A systematic review and meta-analysis of placebo-controlled trials. Pharmacol Res. 2015;99:329-336. doi:10.1016/j.phrs.2015.07.008 6. Emmanuele V, Lopez LC, Berardo A, et al. Heterogeneity of coenzyme Q10 deficiency: patient study and literature review. Arch Neurol. 2012;69(8):978-983. doi:10.1001/archneurol.2012.206

TQ10
63148

Coenzyme Q10, Total, Plasma

Clinical Information: Coenzyme Q10 (CoQ10) is an essential cofactor in the mitochondrial respiratory chain responsible for oxidative phosphorylation, where it functions as an electron carrier and acts as an antioxidant. It is found in all cell membranes and is carried by lipoproteins in the circulation. Approximately 60% of CoQ10 is associated with low-density lipoprotein (LDL), 25% with high-density lipoprotein, and 15% with other lipoproteins. CoQ10 is present in the body in both the reduced and oxidized forms, with the antioxidant activity of CoQ10 dependent on both its concentration and reduction-oxidation (redox) status. CoQ10 deficiencies, which are clinically and genetically diverse, can occur due to defects in genes involved in the biosynthesis of ubiquinone (primary CoQ10 deficiency) or due to other causes, such as mitochondrial disorders (secondary CoQ10 deficiency). Five major clinical phenotypes of CoQ10 deficiency have been described: -Encephalomyopathy (elevated serum creatine kinase [CK], recurrent myoglobinuria, lactic acidosis) -Cerebellar ataxia and atrophy (neuropathy, hypogonadism) -Severe multisystemic infant form (nystagmus, optic atrophy, sensorineural hearing loss, dystonia, rapidly progressing nephropathy) -Nephropathy, steroid resistant nephrotic syndrome leading to end stage kidney disease -Isolated myopathy (exercise intolerance, fatigue, elevated serum CK) Treatment with CoQ10 in patients with mitochondrial cytopathies can improve mitochondrial respiration in both brain and skeletal muscle. CoQ10 has been implicated in other disease processes, including diabetes, neurodegenerative

conditions such as Parkinson and Alzheimer diseases, as well as in aging and oxidative stress. CoQ10 may also play a role in hydroxymethylglutaryl-CoA reductase inhibitor (statin) therapy and may be relevant to statin-induced myalgia. Additionally, the redox status of CoQ10 may be a useful early marker for the detection of oxidative LDL modification.

Useful For: Diagnosis of primary coenzyme Q10 (CoQ10) deficiencies in some patients who are not supplemented with CoQ10 Monitoring patients receiving statin therapy Monitoring CoQ10 status during treatment of various degenerative conditions, including Parkinson and Alzheimer diseases Providing accurate quantitation of total CoQ10 when specimens are hemolyzed This test is not useful for distinguishing primary CoQ10 deficiencies from acquired CoQ10 deficiencies.

Interpretation: Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:
<18 years: 320-1558 mcg/L
> or =18 years: 433-1532 mcg/L

Miles MV, Horn PS, Tang PH, et al. Age-related changes in plasma coenzyme Q10 concentrations and redox state in apparently healthy children and adults. Clin Chim Acta. 2004;34:139-144

Clinical References: 1. Salviati L, Trevisson E, Agosto C, Doimo M, Navas P. Primary coenzyme Q10 deficiency overview. In: Adam MP, Mirzaa GM, Pagon RA, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2017. Updated June 8, 2023. Accessed November 1, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK410087/ 2. Desbats MA, Lunardi G, Doimo M, Trevisson E, Salviati L. Genetic bases and clinical manifestations of coenzyme Q10 (CoQ 10) deficiency. J Inherit Metab Dis. 2015;38(1):145-56. doi:10.1007/s10545-014-9749-9 3. Littarru GP, Tiano L. Clinical aspects of coenzyme Q10: An update. Nutrition. 2010;26:250-254 4. Hargreaves I, Heaton RA, Mantle D. Disorders of human coenzyme Q10 metabolism: An overview. Int J Mol Sci. 2020;21(18):6695. doi:10.3390/ijms21186695 5. Banach M, Serban C, Ursoniu S, et al. Statin therapy and plasma coenzyme Q10 concentrations-A systematic review and meta-analysis of placebo-controlled trials. Pharmacol Res. 2015;99:329-336. doi:10.1016/j.phrs.2015.07.008 6. Emmanuele V, Lopez LC, Berardo A, et al. Heterogeneity of coenzyme Q10 deficiency: patient study and literature review. Arch Neurol. 2012;69(8):978-983. doi:10.1001/archneurol.2012.206

FCOFE
57525

Coffee (Coffea spp) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.1-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 17.50-49.99 Very High Positive 5 50.00-99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

ML20C
605263

COG Metaphases, 1-19 (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

M25C
605264

COG Metaphases, 20-25 (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MG25C
605265

COG Metaphases, >25 (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

CATTR
614034

Cold Agglutinin Titer, Serum

Clinical Information: The cold agglutinin titer test is to be used as a tool in the evaluation of suspected cold agglutinin syndrome. In this syndrome, cold agglutinins, usually IgM with anti-I specificity, attach to the patient's erythrocytes causing a variety of symptoms. Symptoms may include chronic anemia due to premature removal of the sensitized erythrocytes from circulation by hemolysis, to acrocyanosis of the ears, fingers, or toes due to local blood stasis in the skin capillaries.

Useful For: Detection of cold agglutinins in patients with suspected cold agglutinin disease This test is not recommended to diagnose Mycoplasma pneumoniae infections.

Interpretation: Titers above 64 are considered elevated, but hemolytic anemia resulting from cold-reactive autoagglutinins rarely occurs unless the titer is 1000 or above. Titers below 1000 may be obtained when the autoantibody has a different specificity (eg, anti-i) or if the cold agglutinin is of the less-common low-titer, high-thermal-amplitude type. The test is not a direct measure of clinical significance and must be used in conjunction with other in vitro and in vivo parameters.

Reference Values:
Titer results:
>64: Elevated
>1000: May be indicative of hemolytic anemia

Clinical References: Cohn CS, Delaney M, Johnson ST, Katz LM, Schwartz J. eds: Technical Manual. 21st ed. AABB; 2023

COLIV
70408

Collagen IV Immunostain, Technical Component Only

Clinical Information: Collagen IV stains the basal lamina of capillaries as well as basement membrane structures in all organs. In the kidney, the antibody stains the glomerular and tubular basement membranes and mesangial cells and matrix within the glomerulus.

Useful For: A marker of the basal lamina of capillaries and basement membranes in all organs

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical

history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Abreu-Velez AM, Howard MS. Collagen IV in normal skin and in pathological processes. N Am J Med Sci. 2012 Jan;4(1):1-8 2. Agarwal P, Ballabh R. Expression of type IV collagen in different histological grades of oral squamous cell carcinoma: an immunohistochemical study. J Cancer Res Ther. 2013;9(2):272-275 3. Girolamo F, Errede M, Longo G, et al. Defining the role of NG2-expressing cells in experimental models of multiple sclerosis. A biofunctional analysis of the neurovascular unit in wild type and NG2 null mice. PLoS One. 2019;14(3):e0213508. doi:10.1371/journal.pone.0213508 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FFTYC 91496 Collagen Type II antibody

Interpretation: Anti-collagen II antibodies occur in 22% of patients with idiopathic SNHL, 30% of patients with sudden deafness and 20% of patients with Meniere's disease. Anti-collagen II antibodies also occur in patients with relapsing polychondritis and in rheumatoid arthritis.

Reference Values:
Negative: <20 EU/mL

Borderline/Equivocal: 20-25 EU/mL

Positive: >25 EU/mL

MSCG 615298 Collagenofibrotic Glomerulopathy Confirmation, Mass Spectrometry

Clinical Information: Collagenofibrotic glomerulopathy (CG), also called collagen type III glomerulopathy, is a rare kidney disease characterized by large amounts of atypical type III collagen fibrils in the mesangium and subendothelial space of renal glomeruli. Liquid chromatography tandem mass spectrometry performed on microdissected glomeruli from patients with CG demonstrates a unique proteomic profile. The presence of type III collagen, in the appropriate clinical and pathological context, can be useful to establish a diagnosis of CG.

Useful For: Aiding in the diagnosis of collagenofibrotic glomerulopathy

Interpretation: An interpretation will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Chen X, Wan H, Xu W, Zhu J. Collagen type III glomerulopathy: Case report and review of the literature. Clin Nephrol. 2017;1:39-46 2. Dong J, Wei H, Han M, Guan Y, Wu Y, Li H. Collagen type III glomerulopathy: A case report and review of 20 cases. Exp Ther Med. 2015;10(4):1445-1449 3. Kurien AA, Larsen CP, Cossey N. Collagenofibrotic glomerulopathy. Clin Kidney J. 2015;8(5):543-547 4. Cohen AH. Collagen type III glomerulopathies. Adv Chronic Kidney Dis. 2012;19(2):101-106 5. Duggal R, Nada R, Rayat CS, Sakhuja V, Joshi K. Collagenofibrotic glomerulopathy - a review. Clin Kidney J. 2012;5(1):7-12

CRMTS
43436

Collapsin Response-Mediator Protein-5 (CRMP-5) Neuronal IgG Titer, Serum

Clinical Information: Autoantibodies specific for neurons, glia, and muscle are important serological markers of neurological autoimmunity. Most are highly predictive of specific neoplasms that are metastatic to regional lymph nodes when diagnosed, but usually limited in spread.(1,2) The target autoantigens identified so far include cytoplasmic and nuclear proteins and plasma membrane cation channels.(3) Collapsin response-mediator protein-5 (CRMP-5)-IgG is currently the second most common autoantibody predictive of small-cell lung carcinoma and, sometimes, occurs with thymoma. The neurological presentation of CRMP-5-IgG seropositive patients is usually multifocal and can affect any level of the neuraxis. The presentation frequently mimics a stroke or multiple sclerosis. Syndromic manifestations encountered with lung carcinoma include subacute chorea, blindness, other cranial neuropathies (particularly loss of taste or smell), gastrointestinal dysmotility, myelopathy, and radiculoplexopathy. Fourteen percent of patients have thromboembolic phenomena. Seropositive patients who have thymoma (6%) usually present with neurological manifestations other than, or including, myasthenia gravis (eg, encephalopathy, disorders of continuous muscle fiber activity).

Useful For: Evaluation of neurological autoimmunity particularly that associated with small-cell lung carcinoma and thymoma Reporting an end titer result from serum specimens

Interpretation: Detection of IgG autoantibody specific for the neuronal cytoplasmic antigen collapsin response-mediator protein-5 (CRMP-5) in a patient's serum or spinal fluid confirms that the patient's subacute neurological disorder has an autoimmune basis and predicts a small-cell lung carcinoma or thymoma with 75% to 80% certainty.(1) CRMP-5-IgG titers generally fall after the neoplasm is treated, and a rising titer is indicative of tumor persistence or recurrence.

Reference Values:
Only orderable as a reflex. For more information see:
-PAVAL / Paraneoplastic, Autoantibody Evaluation, Serum
-DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
-ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
-MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
-MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-DYS2 / Dysautonomia, Autoimmune/Paraneoplastic Evaluation, Serum
-GID2 / Gastrointestinal Dysmotility, Autoimmune/Paraneoplastic Evaluation, Serum
-PVLE / Paraneoplastic Vision Loss Evaluation, Serum
-AIAES / Axonal Neuropathy, Autoimmune/Paraneoplastic Evaluation, Serum

<1:240
Note: Titers lower than 1:240 are detectable by recombinant collapsin response-mediator protein-5 (CRMP-5) Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored serum (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call 1-800-533-1710 to request CRMP-5 Western blot.

Neuron-restricted patterns of IgG staining that do not fulfill criteria for CRMP-5-IgG may be reported as "unclassified antineuronal IgG." Complex patterns that include non-neuronal elements may be reported as "uninterpretable."

Clinical References: 1. Yu Z, Kryzer TJ, Griesmann GE, et al: CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. Ann Neurol. 2001 Feb;49(2):146-154 2. Cross SA, Salomao DR, Parisi JE, et al: Paraneoplastic autoimmune optic neuritis with retinitis defined by CRMP-5-IgG. Ann Neurol. 2003 Jul;54(1):38-50 3. Galanis E, Frytak S, Rowland KM, et al: Neuronal

autoantibody titers in the course of small-cell lung carcinoma and platinum associated neuropathy. Cancer Immunol Immunother. 1999 May-June;48(2-3):85-90 4. Vernino S, Tuite P, Adler CH, et al: Paraneoplastic chorea associated with CRMP-5 neuronal antibody and lung carcinoma. Ann Neurol. 2002 May;51(5):625-630 5. Pittock SJ, Kryzer TJ, Lennon VA: Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. Ann Neurol. 2004 Nov;56(5):715-719 6. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul 15;20(14):3862-3869

CRMTC
43445

Collapsin Response-Mediator Protein-5 (CRMP-5) Neuronal IgG Titer, Spinal Fluid

Clinical Information: Autoantibodies specific for neurons, glia, and muscle are important serological markers of neurological autoimmunity. Most are highly predictive of specific neoplasms that are metastatic to regional lymph nodes when diagnosed but usually limited in spread.(1,2) The target auto-antigens identified so far include cytoplasmic and nuclear proteins and plasma membrane cation channels.(3) Collapsin response-mediator protein-5 (CRMP-5)-IgG is currently the second most common autoantibody predictive of small-cell lung carcinoma and, sometimes, occurs with thymoma. The neurological presentation of CRMP-5-IgG seropositive patients is usually multifocal and can affect any level of the neuraxis. The presentation frequently mimics a stroke or multiple sclerosis. Syndromic manifestations encountered with lung carcinoma include subacute chorea, blindness, other cranial neuropathies (particularly loss of taste or smell), gastrointestinal dysmotility, myelopathy, and radiculoplexopathy. Fourteen percent of patients have thromboembolic phenomena. Seropositive patients who have thymoma (6%) usually present with neurological manifestations other than, or including, myasthenia gravis (eg, encephalopathy, disorders of continuous muscle fiber activity).

Useful For: Evaluation of neuroautoimmunity, particularly small-cell lung carcinoma and thymoma, in conjunction with other antineuronal antibodies Reporting an end titer result from cerebrospinal fluid specimens

Interpretation: Detection of IgG autoantibody specific for the neuronal cytoplasmic antigen collapsin response-mediator protein-5 (CRMP-5) in a patient's serum or spinal fluid confirms that the patient's subacute neurological disorder has an autoimmune basis and predicts a small-cell lung carcinoma or thymoma with 75% to 80% certainty.(1) CRMP-5-IgG titers generally fall after the neoplasm is treated, and a rising titer is indicative of tumor persistence or recurrence.

Reference Values:
Only orderable as a reflex. For more information see:
-DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

<1:2
Note: Titers lower than 1:2 are detectable by recombinant collapsin response-mediator protein-5 (CRMP-5) Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored spinal fluid (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call the Neuroimmunology Laboratory at 800-533-1710 to request CRMP-5 Western blot.

Neuron-restricted patterns of IgG staining that do not fulfill criteria for CRMP-5-IgG may be reported as "unclassified anti-neuronal IgG." Complex patterns that include nonneuronal elements may be

reported as "uninterpretable."

Clinical References: 1. Yu Z, Kryzer TJ, Griesmann GE, et al: CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. Ann Neurol. 2001 Feb;49(2):146-154 2. Galanis E, Frytak S, Rowland KM, et al: Neuronal autoantibody titers in the course of small-cell lung carcinoma and platinum associated neuropathy. Cancer Immunol Immunother. 1999 May-June;48(2-3):85-90 3. Lennon VA: Calcium channel and related paraneoplastic disease autoantibodies. In: Peter JB, Schoenfeld Y, eds. Textbook of Autoantibodies. Elsevier Science Publishers, BV, The Netherlands, 1996;139-147 4. Vernino S, Tuite P, Adler CH, et al: Paraneoplastic chorea associated with CRMP-5 neuronal antibody and lung carcinoma. Ann Neuro. 2002 May;51(5):625-630 5. Pittock SJ, Kryzer TJ, Lennon VA: Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. Ann Neurol. 2004 Nov;56(5):715-719 6. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul 15;20(14):3862-3869

CRMWS 83107 Collapsin Response-Mediator Protein-5-IgG, Western Blot, Serum

Clinical Information: Autoantibodies specific for neurons and muscle are important serological markers of neurological autoimmunity. Most are highly predictive of specific neoplasms that are metastatic when diagnosed, but usually limited in spread to regional lymph nodes and adjacent structures.(1-4) Collapsin response-mediator protein-5 (CRMP-5) is highly expressed in small-cell lung carcinomas (SCLC), in neurons throughout the adult central and peripheral nervous systems, and in a subset of glial cells.(1) In Western blot analyses the native antigen is a 62-kDa protein (recombinant human CRMP-5 is 68-kDa).(1) CRMP-5-IgG (also known as anti-CV-2)(4,5) is a more common autoantibody accompaniment of SCLC than antineuronal nuclear antibodies-1 (ANNA-1; anti-Hu) and sometimes occurs with thymoma. The neurological presentation of CRMP-5 seropositive patients is usually multifocal, and can affect any level of the neuraxis. Neurological presentations that suggest a CRMP-5-IgG-related syndrome include subacute chorea or cranial neuropathy (particularly loss of vision, taste, or smell), dementia, myelopathy and gastrointestinal dysmotility in a patient with risk factors for lung cancer, or encephalopathy or neuromuscular hyperexcitability in a patient with serological or clinical evidence of myasthenia gravis.(1) Fourteen percent of patients have thromboembolic phenomena. Seropositive patients who have thymoma usually present with other myasthenia gravis neurological manifestations (eg, encephalopathy, disorders of continuous muscle fiber activity).(3) CRMP-5-IgG is defined in serum or spinal fluid by its characteristic immunofluorescence (IF) staining pattern on a mixed tissue substrate of adult mouse central and peripheral neurons. However, CRMP-5-IgG is not detectable by standard IF screening if the titer is low (serum <1:240; CSF <1:2) or if coexisting autoantibodies, either neuron-specific or nonorgan-specific antinuclear and antimitochondrial antibodies, preclude identification of CRMP-5-IgG with certainty. In these situations, CRMP-5-IgG may be detected by Western blot analysis.

Useful For: Evaluation of cases of chorea, vision loss, cranial neuropathy and myelopathy

Interpretation: A positive result confirms that a patient's subacute neurological disorder has an autoimmune basis, and is likely to be associated with a small-cell lung carcinoma (SCLC) or thymoma, which may be occult.(1,2) A positive result has a predictive value of 90% for neoplasm (77% SCLC, 6% thymoma).(1) Seropositivity is found in approximately 3% of patients who have SCLC with limited metastasis without evidence of neurological autoimmunity.(6) Clinical-serological correlations have not yet been established for children. Western blot analysis is indicated when interfering nonorgan-specific or coexisting neuron-specific autoantibodies in serum or spinal fluid preclude unambiguous detection of CRMP-5-IgG by indirect immunofluorescence assay, or when the immunofluorescence assay is negative in a patient whose neurological presentation suggests a CRMP-5-IgG-related syndrome.

Reference Values:
Negative

Clinical References: 1. Yu Z, Kryzer TJ, Griesmann GE, et al. CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. Ann Neurol. 2001;49(2):146-154 2. Vernino S, Tuite P, Adler CH, et al. Paraneoplastic chorea associated with CRMP-5 neuronal antibody and lung carcinoma. Ann Neurol. 2002;51(5):625-630 3. Vernino S, Lennon VA. Autoantibody profiles and neurological correlations of thymoma. Clin Cancer Res. 2004;10(21):7270-7275 4. Galanis E, Frytak S, Rowland KM Jr, et al. Neuronal autoantibody titers in the course of small cell lung carcinoma and platinum associated neuropathy. Cancer Immunol Immunother. 1999;48(2-3):85 5. Klein CJ. Autoimmune-mediated peripheral neuropathies and autoimmune pain. In: Pittock SJ, Vincent A, eds. Handbook of Clinical Neurology; Autoimmune Neurology. Elsevier; 2016 pp 417-446

CRMWC 21747 Collapsin Response-Mediator Protein-5-IgG, Western Blot, Spinal Fluid

Clinical Information: Autoantibodies specific for neurons and muscle are important serological markers of neurological autoimmunity. Most are highly predictive of specific neoplasms that are metastatic when diagnosed, but usually limited in spread to regional lymph nodes and adjacent structures.(1-4) Collapsin response-mediator protein-5 (CRMP-5) is highly expressed in small-cell lung carcinomas (SCLC), in neurons throughout the adult central and peripheral nervous systems, and in a subset of glial cells.(1) In Western blot analyses, the native antigen is a 62-kDa protein (recombinant human CRMP-5 is 68 kDa).(1) CRMP-5-IgG (also known as "anti-CV-2")(4,5) is a more common autoantibody accompaniment of SCLC than antineuronal nuclear antibodies-1 (ANNA-1; anti-Hu) and sometimes occurs with thymoma. The neurological presentation of CRMP-5 seropositive patients is usually multifocal, and can affect any level of the neuraxis. Neurological presentations that suggest a CRMP-5-IgG-related syndrome include subacute chorea or cranial neuropathy (particularly loss of vision, taste, or smell), dementia, myelopathy and gastrointestinal dysmotility in a patient with risk factors for lung cancer, or encephalopathy or neuromuscular hyperexcitability in a patient with serological or clinical evidence of myasthenia gravis.(1) Fourteen percent of patients have thromboembolic phenomena. Seropositive patients who have thymoma usually present with other myasthenia gravis neurological manifestations (eg, encephalopathy, disorders of continuous muscle fiber activity).(3) CRMP-5-IgG is defined in serum or spinal fluid by its characteristic immunofluorescence (IF) staining pattern on a mixed tissue substrate of adult mouse central and peripheral neurons. However, CRMP-5-IgG is not detectable by standard IF screening if the titer is low (serum <1:240; CSF <1:2) or if coexisting autoantibodies, either neuron-specific or nonorgan-specific antinuclear and antimitochondrial antibodies, preclude identification of CRMP-5-IgG with certainty. In these situations, CRMP-5-IgG may be detected by Western blot analysis.

Useful For: Evaluation of cases of chorea, vision loss, cranial neuropathy and myelopathy

Interpretation: A positive result confirms that a patient's subacute neurological disorder has an autoimmune basis and is likely to be associated with a small-cell lung carcinoma (SCLC) or thymoma, which may be occult.(1,2) A positive result has a predictive value of 90% for neoplasm (77% SCLC, 6% thymoma).(1) Seropositivity is found in approximately 3% of patients who have SCLC with limited metastasis without evidence of neurological autoimmunity.(6) Clinical-serological correlations have not yet been established for children. Western blot analysis is indicated when interfering nonorgan-specific or coexisting neuron-specific autoantibodies in serum or spinal fluid preclude unambiguous detection of CRMP-5-IgG by indirect immunofluorescence assay, or when the immunofluorescence assay is negative in a patient whose neurological presentation suggests a CRMP-5-IgG-related syndrome.

Reference Values:

Negative

Clinical References: 1. Yu Z, Kryzer TJ, Griesmann GE, et al. CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. Ann Neurol. 2001;49(2):146-154 2. Vernino S, Tuite P, Adler CH, et al. Paraneoplastic chorea associated with CRMP-5 neuronal antibody and lung carcinoma. Ann Neurol. 2002;51(5):625-630 3. Vernino S, Lennon VA. Autoantibody profiles and neurological correlations of thymoma. Clin Cancer Res. 2004;10(21):7270-7275 4. Galanis E, Frytak S, Rowland KM Jr, et al. Neuronal autoantibody titers in the course of small cell lung carcinoma and platinum associated neuropathy. Cancer Immunol Immunother 1999;48(2-3):85-90 5. Klein CJ. Autoimmune-mediated peripheral neuropathies and autoimmune pain. In: Pittock SJ, Vincent A, eds. Handbook of Clinical Neurology; Autoimmune Neurology. Elsevier; 2016 pp 417-446

COMID 621533 Combined Humoral and Cell-Mediated Immunodeficiency Gene Panel, Varies

Clinical Information:

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of a hereditary combined humoral and cell-mediated immunodeficiency (CID) Establishing a diagnosis of a combined immunodeficiency associated with known causal genes Identifying variants within genes known to be associated with inherited CID, allowing for predictive testing of at-risk family members and/or determination of targeted management (anticipatory guidance, management changes, specific therapies)

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507. doi:10.1007/s10875-022-01289-3 3. Bousfiha A, Moundir A, Tangye SG, et al. The 2022 Update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity. J Clin Immunol. 2022;42(7):1508-1520. doi:10.1007/s10875-022-01352-z 4. Bosticardo M, Yamazaki Y, Cowan J, et al. Heterozygous FOXN1 variants cause low TRECs and severe T cell lymphopenia, revealing a crucial role of FOXN1 in supporting early thymopoiesis. Am J Hum Genet. 2019;105(3):549-561. doi:10.1016/j.ajhg.2019.07.014 5. Dvorak CC, Haddad E, Heimall J, et al. The diagnosis of severe combined immunodeficiency (SCID): The Primary Immune Deficiency Treatment Consortium (PIDTC) 2022 Definitions. J Allergy Clin Immunol. 2023;151(2):539-546. doi:10.1016/j.jaci.2022.10.022 6. Yagi H, Furutani Y, Hamada H, et al. Role of TBX1 in human del22q11.2 syndrome. Lancet. 2003;362(9393):1366-1373. doi:10.1016/s0140-6736(03)14632-6 7. Verhagen JM, Diderich KE, Oudesluijs G, et al. Phenotypic variability of atypical 22q11.2 deletions not including TBX1. Am J Med Genet A. 2012;158A(10):2412-2420. doi:10.1002/ajmg.a.35517

CMITO
617103

Combined Mitochondrial Full Genome and Nuclear Gene Panel, Varies

Clinical Information: The mitochondrion occupies a unique position in eukaryotic biology. It is the site of energy metabolism, and it is the sole subcellular organelle that is composed of proteins derived from 2 genomes, mitochondrial and nuclear. A group of hereditary disorders due to variants in either the mitochondrial genome or nuclear mitochondrial genes have been well characterized. The diagnosis of mitochondrial disease can be particularly challenging as the presentation can occur at any age, involve virtually any organ system, and be associated with widely varying severities. Due to the considerable overlap in the clinical phenotypes of various mitochondrial disorders, it is often difficult to distinguish these specific inherited disorders without genetic testing. This test utilizes massively parallel sequencing, also termed next-generation sequencing (NGS), to analyze 221 nuclear-encoded genes implicated in mitochondrial disease and to determine the exact sequence of the entire 16,569 base-pair mitochondrial genome. The utility of this test is to assist in the diagnosis of mitochondrial diseases that result from variants in both nuclear encoded genes and in the mitochondrial genome. Those diseases involving nuclear genes include disorders of mitochondrial protein synthesis, coenzyme Q10 biosynthesis, respiratory chain complexes, and mitochondrial DNA (mtDNA) maintenance (ie, mtDNA depletion disorders). Disorders of the mitochondrial genome include those caused by point alterations, such as mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), mitochondrial myopathy (MM), neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP), Leigh syndrome, Leber hereditary optic neuropathy (LHON), and chronic progressive external ophthalmoplegia (CPEO). In addition to the detection of single base changes with these disorders, large deletions, such as those associated with Kearns-Sayre or Pearson syndromes, are also detected. In contrast to variants in nuclear genes, which are present in either 0, 1, or 2 copies, mitochondrial variants can be present in any fraction of the total organelles, a phenomenon known as heteroplasmy. Typically, the severity of disease presentation is a function of the degree of heteroplasmy. Individuals with a higher fraction of altered mitochondria present with more severe disease than those with lower percentages of altered alleles. The sensitivity for the detection of altered alleles in a background of wild-type (or normal) mitochondrial sequences by NGS is approximately 10%.

Useful For: Diagnosing mitochondrial disease that results from variants in either nuclear-encoded genes or the mitochondrial genome A second-tier test for patients in whom previous targeted gene variant analyses for specific mitochondrial disease-related genes were negative Identifying variants known to be associated with mitochondrial disease, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1-2) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. McCormick EM, Lott MT, Dulik MC, et al. Specifications of the ACMG/AMP standards and guidelines for mitochondrial DNA variant interpretation. Hum Mutat. 2020;41(12):2028-2057 3. Munnich A, Rotig A, Cormier-Daire V, Rustin P. Clinical presentation of respiratory chain deficiency. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill; 2019. Accessed March

8, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225086827 4. Wallace DC, Lott MT, Brown MD, Kerstann K. Mitochondria and neuro-ophthalmologic diseases. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill; 2019. Accessed March 8, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225088522 5. Wong LJ. Molecular genetics of mitochondrial disorders. Dev Disabil Res Rev. 2010;16(2):154-162 6. Barca E, Long Y, Cooley V, et al. Mitochondrial disease in North America: An analysis of the NAMDC Registry. Neurol Genet. 2020;6(2):e402

CMIL
82833

Common Millet, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to common millet Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

REED
82902

Common Reed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to common reed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CO4D
70407

Complement 4d Immunostain, Technical Component Only

Clinical Information: Complement 4d (C4d) is a split product resulting from complement activation. The deposition of C4d on the walls of peritubular capillaries in kidney allografts or capillaries in cardiac allografts has been associated with antibody-mediated transplant rejection.

Useful For: Identification of antibody-mediated transplant rejection

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Roden AC, Maleszewski JJ, Yi ES, et al. Reproducibility of complement 4d deposition by immunofluorescence and immunohistochemistry in lung allograft biopsies. J Heart Lung Transplant. 2014;33(12):1223-1232. doi:10.1016/j.healun.2014.06.006 2. Miller DV, Roden AC, Gamez JD, Tazelaar HD. Detection of C4d deposition in cardiac allografts: a comparative study of immunofluorescence and immunoperoxidase methods. Arch Pathol Lab Med. 2010;134(11):1679-1684. doi:10.1043/2009-0511-OAR1.1 3. Troxell ML, Lanciault C: Practical applications in immunohistochemistry: Evaluation of rejection and infection in organ transplantation. Arch Pathol Lab Med. 2016;140(9):910-925. doi:10.5858/arpa.2015-0275-CP 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

C1Q
8851

Complement C1q, Serum

Clinical Information: The first component of complement (C1) is composed of 3 subunits designated as C1q, C1r, and C1s. C1q recognizes and binds to immunoglobulin complexed to antigen and initiates the complement cascade. Congenital deficiencies of any of the early complement components (C1, C2, C4) results in an inability to clear immune complexes. Inherited deficiency of C1 is rare. Like the more common C2 deficiency, C1 deficiency is associated with increased incidence of immune complex disease (systemic lupus erythematosus, polymyositis, glomerulonephritis, and Henoch-Schonlein purpura). Low C1 levels have also been reported in patients with abnormal immunoglobulin levels (Bruton and common variable hypogammaglobulinemia and severe combined immunodeficiency). This is most likely due to increased catabolism. The measurement of C1q is an indicator of the amount of C1 present.

Useful For: Assessment of an undetectable total complement level Diagnosing congenital C1 (first component of complement) deficiency Diagnosing acquired deficiency of C1 inhibitor

Interpretation: An undetectable C1q in the presence of an absent total complement and normal C2, C3, and C4 suggests a congenital C1 (first component of complement) deficiency. A low C1q in combination with a low C1 inhibitor and low C4 suggests an acquired C1 inhibitor deficiency.

Reference Values:
12-22 mg/dL

Clinical References: 1. Stegert M, Bock M, Trendelenburg M. Clinical presentation of human C1q deficiency: How much of a lupus? Mol Immunol. 2015;67(1):3-11 2. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507 3. Beurskens FJ,

van Schaarenburg RA, Trouw LA. C1q, antibodies and anti-C1q autoantibodies. Mol Immunol. 2015;68(1):6-13

C341Q
621739

Complement C3 and C4 with Anti-C1q Antibodies, Serum

Clinical Information:

Useful For: Evaluating patients with suspected anti-C1q vasculitis Predicting renal involvement in patients with systemic lupus erythematosus

Interpretation: A positive result for anti-C1q antibodies may support a diagnosis of anti-C1q vasculitis or renal involvement in patients with systemic lupus erythematosus in the appropriate clinical context. A negative result indicates no detectable IgG antibodies to C1q and does not rule out a diagnosis. A decrease in C3 levels to the abnormal range is consistent with disease activation in systemic lupus erythematosus.

Reference Values:

C3:
75-175 mg/dL

C4:
14-40 mg/dL

AC1Q:
<20 U/mL (Negative)
20-39 U/mL (Weak Positive)
40-80 U/mL (Moderate Positive)
>80 U/mL (Strong Positive)

Clinical References: 1. Dragon-Durey MA, Blanc C, Marinozzi MC, van Schaarenburg RA, Trouw LA. Autoantibodies against complement components and functional consequences. Mol Immunol. 2013;56(3):213-221 2. Defendi F, Thielens NM, Clavarino G, Cesbron JY, Dumestre-Perard C. The immunopathology of complement proteins and innate immunity in autoimmune disease. Clin Rev Allergy Immunol. 2020;58(2):229-251 3. Marzano AV, Maronese CA, Genovese G, et al. Urticarial vasculitis: Clinical and laboratory findings with a particular emphasis on differential diagnosis. J Allergy Clin Immunol. 2022;149(4):1137-1149 4. Hristova MH, Stoyanova VS. Autoantibodies against complement components in systemic lupus erythematosus - role in the pathogenesis and clinical manifestations. Lupus. 2017;26(14):1550-1555 5. Jachiet M, Flageul B, Deroux A, et al. The clinical spectrum and therapeutic management of hypocomplementemic urticarial vasculitis: data from a French nationwide study of fifty-seven patients. Arthritis Rheumatol. 2015;67(2):527-534 6. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1-11 7. Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. J Am Acad Dermatol. 1992;26(3 Pt 2):441-448 8. Damman J, Mooyaart AL, Seelen MAJ, van Doorn MBA. Dermal C4d deposition and neutrophil alignment along the dermal-epidermal junction as a diagnostic adjunct for hypocomplementemic urticarial vasculitis (anti-C1q vasculitis) and underlying systemic disease. Am J Dermatopathol. 2020;42(6):399-406 9. Marto N, Bertolaccini ML, Calabuig E, Hughes GR, Khamashta MA. Anti-C1q antibodies in nephritis: correlation between titres and renal disease activity and positive predictive value in systemic lupus erythematosus. Ann Rheum Dis. 2005;64(3):444-448 10. Fava A, Wagner CA, Guthridge CJ, et al. Association of autoantibody concentrations and trajectories with lupus nephritis histological features and treatment response. Arthritis Rheumatol. Published online July 4, 2024. doi:10.1002/art.42941

C3
8174

Complement C3, Serum

Clinical Information: The complement system is an integral part of the body's immune defenses. It can be activated via immune complexes (classic pathway) or by bacterial polysaccharides (alternative pathway). The primary complement pathway consists of recognition (Clq, Clr, Cls), activation (C4, C2, C3), and attack (C5, C6, C7, C8, C9) mechanisms with respect to their role in antibody-mediated cytolysis. Complement component 3 activation involves cleavage by C3 convertase into C3a and C3b. When immune complexes are not involved, the alternate method of complement activation initiates the reactant sequence at C3, bypassing C1, C4, and C2. Severe recurrent bacterial infections occur in patients with homozygous C3 deficiency and in those patients with low levels of C3 secondary to the absence of C3b activator. Decreased C3 may be associated with acute glomerulonephritis, membranoproliferative glomerulonephritis, immune complex disease, active systemic lupus erythematosus, septic shock, and end-stage liver disease.

Useful For: Assessing disease activity in systemic lupus erythematosus Investigating an undetectable total complement level

Interpretation: A decrease in C3 levels to the abnormal range is consistent with disease activation in systemic lupus erythematosus.

Reference Values:
75-175 mg/dL

Clinical References: 1. Willrich MAV, Braun KMP, Moyer AM, Jeffrey DH, Frazer-Abel A. Complement testing in the clinical laboratory. Crit Rev Clin Lab Sci. 2021;58(7):447-478. doi:10.1080/10408363.2021.19072972 2. Wong EKS, Kavanagh D. Diseases of complement dysregulation-an overview. Semin Immunopathol. 2018;40(1):49-64. doi:10.1007/s00281-017-0663-8 3. Prohaszka Z, Kirschfink M, Frazer-Abel A. Complement analysis in the era of targeted therapeutics. Mol Immunol. 2018;102:84-88. doi:10.1016/j.molimm.2018.06.001 4. Brodszki N, Frazer-Abel A, Grumach AS, et al. European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA) Complement Guideline: Deficiencies, Diagnosis, and Management. J Clin Immunol. 2020;40(4):576-591. doi:10.1007/s10875-020-00754-1

C4
8171

Complement C4, Serum

Clinical Information: The complement system is an integral part of the immune defenses. It can be activated via immune complexes (classic pathway) or by bacterial polysaccharides (alternative pathway). The classic complement pathway consists of recognition, (C1q, C1r, C1s), activation (C2, C3, C4), and attack (C5, C6, C7, C8, C9) mechanisms with respect to their role in antibody-mediated cytolysis. C4 is one of the activation proteins of the classic pathway. In the absence of C4, immune complexes will not be cleared by C3 activation peptides, but bacterial infections can still be defended via the alternative pathway. Complement component 4 may be decreased in systemic lupus erythematosus, early glomerulonephritis, immune complex disease, cryoglobulinemia, hereditary angioedema, and congenital C4 deficiency.

Useful For: Investigating an undetectable total complement Confirming hereditary angioedema (with low C1 inhibitor) Assessing disease activity in systemic lupus erythematosus, proliferative glomerulonephritis, rheumatoid arthritis, and autoimmune hemolytic anemia

Interpretation: Complement component 4 levels will be decreased in acquired autoimmune disorders, in the active phase of lupus erythematosus, and in rheumatoid arthritis. An undetectable C4 level (with

normal C3) suggests a congenital C4 deficiency. Levels will be increased in patients with autoimmune hemolytic anemia.

Reference Values:
14-40 mg/dL

Clinical References: 1. Willrich MAV, Braun KMP, Moyer AM, Jeffrey DH, Frazer-Abel A. Complement testing in the clinical laboratory. Crit Rev Clin Lab Sci. 2021;58(7):447-478. doi:10.1080/10408363.2021.19072972 2. Wong EKS, Kavanagh D. Diseases of complement dysregulation-an overview. Semin Immunopathol. 2018;40(1):49-64. doi:10.1007/s00281-017-0663-8 3. Prohaszka Z, Kirschfink M, Frazer-Abel A. Complement analysis in the era of targeted therapeutics. Mol Immunol. 2018;102:84-88. doi:10.1016/j.molimm.2018.06.001 4. Brodszki N, Frazer-Abel A, Grumach AS, et al. European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA) Complement Guideline: Deficiencies, Diagnosis, and Management. J Clin Immunol. 2020;40(4):576-591. doi:10.1007/s10875-020-00754-1

COM
8167

Complement, Total, Serum

Clinical Information: Complement (C) proteins are components of the innate immune system. There are 3 pathways to complement activation: the classical pathway, the alternative (or properdin) pathway, and the lectin (or mannan-binding lectin) pathway. The classical pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. A single IgM molecule or two IgG molecules are sufficient to trigger activation of the recognition complex initiated by C1q. The activation process triggers a cascade that includes an amplification loop. The amplification loop is mediated by C3, with cleavage of a series of proteins, and results in three main end products: anaphylatoxins which promote inflammation (C3a, C5a); opsonization peptides that are chemotactic for neutrophils (C3b) and facilitate phagocytosis; and the membrane attack complex (MAC), which promotes cell lysis. The absence of early components (C1, C2, C3, C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate the peptides that are necessary to clear immune complexes and to attract neutrophils or to generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease; complement deficiency may be an etiologic factor in the development of autoimmune disease. Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC and may have increased susceptibility to neisserial infections. Undetectable complement levels are found in patients with specific component deficiencies. Decreased complement levels are found in infectious and autoimmune diseases due to fixation and consumption of complement.

Useful For: Detection of individuals with an ongoing immune process First-tier screening test for congenital complement deficiencies

Interpretation: Low levels of total complement (total hemolytic complement) may occur during infections, disease exacerbation in patients with systemic lupus erythematosus, and in patients with immune complex diseases such as glomerulonephritis. Undetectable levels suggest the possibility of a complement component deficiency. Individual complement component assays are useful to identify the specific deficiency.

Reference Values:
30-75 U/mL

Clinical References: 1. Daha MR. Role of complement in innate immunity and infections. Crit Rev Immunol. 2010;30(1):47-52. doi:10.1615/critrevimmunol.v30.i1.30 2. Prohaszka Z, Varga L, Fust G. The use of 'real-time' complement analysis to differentiate atypical haemolytic uraemic syndrome from other forms of thrombotic microangiopathies. Br J Haematol. 2012;158(3):424-425. doi:10.1111/j.1365-2141.2012.09168.x 3. Cataland SR, Holers VM, Geyer S, Yang S, Wu HM. Biomarkers of terminal complement activation confirm the diagnosis of aHUS and differentiate aHUS from TTP. Blood. 2014;123(24):3733-3738. doi:10.1182/blood-2013-12-547067 4. Frazer-Abel A, Sepiashvili L, Mbughuni MM, Willrich MA. Overview of laboratory testing and clinical presentations of complement deficiencies and dysregulation. Adv Clin Chem. 2016;77:1-75. doi:10.1016/bs.acc.2016.06.001

CBC
9109

Complete Blood Cell Count (CBC) with Differential, Blood

Clinical Information: RBCs, WBCs, and platelets are produced in the bone marrow and released into the peripheral blood. The primary function of the RBC is to deliver oxygen to tissues. WBCs are key components of the immune system. Platelets play a vital role in blood clotting. Mean corpuscular volume (MCV) is a measure of the size of the average RBC. Anemias are characterized as microcytic (MCV <80), macrocytic (MCV >100), or normocytic. The red cell distribution width (RDW) is a measure of the degree of variation in RBC size (anisocytosis). RDW may be helpful in distinguishing between some anemias. For example, iron deficiency anemia is characterized by a high RDW, while thalassemia is characterized by a low RDW. These counts are used as clinical guides in the diagnosis or monitoring of many diseases.

Useful For: Screening tool to confirm a hematologic disorder, to establish or rule out a diagnosis, to detect an unsuspected hematologic disorder, or to monitor effects of radiation or chemotherapy

Interpretation: Results outside of normal value ranges may reflect a primary disorder of the cell-producing organs or an underlying disease. Results should be interpreted in conjunction with the patient's clinical picture and appropriate additional testing performed.

Reference Values:

RED BLOOD CELL COUNT (RBC)

Males:
0-14 days: 4.10-5.55 x 10(12)/L
15 days-4 weeks: 3.16-4.63 x 10(12)/L
5 weeks-7 weeks: 3.02-4.22 x 10(12)/L
8 weeks-5 months: 3.43-4.80 x 10(12)/L
6 months-23 months: 4.03-5.07 x 10(12)/L
24 months-35 months: 3.89-4.97 x 10(12)/L
3-5 years: 4.00-5.10 x 10(12)/L
6-10 years: 4.10-5.20 x 10(12)/L
11-14 years: 4.20-5.30 x 10(12)/L
15-17 years: 4.30-5.70 x 10(12)/L
Adults: 4.35-5.65 x 10(12)/L

Females:
0-14 days: 4.12-5.74 x 10(12)/L
15 days-4 weeks: 3.32-4.80 x 10(12)/L
5 weeks-7 weeks: 2.93-3.87 x 10(12)/L
8 weeks-5 months: 3.45-4.75 x 10(12)/L
6 months-23 months: 3.97-5.01 x 10(12)/L
24 months-35 months: 3.84-4.92 x 10(12)/L

3-5 years: 4.00-5.10 x 10(12)/L
6-10 years: 4.10-5.20 x 10(12)/L
11-14 years: 4.10-5.10 x 10(12)/L
15-17 years: 3.80-5.00 x 10(12)/L
Adults: 3.92-5.13 x 10(12)/L

HEMOGLOBIN
Males:
0-14 days: 13.9-19.1 g/dL
15 days-4 weeks: 10.0-15.3 g/dL
5 weeks-7 weeks: 8.9-12.7 g/dL
8 weeks-5 months: 9.6-12.4 g/dL
6 months-23 months: 10.1-12.5 g/dL
24 months-35 months: 10.2-12.7 g/dL
3-5 years: 11.4-14.3 g/dL
6-8 years: 11.5-14.3 g/dL
9-10 years: 11.8-14.7 g/dL
11-14 years: 12.4-15.7 g/dL
15-17 years: 13.3-16.9 g/dL
Adults: 13.2-16.6 g/dL

Females:
0-14 days: 13.4-20.0 g/dL
15 days-4 weeks: 10.8-14.6 g/dL
5 weeks-7 weeks: 9.2-11.4 g/dL
8 weeks-5 months: 9.9-12.4 g/dL
6 months-35 months: 10.2-12.7 g/dL
3-5 years: 11.4-14.3 g/dL
6-8 years: 11.5-14.3 g/dL
9-10 years: 11.8-14.7 g/dL
11-17 years: 11.9-14.8 g/dL
Adults: 11.6-15.0 g/dL

HEMATOCRIT
Males:
0-14 days: 39.8-53.6%
15 days-4 weeks: 30.5-45.0%
5 weeks-7 weeks: 26.8-37.5%
8 weeks-5 months: 28.6-37.2%
6 months-23 months: 30.8-37.8%
24 months-35 months: 31.0-37.7%
3-7 years: 34-42%
8-11 years: 35-43%
12-15 years: 38-47%
16-17 years: 40-50%
Adults: 38.3-48.6%

Females:
0-14 days: 39.6-57.2%
15 days-4 weeks: 32.0-44.5%
5 weeks-7 weeks: 27.7-35.1%
8 weeks-5 months: 29.5-37.1%
6 months-23 months: 30.9-37.9%
24 months-35 months: 31.2-37.8%

3-7 years: 34-42%
8-17 years: 35-43%
Adults: 35.5-44.9%

MEAN CORPUSCULAR VOLUME (MCV)
Males:
0-14 days: 91.3-103.1 fL
15 days-4 weeks: 89.4-99.7 fL
5 weeks-7 weeks: 84.3-94.2 fL
8 weeks-5 months: 74.1-87.5 fL
6 months-23 months: 69.5-81.7 fL
24 months-35 months: 71.3-84.0 fL
3-5 years: 77.2-89.5 fL
6-11 years: 77.8-91.1 fL
12-14 years: 79.9-93.0 fL
15-17 years: 82.5-98.0 fL
Adults: 78.2-97.9 fL

Females:
0-14 days: 92.7-106.4 fL
15 days-4 weeks: 90.1-103.0 fL
5 weeks-7 weeks: 83.4-96.4 fL
8 weeks-5 months: 74.8-88.3 fL
6 months-23 months: 71.3-82.6 fL
24 months-35 months: 72.3-85.0 fL
3-5 years: 77.2-89.5 fL
6-11 years: 77.8-91.1 fL
12-14 years: 79.9-93.0 fL
15-17 years: 82.5-98.0 fL
Adults: 78.2-97.93 fL

RED CELL DISTRIBUTION WIDTH (RDW)
Males:
0-14 days: 14.8-17.0%
15 days-4 weeks: 14.3-16.8%
5 weeks-7 weeks: 13.8-16.1%
8 weeks-5 months: 12.4-15.3%
6 months-23 months: 12.9-15.6%
24 months-35 months: 12.5-14.9%
3-5 years: 11.3-13.4%
6-17 years: 11.4-13.5%
Adults: 11.8-14.5%

Females:
0-14 days: 14.6-17.3%
15 days-4 weeks: 14.4-16.2%
5 weeks-7 weeks: 13.6-15.8%
8 weeks-5 months: 12.2-14.3%
6 months-23 months: 12.7-15.1%
24 months-35 months: 12.4-14.9%
3-5 years: 11.3-13.4%
6-17 years: 11.4-13.5%
Adults: 12.2-16.1%

WHITE BLOOD CELL COUNT (WBC)
Males:
0-14 days: 8.0-15.4 x 10(9)/L
15 days-4 weeks: 7.8-15.9 x 10(9)/L
5 weeks-7 weeks: 8.1-15.0 x 10(9)/L
8 weeks-5 months: 6.5-13.3 x 10(9)/L
6 months-23 months: 6.0-13.5 x 10(9)/L
24 months-35 months: 5.1-13.4 x 10(9)/L
3-5 years: 4.4-12.9 x 10(9)/L
6-17 years: 3.8-10.4 x 10(9)/L
Adults: 3.4-9.6 x 10(9)/L

Females:
0-14 days: 8.2-14.6 x 10(9)/L
15 days-4 weeks: 8.4-14.4 x 10(9)/L
5 weeks-7 weeks: 7.1-14.7 x 10(9)/L
8 weeks-5 months: 6.0-13.3 x 10(9)/L
6 months-23 months: 6.5-13.0 x 10(9)/L
24 months-35 months: 4.9-13.2 x 10(9)/L
3-5 years: 4.4-12.9 x 10(9)/L
6-17 years: 3.8-10.4 x 10(9)/L
Adults: 3.4-9.6 x 10(9)/L

PLATELETS
Males:
0-14 days: 218-419 x 10(9)/L
15 days-4 weeks: 248-586 x 10(9)/L
5 weeks-7 weeks: 229-562 x 10(9)/L
8 weeks-5 months: 244-529 x 10(9)/L
6 months-23 months: 206-445 x 10(9)/L
24 months-35 months: 202-403 x 10(9)/L
3-5 years: 187-445 x 10(9)/L
6-9 years: 187-400 x 10(9)/L
10-13 years: 177-381 x 10(9)/L
14-17 years: 139-320 x 10(9)/L
Adults: 135-317 x 10(9)/L

Females:
0-14 days: 144-449 x 10(9)/L
15 days-4 weeks: 279-571 x 10(9)/L
5 weeks-7 weeks: 331-597 x 10(9)/L
8 weeks-5 months: 247-580 x 10(9)/L
6 months-23 months: 214-459 x 10(9)/L
24 months-35 months: 189-394 x 10(9)/L
3-5 years: 187-445 x 10(9)/L
6-9 years: 187-400 x 10(9)/L
10-13 years: 177-381 x 10(9)/L
14-17 years: 158-362 x 10(9)/L
Adults: 157-371 x 10(9)/L

NEUTROPHILS
Males:
0-14 days: 1.60-6.06 x 10(9)/L
15 days-4 weeks: 1.18-5.45 x 10(9)/L

5 weeks-7 weeks: 0.83-4.23 x 10(9)/L
8 weeks-5 months: 0.97-5.45 x 10(9)/L
6 months-23 months: 1.19-7.21 x 10(9)/L
24 months-35 months: 1.54-7.92 x 10(9)/L
3-5 years: 1.60-7.80 x 10(9)/L
6-16 years: 1.40-6.10 x 10(9)/L
17 years: 1.80-7.20 x 10(9)/L
Adults: 1.56-6.45 x 10(9)/L

Females:
0-14 days: 1.73-6.75 x 10(9)/L
15 days-4 weeks: 1.23-4.80 x 10(9)/L
5 weeks-7 weeks: 1.00-4.68 x 10(9)/L
8 weeks-5 months: 1.04-7.20 x 10(9)/L
6 months-23 months: 1.27-7.18 x 10(9)/L
24 months-35 months: 1.60-8.29 x 10(9)/L
3-5 years: 1.60-7.80 x 10(9)/L
6-14 years: 1.50-6.50 x 10(9)/L
15-17 years: 2.00-7.40 x 10(9)/L
Adults: 1.56-6.45 x 10(9)/L

LYMPHOCYTES
Males:
0-14 days: 2.07-7.53 x 10(9)/L
15 days-4 weeks: 2.11-8.38 x 10(9)/L
5 weeks-7 weeks: 2.47-7.95 x 10(9)/L
8 weeks-5 months: 2.45-8.89 x 10(9)/L
6 months-23 months: 1.56-7.83 x 10(9)/L
24 months-35 months: 1.13-5.52 x 10(9)/L
3-5 years: 1.60-5.30 x 10(9)/L
6-11 years: 1.40-3.90 x 10(9)/L
12-17 years: 1.00-3.20 x 10(9)/L
Adults: 0.95-3.07 x 10(9)/L

Females:
0-14 days: 1.75-8.00 x 10(9)/L
15 days-4 weeks: 2.42-8.20 x 10(9)/L
5 weeks-7 weeks: 2.29-9.14 x 10(9)/L
8 weeks-5 months: 2.14-8.99 x 10(9)/L
6 months-23 months: 1.52-8.09 x 10(9)/L
24 months-35 months: 1.25-5.77 x 10(9)/L
3-5 years: 1.60-5.30 x 10(9)/L
6-11 years: 1.40-3.90 x 10(9)/L
12-17 years: 1.00-3.20 x 10(9)/L
Adults: 0.95-3.07 x 10(9)/L

MONOCYTES
Males:
0-14 days: 0.52-1.77 x 10(9)/L
15 days-4 weeks: 0.28-1.38 x 10(9)/L
5 weeks-7 weeks: 0.28-1.05 x 10(9)/L
8 weeks-5 months: 0.28-1.07 x 10(9)/L
6 months-23 months: 0.25-1.15 x 10(9)/L
24 months-35 months: 0.19-0.94 x 10(9)/L

3-5 years: 0.30-0.90 x 10(9)/L
6-17 years: 0.20-0.80 x 10(9)/L
Adults: 0.26-0.81 x 10(9)/L

Females:
0-14 days: 0.57-1.72 x 10(9)/L
15 days-4 weeks: 0.42-1.21 x 10(9)/L
5 weeks-7 weeks: 0.28-1.21 x 10(9)/L
8 weeks-5 months: 0.24-1.17 x 10(9)/L
6 months-23 months: 0.26-1.08 x 10(9)/L
24 months-35 months: 0.24-0.92 x 10(9)/L
3-5 years: 0.30-0.90 x 10(9)/L
6-17 years: 0.20-0.80 x 10(9)/L
Adults: 0.26-0.81 x 10(9)/L

EOSINOPHILS
Males:
0-14 days: 0.12-0.66 x 10(9)/L
15 days-4 weeks: 0.08-0.80 x 10(9)/L
5 weeks-7 weeks: 0.05-0.57 x 10(9)/L
8 weeks-5 months: 0.03-0.61 x 10(9)/L
6 months-23 months: 0.02-0.82 x 10(9)/L
24 months-35 months: 0.03-0.53 x 10(9)/L
3-11 years: 0.00-0.50 x 10(9)/L
12-17 years: 0.10-0.20 x 10(9)/L
Adults: 0.03-0.48 x 10(9)/L

Females:
0-14 days: 0.09-0.64 x 10(9)/L
15 days-4 weeks: 0.06-0.75 x 10(9)/L
5 weeks-7 weeks: 0.04-0.63 x 10(9)/L
8 weeks-5 months: 0.02-0.74 x 10(9)/L
6 months-23 months: 0.02-0.58 x 10(9)/L
24 months-35 months: 0.03-0.46 x 10(9)/L
3-11 years: 0.00-0.50 x 10(9)/L
12-17 years: 0.10-0.20 x 10(9)/L
Adults: 0.03-0.48 x 10(9)/L

BASOPHILS
Males:
0-14 days: 0.02-0.11 x 10(9)/L
15 days-7 weeks: 0.01-0.07 x 10(9)/L
8 weeks-35 months: 0.01-0.06 x 10(9)/L
3-17 years: 0.00-0.10 x 10(9)/L
Adults: 0.01-0.08 x 10(9)/L

Females:
0-14 days: 0.02-0.07 x 10(9)/L
15 days-4 weeks: 0.01-0.06 x 10(9)/L
5 weeks-7 weeks: 0.01-0.05 x 10(9)/L
8 weeks-5 months: 0.01-0.07 x 10(9)/L
6 months-35 months: 0.01-0.06 x 10(9)/L
3-17 years: 0.00-0.10 x 10(9)/L
Adults: 0.01-0.08 x 10(9)/L

Clinical References: 1. Adel K, Raizman J, Chen Y, et al: Complex biological profile of hematologic markers across pediatric, adult, and geriatric ages: establishment of robust pediatric and adult reference intervals on the basis of the Canadian Health Measures Survey. Clin Chem 2015;61:8 2. CLSI. Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline, Third Edition. CLSI document EP28-A3c. Wayne, PA, Clinical and Laboratory Standards Institute, 2008 3. Soldin J, Brugnara C, Wong EC: Pediatric Reference Intervals. Fifth Edition. AACC Press. Washington, DC, 2005. ISBN 1-594250-32-4

CACMG 617141 Comprehensive Arrhythmia and Cardiomyopathy Gene Panel, Varies

Clinical Information: The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by either genetic (inherited) factors or nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. The hereditary forms of cardiomyopathy include hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC or AC), left ventricular noncompaction, and restrictive cardiomyopathy.(1) Cardiomyopathy may also be a feature of an underlying systemic condition such as Noonan syndrome, a mitochondrial disorder, a muscular dystrophy, or a metabolic storage disorder.(1) In these cases, cardiomyopathy may be the first feature to come to attention clinically. Cardiac arrhythmias are a group of conditions characterized by abnormal heart rhythms. Arrhythmias can be caused by either genetic (inherited) factors or by nongenetic (acquired) causes such as medications and infection. The more common hereditary forms of cardiac arrhythmias include long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome.(2) Other inherited forms of arrhythmia can include, but are not limited to, ARVC and atrial fibrillation.(2) Additionally, other forms of inherited cardiomyopathies may first come to medical attention due to an associated arrhythmia. Cardiac arrhythmias can also be a feature of rarer, syndromic conditions including Andersen-Tawil syndrome, Cantu syndrome, Carvajal syndrome, Jervell and Lange-Nielsen syndrome, Naxos disease, Timothy syndrome, and Emery-Dreifuss muscular dystrophy.(2) Inherited cardiomyopathies and inherited cardiac arrhythmias can follow autosomal dominant, autosomal recessive, X-linked, and digenic patterns of inheritance. Genes associated with mitochondrial inheritance of cardiomyopathy and cardiac arrhythmia are not assessed on this panel.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of a hereditary form of either a cardiomyopathy or cardiac arrhythmia Establishing a diagnosis of a hereditary form of either a cardiomyopathy or cardiac arrhythmia.

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Hershberger RE, Givertz MM, Ho CY, et al. Genetic Evaluation of Cardiomyopathy-A Heart Failure Society of America Practice Guideline. J Card Fail. 2018 May;24(5):281-302. doi: 10.1016/j.cardfail.2018.03.004 2. Schwartz PJ, Ackerman MJ, Antzelevitch C, et al. Inherited cardiac arrhythmias. Nat Rev Dis Primers. 2020 Jul 16;6(1):58.. doi: 10.1038/s41572-020-0188-7 3. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015

May;17(5):405-424. doi: 10.1038/gim.2015.30

CARGG 617169 Comprehensive Arrhythmia Gene Panel, Varies

Clinical Information: Cardiac arrhythmias are a group of conditions characterized by abnormal heart rhythms. Arrhythmias can be caused by either genetic (inherited) factors or nongenetic (acquired) causes such as medications and infection. Hereditary forms of cardiac arrhythmias assessed for on this panel include, but are not limited to, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and familial atrial fibrillation.(1) This panel also assesses genes associated with rarer, syndromic conditions in which cardiac arrhythmia is a major feature, such as Andersen-Tawil syndrome, Carvajal syndrome, Jervell and Lange-Nielsen syndrome, Naxos disease, Timothy syndrome, and Emery-Dreifuss muscular dystrophy.(1-3) Inherited cardiac arrhythmias can follow autosomal dominant, autosomal recessive, X-linked, and digenic patterns of inheritance. Genes associated with mitochondrial inheritance of cardiac arrhythmias are not assessed on this panel.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of a hereditary form of cardiac arrhythmia Establishing a diagnosis of a hereditary form of cardiac arrhythmia

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(4) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Schwartz PJ, Ackerman MJ, Antzelevitch C, et al: Inherited cardiac arrhythmias. Nat Rev Dis Primers. 2020 Jul 16;6(1):58. doi: 10.1038/s41572-020-0188-7 2. Ackerman MJ, Priori SG, Willems S, et al: HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011 Aug;8(8):1308-1339. doi: 10.1016/j.hrthm.2011.05.020 3. Bonne G, Leturcq F, Ben Yaou R: Emery-Dreifuss Muscular Dystrophy. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated August 15, 2019. Accessed July 14, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1436/ 4. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

CCMGG 617183 Comprehensive Cardiomyopathy Gene Panel, Varies

Clinical Information: Cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by either inherited, genetic factors or nongenetic (acquired) causes, such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC or AC), and left ventricular noncompaction (LVNC).(1) The hereditary form of HCM is characterized by left ventricular

hypertrophy in the absence of other cardiac or systemic causes that may cause hypertrophy of the heart muscle, such as longstanding, uncontrolled hypertension or aortic stenosis. The incidence of HCM in the general population is approximately 1:200 to 1:500, and it is estimated that 30% to 60% of cases can be attributed to a genetic etiology.(2) Hereditary forms of HCM are most often caused by genes encoding proteins of the cardiac sarcomere, the functional contractile unit of the heart muscle. Hereditary forms of DCM are characterized by ventricular dilation with reduced cardiac performance in the absence of other cardiac or systemic causes that may cause dilation of the heart muscle, such as hypertension and ischemic heart disease. The incidence of DCM in the general population is approximately 1 in 2500, and it is estimated that approximately 50% of cases can be attributed to a genetic etiology.(3) Hereditary forms of DCM are most often caused by genes encoding proteins of the cardiac cytoskeleton and sarcomere. LVNC is characterized by prominent trabeculations of the left ventricle with trabecular recesses extending into the ventricular cavity. The incidence of LVNC in the general population is estimated to be 1 in 5000.(3) It is currently unclear if LVNC represents a genetically distinct form of cardiomyopathy, as many familial cases of LVNC have been linked to the same genes associated with other forms of hereditary cardiomyopathies and many affected individuals also meet diagnostic criteria for DCM or HCM.(3,4) Arrhythmogenic cardiomyopathy (ACM) is characterized by the presence of arrhythmogenic cardiac muscle in the absence of ischemic, hypertensive, or valvular cardiac disease. ARVC, the most well-defined form of ACM, is characterized by the breakdown of the myocardium and replacement of right ventricular muscle tissue with fibrofatty tissue, resulting in an increased risk of arrhythmia and sudden death. In some cases, there may also be left ventricular involvement. The prevalence of ARVC (genetic and acquired) is estimated to be 1 in 2000 to 1 in 5000 in the general population.(5) Hereditary forms of cardiomyopathy may be an isolated finding or may be a feature of an underlying systemic condition. Hereditary forms of cardiomyopathy can follow autosomal dominant, autosomal recessive, X-linked, and digenic patterns of inheritance. Mitochondrial inheritance is also possible, however, genes associated with mitochondrial inheritance of cardiomyopathy are not assessed on this panel.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of a hereditary form of cardiomyopathy Establishing a diagnosis of a hereditary form of cardiomyopathy

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Hershberger RE, Givertz MM, Ho CY, et al: Genetic evaluation of cardiomyopathy-a heart failure society of America practice guideline. J Card Fail. 2018;24(5):281-302. doi: 10.1016/j.cardfail.2018.03.004 2. Ommen SR, Mital S, Burke MA, et al: 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: Executive Summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. Circulation. 2020;142(25):e533-e557. doi: 10.1161/CIR.0000000000000938 3. Bozkurt B, Colvin M, Cook J, et al: Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association [published correction appears in Circulation. 2016 Dec 6;134(23):e652]. Circulation. 2016;134(23):e579-e646. doi: 10.1161/CIR.0000000000000455 4. Aung N, Doimo S, Ricci F, et al: Prognostic significance of left ventricular noncompaction: Systematic review and meta-analysis of observational studies. Circ Cardiovasc Imaging. 2020 Jan;13(1):e009712. doi: 10.1161/CIRCIMAGING.119.009712 5. Corrado D, Link MS, Calkins H: Arrhythmogenic right ventricular cardiomyopathy. N Engl J Med. 2017 Jan;376(1):61-72. doi: 10.1056/NEJMra1509267 6. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424. doi: 10.1038/gim.2015.30

CVHBG
617225

Comprehensive Cerebrovascular Gene Panel, Varies

Clinical Information: There are many known monogenic conditions that increase an individual's risk for cerebrovascular accident or stroke. Most of these conditions are characterized by abnormal vascular development, abnormal intracranial blood flow, and weakening of the cerebral vessels. Depending on the pathophysiology of the associated condition, risk may be increased for ischemic stroke, hemorrhagic stroke, or both.(1) Several vascular malformation syndromes are associated with an increased risk for stroke due to abnormalities in vascular development throughout the body.(1) Pulmonary arteriovenous malformations (AVM) are common features of autosomal dominant hereditary hemorrhagic telangiectasia and autosomal dominant capillary malformation-AVM. Pulmonary AVM increase the risk for ischemic stroke by allowing emboli to bypass the lungs and enter the cerebral vasculature.(1) Autosomal dominant familial cerebral cavernous malformation causes abnormal development of capillary channels within the brain and is associated with an increased risk for hemorrhagic stroke.(1,2) Several monogenic connective tissue conditions leading to vascular fragility are associated with an increased risk for arterial dissection and ischemic stroke.(1) These conditions lead to defects impacting the structural integrity of blood vessels throughout the body resulting in a high risk for vessel rupture. This panel assesses several vascular fragility syndromes, including autosomal dominant vascular Ehlers-Danlos syndrome, autosomal dominant Loeys-Dietz syndrome, autosomal dominant familial aortic aneurysm and dissection, and autosomal recessive arterial tortuosity syndrome.(3-6) Hereditary cerebral small vessel disease (SVD) is a group of conditions generally characterized by lacunar infarcts and white matter hyperintensities on magnetic resonance imaging and an increased risk for ischemic and/or hemorrhagic stroke.(1,7) The monogenic SVDs assessed on this panel include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), autosomal dominant retinal vasculopathy with leukodystrophy, autosomal dominant COL4A1-associated SVD, and autosomal dominant COL4A2-associated SVD.(1, 7) Moyamoya disease, a condition characterized by progressive narrowing of the blood vessels and an increased risk for ischemic stroke, can be inherited in an autosomal dominant manner. However, in most individuals, the genetic etiology (if any) remains unknown.(1,8) Other conditions associated with increased risk for ischemic and hemorrhagic stroke assessed on this panel include X-linked Fabry disease, autosomal recessive homocystinuria due to variants in the CBS gene, and autosomal recessive adenosine deaminase 2 deficiency.(1,9)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of a monogenic condition in which there is an increased risk for a cerebrovascular accident Establishing a diagnosis of a monogenic condition in which there is an increased risk for a cerebrovascular accident

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(10) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Tan RY, Markus HS. Monogenic causes of stroke: now and the future. J Neurol. 2015;262(12):2601-2616. doi:10.1007/s00415-015-7794-4 2. Zafar A, Quadri SA, Farooqui M, et al. Familial cerebral cavernous malformations. Stroke. 2019;50(5):1294-1301. doi:10.1161/STROKEAHA.118.022314 3. Byers PH. Vascular Ehlers-Danlos syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated February 21, 2019. Accessed September 6, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1494/ 4. Loeys BL, Dietz HC. Loeys-Dietz syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2008. Updated March 1, 2018. Accessed September 6, 2024. Available at

www.ncbi.nlm.nih.gov/books/NBK1133/ 5. Milewicz DM, Regalado E: Heritable thoracic aortic disease overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated May 4, 2023. Accessed September 6, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1120/ 6. Callewaert B, De Paepe A, Coucke P: Arterial Tortuosity Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2014. Updated February 23, 2023. Accessed September 6, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK253404/ 7. Litak J, Mazurek M, Kulesza B, et al. Cerebral small vessel disease. Int J Mol Sci. 2020;21(24):9729. doi:10.3390/ijms21249729 8. Shang S, Zhou D, Ya J, et al. Progress in moyamoya disease. Neurosurg Rev. 2020;43(2):371-382. doi:10.1007/s10143-018-0994-5 9. Aksentijevich I, Sampaio Moura N, Barron K. Adenosine deaminase 2 deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2019. Accessed September 6, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK544951 10. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

DWPAN
617545

Comprehensive Distal Weakness Gene Panel, Varies

Clinical Information: Peripheral neuropathy and distal myopathy are well-established inherited neuromuscular disorders characterized by progressive weakness and atrophy of the distal limb muscles. Inherited peripheral neuropathies are common neurologic disorders that represent a spectrum of diseases with different etiologies. Based on the pattern of inheritance and nerve conduction studies, there are 3 major categories of inherited peripheral neuropathies with isolated nerve involvement. The first group is hereditary motor and sensory neuropathy, also referred to as Charcot-Marie-Tooth (CMT) disease. Individuals with CMT typically present with slowly progressive muscle weakness and atrophy primarily affecting the distal extremities. The second group is hereditary sensory and autonomic neuropathy (HSAN) or hereditary sensory neuropathy if autonomic dysfunction is absent. They predominantly feature slowly progressive loss of multimodal sensation and autonomic dysfunction, with the most common features of HSANs being the loss of sensation of pain and temperature. The third group is distal hereditary motor neuropathy, which is characterized by length-dependent lower motor neuron dysfunction. The clinical phenotype is variable but includes progressive weakness and atrophy of the distal muscles, foot deformities, and decreased reflexes. Inherited peripheral neuropathies may also show involvement of the central nervous system (brain or spinal cord), as in hereditary spastic paraplegia with neuropathy or be part of a systemic syndromic or metabolic disorder. It is important to note that this assay includes testing for TTR-associated with familial amyloidosis. Distal myopathies are characterized by distal weakness and atrophy that starts in the muscles of the hands or feet and lack of cranial involvement or sensory loss. Distal myopathies are classified based on clinical features, inheritance pattern, and histopathological findings, such as the presence of rimmed vacuoles. Categories of distal myopathies include late adult-onset autosomal dominant forms, adult-onset autosomal dominant forms, early-onset autosomal dominant forms, early-onset autosomal recessive forms, and early adult-onset autosomal recessive forms. Additionally, inclusion body myositis presents with distal muscle weakness and may be in the differential with the distal myopathies. Given the considerable overlap in clinical phenotype of various disorders with distal weakness, multigene panels can be an efficient and cost-effective way to establish a molecular diagnosis.

Useful For: Establishing a molecular diagnosis for patients with distal weakness Identifying variants within genes known to be associated with distal weakness, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 201517(5):405-424 2. Klein CJ, Duan X, Shy ME: Inherited neuropathies: Clinical overview and update. Muscle Nerve. 2013;48(4):604-622 3. Udd B: Distal myopathies. Curr Neurol Neurosci Rep. 2014;14(3):434. doi:10.1007/s11910-013-0434-4 4. Savarese M, Sarparanta J, Vihola A, et al: Panorama of the distal myopathies. Acta Myol. 2020;39(4):245-265. doi:10.36185/2532-1900-028

FCDSU 75775 Comprehensive Drug Screen, Umbilical Cord Tissue

Reference Values:
Reporting limit(s) determined each analysis.

None Detected ng/g

EPPAN 616550 Comprehensive Epilepsy With or Without Encephalopathy Gene Panel, Varies

Clinical Information: Epilepsy is a chronic neurological disorder characterized by recurrent and unprovoked seizures. Epilepsy is common, impacting just over 1% of the population. The underlying cause of epilepsy is multifactorial, with both genetic and nongenetic etiologies. Inherited forms of epilepsy may present with varying seizure types, age of onset, comorbidities and underlying molecular causes, including channelopathies, metabolic conditions, and disorders associated with structural brain anomalies. Different hereditary epilepsies may follow autosomal dominant, autosomal recessive, or X-linked patterns of inheritance, or may occur as a result of a de novo pathogenic variant; therefore, identification of a specific molecular cause is essential to assess recurrence risk and impact to at risk family members. Clinical diagnoses can be challenging as pathogenic variants in different genes may be associated with strikingly similar clinical presentations. Comprehensive diagnostic genetic testing is useful to determine the molecular etiology which in turn can assist in establishing long-term prognosis and identifying appropriate therapeutic and management strategies.

Useful For: Establishing a diagnosis of an epilepsy or seizure disorder associated with known causal genes Identifying disease-causing variants within genes known to be associated with inherited epilepsy or seizure disorders, allowing for predictive testing of at-risk family members Impacting patient treatment and management through the identification of a specific underlying etiology for epilepsy (eg, directing appropriate use of antiepileptic drugs and other treatment modalities)

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Reference values for CSTB repeat expansion assay Normal: <5 dodecamer repeats Repeat Size of Uncertain Significance: 5-29 dodecamer repeats Full Penetrance Expansion: >29 dodecamer repeats

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-42. 2. Martinez L, Lai Y, Holder J, et al: Genetics in epilepsy. Neurol Clin. 2021 Aug; 39(3):743-777 3. Helbig I, Ellis C: Personalized medicine in genetic epilepsies-possibilities, challenges, and new frontiers. Neuropharmacology. 2020 Aug 1;172:107970

CAORG 617155 Comprehensive Marfan, Loeys-Dietz, Ehlers-Danlos, and Aortopathy Gene Panel, Varies

Clinical Information: Inherited forms of aortic disease, or aortopathies, may be associated with isolated thoracic aortic aneurysms and dissections or conditions with multi-system involvement. This gene panel includes genes for multiple conditions that may have aortopathy as a feature, including Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, arterial tortuosity syndrome, and heritable thoracic aortic disease (also known as familial thoracic aortic aneurysm/dissection: FTAAD). Other heritable conditions with overlapping clinical presentations are also covered by this panel. Confirming a genetic diagnosis in the setting of aortopathy may aid in differentiating the genetic etiology of complex or ambiguous clinical presentations, treatment decisions, and genetic counseling. Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue that occurs in approximately 1 to 2 per 10,000 individuals. It is characterized by the presence of skeletal, ocular, and cardiovascular manifestations and is caused by variants in the FBN1 gene. Skeletal findings may include tall stature, chest wall deformity, scoliosis, and joint hypermobility. Lens dislocation (ectopia lentis) is the cardinal ocular feature with mitral valve prolapse and aortic root dilatation/dissection the main cardiovascular features.(1) Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with significant overlap with Marfan syndrome but may include involvement of other organ systems and is primarily caused by variants in TGFBR1 and TGFBR2.(2,3) Features of LDS that are not typical of MFS include craniofacial and neurodevelopmental abnormalities and arterial tortuosity with increased risk for aneurysm and dissection throughout the arterial tree. Variants in the SMAD3 gene have been reported in families with an LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis. Variants in the TGFB3 gene have also been reported in families with an LDS-like phenotype, although these individuals tended to not have arterial tortuosity. Heritable thoracic aortic disease (FTAAD) is a genetic condition primarily involving dilatation and dissection of the thoracic aorta but may also include aneurysm and dissection of other arteries. This condition has a highly variable age of onset and presentation and may involve additional features such as congenital heart defects and other features of connective tissue disease or smooth muscle abnormalities depending on the causative gene. The gene most commonly involved in FTAAD is ACTA2.(4,5) Vascular Ehlers-Danlos syndrome (also known as vEDS or EDS IV) is an autosomal dominant connective tissue disease caused by variants in the COL3A1 gene. vEDS may present with characteristic facial features, thin, translucent skin, easy bruising, and arterial, intestinal, and uterine fragility. Arterial rupture may be preceded by aneurysm or dissection or may occur spontaneously.(6) Classic Ehlers-Danlos syndrome types I and II (also known as cEDS) are caused by variants in the COL5A1 and COL5A2 genes. Aortic root dilation and, more rarely, spontaneous vessel rupture have been reported in cEDS.(7) Other genes included on this panel cause conditions with clinical overlap with those above. Examples include genes associated with rare, autosomal recessive forms of Ehlers-Danlos syndrome, the FLNA gene associated with periventricular nodular heterotopia, the FBN2 gene associated with congenital contractural arachnodactyly, the CBS gene associated with homocystinuria, the SLC2A10 gene associated with autosomal recessive arterial tortuosity syndrome, and the NOTCH1 gene associated with aortic valve disease and severe valve calcification. Currently, expert consensus indicates NOTCH1 variants may be predictive of thoracic aortic enlargement without evidence of progression to aortic dissection.(8-12)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of hereditary aortic disease Establishing a diagnosis for a variety of hereditary conditions involving aortic

disease or overlapping clinical presentations including Marfan syndrome, Loeys-Dietz syndrome, multiple forms of Ehlers-Danlos syndrome, heritable thoracic aortic disease/aortopathy, and others

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(13) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Loeys BL, Dietz HC, Braverman AC, et al: The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010 Jul;47(7):476-485 2. Loeys BL, Schwarze U, Holm T, et al: Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med. 2006 Aug 24;355(8):788-798 3. Loeys BL, Chen J, Neptune ER, et al: A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet. 2005 Mar;37(3):275-281 4. Milewicz DM, Regalado E: Heritable thoracic aortic disease overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated December 14, 2017. Accessed September 22, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1120/ 5. Guo DC, Pannu H, Tran-Fadulu V, et al: Mutations in smooth muscle a-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. Nat Genet. 2007 Dec;39(12):1488-1493 6. Pepin M, Schwarze U, Superti-Furga A, Byers PH: Clinical and genetic features of Ehlers-Danlos syndrome type IV, The vascular type. N Engl J Med. 2000 Mar 9;342(10):673-680 7. Malfait F, Wenstrup R, Paepe AD: Classic Ehlers-Danlos syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2007. Updated July 26, 2018. Accessed September 22, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1244/ 8. Chen MH, Walsh CA: FLNA-related periventricular nodular heterotopia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated September 17, 2015. Accessed September 22, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1213/ 9. Callewaert B. Congenital contractural arachnodactyly. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated October 21, 2019. Accessed September 30, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1386/ 10. Sacharow SJ, Picker JD, Levy HL: Homocystinuria caused by cystathionine beta-synthase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated May 18, 2017. Accessed September 30, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1524/ 11. Coucke PJ, Willaert A, Wessels MW, et al: Mutations in the facilitative glucose transporter GLUT10 alter angiogenesis and cause arterial tortuosity syndrome. Nat Genet. 2006 Apr;38(4):452-457 12. Clinical Genome Resource: Gene-Disease Validity Classification Summary for NOTCH1-familial thoracic aortic aneurysm and aortic dissection. ClinGen; 2016. Accessed July 14, 2022. Available at https://search.clinicalgenome.org/kb/gene-validity/CGGCIEX:assertion_8269 13. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

CMAMA
113631

Comprehensive Metabolic Panel, Serum

Clinical Information: The comprehensive metabolic panel measures 14 analytes and calculates an anion gap. It is used to assess kidney or liver status, electrolyte and acid/base balance, and blood glucose This comprehensive metabolic panel can also provide information about a patient's response to medications that would impact kidney or liver function.

Useful For: Routine health monitoring Patient monitoring while hospitalized for information regarding metabolism, including the current kidney status, electrolyte and acid/base balance, and blood glucose

Interpretation: Comprehensive metabolic panel results are usually evaluated in conjunction with each other for patterns of results. The pattern of abnormal results can help identify the possible conditions or diseases present. Many conditions will cause abnormal results including kidney failure, breathing problems, and diabetes-related complications.

Reference Values:

SODIUM
<1 year: Not established
> or =1 year: 135-145 mmol/L

POTASSIUM
<1 year: Not established
> or =1 year: 3.6-5.2 mmol/L

CHLORIDE
1-17 years: 102-112 mmol/L
> or =18 years: 98-107 mmol/L
Reference values have not been established for patients who are younger than 12 months of age.

BICARBONATE
Males
12-24 months: 17-25 mmol/L
3 years: 18-26 mmol/L
4-5 years: 19-27 mmol/L
6-7 years: 20-28 mmol/L
8-17 years: 21-29 mmol/L
> or =18 years: 22-29 mmol/L

Females
1-3 years: 18-25 mmol/L
4-5 years: 19-26 mmol/L
6-7 years: 20-27 mmol/L
8-9 years: 21-28 mmol/L
> or =10 years: 22-29 mmol/L
Reference values have not been established for patients that are younger than 12 months of age.

ANION GAP
> or =7 years: 7-15
Reference values have not been established for patients who are younger than 7 years of age.

BLOOD UREA NITROGEN (BUN)
Males
1-17 years: 7-20 mg/dL
> or =18 years: 8-24 mg/dL
Reference values have not been established for patients who are younger than 12 months of age.

Females
1-17 years: 7-20 mg/dL
> or =18 years: 6-21 mg/dL
Reference values have not been established for patients who are younger than 12 months of age

CREATININE
Males:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL

Females:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL

ESTIMATED GLOMERULAR FILTRATION RATE (eGFR)
>= 18 years old: > or =60 mL/min/BSA
Estimated GFR calculated using the 2021 CKD_EPI creatinine equation.

Note: eGFR results will not be calculated for patients younger than 18 years old.

CALCIUM
<1 year: 8.7-11.0 mg/dL
1-17 years: 9.3-10.6 mg/dL
18-59 years: 8.6-10.0 mg/dL
60-90 years: 8.8-10.2 mg/dL
>90 years: 8.2-9.6 mg/dL

GLUCOSE
0-11 months: Not established
> or =1 year: 70-140 mg/dL

TOTAL PROTEIN
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients who are younger than 12 months of age.

ALBUMIN
> or =12 months: 3.5-5.0 g/dL
Reference values have not been established for patients who are younger than 12 months of age.

ASPARTATE AMINOTRANSFERASE (AST)
Males:
0-11 months: Not established
1-13 years: 8-60 U/L
> or =14 years: 8-48 U/L

Females:
0-11 months: Not established
1-13 years: 8-50 U/L
> or =14 years: 8-43 U/L

ALKALINE PHOSPHATASE (ALP)
Males
0-14 days: 83-248 U/L

15 days-<1 year: 122-469 U/L
1-<10 years: 142-335 U/L
10-<13 years: 129-417 U/L
13-<15 years: 116-468 U/L
15-<17 years: 82-331 U/L
17-<19 years: 55-149 U/L
> or =19 years: 40-129 U/L

Females
0-14 days: 83-248 U/L
15 days-<1 year: 122-469 U/L
1-<10 years: 142-335 U/L
10-<13 years: 129-417 U/L
13-<15 years: 57-254 U/L
15-<17 years: 50-117 U/L
> or =17 years: 35-104 U/L

ALANINE AMINOTRANSFERASE (ALT)
Males:
> or =1 year: 7-55 U/L
Reference values have not been established for patients who are younger than 12 months of age.

Females:
> or =1 year: 7-45 U/L
Reference values have not been established for patients who are younger than 12 months of age.

TOTAL BILIRUBIN
0-6 days: Refer to www.bilitool.org for information on age-specific (postnatal hour of life) serum bilirubin values.
7-14 days: 0.0-14.9 mg/dL
15 days to 17 years: 0.0-1.0 mg/dL
>18 years 0.0-1.2 mg/dL

Clinical References: Comprehensive Metabolic Panel (CMP). Testing.com; Updated July 29, 2022. Accessed September 19, 2023. Available at www.testing.com/tests/comprehensive-metabolic-panel-cmp/

NGHMM 620041 Comprehensive Myeloid Next-Generation Sequencing Assay, Bone Marrow

Clinical Information: This next-generation sequencing test provides a comprehensive genomic profile, including gene mutations and fusions, for myeloid neoplasms in a single assay. Many hematologic neoplasms are characterized by morphologic or phenotypic similarities but can have characteristic somatic mutations in many genes or a specific gene fusion that enables specific disease classification. In addition, many myeloid neoplasms lack a clonal cytogenetic finding at diagnosis (normal karyotype) but can be diagnosed, confirmed, and classified according to the gene mutation profile. Patients with unexplained cytopenias may harbor acquired genetic alterations in hematopoietic cells (clonal cytopenias of uncertain significance) which may carry risk of developing overt myeloid malignancies. Detection of a specific gene fusion or gene mutations in known or suspected myeloid neoplasm can provide critical diagnostic, prognostic, and therapeutic information to help guide management for the patient's healthcare professional.

Useful For: Evaluating known or suspected hematologic neoplasms, specifically of myeloid origin (eg,

acute myeloid leukemia, myelodysplastic syndrome, myeloproliferative neoplasm, myelodysplastic/myeloproliferative neoplasm, unexplained cytopenias) at the time of diagnosis or, possibly, disease relapse As an aid in determining diagnostic classification using bone marrow specimens Providing prognostic or therapeutic information for guiding clinical management Determining the presence of new clinically important gene mutation changes at relapse

Interpretation: Detailed variant assessment and interpretive comments will be provided for all reportable genetic alterations. If this test is ordered in the setting of erythrocytosis and suspicion of polycythemia vera, interpretation requires correlation with a concurrent or recent prior bone marrow evaluation.

Reference Values:
An interpretive report will be provided.

Clinical References:

NEPHP
618086

Comprehensive Nephrology Gene Panel, Varies

Clinical Information: Monogenic kidney disease spans a clinical spectrum of conditions with etiologies that can include structural, metabolic, immune, or endocrine abnormalities. Many heritable kidney diseases exhibit overlapping or complex phenotypes leading to a broad clinical differential. This gene panel assesses over 300 genes associated with a diverse spectrum of monogenic kidney diseases spanning the structural, metabolic, immune, and endocrine phenotypes. Assessing genetic etiologies across this phenotypic spectrum may aid in differentiating the genetic etiology of complex or ambiguous clinical presentations.(1-6) Renal phenotypes assessed on this panel include: focal segmental glomerulosclerosis, nephritic/nephrotic syndrome, Alport syndrome, cystic kidney diseases (including polycystic kidney disease), nephronophthisis, tubulointerstitial disease, congenital anomalies of kidney and urinary tract, nephrocalcinosis, nephrolithiasis (kidney stones), renal electrolyte imbalances (including Bartter syndrome), C3 glomerulopathy, and complement-mediated thrombotic microangiopathy (CM-TMA; also known as atypical hemolytic uremic syndrome [aHUS]). Many hereditary kidney diseases exhibit autosomal dominant, autosomal recessive, and/or X-linked inheritance. However, some hereditary kidney diseases exhibit complex or multifactorial inheritance. These complex and environmental etiologies are not assessed on this gene panel. Several risk alleles associated with increased susceptibility to kidney disease are also included on this panel to aid in risk assessment: -APOL1 Genotype: Two alleles, commonly called G1 and G2, have been associated with increased risk for development or progression of nondiabetic chronic kidney diseases.(7) -CFH-H3 Risk Haplotype: The variants that comprise this risk haplotype are common in the general population, but in the context of additional pathogenic genetic and environmental factors, the presence of this risk haplotype is associated with an increased risk for development or progression of atypical hemolytic uremic syndrome.(8) -MCP/CD46 Risk Haplotype: The variants that comprise this risk haplotype are common in the general population, but in the context of additional pathogenic genetic and environmental factors, the presence of this risk haplotype is associated with an increased risk for development or progression of atypical hemolytic uremic syndrome.(8) -Finally, two variants in C5 (p.Arg885His and p.Arg885Cys) that are associated with poor response to eculizumab can be detected by this panel.(9)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of hereditary kidney disease Establishing a diagnosis for a variety of hereditary kidney conditions including focal segmental glomerulosclerosis, nephritic/nephrotic syndrome, Alport syndrome, cystic kidney diseases (including polycystic kidney disease), nephronophthisis, tubulointerstitial disease, congenital anomalies of kidney and urinary tract, nephrocalcinosis, nephrolithiasis (kidney stones), renal electrolyte imbalances (including Bartter syndrome), C3 glomerulopathy, and complement-

mediated thrombotic microangiopathy (also known as atypical hemolytic uremic syndrome)

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(10) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Lemaire M, Noone D, Lapeyraque AL, Licht C, Fremeaux-Bacchi V. Inherited kidney complement diseases. Clin J Am Soc Nephrol. 2021;16(6):942-956. doi:10.2215/CJN.11830720 2. Lanktree MB, Haghighi A, di Bari I, Song X, Pei Y. Insights into autosomal dominant polycystic kidney disease from genetic studies. Clin J Am Soc Nephrol. 2021;16(5):790-799. doi:10.2215/CJN.02320220 3. Quinlan C, Rheault MN. Genetic basis of type IV collagen disorders of the kidney. Clin J Am Soc Nephrol. 2021;16(7) 1101-1109. doi:10.2215/CJN.19171220 4. Downie ML, Lopez Garcia SC, Kleta R, Bockenhauer D Inherited tubulopathies of the kidney: Insights from genetics. Clin J Am Soc Nephrol. 2021;16(4):620-630. doi:10.2215/CJN.14481119 5. Westland R, Renkema KY, Knoers NVAM. Clinical integration of genome diagnostics for congenital anomalies of the kidney and urinary tract. Clin J Am Soc Nephrol. 2020;16(1):128-137. doi:10.2215/CJN.14661119 6. Li AS, Ingham JF, Lennon R. Genetic disorders of the glomerular filtration barrier. Clin J Am Soc Nephrol. 2020;15(12):1818-1828. doi:10.2215/CJN.11440919 7. Parsa A, Kao WH, Xie D, et al. APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med. 2013;369(23):2183-2196. doi:10.1056/NEJMoa1310345 8. Bernabeu-Herrero ME, Jimenez-Alcazar M, Anter J, et al. Complement factor H, FHR-3 and FHR-1 variants associate in an extended haplotype conferring increased risk of atypical hemolytic uremic syndrome. Mol Immunol. 2015;67(2 Pt B):276-286. doi:10.1016/j.molimm.2015.06.021 9. Nishimura J, Yamamoto M, Hayashi S, et al. Genetic variants in C5 and poor response to eculizumab. N Engl J Med. 2014;370(7):632-639. doi:10.1056/NEJMoa1311084 10. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

MUPAN
617662

Comprehensive Neuromuscular Gene Panel, Varies

Clinical Information: age, but mostly they affect infants, children, and teenagers. While some neuromuscular disorders are acquired, the vast majority are genetic. Diagnosis of neuromuscular disorders involves clinical presentation, electromyography, muscle and nerve biopsy, and biochemical and genetic testing. This panel includes genes associated with muscular dystrophy, myopathy, rhabdomyolysis, congenital myasthenic syndrome, and skeletal muscular channelopathy disorders.

Useful For: Establishing a molecular diagnosis for patients with a neuromuscular disorder Identifying variants within genes known to be associated with neuromuscular disorders allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Laing NG. Genetics of neuromuscular disorders. Crit Rev Clin Lab Sci. 2012;49(2):33-48

PEPAN 617688 Comprehensive Peripheral Neuropathy Gene Panel, Varies

Clinical Information: Inherited peripheral neuropathies are common neurologic disorders that represent a spectrum of diseases with different etiologies. Based on the pattern of inheritance and nerve conduction studies, there are 3 major categories of inherited peripheral neuropathies with isolated nerve involvement. The first group is hereditary motor and sensory neuropathy, also referred to as Charcot-Marie-Tooth (CMT) disease. Individuals with CMT typically present with slowly progressive muscle weakness and atrophy, primarily affecting the distal extremities. The second group is hereditary sensory and autonomic neuropathy (HSAN) or hereditary sensory neuropathy if autonomic dysfunction is absent. They predominantly feature slowly progressive loss of multimodal sensation and autonomic dysfunction, with the most common features of HSANs being the loss of sensation of pain and temperature. The third group is distal hereditary motor neuropathy, which is characterized by length-dependent lower motor neuron dysfunction. The clinical phenotype is variable but includes progressive weakness and atrophy of the distal muscles, foot deformities, and decreased reflexes. Inherited peripheral neuropathies may also show involvement of the central nervous system (brain or spinal cord), as seen in hereditary spastic paraplegia with neuropathy, or they may be part of a systemic syndromic or metabolic disorder. The inherited peripheral neuropathies are a relatively common and heterogeneous group of disorders. Due to the considerable overlap in the clinical phenotypes of various neuropathies, it is often difficult to distinguish these specific inherited disorders from sporadic, idiopathic, or acquired forms of neuropathy without genetic testing. Additionally, peripheral neuropathy may be part of an inherited systemic syndromic or metabolic disorder caused by genes in metabolic pathways. Therefore, multigene panels can be an efficient and cost-effective way to establish a molecular diagnosis for individuals with peripheral neuropathy.

Useful For: Establishing a molecular diagnosis for patients with peripheral neuropathy Identifying variants within genes known to be associated with peripheral neuropathy, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Klein CJ, Duan X, Shy ME. Inherited neuropathies: clinical overview and update. Muscle Nerve. 2013;48(4):604-622

TBT 80667 Concentration, Mycobacteria (Bill Only)

Reference Values:

This test is for billing purposes only.
This is not an orderable test.

FFCAH
75305

Congenital Adrenal Hyperplasia (CAH) Pediatric Profile 6, Comprehensive Screen

Interpretation:

Reference Values:

Androstenedione	
Units: ng/dL	
Age	Range
Premature (26-28w) Day 4	63-935
Premature (31-35w) Day 4	50-449
Full Term (1-7 days)	
Levels decrease rapidly to	
Androstenedione gradually decreases during the first six months to prepubertal levels. Prepubertal Children	
Adult Males	44-186
Adult Females	2 -230
Females Postmenopausal	
Cortisol	
Units: ug/dL	
Age	Range
Premature (26-28w) Day 4	1.0-11
Premature (31-35w) Day 4	2.5-9.1
Full Term Day 3	1.7-14
Full Term Day 7	2.0-11
31d - 11m	2.8-23
12m - 15y (8:00 AM)	3 .0-21
Adults	
8:00 AM	8.0-19
4:00 PM	4.0-11

Deoxycorticosterone (DOC)	
Units: ng/dL	
Age	Range
Premature (26-28w) Day 4	20-105
Premature (34-36w) Day 4	28-78
Newborn: Levels are markedly elevated at birth and decrease rapidly during the first week to the range of 7-49 as found in older infants. 1-11m	7-49
Prepubertal Children	2-34
Pubertal Children and Adults 8:00 AM	2-19
Dehydroepiandrosterone (DHEA)	
Units: ng/dL	
Age	Range
Premature (26-31w)	82-1484
Premature (32-35w)	56-1853
Full Term (2-7d)	41-1292
8d-5m	
6-12m	
1-5 y	
6-7 y	
8-10 y	
11-12 y	
13-14 y	
15-16 y	39-481
17-19 y	40-491
20 50 y	31-701
>50 y	21-402
11-Desoxycortisol	
Units: ng/dL	
Age	Range
Premature (26-28w) Day 4	110-1376
Premature (31-35w) Day 4	48-579

Newborn Day 3	13-147
1-11m	
Prepubertal 8:00 AM	20-155
Pubertal Children and Adults 8:00 AM	12-158
17-OH Pregnenolone	
Units: ng/dL	
Age	Range
Premature (26-28w) Day 4	375-3559
Premature (31-35w) Day 4	64-2380
3 Days	10-829
1-5m	36-763
6-11m	42-540
12-23m	14-207
24m-5y	10-103
6-9y	10-186
Pubertal	44-235
Adults	53-357
Progesterone	
Units: ng/dL	
Males	
Age	Range
1-16y	
Adults	
Females	
Age	Range
1-10y	
11y	
12y	
13y	
14y	
15y	
16y	
Adult	
Cycle Days	Range
1-6	

7-12	
13-15	
16-28	
Post Menopausal	
Note: Luteal progesterone peaked from 350 to 3750 ng/dL on days ranging from 17 to 23. 17-Alpha-Hydroxyprogesterone 17-OHP	
Units: ng/dL	
Age	Range
Premature (26-28w) Day 4	124-841
Premature (31-35w) Day 4	26-568
Full-Term Day 3	
Males: Levels increase after the first week to peak values ranging from 40-200 between 30 and 60 days. Values then decline to a prepubertal value of	
Adult Males	27-199
Females	
1-11m	13-106
Prepubertal	
Adult Females	
Follicular	15-70
Luteal	35-290
Testosterone, Total	
Units: ng/dL	
Age	Range
Males	
Premature (26-28w) Day 4	59-125
Premature (31-35w) Day 4	37-198
Newborns	75-400
1-7m: Levels decrease rapidly the first week to 20-50, then increase to 60-400 between 20-60 days. Levels then decline	

to prepubertal range levels of	
Premature (26-28w) Day 4	5-16
Premature (31-35w) Day 4	5-22
Newborns	20-64
1-7m: Levels decrease during the first month to less than 10 and remain there until puberty. Prepubertal Males and Females	
Adult Males >18 years	264-916
Adult Females	
Premenopausal	10-55
Postmenopausal	7-40
Males	
Tanner Stage	Age (years)
1	
2	9.8-14.5
3	10.7-15.4
4	11.8-16.2
5	12.8-17.3
Females	
Tanner Stage	Age (years)
1	
2	9.2-13.7
3	10.0-14.4
4	10.7-15.6
5	11.8-18.6

CAH21
87815

Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency, Serum

Clinical Information: The cause of congenital adrenal hyperplasia (CAH) is an inherited genetic defect that results in decreased formation of one of the many enzymes that are involved in the production of cortisol. The enzyme defect results in reduced glucocorticoids and mineralocorticoids and elevated 17-hydroxyprogesterone (OHPG) and androgens. The resulting hormone imbalances can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized female patients. Adult-onset CAH may result in hirsutism or infertility in women. The adrenal glands, ovaries, testes, and placenta produce OHPG. It is hydroxylated at the 11 and 21 positions to produce cortisol.

Deficiency of either 11- or 21-hydroxylase results in decreased cortisol synthesis, and the feedback inhibition of adrenocorticotropic hormone (ACTH) secretion is lost. Consequently, increased pituitary release of ACTH increases production of OHPG. In contrast, if 17-alpha-hydroxylase (which allows formation of OHPG from progesterone) or 3-beta-ol-dehydrogenase (which allows formation of 17-hydroxyprogesterone formation from 17-hydroxypregnenolone) are deficient, OHPG levels are low with possible increase in progesterone or pregnenolone, respectively. Most (90%) cases of CAH are due to mutations in the 21-hydroxylase gene (CYP21A2). CAH due to 21-hydroxylase deficiency is diagnosed by confirming elevations of OHPG and androstenedione with decreased cortisol. By contrast, in 2 less common forms of CAH, due to 17-hydroxylase or 11-hydroxylase deficiency, OHPG and androstenedione levels are not significantly elevated and measurement of progesterone (PGSN / Progesterone, Serum) and deoxycorticosterone (DOCS / 11-Deoxycorticosterone, Serum), respectively, are necessary for diagnosis. OHPG is bound to both transcortin and albumin, and total OHPG is measured in this assay. OHPG is converted to pregnanetriol, which is conjugated and excreted in the urine. In all instances, more specific tests than pregnanetriol measurement are available to diagnose disorders of steroid metabolism.

Useful For: Preferred screening test for congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency Part of a battery of tests to evaluate women with hirsutism or infertility, which can result from adult-onset CAH

Interpretation: Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to 21-hydroxylase gene (CYP21A2) variants usually have very high levels of androstenedione, often 5- to 10-fold elevations. 17-Hydroxyprogesterone (OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. In the much less common CYP11A variant, androstenedione levels are elevated to a similar extent as in CYP21A2 variant, and cortisol is also low, but OHPG is only mildly, if at all, elevated. Also less common is 3-beta hydroxysteroid dehydrogenase (HSD) type 2 deficiency, characterized by low cortisol and substantial elevations in dehydroepiandrosterone sulfate (DHEA-S) and 17-alpha-hydroxypregnenolone, while androstenedione is either low, normal, or rarely, very mildly elevated (as a consequence of peripheral tissue androstenedione production by 3-beta HSD-1). In the very rare StAR (steroidogenic acute regulatory) protein deficiency, all steroid hormone levels are low and cholesterol is elevated. In the very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, OHPG, DHEA-S), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors, in particular progesterone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone, are increased. The goal of CAH treatment is normalization of cortisol levels and, ideally, of sex-steroid levels also. OHPG is measured to guide treatment, but this test correlates only modestly with androgen levels. Therefore, androstenedione and testosterone should also be measured and used to guide treatment modifications. Normal prepubertal levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels up to 100 ng/dL are usually regarded as acceptable.

Reference Values:

CORTISOL 5-25 mcg/dL (a.m.) 2-14 mcg/dL (p.m.) Pediatric reference ranges are the same as adults, as confirmed by peer-reviewed literature. Petersen KE. ACTH in normal children and children with pituitary and adrenal diseases. I.	**Age (Years)**	**Reference range (ng/dL)**

Measurement in plasma by radioimmunoassay-basal values. Acta Paediatr Scand. 1981;70(3):341-345 ANDROSTENEDIONE PEDIATRICS* Premature infants 26-28 weeks, day 4: 92-282 ng/dL 31-35 weeks, day 4: 80-446 ng/dL Full-term infants 1-7 days: 20-290 ng/dL 1 month-1 year:

Stage I (prepubertal)		
Stage II	9.8-14.5	31-65
Stage III	10.7-15.4	50-100
Stage IV	11.8-16.2	48-140
Stage V	12.8-17.3	65-210
Females* Tanner stages	Age (Years)	Reference range (ng/dL)
Stage I (prepubertal)		
Stage II	9.2-13.7	42-100
Stage III	10.0-14.4	80-190
Stage IV	10.7-15.6	77-225
Stage V	11.8-18.6	80-240

Clinical References:

CAH2T
42202

Congenital Adrenal Hyperplasia Newborn Screen, Blood Spot

Clinical Information: Congenital adrenal hyperplasia (CAH) is a group of disorders caused by inherited defects in steroid biosynthesis, most commonly, 21-hydroxylase deficiency (approximately 90% of cases) and 11-beta hydroxylase deficiency (approximately 5% of cases). The overall incidence of CAH due to 21-hydroxylase deficiency is approximately 1 in 15,000 live births. Individuals with CAH may present with life-threatening salt-wasting crises in the newborn period and incorrect sex assignment of virilized females, which occurs due to in utero exposure to reduced glucocorticoids and mineralocorticoids and elevated 17-hydroxyprogesterone (17-OHP) and androgens. Hormone replacement therapy, when initiated early, results in a significant reduction in morbidity and mortality. Therefore, newborn screening for CAH is desirable and has been implemented in all 50 states. Immunoassays are typically used to quantify 17-OHP as a marker for CAH in the newborn screen setting. However, these immunoassays are hampered by cross-reactivity of the antibodies with other steroids, yielding a high rate of false-positive results. Tandem mass spectrometry allows for the simultaneous specific determination of 17-OHP and other steroids, such as androstenedione, cortisol, 11-deoxycortisol, and 21-deoxycortisol. Application of this technology to the determination of steroids in newborn blood spots significantly enhances the correct identification of patients with CAH and reduces the number of false-positive screening results when implemented as a second-tier analysis performed prior to reporting of initial newborn screen results.

Useful For: Second-tier testing of newborns with abnormal screening result for congenital adrenal hyperplasia

Interpretation: Findings of a 17-hydroxyprogesterone (17-OHP) value greater than 15.0 ng/mL and a high (17-OHP + androstenedione)/cortisol ratio (> or =1) are supportive of the initial abnormal newborn screening result. Findings of an 11-deoxycortisol value greater than 15.0 ng/mL or 21-deoxycortisol greater than 4.0 ng/mL with elevated 17-OHP further support the abnormal newborn screening result and increase the diagnostic specificity. Clinical and laboratory follow-up is strongly recommended.

Reference Values:
17-HYDROXYPROGESTERONE (17-OHP)
<15.1 ng/mL

ANDROSTENEDIONE
<3.1 ng/mL

CORTISOL
Not applicable

11-DEOXYCORTISOL
<15.1 ng/mL

21-DEOXYCORTISOL
<4.1 ng/mL

(17-OHP + ANDROSTENEDIONE)/CORTISOL RATIO
<1.1
Note: Abnormal (17-OHP + Androstenedione)/Cortisol Ratio: > or =1.1 is only applicable when 17-OHP is elevated

11-DEOXYCORTISOL/CORTISOL RATIO
Not applicable

Clinical References: 1. Claahsen-van der Grinten HL, Speiser PW, et al. Congenital adrenal hyperplasia-Current insights in pathophysiology, diagnostics, and management. Endocr Rev. 2022;43(1):91-159. doi:10.1210/endrev/bnab016 2. Minutti CZ, Lacey JM, Magera MJ, et al. Steroid profiling by tandem mass spectrometry improves the positive predictive value of newborn screening for congenital adrenal hyperplasia. J Clin Endo Met. 2004;89:3687-3693 3. Turcu AF, Auchus RJ. The next 150 years of congenital adrenal hyperplasia. J Steroid Biochem Mol Biol. 2015;153:63-714 4. Witchel SF, Azziz R. Congenital adrenal hyperplasia. Pediatri Adolesc Gynecol. 2011;24:116-126

CCMVS 620659 Congenital Cytomegalovirus (cCMV), Molecular Detection, PCR, Saliva

Clinical Information: Cytomegalovirus (CMV) is a double-stranded DNA virus of the Herpesviridae family. CMV is transmitted through direct contact from a variety of infected body fluids, as well as through sexual contact, organ transplantation, and intrauterine transmission during pregnancy.(1) CMV infection may be asymptomatic but can cause a wide range of symptoms in immunocompromised individuals. Congenitally acquired CMV (cCMV) may lead to long-term sequelae, including visual and hearing impairments, and cognitive and motor deficits.(2) Current recommendations indicate testing urine and saliva swabs for cCMV using a nucleic acid amplification detection method.(3)

Useful For: Aiding in the rapid diagnosis of cytomegalovirus (CMV) infections in neonates 21 days of age or younger using saliva specimens

Interpretation: A positive result indicates the presence of cytomegalovirus (CMV) DNA in the patient sample. A negative result indicates the absence of CMV DNA in the patient sample. An invalid result indicates inability to conclusively determine presence or absence of CMV DNA in the patient sample.

Reference Values:
Negative

Clinical References: 1. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev. 2013;26(1):86-102. doi:10.1128/CMR.00062-12 2. Cannon MJ, Griffiths PD, Aston V, Rawlinson WD. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit?. Rev Med Virol. 2014;24(5):291-307. doi:10.1002/rmv.1790 3. Rawlinson WD, Boppana SB, Fowler KB, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis. 2017;17(6):e177-e188. doi:10.1016/S1473-3099(17)30143-3 4. Binnicker MJ, Espy ME. Comparison of six real-time PCR assays for qualitative detection of cytomegalovirus in clinical specimens. J Clin Microbiol. 2013;51(11):3749-3752. doi:10.1128/JCM.02005-13 5. Fernholz EC, Vidal-Folch N, Hasadsri L. Rapid and direct detection of congenital cytomegalovirus using a commercial real-time PCR assay. J Clin Microbiol. 2023;61(3):e0178122. doi:10.1128/jcm.01781-22

CCMVU 620658 Congenital Cytomegalovirus (cCMV), Molecular Detection, PCR, Urine

Clinical Information: Cytomegalovirus (CMV) is a double-stranded DNA virus of the Herpesviridae family. CMV is transmitted through direct contact from a variety of infected body fluids, as well as through sexual contact, organ transplantation, and intrauterine transmission during pregnancy.(1) CMV infection may be asymptomatic but can cause a wide range of symptoms, especially in immunocompromised individuals. Congenitally acquired CMV (cCMV) may lead to long-term sequelae, including visual and hearing impairments, and cognitive and motor deficits.(2) Current recommendations indicate testing urine and saliva swabs for cCMV using a nucleic acid amplification detection method.(3)

Useful For: Aiding in the rapid diagnosis of cytomegalovirus infections in neonates 21 days of age or younger using urine specimens

Interpretation: A positive result indicates the presence of cytomegalovirus (CMV) DNA in the patient sample. A negative result indicates the absence of CMV DNA in the patient sample. An invalid result indicates inability to conclusively determine presence or absence of CMV DNA in the patient sample.

Reference Values:
Negative

Clinical References: 1. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev. 2013;26(1):86-102. doi:10.1128/CMR.00062-12 2. Cannon MJ, Griffiths PD, Aston V, Rawlinson WD. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit?. Rev Med Virol. 2014;24(5):291-307. doi:10.1002/rmv.1790 3. Rawlinson WD, Boppana SB, Fowler KB, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis. 2017;17(6):e177-e188. doi:10.1016/S1473-3099(17)30143-3 4. Binnicker MJ, Espy ME. Comparison of six real-time PCR assays for qualitative detection of cytomegalovirus in clinical specimens. J Clin Microbiol. 2013;51(11):3749-3752. doi:10.1128/JCM.02005-13 5. Fernholz EC, Vidal-Folch N, Hasadsri L. Rapid and direct detection of congenital cytomegalovirus using a commercial real-time PCR assay. J Clin Microbiol. 2023;61(3):e0178122. doi:10.1128/jcm.01781-22

CDGGP
608010

Congenital Disorders of Glycosylation Gene Panel, Varies

Clinical Information: Congenital disorders of glycosylation (CDG), formerly known as carbohydrate-deficient glycoprotein syndrome, are a group of disorders affecting several steps of the pathway involved in the glycosylation of proteins. CDG are classified into 5 groups. CDG types I and II will have abnormal biochemical findings detected by serum transferrin and serum total N-glycan analyses (see CDG / Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum). In the other 3 groups these analyses will be normal. CDG type I disorders are characterized by defects in the assembly or transfer of the dolichol-linked glycan, while CDG type II includes defects of the glycan moiety processing. The third group includes disorders of glycosylphosphatidyl inositol anchor protein glycosylation. If clinically suspected, a flow cytometry analysis could facilitate the diagnostic workup. The fourth group involves disorders of O-mannosylation, a process that takes place predominantly in the muscle and brain tissues. The fifth group involves deglycosylation defects (eg, NAGLY1-CDG). The urine oligosaccharide profile by matrix-assisted laser desorption/ionization time-of-flight/time-of-flight mass spectrometer (MALDI-TOF/TOF-MS) may be abnormal and facilitate the diagnostic workup. CDG typically present as multisystemic disorders with a broad range of clinical features including developmental delay, hypotonia, abnormal magnetic resonance imaging findings, skin manifestations, and coagulopathy. There is considerable variation in the severity of this group of diseases, ranging from hydrops fetalis to a mild presentation in adults. Almost all types of CDG are autosomal recessive in inheritance, but some are X-linked. The broad clinical spectrum and genetic heterogeneity of CDG make a comprehensive panel a helpful tool in establishing a diagnosis for patients with suggestive clinical features.

Useful For: Establishing a molecular diagnosis for patients with congenital disorders of glycosylation Identifying variants within genes known to be associated with congenital disorders of glycosylation, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 2. Freeze HH, Chong JX, Bamshad MJ, Ng BG: Solving glycosylation disorders: fundamental approaches reveal complicated pathways. Am J Hum Genet. 2014;94(2):161-175 3. Krasnewich D: Human glycosylation disorders. Cancer Biomark. 2014 Jan;14(1):3-16

CDGN
65485

Congenital Disorders of N-Glycosylation, Serum

Clinical Information: Congenital disorders of glycosylation (CDG) are a group of over 150 inherited metabolic disorders largely affecting N- and O-glycosylation of proteins. The majority of CDG are attributed to congenital defects in N-glycosylation, which take place primarily in the cytoplasm and in the membranes of the endoplasmic reticulum. O-glycosylation defects are frequently tissue specific and present differently than classic N-linked defects. CDG are currently classified into 2 main groups. Type I CDG is characterized by defects in the assembly or transfer of the dolichol-linked glycan (sugar chain), while type II involves processing defects of the glycan. Depending on the specific defect, an N-glycosylation disorder can be either a type I or type II CDG. N-linked CDG are

phenotypically diverse, usually presenting as clinical syndromes with multisystemic involvement and a broad clinical spectrum. There is considerable variation in the severity of this group of diseases ranging from a mild presentation in adults to severe multi-organ dysfunction causing infantile lethality. Intellectual disability is common, although in some subtypes, phosphomannose isomerase-CDG (MPI-CDG or CDG type Ib) in particular, intellect is preserved. CDG should be considered in all patients with multisystem disease and in those with neurologic abnormalities, including developmental delay and seizures; brain abnormalities, such as cerebellar atrophy or hypoplasia; and unexplained liver dysfunction. Additional common symptoms that may be present include abnormal subcutaneous fat distribution; gastrointestinal issues, such as vomiting, chronic diarrhea, and protein-losing enteropathy; eye abnormalities, including retinal degeneration and strabismus; and cardiomyopathy. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry analysis of released N-linked oligosaccharides, as performed in this assay, is a global assessment of N-linked glycosylation. This complements the also performed transferrin and apolipoprotein CIII isoform analysis (see CDG / Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum) by providing additional information on specific structural oligosaccharide abnormalities that can guide molecular testing.

Useful For: Screening for N-linked congenital disorders of glycosylation Providing information on specific structural oligosaccharide abnormalities to potentially direct further genetic testing

Interpretation: The results of the transferrin and apolipoprotein CIII isoform analysis are followed up with matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry analysis of released N-linked oligosaccharides to assess N-linked glycosylation. Reports of abnormal results will include recommendations for additional biochemical and molecular genetic studies to identify more precisely the specific congenital disorder of glycosylation. If applicable, treatment options, the name and telephone number of contacts who may provide studies, and a telephone number for one of the laboratory directors (if the referring physician has additional questions) will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Sparks SE, Krasnewich DM. Congenital disorders of N-linked glycosylation and multiple pathway overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2005. Updated January 12, 2017. Accessed March 1, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1332/ 2. Chang IJ, He M, Lam CT. Congenital disorders of glycosylation. Ann Transl Med. 2018;6(24):477. doi:10.21037/atm.2018.10.45 3. Francisco R, Marques-da-Silva D, Brasil S, et al. The challenge of CDG diagnosis. Mol Genet Metab. 2019;126(1):1-5. doi:10.1016/j.ymgme.2018.11.003 4. Freeze HH, Chong JX, Bamshad MJ, Ng BG. Solving glycosylation disorders: fundamental approaches reveal complicated pathways. Am J Hum Genet. 2014;94(2):161-175. doi:10.1016/j.ajhg.2013.10.024 5. Verheijen J, Tahata S, Kozicz T, et al. Therapeutic approaches in congenital disorders of glycosylation (CDG) involving N-linked glycosylation: an update. Genet Med. 2020;22(2):268-279. doi:10.1038/s41436-019-0647-2 6. Francisco R, Brasil S, Poejo J, et al. Congenital disorders of glycosylation (CDG): state of the art in 2022. Orphanet J Rare Dis. 2023;18(1):329. doi:10.1186/s13023-023-02879-z

NCDA
619075

Congenital Dyserythropoietic Anemia Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Next-generation sequencing is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene variants can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. This panel aids in the diagnosis and genetic counseling of individuals with clinical or familial features of congenital

dyserythropoietic anemia (CDA). CDA is a disorder of ineffective erythropoiesis clinically subdivided into subtypes with various phenotypic findings that segregate into different gene associations.(1-6) These disorders have distinctive cytopathologic findings consisting of nuclear abnormalities in bone marrow erythroid precursors. Types I and II CDA are inherited in an autosomal recessive pattern, whereas types III and IV are autosomal dominant.

Useful For: Confirming the diagnosis or carrier variant status of genes associated with congenital dyserythropoietic anemia Identifying variants within genes associated with phenotypic severity, allowing for predictive testing and further genetic counseling

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:

An interpretive report will be provided.

Clinical References: 1. Orkin SH, Nathan DG, Ginsburg D, et al, eds. Nathan and Oski's Hematology of Infancy and Childhood. 7th ed. Saunders Elsevier; 2009:360-364 2. Iolascon A, Andolfo I, Russo R. Congenital dyserythropoietic anemias. Blood. 2020;136(11):1274-1283. doi:10.1182/blood.2019000948 3. Kamiya T, Manabe A. Congenital dyserythropoietic anemia. Int J Hematol. 2010;92(3):432-348. doi:10.1007/s12185-010-0667-9 4. Iolascon A, Heimpel H, Wahlin A, Tamary H. Congenital dyserythropoietic anemias: molecular insights and diagnostic approach. Blood. 2013;122(13):2162-2166 5. Arnaud L, Saison C, Helias V, et al. A dominant mutation in the gene encoding the erythroid transcription factor KLF1 causes a congenital dyserythropoietic anemia. Am J Hum Genet. 2010;87(5):721-727 6. Iolascon A, Andolfo I, Barcellini W, et al. Recommendations for splenectomy in hereditary hemolytic anemias. Haematologica. 2017;102(8):1304-1313. doi:10.3324/haematol.2016.161166 7. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

GNFIB
619159

Congenital Fibrinogen Disorders, FGA, FGB, and FGG Genes, Next-Generation Sequencing, Varies

Clinical Information: Congenital fibrinogen disorders (CFD) are rare bleeding abnormalities associated with germline variants in the FGA, FGB, and FGG genes. They manifest as one of 2 broad subtypes: autosomal recessive afibrinogenemia/hypofibrinogenemia (also known as a type I fibrinogen defect) or autosomal dominant dysfibrinogenemia (also known as a type II defect). Afibrinogenemia and hypofibrinogenemia are considered quantitative defects characterized by undetectable or low levels of fibrinogen, respectively. Afibrinogenemia often presents in the neonatal period as umbilical cord bleeding. However, a later age of onset is not unusual and bleeding in the skin, oral cavity, gastrointestinal tract, genitourinary tract, and the central nervous system can occur. Individuals with hypofibrinogenemia are typically asymptomatic due to fibrinogen levels that, while lower than normal, are adequate to protect against spontaneous bleeding. Dysfibrinogenemia is considered a qualitative defect. It is caused by structural changes in fibrinogen that modify its function, resulting in impaired

clotting ability. Individuals with dysfibrinogenemia are commonly asymptomatic or have episodic symptoms. Cases are frequently discovered incidentally during routine coagulation testing or because of a positive family history. Patients with CFD can also present with thrombotic events. Affected women are at increased risk of obstetric complications, including pregnancy loss, placental abruption, and postpartum hemorrhage.(3-6) Causes of acquired (nongenetic) fibrinogen disorders should be excluded prior to genetic testing, including liver disease, consumptive coagulopathy (eg, disseminated intravascular coagulopathy, trauma-induced coagulopathy, medications (eg, L-asparaginase), malignancy (eg, multiple myeloma), the use of plasma exchange using albumin as a replacement fluid, and autoimmune conditions resulting in antifibrinogen antibodies (e.g., rheumatoid arthritis and systemic lupus erythematosus).(3,4) The United Kingdom Haemophilia Centre Doctors' Organization provides guidelines regarding diagnosis and management for individuals with inherited bleeding disorders including fibrinogen deficiency.(7)

Useful For: Evaluating congenital fibrinogen disorders (CFD) in patients with a personal or family history suggestive of a fibrinogen disorder Confirming a CFD diagnosis with the identification of known or suspected disease-causing alterations in the FGA, FGB, or FGG genes Determining the disease-causing alterations within the FGA, FGB, or FGG genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of suggestive of CFD Identifying the causative alterations for genetic counseling purposes Prognosis and risk assessment based on the genotype-phenotype correlations Carrier testing for close family members of an individual with autosomal recessive afibrinogenemia/hypofibrinogenemia

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Mackie IJ, Kitchen S, Machin SJ, Lowe GDO: Guidelines on fibrinogen assays. Br J Haematol. 2003 May;121(3):396-404 2. Boender J, Kruip MJHA, Leebeek FWG: A diagnostic approach to mild bleeding disorders. J Thromb Haemost. 2016 Aug;14(8):1507-1516 3. May JE, Wolberg AS, Lim MY: Disorders of fibrinogen and fibrinolysis. Hematol Oncol Clin North Am. 2021 Dec;35(6):1197-1217 4. Tiscia GL, Margaglione M: Human fibrinogen: Molecular and genetic aspects of congenital disorders. Int J Mol Sci. 2018 May 29;19(6):1597 5. Palla R, Peyvandi F, Shapiro AD: Rare bleeding disorders: diagnosis and treatment. Blood. 2015 Mar 26;125(13):2052-2061 6. de Moerloose P, Casini A, Neerman-Arbez M: Congenital fibrinogen disorders: an update. Semin Thromb Hemost. 2013 Sep;39(6):585-595 7. Mumford AD, Ackroyd S, Alikhan R: Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2014 Nov;167(3):304-326 8. Richards S, Aziz N, Bale S et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

CHDGG
617197

Congenital Heart Disease Gene Panel, Varies

Clinical Information:

Useful For: Providing a genetic evaluation for patients with a personal or family history of congenital heart disease Establishing a diagnosis of a genetic condition associated with congenital heart disease

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(2) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Ison HE, Griffin EL, Parrott A, et al: Genetic counseling for congenital heart disease-Practice resource of the National Society of Genetic Counselors. J Genet Couns. 2022 Feb;31(1):9-33 2. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

CILPF 614180 Congenital Infantile Leukemia, FISH, Tissue

Clinical Information:

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities and classic rearrangements seen in infant patients with leukemia using tissue specimens

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. A positive result is not diagnostic for congenital or infantile leukemia but may provide relevant prognostic information. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow SH, Campo E, Harris NL, et al, eds: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017 2. Tomizawa D: Recent progress in the treatment of infant acute lymphoblastic leukemia. Pediatr Int. 2015;57(5):811-819. doi: 10.1111/ped.12758 3. Inaba H, Zhou Y, Abla O, et al: Heterogeneous cytogenetic subgroups and outcomes in childhood acute megakaryoblastic leukemia: a retrospective international study. Blood. 2015;126(13):1575-1584. doi: 10.1182/blood-2015-02-629204 4. Coenen EA, Zwaan CM, Reinhardt D, et al: Pediatric acute myeloid leukemia with t(8;16)(p11;p13), a distinct clinical and biological entity: a collaborative study by the International-Berlin-Frankfurt-Munster AML-study group. Blood. 2013;122(15):2704-2713. doi: 10.1182/blood-2013-02-485524

CLADP 608019 Congenital Lactic Acidosis Panel, Varies

Clinical Information: Congenital lactic acidosis (CLA) is a rare, but serious, condition that presents in newborns with extreme elevations of lactic acid and is caused by a variety of biochemical disorders, resulting in impaired mitochondrial activity. Elevated lactate in multiple specimen types such as blood and cerebrospinal fluid (CSF) are typically observed. However, additional symptoms are extremely variable, as any high-energy organ or tissue may be impaired, resulting in a need for multisystem screening that may involve biopsies and biochemical analysis. CLA can be caused by pathogenic variants in genes encoding enzymes involved in gluconeogenesis, pyruvate oxidation, the Krebs cycle, and mitochondrial function. A comprehensive gene panel with mitochondrial genome analysis is an essential tool to establish a diagnosis for patients with congenital lactic acidosis. As

biomarker testing and multisystem organ assessments are not specific and can yield complex results, genetic testing is required to distinguish among the spectrum of conditions that can cause CLA. This panel analyzes a combination of nuclear genes for single-gene biochemical disorders known to cause CLA, as well as analysis of the mitochondrial genome.

Useful For: Follow up for abnormal biochemical results suggestive of congenital lactic acidosis Establishing a molecular diagnosis for patients with congenital lactic acidosis Identifying variants within genes known to be associated with congenital lactic acidosis, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 2. Bravo-Alonso I, Navarrette R, Vega AI, et al: Genes and variants underlying human congenital lactic acidosis-from genetics to personalized treatment. J Clin Med. 2019;8(11):1811

CTDC
83631

Connective Tissue Diseases Cascade, Serum

Clinical Information:

Useful For: Evaluation of patients with signs and symptoms compatible with connective tissue diseases Initial evaluation of patients in clinical situations in which the prevalence of disease is low (6) This test is not recommended for: -Testing in clinical situations in which there is a high prevalence of connective tissue diseases (eg, rheumatology specialty practice) -Follow-up evaluation of patients with known connective tissue diseases

Interpretation: Interpretive comments are provided. Differential testing for Ro52 and Ro60 antibodies in SS-A/Ro positive patients may be useful in the diagnosis of specific CTD clinical subset, disease stratification, and prognosis. Consider testing for Ro52 and Ro60 antibodies (ROPAN / Ro52 and Ro60 Antibodies, IgG, Serum) if the patient is positive for SS-A/Ro.

Reference Values:
ANTINUCLEAR ANTIBODIES (ANA)
< or =1.0 U (Negative)
1.1-2.9 U (Weakly positive)
3.0-5.9 U (Positive)
> or =6.0 U (Strongly positive)
Reference values apply to all ages.

CYCLIC CITRULLINATED PEPTIDE ANTIBODIES, IgG
<20.0 U (Negative)
20.0-39.9 U (Weak positive)
40.0-59.9 U (Positive)
> or =60.0 U (Strong positive)

Reference values apply to all ages.

Clinical References:

SLSUR 622224 Consult Slide Surcharge (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

CRHPC 113329 Consult, w/Comp Rvw of His (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

CSPPC 113327 Consult, w/Slide Prep (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

CUPPC 113328 Consult, w/USS Prof (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

CONCS 616442 Contactin-1 IgG Cell Binding Assay, Serum

Clinical Information: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired, immune-mediated condition effecting peripheral nerves and nerve roots and is characterized by electrodiagnostic features of demyelination with a chronic onset that leads to significant disability. The prevalence of CIDP is estimated at approximately 2 to 4 cases per 100,000 persons. Although a rarer cause of polyneuropathy, it is important to recognize as it is treatable with the appropriate use of immunomodulating therapies. Although the exact immunological trigger of CIDP remains unclear, a subset of patients with suspected CIDP have been identified with autoantibodies targeting nodal-paranodal proteins. These patients share common immunopathological mechanisms of disease, clinical features, and treatment responses that are distinct from classic CIDP. A common target of these autoantibodies is the neurofascin-155 (NF155)-contactin-1 (CNTN1) complex. NF155 is expressed at the paranodal loops of Schwann cells where it interacts with CNTN1 expressed on adjacent axons. This interaction stabilizes and allows the proper organization of the paranodal axoglial junction. Antibody-mediated disruption of this interaction in animal models recapitulates the pathophysiology observed in humans. Contactin-1 IgG antibodies are present in approximately 2% of patients with CIDP-like presentations. CNTN1 IgG-positive cases are more likely to present with neuropathic pain, sensory ataxia, and subacute progressive demyelinating polyradiculoneuropathy or polyradiculopathy. The majority of seropositive patients have been reported to be refractory to treatment with intravenous

immune globulin (IVIg). However, some of these patients respond well to B-cell depleting therapies such as rituximab. Up to half of CNTN1 IgG-positive patients with CIDP or CIDP-like presentations have been reported to develop membranous nephropathy and, thus, screening for proteinuria may be warranted.

Useful For: Evaluating for chronic inflammatory demyelinating polyradiculoneuropathy and related demyelinating peripheral neuropathies Determining contactin-1 IgG results as a part of a profile

Interpretation: Seropositivity for contactin-1 IgG is consistent with an immune-mediated demyelinating polyradiculoneuropathy/polyradiculopathy.

Reference Values:
Only orderable as part of a profile. For more information see:
-CIDP / Chronic Inflammatory Demyelinating Polyradiculoneuropathy/Nodopathy Evaluation, Serum
-DMNES / Peripheral Nervous System Demyelinating Neuropathy, Autoimmune Evaluation, Serum

Negative

Clinical References: 1. Dubey D, Honorat JA, Shelly S, et al. Contactin-1 autoimmunity: Serologic, neurologic, and pathologic correlates. Neurol Neuroimmunol Neuroinflamm. 2020;7(4):e771 2. Cortese A, Lombardi R, Briani C, et al. Antibodies to neurofascin, contactin-1, and contactin-associated protein 1 in CIDP: Clinical relevance of IgG isotype. Neurol Neuroimmunol Neuroinflamm. 2020;7(1):e639 3. Manso C, Querol L, Mekaouche M, Illa I, Devaux JJ. Contactin-1 IgG4 antibodies cause paranode dismantling and conduction defects. Brain. 2016;139(Pt 6):1700-1712 4. Le Quintrec M, Teisseyre M, Bec N, et al. Contactin-1 is a novel target antigen in membranous nephropathy associated with chronic inflammatory demyelinating polyneuropathy. Kidney Int. 2021;100(6):1240-1249 5. Ogata H, Yamasaki R, Hiwatashi A, et al. Characterization of IgG4 anti-neurofascin 155 antibody-positive polyneuropathy. Ann Clin Transl Neurol. 2015;2(10):960-971 6. Cortese A, Lombardi R, Briani C, et al. Antibodies to neurofascin, contactin-1, and contactin-associated protein 1 in CIDP: Clinical relevance of IgG isotype. Neurol Neuroimmunol Neuroinflamm. 2020;7(1):e639 7. Querol L, Nogales-Gadea G, Rojas-Garcia R, et al. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. Neurology. 2014;82(10):879-886 8. Shelly S, Klein CJ, Dyck PJB, et al. Neurofascin-155 immunoglobulin subtypes: Clinicopathologic associations and neurologic outcomes. Neurology. 2021;97(24):e2392-e2403

CSMEU
615907

Controlled Substance Monitoring Enhanced Profile with Reflex, 21 Drug Classes, High Resolution Mass Spectrometry and Immunoassay Screen, Random, Urine

Clinical Information: This test uses screening techniques that involves immunoassay testing and high-resolution accurate mass spectrometry screening for drugs by class. All positive immunoassay screening results are confirmed by gas chromatography mass spectrometry (GC-MS) or liquid chromatography tandem mass spectrometry (LC-MS/MS) and quantitated before a positive result is reported. The following drugs/drug classes are tested by immunoassay and confirmed by GC-MS:
-Barbiturates -Cocaine The following drugs/drug classes are tested by immunoassay and confirmed by LC-MS/MS -Carboxy-tetrahydrocannabinol -Ethyl glucuronide The targeted opioid, benzodiazepine, and stimulant screen portions are performed using liquid chromatography tandem mass spectrometry, high-resolution accurate mass and are completed for all opioids, benzodiazepines, and stimulants. Opioids are a large class of medications commonly used to relieve acute and chronic pain or help manage opioid abuse and dependence. Medications that fall into this class include buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, and others. Opioids work by binding to the opioid receptors that are found in the brain, spinal cord,

gastrointestinal tract, and other organs. Common side effects for opioids include drowsiness, confusion, nausea, constipation, and, in severe cases, respiratory depression. These are dose dependant and vary with tolerance. These medications can also produce physical and psychological dependence and have a high risk for abuse and diversion, which is one of the main reasons many professional practice guidelines recommend compliance testing in patients prescribed these medications. Opioids are readily absorbed from the gastrointestinal tract, nasal mucosa, lungs, and after subcutaneous or intermuscular injection. Opioids are primarily excreted from the kidney in both free and conjugated forms. This assay does not hydrolyze the urine sample and looks for both parent drugs and metabolites (including glucuronide forms). The detection window for most opioids in urine is approximately 1 to 3 days with longer detection times for some compounds (ie, methadone). Benzodiazepines represent a large family of medications used to treat a wide range of disorders from anxiety to seizures and are also used in pain management. With a high risk for abuse and diversion, professional practice guidelines recommend compliance monitoring for these medications using urine drug tests. However, traditional benzodiazepine immunoassays suffer from a lack of cross-reactivity with all the benzodiazepines, so many compliant patients taking either clonazepam (Klonopin) or lorazepam (Ativan) may screen negative by immunoassay but are positive when confirmatory testing is done. The new targeted benzodiazepine screening test provides a more sensitive and specific test to check for compliance to all the commonly prescribed benzodiazepines and looks for both parent drugs and metabolites in the urine. Stimulants are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Amphetamine and methamphetamine are also prescription drugs used in the treatment of narcolepsy and attention-deficit disorder/attention-deficit hyperactivity disorder (ADHD). Methylphenidate is another stimulant used to treat ADHD. Phentermine is indicated for the management of obesity. All other amphetamines (eg, methylenedioxymethamphetamine: MDMA) are Drug Enforcement Administration-scheduled Class I compounds. Due to their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis. Ethyl glucuronide is a direct metabolite of ethanol that is formed by enzymatic conjugation of ethanol with glucuronic acid. Alcohol in urine is normally detected for only a few hours, whereas ethyl glucuronide can be detected in the urine for 1 to 5 days. This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (eg, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate to the antibody's ability to cross-react with different drugs in the class being screened. This test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

Useful For: Detecting drug use involving stimulants, barbiturate, benzodiazepines, cocaine, opioids, tetrahydrocannabinol, and alcohol This test is not intended for use in employment-related testing.

Interpretation: A positive result derived by this testing indicates that the patient has used one of the drugs detected by these techniques in the recent past. For information about drug testing, including estimated detection times and Result Interpretations, see Controlled Substance Monitoring on MayoClinicLabs.com.

Reference Values:

ADULTERANT SURVEY:
Cutoff concentrations
Oxidants: 200 mg/L
Nitrites: 500 mg/L

DRUG IMMUNOASSAY PANEL:
Negative
Screening cutoff concentrations:

Barbiturates: 200 ng/mL
Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

TARGETED OPIOID SCREEN:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Codeine: 25 ng/mL
Codeine-6-beta-glucuronide: 100 ng/mL
Morphine: 25 ng/mL
Morphine-6-beta-glucuronide: 100 ng/mL
6-Monoacetylmorphine: 25 ng/mL
Hydrocodone: 25 ng/mL
Norhydrocodone: 25 ng/mL
Dihydrocodeine: 25 ng/mL
Hydromorphone: 25 ng/mL
Hydromorphone-3-beta-glucuronide: 100 ng/mL
Oxycodone: 25 ng/mL
Noroxycodone: 25 ng/mL
Oxymorphone: 25 ng/mL
Oxymorphone-3-beta-glucuronide: 100 ng/mL
Noroxymorphone: 25 ng/mL
Fentanyl: 2 ng/mL
Norfentanyl: 2 ng/mL
Meperidine: 25 ng/mL
Normeperidine: 25 ng/mL
Naloxone: 25 ng/mL
Naloxone-3-beta-glucuronide: 100 ng/mL
Methadone: 25 ng/mL
2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP): 25 ng/mL
Propoxyphene: 25 ng/mL
Norpropoxyphene: 25 ng/mL
Tramadol: 25 ng/mL
O-desmethyltramadol: 25 ng/mL
Tapentadol: 25 ng/mL
N-desmethyltapentadol: 50 ng/mL
Tapentadol-beta-glucuronide: 100 ng/mL
Buprenorphine: 5 ng/mL
Norbuprenorphine: 5 ng/mL
Norbuprenorphine glucuronide: 20 ng/mL

TARGETED BENZODIAZEPINE SCREEN:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Alprazolam: 10 ng/mL
Alpha-hydroxyalprazolam: 10 ng/mL
Alpha-hydroxyalprazolam glucuronide: 50 ng/mL
Chlordiazepoxide: 10 ng/mL
Clobazam: 10 ng/mL

N-desmethylclobazam: 200 ng/mL
Clonazepam: 10 ng/mL
7-Aminoclonazepam: 10 ng/mL
Diazepam: 10 ng/mL
Nordiazepam: 10 ng/mL
Flunitrazepam: 10 ng/mL
7-Aminoflunitrazepam: 10 ng/mL
Flurazepam: 10 ng/mL
2-Hydroxy ethyl flurazepam: 10 ng/mL
Lorazepam: 10 ng/mL
Lorazepam glucuronide: 50 ng/mL
Midazolam: 10 ng/mL
Alpha-hydroxymidazolam: 10 ng/mL
Oxazepam: 10 ng/mL
Oxazepam glucuronide: 50 ng/mL
Prazepam: 10 ng/mL
Temazepam: 10 ng/mL
Temazepam glucuronide: 50 ng/mL
Triazolam: 10 ng/mL
Alpha-hydroxytriazolam: 10 ng/mL
Zolpidem: 10 ng/mL
Zolpidem phenyl-4-carboxylic acid: 10 ng/mL

TARGETED STIMULANT SCREEN:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Methamphetamine: 100 ng/mL
Amphetamine: 100 ng/mL
3,4-Methylenedioxymethamphetamine (MDMA): 100 ng/mL
3,4-Methylenedioxy-N-ethylamphetamine (MDEA): 100 ng/mL
3,4-Methylenedioxyamphetamine (MDA): 100 ng/mL
Ephedrine: 100 ng/mL
Pseudoephedrine: 100 ng/mL
Phentermine: 100 ng/mL
Phencyclidine (PCP): 20 ng/mL
Methylphenidate: 20 ng/mL
Ritalinic acid: 100 ng/mL

ETHYL GLUCURONIDE SCREEN:
Negative

Screening cutoff concentrations:
Ethyl glucuronide: 500 ng/mL

Clinical References: 1. Physicians' Desk Reference; 60th ed. Medical Economics Company; 2006 2. Bruntman LL, ed. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Book Company; 2006 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 4. Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Companies; 2006 5. Rovine T, Ferrero CL, American Pain Society: Chronic Pain in America: Roadblocks to Relief. Roper Starch Worldwide, Inc; 1999. Updated 2001. Accessed December 12, 2024. Available at http://accurateclinic.com/wp-content/uploads/2016/04/Chronic-Pain-

In-America-Roadblocks-To-Relief-1999.pdf 6. Magnani B, Kwong T. Urine drug testing for pain management. Clin Lab Med. 2012;32(32):379-390 7. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline-using clinical laboratory tests to monitor drug therapy in pain management patients. J Appl Lab Med. 2018;2(4):489-526 8. McMillin GA, Marin SJ, Johnson-Davis KL, Lawlor BG, Strathmann FG. A hybrid approach to urine drug testing using high-resolution mass spectrometry and select immunoassays. Am J Clin Pathol. 2015;143(2):234-240 9. Cone EJ, Caplan YH, Black DL, Robert T, Moser F. Urine drug testing of chronic pain patients: licit and illicit drug patterns. J Anal Toxicol. 2008;32(8):530-543

CSMHU
615293

Controlled Substance Monitoring Hybrid Drug Profile, 20 Drug Classes, High-Resolution Mass Spectrometry and Immunoassay Screen, Random, Urine

Clinical Information: This test uses the simple screening technique that involves immunoassay testing for drugs by class. All positive immunoassay screening results can be confirmed by either gas chromatography mass spectrometry (GC-MS) or liquid chromatography tandem mass spectrometry (LC-MS/MS) and quantitated if applicable. The targeted opioid, benzodiazepine, and stimulant screen portions are performed by LC-MS/MS high-resolution accurate mass and are completed for all opioids, benzodiazepines, and stimulants. Opioids are a large class of medications commonly used to relieve acute and chronic pain or help manage opioid abuse and dependence. Medications that fall into this class include buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, and others. Opioids work by binding to the opioid receptors that are found in the brain, spinal cord, gastrointestinal tract, and other organs. Common side effects for opioids include drowsiness, confusion, nausea, constipation, and, in severe cases, respiratory depression. These are dose dependant and vary with tolerance. These medications can also produce physical and psychological dependence and have a high risk for abuse and diversion, which is one of the main reasons many professional practice guidelines recommend compliance testing in patients prescribed these medications. Opioids are readily absorbed from the gastrointestinal tract, nasal mucosa, lungs, and after subcutaneous or intermuscular injection. Opioids are primarily excreted from the kidney in both free and conjugated forms. This assay does not hydrolyze the urine sample and looks for both parent drugs and metabolites (including glucuronide forms). The detection window for most opioids in urine is approximately 1 to 3 days with longer detection times for some compounds (eg, methadone). Benzodiazepines represent a large family of medications used to treat a wide range of disorders from anxiety to seizures and are also used in pain management. With a high risk for abuse and diversion, professional practice guidelines recommend compliance monitoring for these medications using urine drug tests. However, traditional benzodiazepine immunoassays suffer from a lack of cross-reactivity with all the benzodiazepines, so many compliant patients taking either clonazepam (Klonopin) or lorazepam (Ativan) may screen negative by immunoassay but are positive when confirmatory testing is done. The new targeted benzodiazepine screening test provides a more sensitive and specific test to check for compliance to all the commonly prescribed benzodiazepines and looks for both parent drugs and metabolites in the urine. Stimulants are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Amphetamine and methamphetamine are also prescription drugs used in the treatment of narcolepsy and attention-deficit disorder/attention-deficit hyperactivity disorder (ADHD). Methylphenidate is another stimulant used to treat ADHD. Phentermine is indicated for the management of obesity. All other amphetamines (eg, methylenedioxymethamphetamine: MDMA) are Drug Enforcement Administration-scheduled Class I compounds. Due to their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis. This test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

Useful For: Detecting drug use involving stimulants, barbiturate, benzodiazepines, cocaine, opioids, and tetrahydrocannabinol This test is not intended for use in employment-related testing.

Interpretation: A positive result derived by this testing indicates that the patient has used one of the drugs detected by these techniques in the recent past. For information about drug testing, including estimated detection times and Result Interpretations, see Controlled Substance Monitoring on MayoClinicLabs.com.

Reference Values:

Adulterant Survey:
Cutoff concentrations
Oxidants: 200 mg/L
Nitrites: 500 mg/L

Limited Drug Panel:
Negative
Screening cutoff concentrations:
Barbiturates: 200 ng/mL
Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

Targeted Opioid Screen:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Codeine: 25 ng/mL
Codeine-6-beta-glucuronide: 100 ng/mL
Morphine: 25 ng/mL
Morphine-6-beta-glucuronide: 100 ng/mL
6-Monoacetylmorphine: 25 ng/mL
Hydrocodone: 25 ng/mL
Norhydrocodone: 25 ng/mL
Dihydrocodeine: 25 ng/mL
Hydromorphone: 25 ng/mL
Hydromorphone-3-beta-glucuronide: 100 ng/mL
Oxycodone: 25 ng/mL
Noroxycodone: 25 ng/mL
Oxymorphone: 25 ng/mL
Oxymorphone-3-beta-glucuronide: 100 ng/mL
Noroxymorphone: 25 ng/mL
Fentanyl: 2 ng/mL
Norfentanyl: 2 ng/mL
Meperidine: 25 ng/mL
Normeperidine: 25 ng/mL
Naloxone: 25 ng/mL
Naloxone-3-beta-glucuronide: 100 ng/mL
Methadone: 25 ng/mL
2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP): 25 ng/mL
Propoxyphene: 25 ng/mL
Norpropoxyphene: 25 ng/mL
Tramadol: 25 ng/mL

O-desmethyltramadol: 25 ng/mL
Tapentadol: 25 ng/mL
N-desmethyltapentadol: 50 ng/mL
Tapentadol-beta-glucuronide: 100 ng/mL
Buprenorphine: 5 ng/mL
Norbuprenorphine: 5 ng/mL
Norbuprenorphine glucuronide: 20 ng/mL

Targeted Benzodiazepine Screen:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Alprazolam: 10 ng/mL
Alpha-hydroxyalprazolam: 10 ng/mL
Alpha-hydroxyalprazolam glucuronide: 50 ng/mL
Chlordiazepoxide: 10 ng/mL
Clobazam: 10 ng/mL
N-desmethylclobazam: 200 ng/mL
Clonazepam: 10 ng/mL
7-Aminoclonazepam: 10 ng/mL
Diazepam: 10 ng/mL
Nordiazepam: 10 ng/mL
Flunitrazepam: 10 ng/mL
7-Aminoflunitrazepam: 10 ng/mL
Flurazepam: 10 ng/mL
2-Hydroxy ethyl flurazepam: 10 ng/mL
Lorazepam: 10 ng/mL
Lorazepam glucuronide: 50 ng/mL
Midazolam: 10 ng/mL
Alpha-hydroxymidazolam: 10 ng/mL
Oxazepam: 10 ng/mL
Oxazepam glucuronide: 50 ng/mL
Prazepam: 10 ng/mL
Temazepam: 10 ng/mL
Temazepam glucuronide: 50 ng/mL
Triazolam: 10 ng/mL
Alpha-hydroxytriazolam: 10 ng/mL
Zolpidem: 10 ng/mL
Zolpidem phenyl-4-carboxylic acid: 10 ng/mL

Targeted Stimulant Screen:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Methamphetamine: 100 ng/mL
Amphetamine: 100 ng/mL
3,4-Methylenedioxymethamphetamine (MDMA): 100 ng/mL
3,4-Methylenedioxy-N-ethylamphetamine (MDEA): 100 ng/mL
3,4-Methylenedioxyamphetamine (MDA): 100 ng/mL
Ephedrine: 100 ng/mL
Pseudoephedrine: 100 ng/mL
Phentermine: 100 ng/mL
Phencyclidine (PCP): 20 ng/mL
Methylphenidate: 20 ng/mL

Ritalinic acid: 100 ng/mL

Clinical References: 1. Physicians' Desk Reference. 60th ed. Medical Economics Company; 2006 2. Bruntman LL Lazo JS, Parker KL, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Book Company; 2006 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 4. Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Companies; 2006:chap 21 5. Rovine T, Ferrero CL, American Pain Society: Chronic Pain in America: Roadblocks to Relief. Roper Starch Worldwide, Inc; 1999. Updated 2001. Accessed December 16, 2024. Available at http://accurateclinic.com/wp-content/uploads/2016/04/Chronic-Pain-In-America-Roadblocks-To-Relief-1999.pdf 6. Magnani B, Kwong T. Urine drug testing for pain management. Clin Lab Med. 2012;32(3):379-390 7. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline-using clinical laboratory tests to monitor drug therapy in pain management patients. J Appl Lab Med. 2018;2(4):489-526 8. McMillin GA, Marin SJ, Johnson-Davis KL, Lawlor BG, Strathmann FG. A hybrid approach to urine drug testing using high-resolution mass spectrometry and select immunoassays. Am J Clin Pathol. 2015;143(2):234-240 9. Cone EJ, Caplan YH, Black DL, Robert T, Moser F. Urine drug testing of chronic pain patients: licit and illicit drug patterns. J Anal Toxicol. 2008;32(8):530-543

CSMOF
621483

Controlled Substance Monitoring Panel, 11 Drug Classes, Screen Only, Immunoassay, Oral Fluid

Clinical Information: Drug abuse is a major social and medical issue and usually requires costly interventions for the treatment and rehabilitation of abusers. This qualitative test screens for commonly prescribed and/or abused drugs/drug classes in human oral fluid specimens. It uses a noninvasive specimen collection method, which can be observed. This test may be used for screening samples for compliance monitoring of prescription drugs in a point of care setting.

Useful For: Monitoring acute (ie, short-term) drug use in addiction treatment or pain management settings as part of a rotational drug testing strategy Presumptive screening for amphetamine, methamphetamine, opioids/opiates (targeting morphine, oxymorphone, oxycodone, hydrocodone, 6-monoacetylmorphine, tramadol, buprenorphine, fentanyl, and methadone), PCP (phencyclidine), cocaine metabolite (targeting benzoylecgonine), benzodiazepines (targeting oxazepam, lorazepam, and clonazepam), zolpidem, barbiturates (targeting phenobarbital), methylphenidate, and THC-COOH (marijuana metabolite) in oral fluid specimens This test is not intended for forensic or medico-legal purposes (ie, employee drug testing or settings where chain-of-custody is required).

Interpretation: This test is intended to screen for amphetamine, methamphetamine, opioids/opiates (targeting morphine, oxymorphone, oxycodone, hydrocodone, 6-monoacetylmorphine, tramadol, buprenorphine, fentanyl, and methadone), PCP (phencyclidine), cocaine metabolite (targeting benzoylecgonine), benzodiazepines (targeting oxazepam, lorazepam, and clonazepam), zolpidem, barbiturates (targeting phenobarbital), methylphenidate, and THC-COOH (marijuana metabolite) in oral fluid specimens. The limit of detection for each of these drug groups varies (see Reference Values). A positive finding for one of these drugs or metabolites is an indication for the presence of the drug of abuse or cross reactivity with other structurally similar commonly prescribed drugs.

Reference Values:
Not detected

Positives are reported with a qualitative result.

Cutoff concentrations by competitive chemiluminescent immunoassay:
Opioids:
6-Acetylmorphine: 5 ng/mL
Morphine: 10 ng/mL
Hydrocodone: 10 ng/mL
Oxycodone: 10 ng/mL
Oxymorphone: 10 ng/mL
Methadone: 10 ng/mL
Fentanyl: 1 ng/mL
Tramadol: 5 ng/mL
Buprenorphine: 1 ng/mL

Benzodiazepines:
Oxazepam: 10 ng/mL
Clonazepam: 10 ng/mL
Lorazepam: 10 ng/mL

Non-Benzodiazepine: Zolpidem: 10 ng/mL

Stimulants:
Amphetamine: 20 ng/mL
Methamphetamine: 10 ng/mL
Methylphenidate: 100 ng/mL
Cocaine Metabolite (BE): 30 ng/mL

PCP, Phencyclidine: 5 ng/mL
Marijuana metabolite (THC-COOH): 10 ng/mL
Barbiturates, Phenobarbital: 50 ng/mL

Clinical References: 1. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive Summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline-Using Clinical Laboratory Tests to Monitor Drug Therapy in Pain Management Patients. J Appl Lab Med. 2018;2(4):489-526. doi:10.1373/jalm.2017.023341 2. Bosker WM, Huestis MA. Oral fluid testing for drugs of abuse. Clin Chem. 2009;55(11):1910-31. doi:10.1373/clinchem.2008.108670. 3. Huestis MA, Verstraete A, Kwong TC, Morland J, Vincent MJ, de la Torre R. Oral fluid testing: promises and pitfalls. Clin Chem. 2011;57(6):805-10. doi:10.1373/clinchem.2010.152124

CSMPU
610271

Controlled Substance Monitoring Panel, Random, Urine

Clinical Information: This test uses the simple screening technique that involves immunoassay testing for drugs by class. All positive immunoassay screening results are confirmed by gas chromatography mass spectrometry (GC-MS) or liquid chromatography tandem mass spectrometry (LC-MS/MS) and quantitated before a positive result is reported. This assay was designed to test for and confirm by GC-MS the following: -Barbiturates -Cocaine The following drugs/drug classes are tested by immunoassay and confirmed by LC-MS/MS -Carboxy-tetrahydrocannabinol The targeted opioid, benzodiazepine, and stimulant screen portions are performed by LC-MS/MS high-resolution accurate mass and are completed for all opioids, benzodiazepines, and stimulants. Opioids are a large class of medications commonly used to relieve acute and chronic pain or help manage opioid abuse and dependence. Medications that fall into this class include buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, and others. Opioids work by binding to the opioid receptors that are found in the brain, spinal cord, gastrointestinal tract, and other organs. Common side effects for opioids include drowsiness, confusion, nausea, constipation, and, in severe cases, respiratory depression. These are dose dependant and vary with

tolerance. These medications can also produce physical and psychological dependence and have a high risk for abuse and diversion, which is one of the main reasons many professional practice guidelines recommend compliance testing in patients prescribed these medications. Opioids are readily absorbed from the gastrointestinal tract, nasal mucosa, lungs, and after subcutaneous or intermuscular injection. Opioids are primarily excreted from the kidney in both free and conjugated forms. This assay does not hydrolyze the urine sample and looks for both parent drugs and metabolites (including glucuronide forms). The detection window for most opioids in urine is approximately 1 to 3 days with longer detection times for some compounds (ie, methadone). Benzodiazepines represent a large family of medications used to treat a wide range of disorders from anxiety to seizures and are also used in pain management. With a high risk for abuse and diversion, professional practice guidelines recommend compliance monitoring for these medications using urine drug tests. However, traditional benzodiazepine immunoassays suffer from a lack of cross-reactivity with all the benzodiazepines, so many compliant patients taking either clonazepam (Klonopin) or lorazepam (Ativan) may screen negative by immunoassay but are positive when confirmatory testing is done. The new targeted benzodiazepine screening test provides a more sensitive and specific test to check for compliance to all the commonly prescribed benzodiazepines and looks for both parent drugs and metabolites in the urine. Stimulants are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Amphetamine and methamphetamine are also prescription drugs used in the treatment of narcolepsy and attention-deficit disorder/attention-deficit hyperactivity disorder (ADHD). Methylphenidate is another stimulant used to treat ADHD. Phentermine is indicated for the management of obesity. All other amphetamines (eg, methylenedioxymethamphetamine: MDMA) are Drug Enforcement Administration scheduled Class I compounds. Due to their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis. This test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

Useful For: Detecting drug use involving stimulants, barbiturates, benzodiazepines, cocaine, opioids, and tetrahydrocannabinol This test is not intended for use in employment-related testing.

Interpretation: A positive result derived by this testing indicates that the patient has used one of the drugs detected by these techniques in the recent past. For information about drug testing, including estimated detection times and Result Interpretations, see Controlled Substance Monitoring on MayoClinicLabs.com.

Reference Values:

ADULTERANT SURVEY:
Cutoff concentrations
Oxidants: 200 mg/L
Nitrites: 500 mg/L

DRUG IMMUNOASSAY PANEL:
Negative
Screening cutoff concentrations:
Barbiturates: 200 ng/mL
Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL
This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

TARGETED OPIOID SCREEN:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:

Codeine: 25 ng/mL
Codeine-6-beta-glucuronide: 100 ng/mL
Morphine: 25 ng/mL
Morphine-6-beta-glucuronide: 100 ng/mL
6-Monoacetylmorphine: 25 ng/mL
Hydrocodone: 25 ng/mL
Norhydrocodone: 25 ng/mL
Dihydrocodeine: 25 ng/mL
Hydromorphone: 25 ng/mL
Hydromorphone-3-beta-glucuronide: 100 ng/mL
Oxycodone: 25 ng/mL
Noroxycodone: 25 ng/mL
Oxymorphone: 25 ng/mL
Oxymorphone-3-beta-glucuronide: 100 ng/mL
Noroxymorphone: 25 ng/mL
Fentanyl: 2 ng/mL
Norfentanyl: 2 ng/mL
Meperidine: 25 ng/mL
Normeperidine: 25 ng/mL
Naloxone: 25 ng/mL
Naloxone-3-beta-glucuronide: 100 ng/mL
Methadone: 25 ng/mL
2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP): 25 ng/mL
Propoxyphene: 25 ng/mL
Norpropoxyphene: 25 ng/mL
Tramadol: 25 ng/mL
O-desmethyltramadol: 25 ng/mL
Tapentadol: 25 ng/mL
N-desmethyltapentadol: 50 ng/mL
Tapentadol-beta-glucuronide: 100 ng/mL
Buprenorphine: 5 ng/mL
Norbuprenorphine: 5 ng/mL
Norbuprenorphine glucuronide: 20 ng/mL

TARGETED BENZODIAZEPINE SCREEN:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Alprazolam: 10 ng/mL
Alpha-hydroxyalprazolam: 10 ng/mL
Alpha-hydroxyalprazolam glucuronide: 50 ng/mL
Chlordiazepoxide: 10 ng/mL
Clobazam: 10 ng/mL
N-desmethylclobazam: 200 ng/mL
Clonazepam: 10 ng/mL
7-Aminoclonazepam: 10 ng/mL
Diazepam: 10 ng/mL
Nordiazepam: 10 ng/mL
Flunitrazepam: 10 ng/mL
7-Aminoflunitrazepam: 10 ng/mL
Flurazepam: 10 ng/mL
2-Hydroxy ethyl flurazepam: 10 ng/mL
Lorazepam: 10 ng/mL
Lorazepam glucuronide: 50 ng/mL

Midazolam: 10 ng/mL
Alpha-hydroxymidazolam: 10 ng/mL
Oxazepam: 10 ng/mL
Oxazepam glucuronide: 50 ng/mL
Prazepam: 10 ng/mL
Temazepam: 10 ng/mL
Temazepam glucuronide: 50 ng/mL
Triazolam: 10 ng/mL
Alpha-hydroxytriazolam: 10 ng/mL
Zolpidem: 10 ng/mL
Zolpidem phenyl-4-carboxylic acid: 10 ng/mL

TARGETED STIMULANT SCREEN:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Methamphetamine: 100 ng/mL
Amphetamine: 100 ng/mL
3,4-Methylenedioxymethamphetamine (MDMA): 100 ng/mL
3,4-Methylenedioxy-N-ethylamphetamine (MDEA): 100 ng/mL
3,4-Methylenedioxyamphetamine (MDA): 100 ng/mL
Ephedrine: 100 ng/mL
Pseudoephedrine: 100 ng/mL
Phentermine: 100 ng/mL
Phencyclidine (PCP): 20 ng/mL
Methylphenidate: 20 ng/mL
Ritalinic acid: 100 ng/mL

Clinical References: 1. Physicians' Desk Reference; 60th ed. Medical Economics Company; 2006 2. Bruntman LL, ed. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Book Company; 2006 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 4. Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Companies; 2006 5. Rovine T, Ferrero CL, American Pain Society: Chronic Pain in America: Roadblocks to Relief. Roper Starch Worldwide, Inc; 1999. Updated 2001. Accessed December 12, 2024. Available at http://accurateclinic.com/wp-content/uploads/2016/04/Chronic-Pain-In-America-Roadblocks-To-Relief-1999.pdf 6. Magnani B, Kwong T. Urine drug testing for pain management. Clin Lab Med. 2012;32(32):379-390 7. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline-using clinical laboratory tests to monitor drug therapy in pain management patients. J Appl Lab Med. 2018;2(4):489-526 8. McMillin GA, Marin SJ, Johnson-Davis KL, Lawlor BG, Strathmann FG. A hybrid approach to urine drug testing using high-resolution mass spectrometry and select immunoassays. Am J Clin Pathol. 2015;143(2):234-240 9. Cone EJ, Caplan YH, Black DL, Robert T, Moser F. Urine drug testing of chronic pain patients: licit and illicit drug patterns. J Anal Toxicol. 2008;32(8):530-543

CSMTU 615292 Controlled Substance Monitoring Targeted Profile, 17 Drug Classes, Mass Spectrometry, Random, Urine

Clinical Information: The targeted opioid, benzodiazepine, and stimulant screen portions are performed by liquid chromatography tandem mass spectrometry, high-resolution accurate mass (LC-

MS/MS HRAM) and are completed for all opioids, benzodiazepines, and stimulants. Opioids are a large class of medications commonly used to relieve acute and chronic pain or help manage opioid abuse and dependence. Medications that fall into this class include buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, and others. Opioids work by binding to the opioid receptors that are found in the brain, spinal cord, gastrointestinal tract, and other organs. Common side effects of opioids include drowsiness, confusion, nausea, constipation, and, in severe cases, respiratory depression. These are dose dependant and vary with tolerance. These medications can also produce physical and psychological dependence and have a high risk for abuse and diversion, which is one of the main reasons many professional practice guidelines recommend compliance testing in patients prescribed these medications. Opioids are readily absorbed from the gastrointestinal tract, nasal mucosa, lungs, and after subcutaneous or intermuscular injection. Opioids are primarily excreted from the kidney in both free and conjugated forms. This assay does not hydrolyze the urine sample and looks for both parent drugs and metabolites (including glucuronide forms). The detection window for most opioids in urine is approximately 1 to 3 days with longer detection times for some compounds (eg, methadone). Benzodiazepines represent a large family of medications used to treat a wide range of disorders from anxiety to seizures and are also used in pain management. With a high risk for abuse and diversion, professional practice guidelines recommend compliance monitoring for these medications using urine drug tests. However, traditional benzodiazepine immunoassays suffer from a lack of cross-reactivity with all the benzodiazepines, so many compliant patients taking either clonazepam (Klonopin) or lorazepam (Ativan) may screen negative by immunoassay but are positive when confirmatory testing is done. The new targeted benzodiazepine screening test provides a more sensitive and specific test to check for compliance to all the commonly prescribed benzodiazepines and looks for both parent drug and metabolites in the urine. Stimulants are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Amphetamine and methamphetamine are also prescription drugs used in the treatment of narcolepsy and attention-deficit disorder/attention-deficit hyperactivity disorder (ADHD). Methylphenidate is another stimulant used to treat ADHD. Phentermine is indicated for the management of obesity. All other amphetamines (eg, methylenedioxymethamphetamine: MDMA) are Drug Enforcement Administration-scheduled Class I compounds. Due to their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis. This test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

Useful For: Detecting drug use involving stimulants, benzodiazepines, and opioids This test is not intended for use in employment-related testing.

Interpretation: A positive result derived by this testing indicates that the patient has used one of the drugs detected by these techniques in the recent past. For information about drug testing, including estimated detection times and Result Interpretations, see Controlled Substance Monitoring on MayoClinicLabs.com.

Reference Values:

ADULTERANT SURVEY:
Cutoff concentrations
Oxidants: 200 mg/L
Nitrites: 500 mg/L

TARGETED OPIOID SCREEN:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Codeine: 25 ng/mL
Codeine-6-beta-glucuronide: 100 ng/mL

Morphine: 25 ng/mL
Morphine-6-beta-glucuronide: 100 ng/mL
6-Monoacetylmorphine: 25 ng/mL
Hydrocodone: 25 ng/mL
Norhydrocodone: 25 ng/mL
Dihydrocodeine: 25 ng/mL
Hydromorphone: 25 ng/mL
Hydromorphone-3-beta-glucuronide: 100 ng/mL
Oxycodone: 25 ng/mL
Noroxycodone: 25 ng/mL
Oxymorphone: 25 ng/mL
Oxymorphone-3-beta-glucuronide: 100 ng/mL
Noroxymorphone: 25 ng/mL
Fentanyl: 2 ng/mL
Norfentanyl: 2 ng/mL
Meperidine: 25 ng/mL
Normeperidine: 25 ng/mL
Naloxone: 25 ng/mL
Naloxone-3-beta-glucuronide: 100 ng/mL
Methadone: 25 ng/mL
2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP): 25 ng/mL
Propoxyphene: 25 ng/mL
Norpropoxyphene: 25 ng/mL
Tramadol: 25 ng/mL
O-desmethyltramadol: 25 ng/mL
Tapentadol: 25 ng/mL
N-desmethyltapentadol: 50 ng/mL
Tapentadol-beta-glucuronide: 100 ng/mL
Buprenorphine: 5 ng/mL
Norbuprenorphine: 5 ng/mL
Norbuprenorphine glucuronide: 20 ng/mL

TARGETED BENZODIAZEPINE SCREEN:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Alprazolam: 10 ng/mL
Alpha-hydroxyalprazolam: 10 ng/mL
Alpha-hydroxyalprazolam glucuronide: 50 ng/mL
Chlordiazepoxide: 10 ng/mL
Clobazam: 10 ng/mL
N-desmethylclobazam: 200 ng/mL
Clonazepam: 10 ng/mL
7-Aminoclonazepam: 10 ng/mL
Diazepam: 10 ng/mL
Nordiazepam: 10 ng/mL
Flunitrazepam: 10 ng/mL
7-Aminoflunitrazepam: 10 ng/mL
Flurazepam: 10 ng/mL
2-Hydroxy ethyl flurazepam: 10 ng/mL
Lorazepam: 10 ng/mL
Lorazepam glucuronide: 50 ng/mL
Midazolam: 10 ng/mL
Alpha-hydroxymidazolam: 10 ng/mL

Oxazepam: 10 ng/mL
Oxazepam glucuronide: 50 ng/mL
Prazepam: 10 ng/mL
Temazepam: 10 ng/mL
Temazepam glucuronide: 50 ng/mL
Triazolam: 10 ng/mL
Alpha-hydroxytriazolam: 10 ng/mL
Zolpidem: 10 ng/mL
Zolpidem phenyl-4-carboxylic acid: 10 ng/mL

TARGETED STIMULANT SCREEN:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Methamphetamine: 100 ng/mL
Amphetamine: 100 ng/mL
3,4-Methylenedioxymethamphetamine (MDMA): 100 ng/mL
3,4-Methylenedioxy-N-ethylamphetamine (MDEA): 100 ng/mL
3,4-Methylenedioxyamphetamine (MDA): 100 ng/mL
Ephedrine: 100 ng/mL
Pseudoephedrine: 100 ng/mL
Phentermine: 100 ng/mL
Phencyclidine (PCP): 20 ng/mL
Methylphenidate: 20 ng/mL
Ritalinic acid: 100 ng/mL

Clinical References: 1. Physicians' Desk Reference: 60th ed. Medical Economics Company; 2006 2. Bruntman LL Lazo JS, Parker KL, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Book Company; 2006 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 4. Gutstein HB, Akil H: Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Companies; 2006:chap 21 5. Rovine T, Ferrero CL, American Pain Society: Chronic Pain in America: Roadblocks to Relief. Roper Starch Worldwide, Inc; 1999. Updated 2001. Accessed December 12, 2024. Available at http://accurateclinic.com/wp-content/uploads/2016/04/Chronic-Pain-In-America-Roadblocks-To-Relief-1999.pdf 6. Magnani B, Kwong T. Urine drug testing for pain management. Clin Lab Med. 2012;32(3):379-390 7. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline-using clinical laboratory tests to monitor drug therapy in pain management patients. J Appl Lab Med. 2018;2(4):489-526 8. McMillin GA, Marin SJ, Johnson-Davis KL, Lawlor BG, Strathmann FG. A hybrid approach to urine drug testing using high-resolution mass spectrometry and select immunoassays. Am J Clin Pathol. 2015;143(2):234-240 9. Cone EJ, Caplan YH, Black DL, Robert T, Moser F. Urine drug testing of chronic pain patients: licit and illicit drug patterns. J Anal Toxicol. 2008;32(8):530-543

CPAPD
70329

Conventional Smear-Diagnostic, Varies

Clinical Information: Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic) stages, to carcinoma in situ, and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. The etiology of cervical carcinoma is unknown, but the disease is believed to be related to sexual activity and possibly sexually transmitted viral infections such as human papillomavirus (HPV). Most cervical carcinomas and precancerous conditions occur in the transformation zone (squamo-columnar junction), therefore, this area

needs to be sampled if optimum results are to be obtained.

Useful For: Screening for cervical carcinoma and a number of infections of the female genital tract including human papillomavirus, herpes, Candida, and Trichomonas

Interpretation: Standard reporting, as defined by the Bethesda System (TBS) is utilized.

Reference Values:
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.
Note: Abnormal results will be reviewed by a physician at an additional charge.

Clinical References: 1. Wright TC Jr, Cox JT, Massad LS, et al: ASCCP-Sponsored Consensus Conference. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA. 2002 April;287(16):2120-2129 2. Solomon D, Davey D, Kurman R, et al: The 2001 Bethesda System: terminology for reporting results of cervical cytology-Consensus Statement JAMA. 2002 April;287(16):2114-2119

CPAPS
70331

Conventional Smear-Screen, Varies

Clinical Information: Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic, intraepithelial neoplastic, stages II in situ carcinoma, and eventually invasive carcinoma). This sequence is felt to develop over a matter of years in most patients. The etiology of cervical carcinoma is unknown but the disease is believed to be related to sexual activity and possibly sexually transmitted viral infections such as human papilloma virus. Most cervical carcinomas and precancerous conditions occur in the transformation zone (squamo-columnar junction), therefore, this area needs to be sampled if optimum results are to be obtained.

Useful For: Screening for cervical carcinoma and a number of infections of the female genital tract including human papillomavirus, herpes, Candida, and Trichomonas

Interpretation: Standard reporting, as defined by the Bethesda System (TBS) is utilized.

Reference Values:
Satisfactory for evaluation
Negative for intraepithelial lesion or malignancy

Note: Abnormal results will be reviewed by a physician at an additional charge.

Clinical References: 1. Wright TC Jr, Cox JT, Massad LS, et al: ASCCP-Sponsored Consensus Conference. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA 2002 April;287(16):2120-2129 2. Solomon D, Davey D, Kurman R, et al: The 2001 Bethesda System: terminology for reporting results of cervical cytology-Consensus Statement. JAMA 2002 April;287(16):2114-2119

CPAVP
603599

Copeptin proAVP, Plasma

Clinical Information: Arginine vasopressin (AVP) and copeptin (also known as copeptin proAVP or copeptin AVP) are derived from the same precursor peptide. Copeptin has been proposed as a more stable, potentially superior, surrogate marker of AVP in the assessment of water balance disorders. Unlike AVP, copeptin is stable in plasma. Both copeptin and AVP are responsive to osmotic stimuli and

increase in response to water deprivation. In healthy subjects, water deprivation causes the plasma osmolality to rise above approximately 280 to 290 mOsmol/kg, leading to the release of AVP and copeptin into the circulation. Copeptin increases gradually with fasting and water deprivation and declines rapidly after intake of water and food. Diabetes insipidus (DI) is characterized by the inability to appropriately concentrate urine in response to volume and osmolar stimuli. The main causes for DI are decreased AVP production (central DI) or decreased renal response to AVP (nephrogenic DI). The determination of the underlying disease pathology in patients with polyuria and altered plasma osmolality is often difficult. Polyuria can be related to insufficient AVP (central DI), reduced sensitivity to AVP (nephrogenic DI), or excessive water intake. Measurement of plasma copeptin concentration has been shown to be useful in the investigation of these AVP-related disorders. Additionally, utilization of copeptin has been proposed in the assessment of syndrome of inappropriate antidiuretic. Copeptin is also a marker of acute hemodynamic stress and has been reported to aid in the prognosis or diagnosis of several cardiac disorders, such as acute coronary syndrome, stable coronary artery disease, congestive heart failure, and acute ischemic stroke. Some studies have demonstrated that copeptin may improve prediction of mortality and heart disease outcome when combined with natriuretic peptides such as B-type natriuretic peptide (BNP) and N-terminal proBNP.

Useful For: Investigating the differential diagnosis for patients with water balance disorders, including diabetes insipidus, in conjunction with osmolality and hydration status May aid in the evaluation of cardiovascular disease in conjunction with other cardiac markers

Interpretation: While secreted in equimolar concentrations in conjunction with arginine vasopressin (AVP), measured plasma concentrations of copeptin do not correlate strongly with AVP concentrations due to in vivo and in vitro differences in stability. Copeptin is a more stable surrogate biomarker of AVP release. The clinical utility of copeptin of differentiating polyuria and water balance disorders has been demonstrated in a number of studies, when used in conjunction with osmolality and hydration status. In a prospective clinical study, an algorithm was established based on patients with polyuria-polydipsia syndrome (n=55). A non-water deprived baseline copeptin concentration of 21.4 pmol/L or greater was found to be consistent with the presence of nephrogenic diabetes insipidus (DI). In a described algorithm,(1) patients with a copeptin concentrations of under 21.4 pmol/L and a copeptin cut-off of 4.9 pmol/L after fluid deprivation, was used to distinguish between complete or partial DI (<4.9 pmol/L) and primary polydipsia (> or =4.9 pmol/L). Central DI may also be differentiated from nephrogenic DI by measuring copeptin during a stimulus for AVP release such as a water deprivation test. Copeptin concentrations obtained in the process of a water deprivation test can be difficult to interpret because of variation in water deprivation protocols. Patients with psychogenic polydipsia will either have a normal response to water deprivation or, in long-standing cases, show a pattern suggestive of mild nephrogenic DI. Expert consultation is recommended in these circumstances. Although the water-deprivation test is considered the reference standard for the evaluation of DI, measurement of saline stimulated copeptin was shown to be more accurate than the water-deprivation test.(2) In this indirect water deprivation test with a cutoff of 4.9 pmol/L or less indicated central DI while a concentration greater than 4.9 pmol/L indicated primary polydipsia. An elevated plasma copeptin AVP concentration in a hyponatremic patient may be indicative of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). However, copeptin determination alone is not typically sufficient to distinguish SIADH from other hyponatremic disorders.(3) Elevations of plasma copeptin in patients with symptoms of heart failure may be prognostic of short- and long-term mortality. In patients with heart failure (HF) following a myocardial infarction, elevations in copeptin are associated with severity of HF and poorer prognosis.(4) In a cohort of patients with class III or IV HF, copeptin concentrations of 40 pmol/L or greater significantly increased the risk of death or need for cardiac transplantation. The combination of elevated copeptin and hyponatremia was an even stronger predictor of heart failure, independent of B-type natriuretic peptide (BNP) and cardiac troponin (cTn) concentrations.(5)

Reference Values:

Non-water deprived, non-fasting adults*: <13.1 pmol/L
Water deprived, fasting adults**: <15.2 pmol/L

Non-water deprived, non-fasting pediatric patients***: <14.5 pmol/L
Note:
*Keller T, Tzikas S, Zeller T, et al. Copeptin improves early diagnosis of acute myocardial infarction. J Am Coll Cardiol. 2010;55(19):2096-2106. doi:10.1016/j.jacc.2010.01.029

**Internal Mayo Clinic study

***Du JM, Sang G, Jiang CM, He XJ, Han Y. Relationship between plasma copeptin levels and complications of community-acquired pneumonia in preschool children. Peptides. 2013;45:61-65. doi:10.1016/j.peptides.2013.04.015

Clinical References:

CUU
8590

Copper, 24 Hour, Urine

Clinical Information: The biliary system is the major pathway of copper excretion. Biliary excretion of copper requires an adenosine triphosphate (ATP)-dependent transporter protein. Variants in the gene for the transporter protein cause hepatolenticular degeneration (Wilson disease). Ceruloplasmin, the primary copper-carrying protein in the blood, is also reduced in Wilson disease. Urine copper excretion is increased in Wilson disease due to a decreased serum binding of copper to ceruloplasmin or due to allelic variances in cellular metal ion transporters. Hypercupricuria (increased urinary copper) is also found in hemochromatosis, biliary cirrhosis, thyrotoxicosis, various infections, and a variety of other acute, chronic, and malignant diseases (including leukemia). Urine copper concentrations are also elevated during pregnancy and in patients taking contraceptives or estrogens. Low urine copper levels are seen in malnutrition, hypoproteinemias, malabsorption, and nephrotic syndrome. Increased zinc consumption interferes with normal copper absorption from the gastrointestinal tract causing hypocupremia.

Useful For: Investigation of Wilson disease and obstructive liver disease using a 24-hour urine specimen

Interpretation: Humans normally excrete less than 60 mcg/day of copper in the urine. Urinary copper excretion greater than 60 mcg/day may be seen in: -Wilson disease -Obstructive biliary disease (eg, primary biliary cirrhosis, primary sclerosing cholangitis) -Nephrotic syndrome (due to leakage through the kidney) -Chelation therapy -Estrogen therapy -Mega dosing of zinc-containing vitamins Because ceruloplasmin is an acute phase reactant, urine copper is elevated during acute inflammation. During the recovery phase, urine copper is usually below normal, reflecting the expected physiologic response to replace the copper that was depleted during inflammation.

Reference Values:
0-17 years: Not established
> or =18 years: 9-71 mcg/24 h

Clinical References: 1. Zorbas YG, Kakuris KK, Deogenov VA, et al. Copper homeostasis during hypokinesia in healthy subjects with higher and lower copper consumption. Tr Elem Electro. 2008;25:169-178 2. Lech T, Sadlik JK. Contribution to the data on copper concentration in blood and urine in patients with Wilson's disease and in normal subjects. Biol Trace Elem Res. 2007;118(1):16-20 3. Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018 4 .Mohr I, Weiss KH. Biochemical markers for the diagnosis and monitoring of Wilson disease. Clin Biochem Rev. 2019;40(2):59-77. doi:10.33176/AACB-18-00014

CUT
8687

Copper, Liver Tissue

Clinical Information: Homeostatic regulation of copper metabolism is very complex. The liver is the key organ to facilitate copper storage and incorporation of copper into the transport protein ceruloplasmin. Intestinal absorption and biliary excretion also play major roles in the regulation of copper homeostasis. Abnormal copper metabolism is associated with liver disease. Elevated serum copper concentrations are seen in portal cirrhosis, biliary tract disease, and hepatitis, probably due to excess copper that would normally be excreted in the bile is retained in circulation. In primary biliary cirrhosis, ceruloplasmin is high, resulting in high serum copper. Lesser elevations of hepatic copper are found in chronic copper poisoning, obstructive jaundice, and certain cases of hepatic cirrhosis. Reduced serum copper concentration is typical of Wilson disease (hepatolenticular degeneration). Wilson disease is characterized by liver disease, neurologic abnormalities, and psychiatric disturbances. Kayser-Fleischer rings are normally present and urinary copper excretion is increased, while serum copper and ceruloplasmin are low. Labile copper fraction (LBC fraction) is also elevated in untreated Wilson disease.

Useful For: Diagnosing Wilson disease and primary biliary cirrhosis using liver tissue specimens

Interpretation: The constellation of symptoms associated with Wilson disease, which includes Kayser-Fleischer rings, behavior changes, and liver disease, is commonly associated with liver copper concentrations above 250 mcg/g dry weight. VERY HIGH >1000 mcg/g dry weight: This finding is strongly suggestive of Wilson disease. HIGH 250-1000 mcg/g dry weight: This finding is suggestive of possible Wilson disease. MODERATELY HIGH 50-250 mcg/g dry weight: Excessive copper at this level can be associated with cholestatic liver disease, such as primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, and familial cholestatic syndrome. Heterozygous carriers for Wilson disease occasionally have modestly elevated values but rarely higher than 125 mcg/g of dry weight. In general, the liver copper content is higher than 250 mcg/g dried tissue in patients with Wilson disease. If any of the above findings are without supporting histology and other biochemical test results, contamination during collection, handling, or processing should be considered. Genetic testing for Wilson disease is available; order WNDZ / Wilson Disease, ATP7B Full Gene Sequencing with Deletion/Duplication, Varies. If additional assistance is needed, call 800-533-1710. In patients with elevated levels of copper without supporting histology and other biochemical test results, contamination during collection, handling, or processing should be considered.

Reference Values:
<50 mcg/g dry weight

Clinical References:

FCOPP
75391

Copper, RBCs

Reference Values:
Reporting limit determined each analysis.
Units: mcg/dL

NMS Labs derived data for 2.5th-97.5th percentile range is 59-91 mcg/dL (n=1999).

The RBC sample used for analysis was measured by weight and multiplied by the density of human RBC (1.10 g/mL) to obtain mcg/dL units.

CUS1
616155

Copper, Serum

Clinical Information: Copper (Cu) is an important trace element that is associated with a number of metalloproteins. Copper in biological material is complexed with proteins, peptides, and other organic ligands. Up to 90% of copper exported from the liver into peripheral blood is protein bound to ceruloplasmin, transcuprein, or metallothionein. A smaller amount of copper in plasma (<10%) is bound to albumin by specific peptide sequences, and this copper is in equilibrium with plasma amino acids. The ceruloplasmin molecule contains 6 to 8 atoms of Cu per molecule with 6 atoms of Cu involved in the protein's ferroxidase and free radical scavenging activities. The other 1 to 2 atoms of Cu are termed "labile" and may allow ceruloplasmin to act as a copper transporter, with a pool of copper being exchanged between albumin, transcuprein, and the labile sites of ceruloplasmin. Low serum copper, most often due to excess iron or zinc ingestion and infrequently due to dietary copper deficit, results in severe derangement in growth and impaired erythropoiesis. Low serum copper is also observed in hepatolenticular degeneration (Wilson disease) due to a decrease in the synthesis of ceruloplasmin and allelic variances in cellular metal ion transporters. In Wilson disease, the albumin-bound copper may actually be increased, but ceruloplasmin-bound copper is low, resulting in low serum copper. However, during the acute phase of Wilson disease (fulminant hepatic failure), ceruloplasmin and copper levels may be normal; in this circumstance, hepatic inflammation causes increased release of ceruloplasmin. It is useful to relate the degree of liver inflammation to the ceruloplasmin and copper-see discussion on hypercupremia below. Significant hepatic inflammation with normal ceruloplasmin and copper suggest acute Wilson disease. Other disorders associated with decreased serum copper concentrations include malnutrition, hypoproteinemia, malabsorption, nephrotic syndrome, Menkes disease, copper toxicity, and megadosing of zinc-containing vitamins (zinc interferes with normal copper absorption from the gastrointestinal [GI] tract). Hypercupremia is found in primary biliary cholangitis (previously primary biliary cirrhosis), primary sclerosing cholangitis, hemochromatosis, malignant diseases (including leukemia), thyrotoxicosis, and various infections. Serum copper concentrations are also elevated in patients taking contraceptives or estrogens and during pregnancy. Since the GI tract effectively excludes excess copper, it is the GI tract that is most affected by copper ingestion. Increased serum concentration does not, by itself, indicate copper toxicity.

Useful For: Diagnosis of: -Wilson disease -Primary biliary cholangitis -Primary sclerosing cholangitis

Interpretation: Serum copper below the normal range is associated with Wilson disease, as well as a variety of other clinical situations (see Clinical Information). Excess use of denture cream containing zinc can cause hypocupremia. Serum concentrations above the normal range are seen in primary biliary cholangitis (previously primary biliary cirrhosis), primary sclerosing cholangitis, and a variety of other clinical situations (see Clinical Information).

Reference Values:
0-2 months: 40-140 mcg/dL
3-6 months: 40-160 mcg/dL
7-9 months: 40-170 mcg/dL
10-12 months: 80-170 mcg/dL
13 months-10 years: 80-180 mcg/dL
11-17 years: 75-145 mcg/dL
Males:
> or =18 years: 73-129 mcg/dL
Females:
> or =18 years: 77-206 mcg/dL

Clinical References: 1. McCullough AJ, Fleming CR, Thistle JL, et al. Diagnosis of Wilson's disease presenting as fulminant hepatic failure. Gastroenterology. 1983;84:161-167 2. Wiesner RH, LaRusso NF, Ludwig J, Dickson ER. Comparison of the clinicopathologic features of primary sclerosing cholangitis and primary biliary cirrhosis. Gastroenterology. 1985;88:108-114 3. Spain RI, Leist TP, De Sousa EA. When metals compete: a case of copper-deficiency myeloneuropathy and

anemia. Nat Clin Pract Neurol. 2009;5(2):106-111 4. Kale SG, Holmes CS, Goldstein DS, et al. Neonatal diagnosis and treatment of Menkes disease. N Engl J Med. 2008;358(6):605-614 5. Nations SP, Boyer PJ, Love LA, et al. Denture cream: An unusual source of excess zinc, leading to hypocupremia and neurologic disease. Neurology. 2008;71;639-643 6. Strathmann FG, Blum LM: Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

CURCU
615257

Copper/Creatinine Ratio, Random, Urine

Clinical Information: The biliary system is the major pathway of copper excretion. Biliary excretion of copper requires an adenosine triphosphate (ATP)-dependent transporter protein. Variants in the gene for the transporter protein cause hepatolenticular degeneration (Wilson disease). Ceruloplasmin, the primary copper-carrying protein in the blood, is also reduced in Wilson disease. Urine copper excretion is increased in Wilson disease due to a decreased serum binding of copper to ceruloplasmin or due to allelic variances in cellular metal ion transporters. Hypercupriuria (increased urinary copper) is also found in hemochromatosis, biliary cirrhosis, thyrotoxicosis, various infections, and a variety of other acute, chronic, and malignant diseases (including leukemia). Urine copper concentrations are also elevated during pregnancy and in patients taking contraceptives or estrogens. Low urine copper levels are seen in malnutrition, hypoproteinemia, malabsorption, and nephrotic syndrome. Increased zinc consumption interferes with normal copper absorption from the gastrointestinal tract causing hypocupremia.

Useful For: Investigation of Wilson disease and obstructive liver disease using a random urine specimen

Interpretation: Humans normally excrete less than 60 mcg/24 hour in the urine. Urinary copper excretion greater than 60 mcg/24 hour may be seen in: -Wilson disease -Obstructive biliary disease (eg, primary biliary cirrhosis, primary sclerosing cholangitis) -Nephrotic syndrome (due to leakage through the kidney) -Chelation therapy -Estrogen therapy -Mega dosing of zinc-containing vitamins Because ceruloplasmin is an acute phase reactant, urine copper is elevated during acute inflammation. During the recovery phase, urine copper is usually below normal, reflecting the expected physiologic response to replace the copper that was depleted during inflammation.

Reference Values:
COPPER/CREATITINE:
Males:
0-17 years: Not established
> or =18 years: 9-43 mcg/g creatinine
Females:
0-17 years: Not established
> or =18 years: 7-72 mcg/g creatinine

CREATITINE:
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years.

Clinical References: 1. Zorbas YG, Kakuris KK, Deogenov VA, Yerullis KB. Copper homeostasis during hypokinesia in healthy subjects with higher and lower copper consumption. Tr Elem Electro. 2008;25:169-178 2. Lech T, Sadlik JK. Contribution to the data on copper concentration in blood and urine in patients with Wilson's disease and in normal subjects. Biol Trace Elem Res. 2007;118(1):16-20 3. Czlonkowska A, Litwin T, Dusek P, et al. Wilson disease. Nat Rev Dis Primers. 2018;4(1):21. doi:10.1038/s41572-018-0018-3 4. Rifai N, Chiu RWK, Young I, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 9th ed. Elsevier; 2023 5. Mohr I, Weiss KH. Biochemical

Markers for the Diagnosis and Monitoring of Wilson Disease. Clin Biochem Rev. 2019;40(2):59-77. doi:10.33176/AACB-18-00014

CURC
615258

Copper/Creatinine Ratio, Urine

Clinical Information: The biliary system is the major pathway of copper excretion. Biliary excretion of copper requires an adenosine triphosphate (ATP)-dependent transporter protein. Variants in the gene for the transporter protein cause hepatolenticular degeneration (Wilson disease). Ceruloplasmin, the primary copper-carrying protein in the blood, is also reduced in Wilson disease. Urine copper excretion is increased in Wilson disease due to a decreased serum binding of copper to ceruloplasmin or due to allelic variances in cellular metal ion transporters. Hypercupriuria (increased urinary copper) is also found in hemochromatosis, biliary cirrhosis, thyrotoxicosis, various infections, and a variety of other acute, chronic, and malignant diseases (including leukemia). Urine copper concentrations are also elevated during pregnancy and in patients taking contraceptives or estrogens. Low urine copper levels are seen in malnutrition, hypoproteinemia, malabsorption, and nephrotic syndrome. Increased zinc consumption interferes with normal copper absorption from the gastrointestinal tract causing hypocupremia.

Useful For: Measurement of copper concentration of a part of the investigation of Wilson disease and obstructive liver disease using a random urine specimen

Interpretation: Humans normally excrete less than 60 mcg/24 hour in the urine. Urinary copper excretion greater than 60 mcg/24 hour may be seen in: -Wilson disease -Obstructive biliary disease (eg, primary biliary cirrhosis, primary sclerosing cholangitis) -Nephrotic syndrome (due to leakage through the kidney) -Chelation therapy -Estrogen therapy -Mega dosing of zinc-containing vitamins Because ceruloplasmin is an acute phase reactant, urine copper is elevated during acute inflammation. During the recovery phase, urine copper is usually below normal, reflecting the expected physiologic response to replace the copper that was depleted during inflammation.

Reference Values:
Only orderable as part of a profile. For more information see CURCU / Copper/Creatinine Ratio, Random, Urine.

Males:
0-17 years: Not established
> or =18 years: 9-43 mcg/g creatinine

Females:
0-17 years: Not established
> or =18 years: 7-72 mcg/g creatinine

Clinical References: 1. Zorbas YG, Kakuris KK, Deogenov VA, Yerullis KB. Copper homeostasis during hypokinesia in healthy subjects with higher and lower copper consumption. Tr Elem Electro. 2008;25:169-178 2. Lech T, Sadlik JK. Contribution to the data on copper concentration in blood and urine in patients with Wilson's disease and in normal subjects. Biol Trace Elem Res. 2007;118(1):16-20 3. Czlonkowska A, Litwin T, Dusek P, et al. Wilson disease. Nat Rev Dis Primers. 2018;4(1):21. doi: 10.1038/s41572-018-0018-3 4. Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

CORI
82476

Coriander, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to coriander Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FCORG
57526

Corn IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG

alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

FCOR4
57569

Corn IgG4

Interpretation: The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests.

CRNP
82718

Corn Pollen, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For:

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive

4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CORN
82705

Corn-Food, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to corn-food Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive

6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CORTC
88221

Corticosterone, Serum

Clinical Information: Corticosterone is a steroid hormone and a precursor molecule for aldosterone. It is produced from deoxycorticosterone, further converted to 18-hydroxycorticosterone, and ultimately to aldosterone in the mineralocorticoid pathway. The adrenal glands, ovaries, testes, and placenta produce steroid hormones, which can be subdivided into 3 major groups: mineralocorticoids, glucocorticoids, and sex steroids. Synthesis proceeds from cholesterol along 3 parallel pathways, corresponding to these 3 major groups of steroids, through successive side-chain cleavage and hydroxylation reactions. At various levels of each pathway, intermediate products can move into the respective adjacent pathways via additional, enzymatically catalyzed reactions (see Steroid Pathways). Corticosterone is the first intermediate in the corticoid pathway with significant mineralocorticoid activity. Its synthesis from 11-deoxycorticosterone is catalyzed by 11-beta-hydroxylase 2 (CYP11B2) or by 11-beta-hydroxylase 1 (CYP11B1). Corticosterone is in turn converted to 18-hydroxycorticosterone and finally to aldosterone, the most active mineralocorticoid. Both reactions are catalyzed by CYP11B2, which, unlike its sister enzyme CYP11B1, also possesses 18-hydroxylase and 18-methyloxidase (also known as aldosterone synthase) activity. The major diagnostic utility of measurements of steroid synthesis intermediates lies in the diagnosis of disorders of steroid synthesis, in particular congenital adrenal hyperplasia (CAH). All types of CAH are associated with cortisol deficiency with the exception of CYP11B2 deficiency and isolated impairments of the 17-lyase activity of CYP17A1 (this enzyme also has 17 alpha-hydroxylase activity). In cases of severe illness or trauma, CAH predisposes patients to poor recovery or death. Patients with the most common form of CAH (21-hydroxylase deficiency, which accounts for >90% of cases), the third most common form of CAH (3-beta-steroid dehydrogenase deficiency, which accounts for<3% of cases), or the extremely rare StAR (steroidogenic acute regulatory protein) or 20,22 desmolase deficiencies may also suffer mineralocorticoid deficiency, as the enzyme blocks in these disorders are proximal to potent mineralocorticoids. These patients might suffer salt-wasting crises in infancy. By contrast, patients with the second most common form of CAH (11-hydroxylase deficiency, which accounts for <5% of cases) are normotensive or hypertensive, as the block affects either CYP11B1 or CYP11B2 but rarely both, thus ensuring that at least corticosterone is still produced. In addition, patients with all forms of CAH might suffer the effects of substrate accumulation proximal to the enzyme block. In the 3 most common forms of CAH, the accumulating precursors spill over into the sex steroid pathway, resulting in virilization of female patients or, in milder cases, hirsutism, polycystic ovarian syndrome, or infertility, as well as in possible premature adrenarche and pubarche in both sexes. Measurement of the various precursors of mature mineralocorticoid and glucocorticoids, in concert with the determination of sex steroid concentrations, allows diagnosis of CAH and its precise type and serves as an aid in monitoring steroid replacement therapy and other therapeutic interventions. Measurement of corticosterone is used as an adjunct to 11-deoxycorticosterone and 11-deoxycortisol (also known as compound S) measurement in the diagnosis of: -CYP11B1 deficiency (associated with cortisol deficiency) -The less common CYP11B2 deficiency (no cortisol deficiency) -The rare glucocorticoid responsive hyperaldosteronism (where expression of the gene CYP11B2 is driven by the CYP11B1 promoter, thus making it responsive to corticotropin [previously adrenocorticotrophic hormone: ACTH] rather than renin) -Isolated loss of function of the 18-hydroxylase or 18-methyloxidase activity of CYP11B2 For other forms of CAH, the following tests might be relevant: 21-Hydroxylase deficiency: -OHPG / 17-Hydroxyprogesterone, Serum -ANST / Androstenedione, Serum -21DOC / 21-Deoxycortisol, Serum 3-Beta-steroid dehydrogenase deficiency: -17PRN / Pregnenolone and 17-Hydroxypregnenolone, Serum

17-Hydroxylase deficiency or 17-lyase deficiency (CYP17A1 has both activities): -17PRN / Pregnenolone and 17-Hydroxypregnenolone, Serum -PGSN / Progesterone, Serum -OHPG / 17-Hydroxyprogesterone, Serum -DHEA_ / Dehydroepiandrosterone (DHEA), Serum -ANST / Androstenedione, Serum Cortisol should be measured in all cases of suspected CAH. When evaluating for suspected 11-hydroxylase deficiency, this test should be used in conjunction with measurements of 11-deoxycortisol, 11-corticosterone, 18-hydroxycorticosterone, cortisol, renin, and aldosterone. When evaluating infants with positive newborn screening results for congenital adrenal hyperplasia, this test should be used in conjunction with 11-deoxycortisol and 11-deoxycorticosteorone measurements as an adjunct to 17-hydroxyprogesterone, aldosterone, and cortisol measurements.

Useful For: Diagnosis of suspected 11-hydroxylase deficiency, including the differential diagnosis of 11-beta-hydroxylase 1 (CYP11B1) versus 11-beta-hydroxylase 2 (CYP11B2) deficiency, and the diagnosis of glucocorticoid-responsive hyperaldosteronism Evaluating infants with positive newborn screening results for congenital adrenal hyperplasia, when elevations of 17-hydroxyprogesterone are only moderate, thereby suggesting possible 11-hydroxylase deficiency

Interpretation: In 11-beta-hydroxylase 1 (CYP11B1) deficiency, serum concentrations of cortisol will be low (usually <7 microgram/dL for a morning collection). 11-Deoxycortisol and 11-deoxycorticosterone are elevated, usually to at least 2 to 3 times (more typically 20 to 300 times) the upper limit of the normal reference range on a morning blood collection. Elevations in 11-deoxycortisol are usually relatively greater than those of 11-deoxycorticosterone because of the presence of intact 11-beta-hydroxylase 2 (CYP11B2). For this reason, serum concentrations of all potent mineralocorticoids (corticosterone, 18-hydroxycorticosterone, and aldosterone) are typically increased above the normal reference range. Plasma renin activity is correspondingly low or completely suppressed. Caution needs to be exercised in interpreting the mineralocorticoid results in infants younger than 7 days; mineralocorticoid levels are often substantially elevated in healthy newborns in the first few hours of life and only decline to near-adult levels by week 1. Mild cases of CYP11B1 deficiency might require corticotropin (previously adrenocorticotrophic hormone: ACTH)1-24 stimulation testing for definitive diagnosis. In affected individuals, the observed serum 11-deoxycortisol concentration 60 minutes after intravenous or intramuscular administration of 250 microgram of ACTH1-24 will usually exceed 20 ng/mL, or at least a 4-fold rise. Such increments are rarely, if ever, observed in unaffected individuals. The corresponding cortisol response will be blunted (<18 ng/mL peak). In CYP11B2 deficiency, serum cortisol concentrations are usually normal, including a normal response to ACTH1-24. 11-Deoxycorticosterone will be elevated, often more profoundly than in CYP11B1 deficiency, while 11-deoxycortisol may or may not be significantly elevated. Serum corticosterone concentrations can be low, normal, or slightly elevated, while serum 18-hydroxycorticosterone and aldosterone concentrations will be low in the majority of cases. However, if the underlying genetic defect has selectively affected 18-hydroxylase activity, corticosterone concentrations will be substantially elevated. Conversely, if the deficit affects aldosterone synthase function primarily, 18-hydroxycorticosterone concentrations will be very high. Expression of the CYP11B2 gene is normally regulated by renin and not ACTH. In glucocorticoid-responsive hyperaldosteronism, the ACTH-responsive promoter of CYP11B1 exerts aberrant control over CYP11B2 gene expression. Consequently, corticosterone, 18-hydroxycorticosterone, and aldosterone are significantly elevated in these patients and their levels follow a diurnal pattern, governed by the rhythm of ACTH secretion. In addition, the high levels of CYP11B2 lead to 18-hydroxylation of 11-deoxycortisol (an event that is ordinarily rare, as CYP11B1, which has much greater activity in 11-deoxycortisol conversion than CYP11B2, lacks 18-hydroxylation activity). Consequently, significant levels of 18-hydroxycortisol, which normally is only present in trace amounts, might be detected in these patients. Ultimate diagnostic confirmation comes from directly showing responsiveness of mineralocorticoid production to ACTH1-24 injection. Normally, this has little, if any, effect on corticosterone, 18-hydroxycorticosterone, and aldosterone levels. This testing may then be further supplemented by showing that mineralocorticoid levels fall after administration of dexamethasone. Sex steroid levels are moderately to significantly elevated in CYP11B1 deficiency and much less, or minimally, pronounced, in CYP11B2 deficiency. Sex steroid levels in glucocorticoid-responsive hyperaldosteronism are usually normal. Most untreated patients with 21-hydroxylase deficiency have serum 17-hydroxyprogesterone

concentrations well in excess of 1000 ng/dL. For the few patients with levels in the range of greater than 630 ng/dL (upper limit of reference range for newborns) to 2000 or 3000 ng/dL, it might be prudent to consider 11-hydroxylase deficiency as an alternative diagnosis. This is particularly true if serum androstenedione concentrations are also only mildly to modestly elevated, and if the phenotype is not salt wasting but either simple virilizing (female) or normal (female or male). 11-Hydroxylase deficiency, particularly if it affects CYP11B1, can be associated with modest elevations in serum 17-hydroxyprogesterone concentrations. In these cases, testing for CYP11B1 deficiency and CYB11B2 deficiency should be considered and interpreted as described above. Alternatively, measurement of 21-deoxycortisol might be useful in these cases. This minor pathway metabolite accumulates in CYP21A2 deficiency, as it requires 21-hydroxylation to be converted to cortisol, but is usually not elevated in CYP11B1 deficiency, since its synthesis requires 11-hydroxylation of 17-hydroxyprogesterone.

Reference Values:

< or =18 years: 18-1,970 ng/dL
>18 years: 53-1,560 ng/dL

Clinical References: 1. von Schnakenburg K, Bidlingmaier F, Knorr D. 17-hydroxyprogesterone, androstenedione, and testosterone in normal children and in prepubertal patients with congenital adrenal hyperplasia. Eur J Pediatr. 1980;133(3):259-267 2. Therrell BL. Newborn screening for congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. 2001;30(1):15-30 3. Collett-Solberg PF. Congenital adrenal hyperplasia: From genetics and biochemistry to clinical practice, Part 1. Clin Pediatr. 2001;40(1):1-16 4. Forest MG. Recent advances in the diagnosis and management of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Hum Reprod Update. 2004;10(6):469-485 5. Tonetto-Fernandes V, Lemos-Marini SH, Kuperman H, Ribeiro-Neto LM, Verreschi IT, Kater CE. Serum 21-deoxycortisol, 17-hydroxyprogesterone, and 11-deoxycortisol in classic congenital adrenal hyperplasia: clinical and hormonal correlations and identification of patients with 11 beta-hydroxylase deficiency among a large group with alleged 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2006;91(6):2179-2184 6. Idkowiak, J, Cragun, D, Hopkin RJ, Arlt W. Cytochrome P450 oxidoreductase deficiency. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. Gene Reviews [Internet]. University of Washington, Seattle; 2005. Updated August 3, 2017. Accessed March 3, 2025. Available at www.ncbi.nlm.nih.gov/sites/books/NBK1419/ 7. Held PK, Bird IM, Heather NL. Newborn screening for congenital adrenal hyperplasia: review of factors affecting screening accuracy. Int J Neonatal Screen. 2020;6(3):67. doi:10.3390/ijns6030067

CORTO
65484

Cortisol, Free and Total, Serum

Clinical Information: Cortisol, the main glucocorticoid (representing 75%-95% of the plasma corticoids), plays a critical role in glucose metabolism and in the body's response to stress. Both hypercortisolism (Cushing disease) and hypocortisolism (Addison disease) can cause disease. Cortisol is also used to treat skin disease, allergic disorders, respiratory system disease, inflammatory disorders, and nephrotic syndrome. Cortisol levels are regulated by corticotropin (previously adrenocorticotropic hormone: ACTH), which is synthesized by the pituitary in response to corticotropin-releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6 a.m.-8 a.m.) and troughs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to corticosteroid-binding globulin (CBG) and albumin. Normally, less than 5% of circulating cortisol is free (unbound). Only free cortisol can access the enzyme transporters in liver, kidney, and other tissues that mediate metabolic and excretory clearance. Historically, measurements of free cortisol have been achieved from indirect means using a ratio known as the free cortisol index. This measurement takes into account the amount of total cortisol and CBG to give a percentage and, ultimately, absolute value of free cortisol. These methods do not consider the possibility variations in albumin levels. These calculations also rely on CBG, which can be lowered in critically ill patients despite normal adrenal function. Equilibrium dialysis best serves to separate free from bound cortisol

without disrupting the bound fraction. Pathological hypercortisolism due to endogenous or exogenous glucocorticoids is termed Cushing syndrome. Signs and symptoms of pathological hypercortisolism may include central obesity, hypertension, hyperglycemia, hirsutism, muscle weakness, and osteoporosis. However, these symptoms and signs are not specific for pathological hypercortisolism. Most individuals with some or all of the symptoms and signs will not suffer from Cushing syndrome. When Cushing syndrome is present, the most common cause is iatrogenic, due to repeated or prolonged administration of, mostly, synthetic corticosteroids. Spontaneous Cushing syndrome is less common and results from either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype, commonly seen in women in the third through fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made. Hypocortisolism most commonly presents with nonspecific lassitude, weakness, hypotension, and weight loss. Depending on the cause, hyperpigmentation may be present. More advanced cases and patients submitted to physical stress (ie, infection, spontaneous or surgical trauma) also may present with abdominal pain, hyponatremia, hyperkalemia, hypoglycemia, and in extreme cases, cardiovascular shock, and kidney failure. The more common causes of hypocortisolism are: Primary adrenal insufficiency: -Addison disease -Congenital adrenal hyperplasia, defects in enzymes involved in cortisol synthesis Secondary adrenal insufficiency: -Prior, prolonged corticosteroid therapy -Pituitary insufficiency -Hypothalamic insufficiency For more information see Steroid Pathways.

Useful For: Assessment of cortisol status in cases where there is known or a suspected abnormality in cortisol-binding proteins or albumin Assessment of adrenal function in the critically ill or stressed patient, thus preventing unnecessary use of glucocorticoid therapy Second-order testing when cortisol measurement by immunoassay (eg, CORT / Cortisol, Serum) gives results that are not consistent with clinical symptoms, or if patients are known to, or suspected of, taking exogenous synthetic steroids An adjunct in the differential diagnosis of primary and secondary adrenal insufficiency An adjunct in the differential diagnosis of Cushing syndrome

Interpretation: Cortisol is converted to cortisone in human kidneys and cortisone is less active toward the mineralocorticoid receptor. The conversion of cortisol to cortisone in the kidney is mediated by 11-beta-hydroxysteroid dehydrogenase isoform-2. Also, cortisol renal clearance will be reduced when there is a deficiency in the cytochrome P450 3A5 (CYP3A5) enzyme as well as a deficiency in P-glycoprotein. Cortisol-binding globulin (CBG) has a low capacity and high affinity for cortisol, whereas albumin has a high capacity and low affinity for binding cortisol. Variations in CBG and serum albumin due to kidney or liver disease may have a major impact on free cortisol. Based on the study by Bancos,(1) normal ranges of free cortisol found in patients without adrenal insufficiency were: -Free cortisol at baseline: median 0.400 mcg/dL (interquartile range: IQR 2.5%-97.5%: 0.110-1.425 mcg/dL) -Free cortisol at 30 minutes: median 1.355 mcg/dL (IQR 2.5%-97.5%: 0.885-2.440 mcg/dL) -Free cortisol at 60 minutes: median 1.720 mcg/dL (IQR 2.5%-97.5%: 1.230-2.930 mcg/dL) Based on the study by Bancos,(1) the following cutoffs were calculated for exclusion of adrenal insufficiency: -Free cortisol at baseline*: greater than 0.271 mcg/dL (>271 ng/dL, area under the curve: AUC 0.81) -Free cortisol at 30 minutes: greater than 0.873 mcg/dL (>873 ng/dL, AUC 0.99) -Free cortisol at 60 minutes: greater than 1.190 mcg/dL (>1190 ng/dL, AUC 0.99) (*note that baseline free cortisol should not be used to exclude adrenal insufficiency given low performance) The use of free cortisol in the management of glucocorticoid levels in the stressed patient due to major surgery or trauma requires further studies to establish clinical dosing levels and efficacy. Cortisol pediatric reference ranges are generally the same as adults as confirmed by peer-reviewed literature.(2) In primary adrenal insufficiency, corticotropin (previously adrenocorticotropic hormone: ACTH) levels are increased and cortisol levels are decreased; in secondary adrenal insufficiency both ACTH and cortisol levels are decreased. When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is less than 10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), additional studies are needed to establish the diagnosis. The 3 most frequently used tests are the ACTH (cosyntropin) stimulation test, the metyrapone test, and insulin-induced hypoglycemia test. First, the basal plasma ACTH concentration should be measured and the short cosyntropin stimulation test performed. Symptoms or signs of Cushing syndrome in a patient with low

serum and urine cortisol levels suggest possible exogenous synthetic steroid effects.

Reference Values:

FREE CORTISOL
6-10:30 a.m. Collection: 0.121-1.065 mcg/dL

TOTAL CORTISOL
5-25 mcg/dL (a.m.)
2-14 mcg/dL (p.m.)
Pediatric reference ranges are the same as adults, as confirmed by peer-reviewed literature.

Petersen KE. ACTH in normal children and children with pituitary and adrenal diseases. I. Measurement in plasma by radioimmunoassay-basal values. Acta Paediatr Scand. 1981;70(3):341-345

Clinical References: 1. Bancos I, Erickson D, Bryant S, et al. Performance of free versus total cortisol following cosyntropin stimulation testing in an outpatient setting. Endocr Pract. 2015;21(12):1353-1363. doi:10.4158/EP15820.OR 2. Petersen KE. ACTH in normal children and children with pituitary and adrenal diseases. I. Measurement in plasma by radioimmunoassay-basal values. Acta Paediatr Scand. 1981;70(3):341-345. doi:10.1111/j.1651-2227.1981.tb16561.x 3. Petersen KE. ACTH in normal children and children with pituitary and adrenal diseases. I. Measurement in plasma by radioimmunoassay-basal values. Acta Paediatr Scand. 1981;70(3):341-345. doi:10.1111/j.1651-2227.1981.tb16561.x 4. Ho JT, Al-Musalhi H, Chapman MJ, et al. Septic shock and sepsis: a comparison of total and free plasma cortisol levels. J Clin Endocrinol Metab. 2006;91(1):105-114. doi:10.1210/jc.2005-0265 5. le Roux CW, Chapman GA, Kong WM, Dhillo WS, Jones J, Alaghband-Zadeh J. Free cortisol index is better than serum total cortisol in determining hypothalamic-pituitary-adrenal status in patients undergoing surgery. J Clin Endocrinol Metab. 2003;88(5):2045-2048. doi:10.1210/jc.2002-021532 6. Huang W, Kalhorn TF, Baillie M, Shen DD, Thummel KE. Determination of free and total cortisol in plasma and urine by liquid chromatography-tandem mass spectrometry. Ther Drug Monit. 2007;29(2):215-224. doi:10.1097/FTD.0b013e31803d14c0

CORTU
8546

Cortisol, Free, 24 Hour, Urine

Clinical Information: Cortisol is a steroid hormone synthesized from cholesterol by a multienzyme cascade in the adrenal glands. It is the main glucocorticoid in humans and acts as a gene transcription factor influencing a multitude of cellular responses in virtually all tissues. Cortisol plays a critical role in glucose metabolism, maintenance of vascular tone, immune response regulation, and in the body's response to stress. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating cortisol is biologically active (free), with the majority of cortisol inactive (protein bound). As plasma cortisol values increase, free cortisol (ie, unconjugated cortisol or hydrocortisone) increases and is filtered through the glomerulus. Urinary free cortisol (UFC) in the urine correlates well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. Urinary free cortisol is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion, by liquid chromatography tandem mass spectrometry (LC-MS/MS), is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic corticosteroids, which can affect immunoassay-based cortisol results.

Useful For: Preferred screening test for Cushing syndrome Diagnosis of pseudo-hyperaldosteronism due to excessive licorice consumption Test may not be useful in the evaluation of adrenal insufficiency.

Interpretation: Most patients with Cushing syndrome have increased 24-hour urinary excretion of cortisol. Further studies, including suppression or stimulation tests, measurement of serum corticotropin concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have suppressed cortisol. In these circumstances a synthetic glucocorticoid screen might be ordered (SGSU / Synthetic Glucocorticoid Screen, Random, Urine). Suppressed cortisol values may also be observed in primary adrenal insufficiency and hypopituitarism. However, many normal individuals may also exhibit a very low 24-hour urinary cortisol excretion with considerable overlap with the values observed in pathological hypocorticalism. Therefore, without other tests, 24-hour urinary cortisol measurements cannot be relied upon for the diagnosis of hypocorticalism.

Reference Values:
0-2 years: Not established
3-8 years: 1.4-20 mcg/24 h
9-12 years: 2.6-37 mcg/24 h
13-17 years: 4.0-56 mcg/24 h
> or =18 years: 3.5-45 mcg/24 h

Use the factor below to convert from mcg/24 hr to nmol/24 hr:

Conversion factor
Cortisol: mcg/24 h x 2.76=nmol/24 hr (molecular weight=362.5)

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Eisenhofer G, Grebe S, Cheung N-K V.Monoamine-Producing Tumors. In: Rafai N, Horvath AR, Witter CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier, 2018: 1421 2. Lin CL, Wu TJ, Machacek DA, Jiang NS, Kao PC. Urinary free cortisol and cortisone determined by high performance liquid chromatography in the diagnosis of Cushing's syndrome. J Clin Endocrinol Metab. 1997;82(1):151-155 3. Dodds HM, Taylor PJ, Cannell GR, Pond SM. A high-performance liquid chromatography-electrospray-tandem mass spectrometry analysis of cortisol and metabolites in placental perfusate. Anal Biochem. 1997;247(2):342-347. doi:10.1006/abio.1997.2074

CRANR
609741

Cortisol, Free, Random, Urine

Clinical Information: Cortisol is a steroid hormone synthesized from cholesterol by a multienzyme cascade in the adrenal glands. It is the main glucocorticoid in humans and acts as a gene transcription factor influencing a multitude of cellular responses in virtually all tissues. Cortisol plays a critical role in glucose metabolism, maintenance of vascular tone, immune response regulation, and in the body's response to stress. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating cortisol is biologically active (free), with the majority of cortisol inactive (protein bound). As plasma cortisol values increase, free cortisol (ie, unconjugated cortisol or hydrocortisone) increases and is filtered through the glomerulus. Urinary free cortisol (UFC) correlates well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. The UFC assay is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion by liquid chromatography tandem mass spectrometry (LC-MS/MS) is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine

(Tegretol) and synthetic corticosteroids, which can affect immunoassay-based cortisol results.

Useful For: Investigating suspected hypercortisolism when a 24-hour collection is prohibitive (ie, pediatric patients)

Interpretation: Most patients with Cushing syndrome have increased 24-hour urinary excretion of cortisol. Further studies, including suppression or stimulation tests, measurement of serum corticotropin (adrenocorticotropic hormone) concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have suppressed cortisol. In these circumstances a synthetic glucocorticoid screen might be ordered (SGSU / Synthetic Glucocorticoid Screen, Random, Urine). Suppressed cortisol values may also be observed in primary adrenal insufficiency and hypopituitarism. The optimal specimen type for evaluation of primary adrenal insufficiency and hypopituitarism is serum (CORT / Cortisol, Serum).

Reference Values:

Males
0-2 years: 3.0-120 mcg/g creatinine
3-8 years: 2.2-89 mcg/g creatinine
9-12 years: 1.4-56 mcg/g creatinine
13-17 years: 1.0-42 mcg/g creatinine
> or =18 years: 1.0-119 mcg/g creatinine

Females
0-2 years: 3.0-120 mcg/g creatinine
3-8 years: 2.2-89 mcg/g creatinine
9-12 years: 1.4-56 mcg/g creatinine
13-17 years: 1.0-42 mcg/g creatinine
> or =18 years: 0.7-85 mcg/g creatinine

Use the conversion factors below to convert each analyte from mcg/g creatinine to nmol/mol creatinine.

Conversion factor
Cortisol: mcg/g creatinine x 312=nmol/mol creatinine

Cortisol molecular weight=362.5
Creatinine molecular weight=113.12

Clinical References: 1. Taylor RL, Machacek DA, Singh RJ. Validation of a high-throughput liquid chromatography tandem mass spectrometry method for urinary cortisol and cortisone. Clin Chem. 2002;48(9):1511-1519 2. Findling JW, Raff H. Diagnosis and differential diagnosis of Cushing's syndrome. Endocrinol Metab Clin North Am. 2001;30(3):729-747 3. Boscaro M, Barzon L, Fallo F, Sonino N. Cushing's syndrome. Lancet. 2001;357(9258):783-791 4. Suzuki S, Minamidate T, Shiga A, et al. Steroid metabolites for diagnosing and predicting clinicopathological features in cortisol-producing adrenocortical carcinoma. BMC Endocr Disord. 2020;20(1):173. doi:10.1186/s12902-020-00652-y

CORTF 65423 Cortisol, Free, Serum

Clinical Information: Cortisol, the main glucocorticoid (representing 75%-95% of the plasma corticoids), plays a critical role in glucose metabolism and in the body's response to stress. Both hypercortisolism (Cushing disease) and hypocortisolism (Addison disease) can cause disease. Cortisol is also used to treat skin disease, allergic disorders, respiratory system disease, inflammatory disorders, and nephrotic syndrome. Cortisol levels are regulated by corticotropin (previously adrenocorticotropic hormone: ACTH), which is synthesized by the pituitary in response to corticotropin releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6 a.m.-8 a.m.) and troughs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to corticosteroid-binding globulin (CBG) and albumin. Normally, less than 5% of circulating cortisol is free (unbound). Only free cortisol can access the enzyme transporters in liver, kidney, and other tissues that mediate metabolic and excretory clearance. Historically, measurements of free cortisol have been achieved from indirect means using a ratio known as the free cortisol index. This measurement takes into account the amount of total cortisol and CBG to give a percentage and ultimately absolute value of free cortisol. These methods do not take into account the possible variations in albumin levels. These calculations also rely on CBG, which can be lowered in critically ill patients despite normal adrenal function. Equilibrium dialysis best serves to separate free from bound cortisol without disrupting the bound fraction.

Useful For: Assessment of cortisol status in cases where there is known or a suspected abnormality in cortisol-binding proteins or albumin Assessment of adrenal function in the critically ill or stressed patient, thus preventing unnecessary use of glucocorticoid therapy

Interpretation: Cortisol is converted to cortisone in human kidneys and cortisone is less active toward the mineralocorticoid receptor. The conversion of cortisol to cortisone in the kidney is mediated by 11-beta-hydroxysteroid dehydrogenase isoform-2. Also, cortisol renal clearance will be reduced when there is a deficiency in the cytochrome P450 3A5 (CYP3A5) enzyme as well as a deficiency in P-glycoprotein. Cortisol binding globulin (CBG) has a low capacity and high affinity for cortisol, whereas albumin has a high capacity and low affinity for binding cortisol. Variations in CBG and serum albumin due to renal or liver disease may have a major impact on free cortisol. Based on the study by Bancos,(1) normal ranges of free cortisol found in patients without adrenal insufficiency were: -Free cortisol at baseline: median 0.400 mcg/dL (interquartile range: IQR 2.5-97.5%-0.110-1.425 mcg/dL) -Free cortisol at 30 minutes: median 1.355 mcg/dL (IQR 2.5-97.5%-0.885-2.440 mcg/dL) -Free cortisol at 60 minutes: median 1.720 mcg/dL (IQR 2.5-97.5%-1.230-2.930 mcg/dL) Based on the study by Bancos,(1) the following cutoffs were calculated for exclusion of adrenal insufficiency: -Free cortisol at baseline*: greater than 0.271 mcg/dL (>271 ng/dL, area under the curve: AUC 0.81) -Free cortisol at 30 minutes: greater than 0.873 mcg/dL (>873 ng/dL, AUC 0.99) -Free cortisol at 60 minutes: greater than 1.190 mcg/dL (>1190 ng/dL, AUC 0.99) *baseline free cortisol should not be used to exclude adrenal insufficiency given low performance The use of free cortisol in the management of glucocorticoid levels in the stressed patient due to major surgery or trauma requires further studies to establish clinical dosing levels and efficacy.

Reference Values:
6-10:30 a.m. Collection: 0.121-1.065 mcg/dL

Clinical References: 1. Bancos I, Erickson D, Bryant S, et al. Performance of free versus total cortisol following cosyntropin stimulation testing in an outpatient setting. Endocr Pract. 2015;21(12):1353-1363. doi:10.4158/EP15820.OR 2. Hamrahian AH, et al. Measurements of Serum Free Cortisol in Critically Ill Patients. New England Journal of Medicine 2004;350;16:1629-1638 3. le Roux CW, Chapman GA, Kong WM, Dhillo WS, Jones J, Alaghband-Zadeh J. Free cortisol index is better than serum total cortisol in determining hypothalamic-pituitary-adrenal status in patients undergoing surgery. J Clin Endocrinol Metab. 2003;88(5):2045-2048 4. Huang W, Kalhorn TF, Baillie M, Shen DD, Thummel KE. Determination of free and total cortisol in plasma and urine by liquid chromatography-tandem mass spectrometry. Ther Drug Monit. 2007;29(2):215-224

CIVC
6347

Cortisol, Inferior Vena Cava, Serum

Clinical Information: Cortisol, the main glucocorticoid (representing 75%-95% of the plasma corticoids), plays a critical role in glucose metabolism and in the body's response to stress. Both hypercortisolism and hypocortisolism can cause disease. Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6-8 a.m.) and troughs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to corticosteroid-binding globulin and albumin. Normally, less than 5% of circulating cortisol is free (unbound). Free cortisol is the physiologically active form and is filterable by the renal glomerulus. Pathological hypercortisolism due to endogenous or exogenous glucocorticoids is termed Cushing syndrome. Signs and symptoms of pathological hypercortisolism may include central obesity, hypertension, hyperglycemia, hirsutism, muscle weakness, and osteoporosis. However, these symptoms and signs are not specific for pathological hypercortisolism. The majority of individuals with some or all of the symptoms and signs will not suffer from Cushing syndrome. When Cushing syndrome is present, the most common cause is iatrogenic, due to repeated or prolonged administration of, mostly, synthetic corticosteroids. Spontaneous Cushing syndrome is less common and results from either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made. Hypocortisolism most commonly presents with nonspecific lassitude, weakness, hypotension, and weight loss. Depending on the cause, hyperpigmentation may be present. More advanced cases and patients submitted to physical stress (ie, infection, spontaneous or surgical trauma) also may present with abdominal pain, hyponatremia, hyperkalemia, hypoglycemia, and in extreme cases, cardiovascular shock and renal failure. The more common causes of hypocortisolism are: Primary adrenal insufficiency: -Addison disease -Congenital adrenal hyperplasia, defects in enzymes involved in cortisol synthesis Secondary adrenal insufficiency: -Prior, prolonged corticosteroid therapy -Pituitary insufficiency -Hypothalamic insufficiency For more information see Steroid Pathways.

Useful For: Testing cortisol levels in the inferior vena cava Second-order testing wen cortisol measurement by immunoassay gives results that are not consistent with clinical symptoms, or if patients are known to, or suspected of, taking exogenous synthetic steroids An adjunct in the differential diagnosis of primary and secondary adrenal insufficiency An adjunct in the differential diagnosis of Cushing syndrome

Interpretation: In primary adrenal insufficiency, adrenocorticotropic hormone (ACTH) levels are increased and cortisol levels are decreased; in secondary adrenal insufficiency both ACTH and cortisol levels are decreased. When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is <10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), further studies are needed to establish the diagnosis. The 3 most frequently used tests are the ACTH (cosyntropin) stimulation test, the metyrapone test, and insulin-induced hypoglycemia test. First, the basal plasma ACTH concentration should be measured, and the short cosyntropin stimulation test performed. Cushing syndrome is characterized by increased serum cortisol levels. However, the 24-hour urinary free cortisol excretion is the preferred screening test for Cushing syndrome, specifically CORTU / Cortisol, Free, 24 Hour, Urine that utilizes liquid chromatography-tandem mass spectrometry. A normal result makes the diagnosis unlikely. Symptoms or signs of Cushing syndrome in a patient with low serum and urine cortisol levels suggest possible exogenous synthetic steroid effects.

Reference Values:
Not established

Clinical References: 1. Lin CL, Wu TJ, Machacek DA, Jiang NS, Kao PC. Urinary free cortisol and cortisone determined by high-performance liquid chromatography in the diagnosis of Cushing's

syndrome. J Clin Endocrinol Metab. 1997;82:151-155. doi:10.1210/jcem.82.1.3687 2. Findling JW, Raff H. Diagnosis and differential diagnosis of Cushing's syndrome. Endocrinol Metab Clin North Am. 2001;30(3):729-747. doi:10.1016/s0889-8529(05)70209-7 3. Buchman Al. Side effects of corticosteroid therapy. J Clin Gastroenterol. 2001;33(4):289-297. doi:10.1097/00004836-200110000-00006 4. Dodds HM, Taylor PJ, Cannell GR, Pond SM. A high-performance liquid chromatography-electrospray-tandem mass spectrometry analysis of cortisol and metabolites in placental perfusate. Anal Biochem. 1997;247:342-347. doi:10.1006/abio.1997.2074 5. Nordenstrom A, Falhammar H. Diagnosis and management of the patient with non-classic CAH due to 21-hydroxylase deficiency Eur J Endocrinol. 2019;180(3):R127-R145 6. Cengiz H, Demirci T, Varim C, Cetin S. Establishing a new screening 17 hydroxyprogesterone cut-off value and evaluation of the reliability of the long intramuscular ACTH stimulation test in the diagnosis of nonclassical congenital adrenal hyperplasia. Eur Rev Med Pharmacol Sci. 2021;25(16):5235-5240. doi:10.26355/eurrev_202108_26537

CLAV
6346

Cortisol, Left Adrenal Vein, Serum

Clinical Information: Cortisol, the main glucocorticoid (representing 75%-95% of the plasma corticoids), plays a critical role in glucose metabolism and in the body's response to stress. Both hypercortisolism and hypocortisolism can cause disease. Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6-8 a.m.) and troughs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to corticosteroid-binding globulin and albumin. Normally, less than 5% of circulating cortisol is free (unbound). Free cortisol is the physiologically active form and is filterable by the renal glomerulus. Pathological hypercortisolism due to endogenous or exogenous glucocorticoids is termed Cushing syndrome. Signs and symptoms of pathological hypercortisolism may include central obesity, hypertension, hyperglycemia, hirsutism, muscle weakness, and osteoporosis. However, these symptoms and signs are not specific for pathological hypercortisolism. The majority of individuals with some or all of the symptoms and signs will not suffer from Cushing syndrome. When Cushing syndrome is present, the most common cause is iatrogenic, due to repeated or prolonged administration of, mostly, synthetic corticosteroids. Spontaneous Cushing syndrome is less common and results from either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made. Hypocortisolism most commonly presents with nonspecific lassitude, weakness, hypotension, and weight loss. Depending on the cause, hyperpigmentation may be present. More advanced cases and patients submitted to physical stress (ie, infection, spontaneous or surgical trauma) also may present with abdominal pain, hyponatremia, hyperkalemia, hypoglycemia, and in extreme cases, cardiovascular shock and renal failure. The more common causes of hypocortisolism are: Primary adrenal insufficiency: -Addison disease -Congenital adrenal hyperplasia, defects in enzymes involved in cortisol synthesis Secondary adrenal insufficiency: -Prior, prolonged corticosteroid therapy -Pituitary insufficiency -Hypothalamic insufficiency For more information see Steroid Pathways.

Useful For: Testing cortisol levels in the left adrenal vein Second-order testing wen cortisol measurement by immunoassay gives results that are not consistent with clinical symptoms, or if patients are known to, or suspected of, taking exogenous synthetic steroids. An adjunct in the differential diagnosis of primary and secondary adrenal insufficiency An adjunct in the differential diagnosis of Cushing syndrome

Interpretation: In primary adrenal insufficiency, adrenocorticotropic hormone (ACTH) levels are increased and cortisol levels are decreased; in secondary adrenal insufficiency both ACTH and cortisol levels are decreased. When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is <10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), further

studies are needed to establish the diagnosis. The 3 most frequently used tests are the ACTH (cosyntropin) stimulation test, the metyrapone test, and insulin-induced hypoglycemia test. First, the basal plasma ACTH concentration should be measured, and the short cosyntropin stimulation test performed. Cushing syndrome is characterized by increased serum cortisol levels. However, the 24-hour urinary free cortisol excretion is the preferred screening test for Cushing syndrome, specifically CORTU / Cortisol, Free, 24 Hour, Urine that utilizes liquid chromatography-tandem mass spectrometry. A normal result makes the diagnosis unlikely. Symptoms or signs of Cushing syndrome in a patient with low serum and urine cortisol levels suggest possible exogenous synthetic steroid effects.

Reference Values:
No established reference values

Clinical References:

CINP
9369

Cortisol, Mass Spectrometry, Serum

Clinical Information: Cortisol, the main glucocorticoid (representing 75%-95% of the plasma corticoids), plays a critical role in glucose metabolism and in the body's response to stress. Both hypercortisolism and hypocortisolism can cause disease. Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6-8 a.m.) and troughs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to corticosteroid-binding globulin and albumin. Normally, less than 5% of circulating cortisol is free (unbound). Free cortisol is the physiologically active form and is filterable by the renal glomerulus. Pathological hypercortisolism due to endogenous or exogenous glucocorticoids is termed Cushing syndrome. Signs and symptoms of pathological hypercortisolism may include central obesity, hypertension, hyperglycemia, hirsutism, muscle weakness, and osteoporosis. However, these symptoms and signs are not specific for pathological hypercortisolism. The majority of individuals with some or all of the symptoms and signs will not suffer from Cushing syndrome. When Cushing syndrome is present, the most common cause is iatrogenic, due to repeated or prolonged administration of, mostly, synthetic corticosteroids. Spontaneous Cushing syndrome is less common and results from either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made. Hypocortisolism most commonly presents with nonspecific lassitude, weakness, hypotension, and weight loss. Depending on the cause, hyperpigmentation may be present. More advanced cases and patients submitted to physical stress (ie, infection, spontaneous or surgical trauma) also may present with abdominal pain, hyponatremia, hyperkalemia, hypoglycemia, and in extreme cases, cardiovascular shock and renal failure. The more common causes of hypocortisolism are: Primary adrenal insufficiency: -Addison disease -Congenital adrenal hyperplasia, defects in enzymes involved in cortisol synthesis Secondary adrenal insufficiency: -Prior, prolonged corticosteroid therapy -Pituitary insufficiency -Hypothalamic insufficiency For more information see Steroid Pathways.

Useful For: Second-order testing when cortisol measurement by immunoassay (eg, CORT / Cortisol, Serum) gives results that are not consistent with clinical symptoms, or if patients are known to, or suspected of, taking exogenous synthetic steroids (order SGSS / Synthetic Glucocorticoid Screen, Serum to confirm the presence of synthetic steroids) An adjunct in the differential diagnosis of primary and secondary adrenal insufficiency An adjunct in the differential diagnosis of Cushing syndrome This test is not recommended for evaluating response to metyrapone; DOCS / 11- Deoxycorticosterone, Serum is more reliable.

Interpretation: In primary adrenal insufficiency, adrenocorticotropic hormone (ACTH) levels are increased, and cortisol levels are decreased; in secondary adrenal insufficiency both ACTH and cortisol levels are decreased. When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is <10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), further studies are needed to establish the diagnosis. The 3 most frequently used tests are the ACTH (cosyntropin) stimulation test, the metyrapone test, and insulin-induced hypoglycemia test. First, the basal plasma ACTH concentration should be measured, and the short cosyntropin stimulation test performed. Cushing syndrome is characterized by increased serum cortisol levels. However, the 24-hour urinary free cortisol excretion is the preferred screening test for Cushing syndrome, specifically CORTU / Cortisol, Free, 24 Hour, Urine that utilizes liquid chromatography-tandem mass spectrometry. A normal result makes the diagnosis unlikely. Symptoms or signs of Cushing syndrome in a patient with low serum and urine cortisol levels suggest possible exogenous synthetic steroid effects.

Reference Values:

5-25 mcg/dL (a.m.)
2-14 mcg/dL (p.m.)
Pediatric reference ranges are the same as adults, as confirmed by peer-reviewed literature.

Petersen KE. ACTH in normal children and children with pituitary and adrenal diseases. I. Measurement in plasma by radioimmunoassay-basal values. Acta Paediatr Scand. 1981;70:341-345

Clinical References: 1. Lin CL, Wu TJ, Machacek DA, Jiang NS, Kao PC. Urinary free cortisol and cortisone determined by high-performance liquid chromatography in the diagnosis of Cushing's syndrome. J Clin Endocrinol Metab. 1997;82:151-155. doi:10.1210/jcem.82.1.3687. 2. Findling JW, Raff H. Diagnosis and differential diagnosis of Cushing's syndrome. Endocrinol Metab Clin North Am. 2001;30(3):729-747. doi:10.1016/s0889-8529(05)70209-7. 3. Buchman Al. Side effects of corticosteroid therapy. J Clin Gastroenterol. 2001;33(4):289-297. doi:10.1097/00004836-200110000-00006. 4. Dodds HM, Taylor PJ, Cannell GR, Pond SM. A high-performance liquid chromatography-electrospray-tandem mass spectrometry analysis of cortisol and metabolites in placental perfusate. Anal Biochem. 1997;247:342-347. doi:10.1006/abio.1997.2074. 5. Nordenstrom A, Falhammar H. Diagnosis and management of the patient with non-classic CAH due to 21-hydroxylase deficiency Eur J Endocrinol. 2019;180(3):R127-R145 6. Cengiz H, Demirci T, Varim C, Cetin S. Establishing a new screening 17 hydroxyprogesterone cut-off value and evaluation of the reliability of the long intramuscular ACTH stimulation test in the diagnosis of nonclassical congenital adrenal hyperplasia. Eur Rev Med Pharmacol Sci. 2021;25(16):5235-5240. doi:10.26355/eurrev_202108_26537

CRAV
6345

Cortisol, Right Adrenal Vein, Serum

Clinical Information: Cortisol, the main glucocorticoid (representing 75%-95% of the plasma corticoids), plays a critical role in glucose metabolism and in the body's response to stress. Both hypercortisolism and hypocortisolism can cause disease. Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6-8 a.m.) and troughs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to corticosteroid-binding globulin and albumin. Normally, less than 5% of circulating cortisol is free (unbound). Free cortisol is the physiologically active form and is filterable by the renal glomerulus. Pathological hypercortisolism due to endogenous or exogenous glucocorticoids is termed Cushing syndrome. Signs and symptoms of pathological hypercortisolism may include central obesity, hypertension, hyperglycemia, hirsutism, muscle weakness, and osteoporosis. However, these symptoms and signs are not specific for pathological hypercortisolism. The majority of individuals with some or all of the symptoms and signs will not suffer from Cushing syndrome. When Cushing syndrome is present, the most common cause is iatrogenic, due to repeated or prolonged administration of, mostly, synthetic corticosteroids. Spontaneous Cushing syndrome is less common and results from either primary adrenal

disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made. Hypocortisolism most commonly presents with nonspecific lassitude, weakness, hypotension, and weight loss. Depending on the cause, hyperpigmentation may be present. More advanced cases and patients submitted to physical stress (ie, infection, spontaneous or surgical trauma) also may present with abdominal pain, hyponatremia, hyperkalemia, hypoglycemia, and in extreme cases, cardiovascular shock and renal failure. The more common causes of hypocortisolism are: Primary adrenal insufficiency: -Addison disease -Congenital adrenal hyperplasia, defects in enzymes involved in cortisol synthesis Secondary adrenal insufficiency: -Prior, prolonged corticosteroid therapy -Pituitary insufficiency -Hypothalamic insufficiency For more information see Steroid Pathways.

Useful For: Testing cortisol levels in the right adrenal vein Second-order testing when cortisol measurement by immunoassay gives results that are not consistent with clinical symptoms, or if patients are known to, or suspected of, taking exogenous synthetic steroids An adjunct in the differential diagnosis of primary and secondary adrenal insufficiency An adjunct in the differential diagnosis of Cushing syndrome

Interpretation: In primary adrenal insufficiency, adrenocorticotropic hormone (ACTH) levels are increased and cortisol levels are decreased; in secondary adrenal insufficiency both ACTH and cortisol levels are decreased. When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is <10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), further studies are needed to establish the diagnosis. The 3 most frequently used tests are the ACTH (cosyntropin) stimulation test, the metyrapone test, and insulin-induced hypoglycemia test. First, the basal plasma ACTH concentration should be measured, and the short cosyntropin stimulation test performed. Cushing syndrome is characterized by increased serum cortisol levels. However, the 24-hour urinary free cortisol excretion is the preferred screening test for Cushing syndrome, specifically CORTU / Cortisol, Free, 24 Hour, Urine that utilizes liquid chromatography-tandem mass spectrometry. A normal result makes the diagnosis unlikely. Symptoms or signs of Cushing syndrome in a patient with low serum and urine cortisol levels suggest possible exogenous synthetic steroid effects.

Reference Values:
No established reference values

Clinical References:

SALCT
84225

Cortisol, Saliva

Clinical Information: Cortisol levels are regulated by corticotropin (previously adrenocorticotropic hormone: ACTH), which is synthesized by the pituitary in response to corticotropin-releasing hormone (CRH). Cushing syndrome results from overproduction of glucocorticoids because of either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; commonly seen in women in the third through fifth decades of life. Corticotropin-releasing hormone is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (elevated in the morning) and troughs (low in the evening) for plasma ACTH and cortisol levels. The diurnal variation is lost in patients with Cushing syndrome and these patients have elevated levels of evening plasma cortisol. The measurement of late-night salivary cortisol is an effective and convenient screening test for Cushing syndrome.(1) In a recent study from the National Institute of Health, nighttime salivary cortisol measurement was superior to plasma and urine free cortisol assessments in detecting patients with mild Cushing syndrome.(2) The sensitivity of nighttime

salivary cortisol measurements remained superior to all other measures. The distinction between Cushing syndrome and pseudo-Cushing states is most difficult in the setting of mild-to-moderate hypercortisolism. Subtle increases in salivary cortisol collected at midnight (cortisol of nadir) appear to be one of the earliest abnormalities in Cushing syndrome.

Useful For: Screening for Cushing syndrome Diagnosis of Cushing syndrome in patients presenting with symptoms or signs suggestive of the disease

Interpretation: Cushing syndrome is characterized by increased salivary cortisol levels, and late-night saliva cortisol measurements may be the optimum test for the diagnosis of Cushing syndrome. It is standard practice to confirm elevated results at least once. This can be done by repeat late-night salivary cortisol measurements, midnight blood sampling for cortisol (CORT / Cortisol, Serum), 24-hour urinary free cortisol collection (CORTU / Cortisol, Free, 24 Hour, Urine), or overnight dexamethasone suppression testing. Upon confirmation of the diagnosis, the cause of hypercortisolism, adrenal versus pituitary versus ectopic adrenocorticotropic hormone production, needs to be established. This is typically a complex undertaking, requiring dynamic testing of the pituitary adrenal axis and imaging procedures. Referral to specialized centers or in-depth consultation with experts is strongly recommended.

Reference Values:
7 a.m.-9 a.m.: 100-750 ng/dL
3 p.m.-5 p.m.: <401 ng/dL
11 p.m.-midnight: <100 ng/dL

Clinical References:

CORT
8545

Cortisol, Serum

Clinical Information: Cortisol, the main glucocorticoid (representing 75%-90% of the plasma corticoids) plays a central role in glucose metabolism and in the body's response to stress. Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary gland in response to corticotropin-releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6 a.m.-8 a.m.) and troughs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to cortisol-binding globulin (CBG-transcortin) and albumin. Normally, less than 5% of circulating cortisol is free (unbound). The free cortisol is the physiologically active form and is filterable by the renal glomerulus. Although hypercortisolism is uncommon, the signs and symptoms are common (eg, obesity, high blood pressure, increased blood glucose concentration). The most common cause of increased plasma cortisol levels in women is a high circulating concentration of estrogen (eg, estrogen therapy, pregnancy) resulting in increased concentration of cortisol-binding globulin. Spontaneous Cushing syndrome results from overproduction of glucocorticoids as a result of either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made. Causes of hypocortisolism are: -Addison disease-primary adrenal insufficiency -Secondary adrenal insufficiency: --Pituitary insufficiency --Hypothalamic insufficiency -Congenital adrenal hyperplasia-defects in enzymes involved in cortisol synthesis

Useful For: Discrimination between primary and secondary adrenal insufficiency Differential diagnosis of Cushing syndrome This test is not recommended for evaluating response to metyrapone.

Interpretation:

Reference Values:
0 -<3 months: 1.1-19 mcg/dL
3 months-<12 months: 2.6-23 mcg/dL
12 months-<13 years: 2.2-13 mcg/dL
13 years-<16 years: 3.0-17 mcg/dL
16 years -<18 years: 3.8-19 mcg/dL
> or =18 years:
a.m.: 7-25 mcg/dL
p.m.: 2-14 mcg/dL

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

COCOU
82948

Cortisol/Cortisone, Free, 24 Hour, Urine

Clinical Information: Cortisol is a steroid hormone synthesized from cholesterol by a multienzyme cascade in the adrenal glands. It is the main glucocorticoid in humans and acts as a gene transcription factor influencing a multitude of cellular responses in virtually all tissues. Cortisol plays a critical role in glucose metabolism, maintenance of vascular tone, immune response regulation, and in the body's response to stress. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating cortisol is biologically active (free), with the majority of cortisol inactive (protein bound). As plasma cortisol values increase, free cortisol (ie, unconjugated cortisol or hydrocortisone) increases and is filtered through the glomerulus. Urinary free cortisol (UFC) correlates well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. UFC is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion, by liquid chromatography-tandem mass spectrometry (LC-MS/MS), is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic corticosteroids, which can affect immunoassay-based cortisol results. Cortisone, a downstream metabolite of cortisol, provides an additional variable to assist in the diagnosis of various adrenal disorders, including abnormalities of 11-beta-hydroxy steroid dehydrogenase (11-beta HSD), the enzyme that converts cortisol to cortisone. Deficiency of 11-beta HSD results in a state of mineralocorticoid excess because cortisol (but not cortisone) acts as a mineralocorticoid receptor agonist. Licorice (active component glycyrrhetinic acid) inhibits 11-beta HSD and excess consumption can result in similar changes.

Useful For: Screening test for Cushing syndrome (hypercortisolism) Assisting in diagnosing acquired or inherited abnormalities of 11-beta-hydroxy steroid dehydrogenase (cortisol to cortisone ratio) Diagnosis of pseudo-hyperaldosteronism due to excessive licorice consumption This test has limited usefulness in the evaluation of adrenal insufficiency.

Interpretation: Most patients with Cushing syndrome have increased 24-hour urinary excretion of cortisol and/or cortisone. Further studies, including suppression or stimulation tests, measurement of serum corticotropin (adrenocorticotropic hormone) concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have both suppressed cortisol and cortisone. In these circumstances a synthetic glucocorticoid screen might be ordered (call 800-533-1710). Suppressed cortisol and cortisone values may also be observed in primary adrenal insufficiency and hypopituitarism. However, random urine specimens are not useful for evaluation of hypocorticalism. Further, many normal individuals also may exhibit a very low 24-hour urinary cortisol excretion with considerable overlap with the values observed in pathological hypocorticalism. Therefore, without other tests, 24-hour urinary cortisol

measurements cannot be relied upon for the diagnosis of hypocorticalism. Patients with 11-beta hydroxy steroid dehydrogenase deficiency may have cortisone to cortisol ratios <1, whereas a ratio of 2:1 to 3:1 is seen in normal patients. Excessive licorice consumption and use of carbenoxolone, a synthetic derivative of glycyrrhizinic acid used to treat gastroesophageal reflux disease, also may suppress the ratio to <1.

Reference Values:

CORTISOL
0-2 years: not established
3-8 years: 1.4-20 mcg/24 h
9-12 years: 2.6-37 mcg/24 h
13-17 years: 4.0-56 mcg/24 h
> or =18 years: 3.5-45 mcg/24 h

CORTISONE
0-2 years: not established
3-8 years: 5.5-41 mcg/24 h
9-12 years: 9.9-73 mcg/24 h
13-17 years: 15-108 mcg/24 h
> or =18 years: 17-129 mcg/24 h

Use the factors below to convert each analyte from mcg/24 h to nmol/24 h:

Conversion factors
Cortisol: mcg/24 hours x 2.76=nmol/24 h (molecular weight=362.5)
Cortisone: mcg/24 hours x 2.78=nmol/24 h (molecular weight=360)

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Dodds HM, Taylor PJ, Cannell GR, Pond SM. A high performance liquid chromatography-electrospray-tandem mass spectrometry analysis of cortisol and metabolites in placental perfusate. Anal Biochem. 1997;247(2):342-347 2. Lin CL, Wu TJ, Machacek DA, Jiang NS, Kao PC. Urinary free cortisol and cortisone determined by high performance liquid chromatography in the diagnosis of Cushing's syndrome. J Clin Endo Metab 1997;82(1):151-155 3. Eisenhofer G, Grebe S, Cheung NK V. Monoamine-producing tumors. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1421

CCFR
609740

Cortisol/Cortisone, Free, Random, Urine

Clinical Information: Cortisol is a steroid hormone synthesized from cholesterol by a multienzyme cascade in the adrenal glands. It is the main glucocorticoid in humans and acts as a gene transcription factor influencing a multitude of cellular responses in virtually all tissues. It plays a critical role in glucose metabolism, maintenance of vascular tone, immune response regulation, and in the body's response to stress. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating cortisol is biologically active (free), with the majority of cortisol inactive (protein bound). As plasma cortisol values increase, free cortisol (ie, unconjugated cortisol or hydrocortisone) increases and is filtered through the glomerulus. Urinary free cortisol (UFC) correlates well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. UFC is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion by liquid chromatography-tandem mass spectrometry (LC-MS/MS) is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic corticosteroids, which can affect

immunoassay-based cortisol results. Cortisone, a downstream metabolite of cortisol, provides an additional variable to assist in the diagnosis of various adrenal disorders, including abnormalities of 11-beta-hydroxy steroid dehydrogenase (11-beta HSD), the enzyme that converts cortisol to cortisone. Deficiency of 11-beta HSD results in a state of mineralocorticoid excess because cortisol (but not cortisone) acts as a mineralocorticoid receptor agonist. Licorice (active component glycyrrhetinic acid) inhibits 11-beta HSD and excess consumption can result in similar changes.

Useful For: Investigating suspected Cushing syndrome (hypercortisolism), when a 24-hour collection is prohibitive (ie, pediatric patients). Assisting in diagnosing acquired or inherited abnormalities of 11-beta-hydroxy steroid dehydrogenase (cortisol to cortisone ratio) Diagnosis of pseudohyperaldosteronism due to excessive licorice consumption This test has limited usefulness in the evaluation of adrenal insufficiency. This test is not useful for evaluation of hypocorticalism.

Interpretation: Most patients with Cushing syndrome have increased urinary excretion of cortisol and/or cortisone. Further studies, including suppression or stimulation tests, measurement of serum corticotrophin concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have both suppressed cortisol and cortisone. In these circumstances a synthetic glucocorticoid screen might be ordered (SGSU / Synthetic Glucocorticoid Screen, Random, Urine). Suppressed cortisol and cortisone values may also be observed in primary adrenal insufficiency and hypopituitarism. However, random urine specimens are not useful for evaluation of hypocorticalism. Patients with 11-beta HSD deficiency may have cortisone to cortisol ratios less than 1, whereas a ratio of 2 or 3:1 is seen in normal patients. Excessive licorice consumption and use of carbenoxolone, a synthetic derivative of glycyrrhizinic acid used to treat gastroesophageal reflux disease, also may suppress the ratio to less than 1.

Reference Values:

CORTISOL

Males

0-2 years: 3.0-120 mcg/g creatinine
3-8 years: 2.2-89 mcg/g creatinine
9-12 years: 1.4-56 mcg/g creatinine
13-17 years: 1.0-42 mcg/g creatinine
> or =18 years: 1.0-119 mcg/g creatinine

Females

0-2 years: 3.0-120 mcg/g creatinine
3-8 years: 2.2-89 mcg/g creatinine
9-12 years: 1.4-56 mcg/g creatinine
13-17 years: 1.0-42 mcg/g creatinine
> or =18 years: 0.7-85 mcg/g creatinine

CORTISONE

0-2 years: 25-477 mcg/g creatinine
3-8 years: 11-211 mcg/g creatinine
9-12 years: 5.8-109 mcg/g creatinine
13-17 years: 5.4-102 mcg/g creatinine
18-29 years: 5.7-153 mcg/g creatinine
30-39 years: 6.6-176 mcg/g creatinine
40-49 years: 7.6-203 mcg/g creatinine
50-59 years: 8.8-234 mcg/g creatinine
60-69 years: 10-270 mcg/g creatinine
> or =70 years: 12-311 mcg/g creatinine

Use the conversion factors below to convert each analyte from mcg/g creatinine to nmol/mol creatinine:

Conversion factors
Cortisol: mcg/g creatinine x 312=nmol/mol creatinine
Cortisone: mcg/g creatinine x 314=nmol/mol creatinine

Cortisol molecular weight=362.5
Cortisone molecular weight=360.4
Creatinine molecular weight=113.12

Clinical References: 1. Taylor RL, Machacek D, Singh RJ. Validation of a high-throughput liquid chromatography-tandem mass spectrometry method for urinary cortisol and cortisone. Clin Chem. 2002;48:1511-1519 2. Findling JW, Raff H. Diagnosis and differential diagnosis of Cushing's syndrome. Endocrinol Metab Clin North Am. 2001;30:729-747 3. Boscaro M, Barzon L, Fallo F, Sonino N. Cushing's syndrome. Lancet. 2001;357:783-791 4. Suzuki S, Minamidate T, Shiga A, et al. Steroid metabolites for diagnosing and predicting clinicopathological features in cortisol-producing adrenocortical carcinoma. BMC Endocr Disord. 2020;20(1):173. doi:10.1186/s12902-020-00652-y

COTT
82859

Cotton Fiber, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cotton fiber Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CSED
82804

Cottonseed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to cottonseed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CTWD
82748

Cottonwood, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cottonwood Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

COW
82873

Cow Epithelium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cow epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References:

CBBRP
62248

Coxiella burnetii (Q fever), Molecular Detection, PCR, Blood

Clinical Information: Coxiella burnetii, the causative agent of Q fever, is a small obligate intracellular bacterium that is distributed ubiquitously in the environment. Acquired through aerosol exposure, it generally causes mild respiratory disease. A small number of these acute cases will advance to a chronic condition, which typically manifests as endocarditis. If left untreated, cases of Q fever endocarditis are fatal. Current diagnostic methods of Q fever endocarditis include serologic studies and histopathologic examination of excised cardiac tissue. These current methods are subjective and nonspecific, limiting usefulness in patient diagnostics. Evaluation of infected tissue, blood, or serum using polymerase chain reaction (PCR) has been shown to be an effective tool for diagnosing C burnetii infection. Mayo Clinic Laboratories has developed a real-time PCR test that permits rapid identification of C burnetii. The assay targets a unique sequence of the shikimate dehydrogenase gene (aroE) present in C burnetii. The assay targets a unique sequence of the shikimate dehydrogenase gene (aroE) present in C burnetii.

Useful For: Aiding in the diagnosis of Coxiella burnetii infection (eg, Q fever)

Interpretation: A positive result indicates the presence of Coxiella burnetii DNA. A negative result indicates the absence of detectable C burnetii DNA but does not negate the presence of the organism and may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of C burnetii DNA in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. Frangoulidis D, Meyer H, Kahlhofer C, Splettstoesser WD: 'Real-time' PCR-based detection of Coxiella burnetii using conventional techniques. FEMS Immunol Med Microbiol 2012 Feb;64(1):134-136. 2. Liesman RM, Pritt BS, Maleszewski JJ, Patel R. Laboratory diagnosis of infective endocarditis. J Clin Microbiol. 2017 Sep;55(9):2599-2608. doi: 10.1128/jcm.00635-17. 3. Kersh GJ, Bleeker-Rovers CP: Coxiella: Evaluation, interpretation, and reporting results. In: Carroll K, Pfaller M, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:1185-1186. 4. Anderson A, Bijlmer H, Fournier PE, et al: Diagnosis and management of Q fever-United States, 2013: recommendations from CDC and the Q Fever Working Group. MMWR Recomm Rep 2013;62(RR-03):1-30.

CBSRP
62194

Coxiella burnetii (Q Fever), Molecular Detection, PCR, Serum

Clinical Information: Coxiella burnetii, the causative agent of Q fever, is a small obligately intracellular bacterium associated with animals. Acquired through aerosol exposure, it generally causes mild respiratory disease. A small number of acute cases advance to a chronic infection, which typically manifests as endocarditis. Left untreated, Q fever endocarditis may be fatal. Serologic and histopathologic studies may be nonspecific and subjective, respectively, limiting usefulness for patient diagnosis. Evaluation of infected tissue, blood, or serum using polymerase chain reaction (PCR) may be a useful tool for diagnosing some cases of Coxiella burnetii infection. Mayo Clinic Laboratories has developed a real-time PCR test that rapidly detects Coxiella burnetii DNA in clinical specimens by targeting a sequence of the shikimate dehydrogenase gene (aroE) unique to Coxiella burnetii.

Useful For: Aiding in the diagnosis of Coxiella burnetii infection (ie, Q fever) using serum specimens

Interpretation: A positive result indicates the presence of Coxiella burnetii DNA. A negative result indicates the absence of detectable C burnetii DNA but does not negate the presence of the organism and may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of C burnetii DNA in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. Frangoulidis D, Meyer H, Kahlhofer C, Splettstoesser WD: 'Real-time' PCR-based detection of Coxiella burnetii using conventional techniques. FEMS Immunol Med Microbiol 2012 Feb;64(1):134-136 2. Liesman RM, Pritt BS, Maleszewski JJ, Patel R. Laboratory diagnosis of infective endocarditis. J Clin Microbiol. 2017 Sep;55(9):2599-2608. doi: 10.1128/jcm.00635-17 3. Kersh GJ, Bleeker-Rovers CP: Coxiella: Evaluation, interpretation, and reporting results. In: Carroll K, Pfaller M, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:1185-1186 4. Anderson A, Bijlmer H, Fournier PE, et al: Diagnosis and management of Q fever-United States, 2013: recommendations from CDC and the Q Fever Working Group. MMWR Recomm Rep 2013;62(RR-03):1-30

CBRP
62193

Coxiella burnetii (Q fever), Molecular Detection, PCR, Varies

Clinical Information: Coxiella burnetii, the causative agent of Q fever, is a small obligate intracellular bacterium associated with animals. Acquired through aerosol exposure, it generally causes mild respiratory disease. A small number of acute cases advance to a chronic infection, which typically manifests as endocarditis. Left untreated, Q fever endocarditis may be fatal. Serologic and histopathologic studies may be nonspecific and subjective, respectively, limiting usefulness for patient diagnosis. Evaluation of infected tissue, blood, or serum using polymerase chain reaction (PCR) may be a useful tool for diagnosing some cases of C burnetii infection. Mayo Clinic Laboratories has developed a real-time PCR test that rapidly detects C burnetii DNA in clinical specimens by targeting a sequence of the shikimate dehydrogenase gene (aroE) unique to C burnetii.

Useful For: Aiding in the diagnosis of Coxiella burnetii infection (eg, Q fever) using tissue specimens

Interpretation: A positive result indicates the presence of Coxiella burnetii DNA. A negative result indicates the absence of detectable C burnetii DNA, but it does not negate the presence of the organism and may occur due to inhibition of polymerase chain reaction, sequence variability underlying primers or probes, or the presence of C burnetii DNA in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. Frangoulidis D, Meyer H, Kahlhofer C, Splettstoesser WD: 'Real-time' PCR-based detection of Coxiella burnetii using conventional techniques. FEMS Immunol Med Microbiol 2012 Feb;64(1):134-136. 2. Liesman RM, Pritt BS, Maleszewski JJ, Patel R. Laboratory diagnosis of infective endocarditis. J Clin Microbiol. 2017 Sep;55(9):2599-2608. doi: 10.1128/jcm.00635-17. 3. Kersh GJ, Bleeker-Rovers CP: Coxiella: Evaluation, interpretation, and reporting results. In: Carroll K, Pfaller M, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:1185-1186. 4. Anderson A, Bijlmer H, Fournier PE, et al: Diagnosis and management of Q fever-United States, 2013: recommendations from CDC and the Q Fever Working Group. MMWR Recomm Rep 2013;62(RR-03):1-30.

FCRAB
57674

Crab IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

CRAB
82745

Crab, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to crab Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CRANB
86307

Cranberry, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to cranberry Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CRAY
82343

Crayfish, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to crayfish Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CRDPP
606130

Creatine Disorders Panel, Plasma

Clinical Information: Disorders of creatine synthesis (guanidinoacetate methyltransferase [GAMT] deficiency, L-arginine:glycine amidinotransferases [AGAT] deficiency, and creatine transporter deficiency [CTD]) are collectively described as creatine deficiency syndromes (CDS). GAMT and AGAT deficiencies are inherited in an autosomal recessive manner, while CTD is X-linked. All 3 disorders result in a depletion of cerebral creatine and typically present with global developmental delays, especially expressive speech and language delay and intellectual disability. Affected patients may have abnormal magnetic resonance imaging findings and exhibit cerebral creatine deficiency in brain magnetic resonance spectroscopy. Patients with GAMT and male patients with CTD may develop seizures, autistic-like behaviors, and abnormal movements. Female carriers for CTD can be asymptomatic or exhibit features similar to affected male patients, such as intellectual disability, behavioral problems, and seizures. Diagnosis of creatine synthesis disorders relies on measurement of guanidinoacetate (GAA), creatine (Cr), and creatinine (Crn) in plasma and urine. The profiles are specific for each clinical entity. In plasma, patients with GAMT deficiency typically exhibit very elevated GAA, low Cr, and normal to low Crn. Patients with AGAT deficiency typically exhibit low to normal GAA, low Cr, and normal to low Crn. Patients with CTD may have normal or abnormal plasma levels of GAA, Cr and Crn, and measurement of these analytes in urine is also useful for diagnosis in male patients (characteristic findings are elevated Cr, normal to low Crn, and an elevated Cr:Crn ratio in urine). The only consistently reliable method for diagnosis of CTD in female patients is molecular analysis of the SLC6A8 gene. The diagnosis of GAMT, AGAT, and CTD can be confirmed by molecular analysis of GAMT,GATM, and SLC6A8 respectively. Treatment with oral supplementation of creatine monohydrate is available and effective for the AGAT and GAMT deficiencies. Patients with GAMT deficiency may also be treated with supplemental ornithine and dietary arginine restriction. CTD is treated with oral creatine monohydrate and arginine and glycine supplementation. Early treatment has been reported to prevent disease manifestations in affected but presymptomatic newborn siblings of individuals with GAMT or AGAT deficiencies.

Useful For: Evaluating patients with a clinical suspicion of arginine:glycine amidinotransferase deficiency, guanidinoacetate methyltransferase deficiency, and creatine transporter deficiency using plasma specimens

Interpretation: Reports include concentrations of guanidinoacetate, creatine, and creatinine, and the calculated analyte ratios. When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given. This interpretation includes an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing.

Reference Values:

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Accessed December 16, 2024. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Sanders K, Peck D, Bentz Pino G, et al. SLC6A8 creatine transporter deficiency can be detected by plasma creatine and creatinine concentrations. Mol Genet Metab. 2024;142(1):108455. doi:10.1016/j.ymgme.2024.108455 3. Clark JF, Cecil KM. Diagnostic methods and recommendations for the cerebral creatine deficiency syndromes. Pediatr Res. 2015;77(3):398-405 4. Mercimek-Mahmutoglu S, Salomons GS. Creatine deficiency syndromes. In: Adam MP, Mirzaa GM, Pagon RA, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2009. Updated February 10, 2022. Accessed December 16, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK3794/ 5. Stockler S, Schultz PW, Salomons GS. Cerebral creatine deficiency syndromes: clinical aspects, treatment, and pathophysiology. Subcell Biochem. 2007;46:149-166 6. Longo N, Ardon O, Vanzo R, et al. Disorders of creatine transport and metabolism. Am J Med Genet. 2011;157:72-78. doi:10.1002/ajmg.c.30292 7. Fernandes-Pires G, Braissant O. Current and potential new treatment strategies for creatine deficiency syndromes. Mol Genet Metab. 2022;135(1):15-26. doi:10.1016/j.ymgme.2021.12.005

CRDPU
88697

Creatine Disorders Panel, Random, Urine

Clinical Information: Disorders of creatine synthesis (guanidinoacetate methyltransferase [GAMT] deficiency, L-arginine:glycine amidinotransferases [AGAT] deficiency, and creatine transporter deficiency [CTD]) are collectively described as creatine deficiency syndromes (CDS). AGAT and GAMT deficiencies are inherited in an autosomal recessive manner, while the creatine transporter defect is X-linked. All 3 disorders result in a depletion of cerebral creatine and typically present with global developmental delays especially expressive speech and language delay and intellectual disability. Affected patients may have abnormal magnetic resonance imaging findings and exhibit cerebral creatine deficiency in brain magnetic resonance spectroscopy. Patients with GAMT and male patients with CTD may develop seizures, autistic-like behaviors, and abnormal movements. Female carriers for CTD can be asymptomatic or exhibit features similar to affected male patients, such as intellectual disability, behavioral problems, and seizures. Diagnosis is possible by measuring guanidinoacetate (GAA), creatine (Cr), and creatinine (Crn) in plasma and urine. The profiles are specific for each clinical entity. Patients with GAMT deficiency typically exhibit normal to low Cr, very elevated GAA, and low Crn. Patients with AGAT deficiency typically exhibit normal to low Cr, low GAA, and normal to low Crn. In comparison, elevated Cr, normal GAA, normal to low Crn, and an elevated Cr:Crn ratio characterize patients with creatine transporter defect. The only consistently reliable method for diagnosis of CTD in female patients is molecular analysis of the SLC6A8 gene. The diagnosis of GAMT, AGAT, and CTD can be confirmed by molecular analysis of GAMT,GATM, and SLC6A8 respectively. Treatment with oral supplementation of creatine monohydrate is available and effective for the AGAT and GAMT deficiencies. Patients with GAMT deficiency may also be treated with supplemental ornithine and dietary arginine restriction. CTD is treated with oral creatine monohydrate and arginine and glycine supplementation. Early treatment has been reported to prevent disease manifestations in affected but presymptomatic newborn siblings of individuals with GAMT or AGAT deficiencies.

Useful For: Evaluating patients with a clinical suspicion of arginine:glycine amidinotransferase deficiency, guanidinoacetate methyltransferase deficiency, and creatine transporter deficiency

Interpretation: Reports include concentrations of guanidinoacetate, creatine, and creatinine, as well as a calculated creatine:creatinine ratio. When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given. This interpretation includes an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing.

Reference Values:

Males Age	Creatinine (nmol/mL)	Guanidinoacetate (nmol/mL)	Creatine (nmol/mL)	Creatine/ creatinine
< or =31 days	430-5,240	9-210	12-2,930	0.02-0.93
32 days-23 months	313-9,040	16-860	18-10,490	0.02-2.49
2-4 years	1,140-12,820	90-1,260	200-9,210	0.04-1.75
5-18 years	1,190-25,270	40-1,190	60-9,530	0.01-0.96
>18 years (male)	3,854-23,340	30-710	7-470	0.00-0.04
Females Age	Creatinine (nmol/mL)	Guanidinoacetate (nmol/mL)	Creatine (nmol/mL)	Creatine/ creatinine
< or =31 days	430-5,240	9-210	12-2,930	0.02-0.93
32 days-23 months	313-9,040	16-860	18-10,490	0.02-2.49
2-4 years	1,140-12,820	90-1,260	200-9,210	0.04-1.75
5-18 years	1,190-25,270	40-1,190	60-9,530	0.01-0.96
>18 years	1,540-18,050	30-760	5-2810	0.00-0.46

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Accessed December 16, 2024. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Clark JF, Cecil KM. Diagnostic methods and recommendations for the cerebral creatine deficiency syndromes. Pediatr Res. 2015;77(3):398-405 3. Mercimek-Mahmutoglu S, Salomons GS. Creatine deficiency syndromes. In: Adam MP, Mirzaa GM, Pagon RA, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2009. Updated February 10, 2022. Accessed December 16, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK3794/ 4. Stockler S, Schultz PW, Salomons GS. Cerebral creatine deficiency syndromes: clinical aspects, treatment, and pathophysiology. Subcell Biochem. 2007;46:149-166 5. Longo N, Ardon O, Vanzo R, Schwartz E, Pasquali M. Disorders of creatine transport and metabolism. Am J Med Genet. 2011;157:72-78. doi:10.1002/ajmg.c.30292 6. Bahl S, Cordeiro D, MacNeil L, Schulze A, Mercimek-Andrews S. Urine creatine metabolite panel as a screening test in neurodevelopmental disorders. Orphanet J Rare Dis. 2020;15(1):339. doi:10.1186/s13023-020-01617-z 7. Fernandes-Pires G, Braissant O. Current and potential new treatment strategies for creatine deficiency syndromes. Mol Genet Metab. 2022;135(1):15-26. doi:10.1016/j.ymgme.2021.12.005

CRDPS
606131

Creatine Disorders Panel, Serum

Clinical Information: Disorders of creatine synthesis (guanidinoacetate methyltransferase [GAMT], L-arginine:glycine amidinotransferases [AGAT], and creatine transporter deficiency [CTD]) are collectively described as creatine deficiency syndromes (CDS). GAMT and AGAT deficiencies are inherited in an autosomal recessive manner, while CTD is X-linked. All 3 disorders result in a depletion of cerebral creatine and typically present with global developmental delays, especially expressive speech and language delay and intellectual disability. Affected patients may have abnormal magnetic resonance imaging findings and exhibit cerebral creatine deficiency in brain magnetic resonance spectroscopy. Patients with GAMT and male patients with CTD may develop seizures, autistic-like behaviors, and abnormal movements. Female carriers for CTD can be asymptomatic or exhibit features similar to affected male patients, such as intellectual disability, behavioral problems, and seizures. Diagnosis of creatine synthesis disorders relies on measurement of guanidinoacetate (GAA), creatine (Cr), and creatinine (Crn) in serum and urine. The profiles are specific for each clinical entity. In serum, patients with GAMT deficiency typically exhibit very elevated GAA, low Cr, and normal to low Crn. Patients with AGAT deficiency typically exhibit low to normal GAA, low Cr, and normal to low Crn. Patients with CTD may have normal or abnormal serum levels of GAA, Cr and Crn, and measurement of these analytes in urine is also useful for diagnosis in male patients (characteristic findings are elevated Cr, normal to low Crn, and an elevated Cr:Crn ratio in urine). The only consistently reliable method for diagnosis of CTD in female patients is molecular analysis of the SLC6A8 gene. The diagnosis of GAMT,AGAT, and CTD can be confirmed by molecular analysis of GAMT,GATM, and SLC6A8 respectively. Treatment with oral supplementation of creatine monohydrate is available and effective for the AGAT and GAMT deficiencies. Patients with GAMT deficiency may also be treated with supplemental ornithine and dietary arginine restriction. CTD is treated with oral creatine monohydrate and arginine and glycine supplementation. Early treatment has been reported to prevent disease manifestations in affected but presymptomatic newborn siblings of individuals with GAMT or AGAT deficiencies.

Useful For: Evaluating patients with a clinical suspicion of arginine:glycine amidinotransferase deficiency,guanidinoacetate methyltransferase deficiency, and creatine transporter deficiency using serum specimens

Interpretation: Reports include concentrations of guanidinoacetate, creatine, and creatinine, and the calculated analyte ratios. When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given. This interpretation includes an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing.

Reference Values:

Creatine Disorders Panel Reference Values (creatine, creatinine, and guanidinoacetate results reported as nmol/mL)
Female
Creatine
Creatinine
Guanidinoacetate
Creatine/ creatinine

Guanidinoacetate/ creatine
Guanidinoacetate/ creatinine
Female
Creatine
Creatinine
Guanidinoacetate
Creatine/ creatinine
Guanidinoacetate/ creatine
Guanidinoacetate/ creatinine
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Clinical References: 1. ACMG Newborn Screening ACT Sheets. Accessed December 16, 2024. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Sanders K, Peck D, Bentz Pino G, et al. SLC6A8 creatine transporter deficiency can be detected by plasma creatine and creatinine concentrations. Mol Genet Metab. 2024;142(1):108455. doi:10.1016/j.ymgme.2024.108455 3.Clark JF, Cecil KM. Diagnostic methods and recommendations for the cerebral creatine deficiency syndromes. Pediatr Res. 2015;77(3):398-405

4. Mercimek-Mahmutoglu S, Salomons GS. Creatine deficiency syndromes. In: Adam MP, Mirzaa GM, Pagon RA, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2009. Updated February 10, 2022. Accessed December 16, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK3794/ 5. Stockler S, Schultz PW, Salomons GS. Cerebral creatine deficiency syndromes: clinical aspects, treatment, and pathophysiology. Subcell Biochem. 2007;46:149-166 6. Longo N, Ardon O, Vanzo R, Schwartz E, Pasquali M. Disorders of creatine transport and metabolism. Am J Med Genet. 2011;157:72-78. doi:10.1002/ajmg.c.30292 7. Fernandes-Pires G, Braissant O. Current and potential new treatment strategies for creatine deficiency syndromes. Mol Genet Metab. 2022;135(1):15-26. doi:10.1016/j.ymgme.2021.12.005

CK
8336

Creatine Kinase (CK), Serum

Clinical Information: Creatine kinase (CK) is an enzyme that catalyzes the reversible phosphorylation of creatine (Cr) by adenosine triphosphate (ATP). Physiologically, when muscle contracts, ATP is converted to adenosine diphosphate (ADP), and CK catalyzes the rephosphorylation of ADP to ATP using creatine phosphate as the phosphorylation reservoir. The CK enzyme is a dimer composed of subunits derived from either muscle (M) or brain (B). Three isoenzymes have been identified: striated muscle (MM), heart tissue (MB), and brain (BB). Normal serum CK is predominantly the CK-MM isoenzyme. CK activity is greatest in striated muscle (MM isoenzyme), heart tissue (MB isoenzyme), and brain (BB isoenzyme). Serum CK concentrations are reflective of muscle mass causing males to have higher concentrations than females. CK may be measured to evaluate myopathy and to monitor patients with rhabdomyolysis for acute kidney injury.

Useful For: Diagnosing and monitoring myopathies or other trauma, toxin, or drug-induced muscle injury

Interpretation: Serum creatine kinase (CK) activity may increase in patients with acute cerebrovascular disease or neurosurgical intervention and with cerebral ischemia as well as in nearly all patients when injury, inflammation, or necrosis of skeletal or heart muscle occurs, including: -All types of muscular dystrophy particularly in progressive muscular dystrophy (particularly Duchenne sex-linked muscular dystrophy). -Viral myositis, polymyositis, and similar muscle diseases -Malignant hyperthermia, an inherited life-threatening condition characterized by high fever and brought on by administration of inhalation anesthesia -Muscle trauma, which causes CK elevations within 12 hours of onset, peaking within 1 to 3 days, and declining 3 to 5 days after cessation of muscle injury ---Serum CK activities exceeding 200 times the upper reference limit may be found in acute rhabdomyolysis, putting the patient at great risk for developing acute renal failure. -When given at pharmacologic doses, some drugs including statins, fibrates, antiretrovirals, and angiotensin II receptor antagonists -Endocrine myopathy, for which hpothyroidism is a common cause, about 60% of hypothyroid subjects show an average elevation of CK activity 5-fold greater than the upper reference limit -Normal childbirth causes a 6-fold elevation in maternal serum For detection of myocardial infarction, changes in serum CK and its heart tissue (MB) isoenzyme have been largely replaced by the more cardiac-specific nonenzymatic markers, cardiac troponin I or T.

Reference Values:

Males
< or =3 months: not established
>3 months: 39-308 U/L
Females
< or =3 months: not established
>3 months: 26-192 U/L
Reference values have not been established for patients that are less than 3 months of age.
Note: Strenuous exercise or intramuscular injections may cause transient elevation of creatine kinase

(CK).

Clinical References: 1. Tietz Clinical Guide to Laboratory Tests. Fourth edition. Edited by Wu AHB. St. Louis, Saunders Elsevier, 2006;306-307 2. Huerta-Alardin AL, Varon J, Marik PE: Bench-to-bedside review: Rhabdomyolysis -- an overview for clinicians. Crit Care 2005 Apr;9(2):158-169 3. Morandi L, Angelini C, Prelle A, et al: High plasma creatine kinase: review of the literature and proposal for a diagnostic algorithm. Neurol Sci 2006 Nov:27(5):303-311

CRCL
615813

Creatinine Clearance, Serum and 24-Hour Urine

Clinical Information: Estimated glomerular filtration rate (eGFR) using serum creatinine alone is calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: eGFR = 142 x min(standardized Scr/k,1)alpha x max(Scr/k, 1)-1.200 x (0.9938 x age) x 1.012 (if patient is female) where: -age is in years -Scr is serum creatinine concentration -k is 0.7 for females and 0.9 for males -alpha is -0.241 for females and -0.302 for males -min indicates the minimum of Scr/k or 1 -max indicates the maximum of Scr/k or 1 Use of an estimating or prediction equation to estimate GFR from serum creatinine should be employed for people with CKD and those with risk factors for CKD (diabetes, hypertension, cardiovascular disease, and family history of kidney disease). Reasons given for routine reporting of eGFR with every serum creatinine in adult (18 and over) patients include: -GFR and creatinine clearance are poorly inferred from serum creatinine alone. GFR and creatinine clearance are inversely and nonlinearly related to serum creatinine. The effects of age and sex further cloud interpretation. -Creatinine is commonly measured in routine clinical practice. Albuminuria (>30 mg/24 hour or urine albumin to creatinine ratio >30 mg/g) may be a more sensitive marker of early kidney disease, especially among patients with diabetic nephropathy. However, there is poor adherence to guidelines that suggest annual urinary albumin testing of patients with known diabetes. Therefore, if a depressed eGFR is calculated from a serum creatinine measurement, it may help providers recognize early CKD and pursue appropriate follow-up testing and therapeutic intervention. -Monitoring kidney function (by GFR or creatinine clearance) is essential once albuminuria is discovered. Estimated GFR is a more practical means to closely follow changes in GFR over time, when compared to direct measurement using methods such as iothalamate clearance. -The CKD-EPI equation does not require weight or height variables. From a serum creatinine measurement, it generates a GFR result normalized to a standard body surface area (1.73 m[2]) using sex and age. Unlike the Cockcroft-Gault equation, height and weight, which are often not available in the laboratory information system, are not required. The 2021 CKD-EPI Cr equation does not require race, so eGFR values for both African American and non-African American populations are no longer reported. The new 2021 CKD-EPI eGFR values cannot be directly compared to the previous 2009 CKD-EPI Cr eGFR values, which were separately reported for African American and non-African American populations. The Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group clinical practice guidelines,(1) as further defined by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) commentary,(2) provided recommendations for reporting and interpretation of serum creatinine and eGFR, which were revised after development of a refit CKD-EPI Creatinine eGFR equation in 2021 that does not require a mathematical adjustment based on race: 1.4.3: Evaluation of GFR -1.4.3.1: We recommend using serum creatinine and GFR estimating equation for initial assessment. -1.4.3.2: We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. -1.4.3.3: We recommend that clinicians: Use a GFR estimating equation to derive GFR from serum creatinine (eGFRcreat) rather than relying on the serum creatinine concentration alone. Understand clinical settings in which eGFR creat is less accurate. -1.4.3.4: We recommend that clinical laboratories should: Measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology. Report eGFRcreat in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting eGFRcreat. Report eGFRcreat in adults using the 2021 CKD-EPI creatinine equation. When reporting serum creatinine: We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed

as standard international units (mmol/L) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dL). When reporting eGFRcreat: -We recommend that eGFRcreat should be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m(2) in adults using the units mL/min/1.73 m(2). -We recommend eGFRcreat levels less than 60 mL/min/1.73 m(2) should be reported as "decreased". 1.4.3.8: We suggest measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact treatment decisions. Creatinine Clearance: Creatinine is derived from the metabolism of creatine from skeletal muscle and dietary meat intake and is released into the circulation at a relatively constant rate. Thus, the serum creatinine concentration is usually stable. Creatinine is freely filtered by glomeruli and not reabsorbed or metabolized by kidney tubules. Therefore, creatinine clearance can be used to assess GFR. However, approximately 15% of excreted urine creatinine is derived from proximal tubular secretion. Because of the tubular secretion of creatinine, creatinine clearance typically overestimates true GFR by 10% to 15%. Creatinine clearance is usually determined from measurement of creatinine in a 24-hour urine specimen and from a serum specimen obtained during the same collection period. However, shorter time periods can be used. A key consideration is accurate timing and collection of the urine sample. Creatinine clearance normalized to body surface area is calculated by the equation: 2.54 cm=1 inch 1 kg=2.2 pounds (lbs) Patient surface area (SA)=wt (kg)(0.425) X ht (cm)(0.725) X 0.007184 Urine conc (mg/dL) x 24 hr urine volume (mL Uncorr creat clear= 1440 minutes mL/min Serum creat (mg/dL) Urine conc (mg/dL) x 24 hr urine volume (mL) X 1.73 m(2) Patient SA Corr creat clear= 1440 minutes mL/min/1.73m(2) Serum creat (mg/dL)

Useful For: Estimation of glomerular filtration rate

Interpretation: Decreased creatinine clearance indicates decreased glomerular filtration rate (GFR). This can be due to conditions such as progressive kidney disease or result from adverse effect on renal hemodynamics that are often reversible, including drug effects or decreases in effective renal perfusion (eg, volume depletion, heart failure). Increased creatinine clearance is often referred to as hyperfiltration and is most commonly seen during pregnancy or in patients with early diabetes mellitus, before diabetic nephropathy has occurred. It may also occur with large dietary protein intake. A major limitation of creatinine clearance is that its accuracy worsens in relation to the amount of tubular creatinine secretion. Often as GFR declines, the contribution of urine creatinine from tubular secretion increases, further increasing the discrepancy between true GFR and measured creatinine clearance. Estimated GFR: According to the Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group, chronic kidney disease (CKD) is defined as the abnormalities of kidney structure of function, present for more than 3 months, with implications for health.(1,2) CKD should be classified by cause, GFR category, and albuminuria category.(1,2) KDIGO guidelines provide the following GFR categories(1,2): Stage Terms GFR mL/min/1.73 m(2) G1* Normal or high 90 G2* Mildly decreased 60 to 89 G3a Mildly to moderately decreased 45 to 59 G3b Moderately to severely decreased 30-44 G4 Severely decreased 15-29 G5 Kidney failure <15 *In the absence of evidence of kidney damage, neither G1 nor G2 fulfill criteria for CKD. Urinary albumin excretion can also be used to further subdivide CKD stages.

Reference Values:

CREATININE CLEARANCE

Males:

0-18 years: Not established

19-75 years: 77-160 mL/min/body surface area (BSA)

> or =76 years: Not established

Females:

0-17 years: Not established

18-29 years: 78-161 mL/min/BSA

30-39 years: 72-154 mL/min/BSA

40-49 years: 67-146 mL/min/BSA

50-59 years: 62-139 mL/min/BSA

60-72 years: 56-131 mL/min/BSA
> or =73 years: Not established

CREATININE, URINE:
Reported in units of mg/dL

CREATININE, SERUM
Males:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL

Females:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL

Estimated glomerular filtration rate (eGFR)
> or =18 years old: > or =60 mL/min/BSA
eGFR calculated using the 2021 CKD-EPI creatinine equation
Note: eGFR results will not be calculated for patients younger than 18 years old.

Clinical References: 1. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;63(5):713-735. doi:10.1053/j.ajkd.2014.01.416 2. National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. Am J Kidney Dis. 2012;60(5):850-886. doi:10.1053/j.ajkd.2012.07.005. Erratum in: Am J Kidney Dis. 2013 Jun;61(6):1049 3. Inker LA, Perrone RD. Assessment of kidney function. In: Sterns RH, Forman JP, eds. UpToDate; 2021. Updated February 2024. Accessed April 1, 2024. Available at www.uptodate.com/contents/assessment-of-kidney-function 4. Kasiske BL, Keane WF. Laboratory assessment of renal disease: clearance, urinalysis, and renal biopsy. In: Brenner BM, ed. The Kidney. 6th ed. WB Saunders Company; 2000:1129-1170 5. Delaney MP, Lamb EJ. Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1256-1323 6. Miller WG, Kaufman HW, Levey AS, et al. National Kidney Foundation Laboratory Engagement Working Group recommendations for implementing the CKD-EPI 2021 race-free equations for estimated glomerular filtration rate: Practical guidance for clinical laboratories. Clin Chem. 2022;68(4):511-520. doi:10.1093/clinchem/hvab278 7. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737-1749. doi:10.1056/NEJMoa2102953

CRTS1
48216

Creatinine with Estimated Glomerular Filtration Rate (eGFR), Serum

Clinical Information: In muscle metabolism, creatinine is synthesized endogenously from creatine and creatine phosphate. Creatinine is removed from plasma by glomerular filtration into the urine without being reabsorbed by the tubules to any significant extent. Renal tubular secretion also contributes a small quantity of creatinine to the urine. As a result, creatinine clearance often overestimates the true glomerular filtration rate (GFR) by 10% to more than 20%. Determinations of creatinine and renal clearance of creatinine are of value in the assessment of kidney function. Serum or blood creatinine levels in kidney

disease generally do not increase until kidney function is substantially impaired. Estimated GFR (eGFR) is calculated using the 2021 Chronic Kidney Disease (CKD) Epidemiology Collaboration (EPI) Cr equation: eGFR =142 x min(standardized Scr/K,1)alpha x max(Scr/K, 1)-1.200 x 0.9938age x 1.012(if patient is female) -where age is in years -Scr is serum creatinine -k is 0.7 for females and 0.9 for males -alpha is -0.241 for females and -0.302 for males -min indicates the minimum of Scr/k or 1 -max indicates the maximum of Scr/k or 1 Use of an estimating or prediction equation to estimate GFR from serum creatinine should be employed for people with CKD and those with risk factors for CKD (diabetes, hypertension, cardiovascular disease, and family history of kidney disease). Reasons given for routine reporting of eGFR with every serum creatinine in adult (18 and over) patients include: -GFR and creatinine clearance are poorly inferred from serum creatinine alone. GFR and creatinine clearance are inversely and nonlinearly related to serum creatinine. The effects of age and sex further cloud interpretation. -Creatinine is commonly measured in routine clinical practice. Albuminuria (>30 mg/24 hour or urine albumin to creatinine ratio >30 mg/g) may be a more sensitive marker of early kidney disease, especially among patients with diabetic nephropathy. However, there is poor adherence to guidelines that suggest annual urinary albumin testing of patients with known diabetes. Therefore, if a depressed eGFR is calculated from a serum creatinine measurement, it may help providers recognize early CKD and pursue appropriate follow-up testing and therapeutic intervention. -Monitoring of kidney function (by GFR or creatinine clearance) is essential once albuminuria is discovered. Estimated GFR is a more practical means to closely follow changes in GFR over time, when compared to direct measurement using methods such as iothalamate clearance. -The CKD-EPI equation does not require weight or height variables. From a serum creatinine measurement, it generates a GFR result normalized to a standard body surface area (1.73 m[2]) using sex and age. Unlike the Cockcroft-Gault equation, height and weight, which are often not available in the laboratory information system, are not required. The 2021 CKD-EPI Cr equation does not require race, so eGFR values for both African Americans and non-African Americans are no longer reported. The new 2021 CKD-EPI eGFR values cannot be directly compared to the previous 2009 CKD-EPI Cr eGFR values that were separately reported for African American and non-African American populations. The Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group clinical practice guideline,(2) as further defined by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) commentary,(3) provide the following recommendations for reporting and interpretation of serum creatinine and eGFR, which were revised after development of a refit CKD-EPI Creatinine eGFR equation in 2021 that does not require a mathematical adjustment based on race: -1.4.3: Evaluation of GFR -1.4.3.1: We recommend using serum creatinine and a GFR estimating equation for initial assessment. (1A) 1.4.3.2: We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. (2B) 1.4.3.3: We recommend that clinicians (1B): -Use a GFR estimating equation to derive GFR from serum creatinine (eGFRcreat) rather than relying on the serum creatinine concentration alone. -Understand clinical settings in which eGFRcreat is less accurate. 1.4.3.4: We recommend that clinical laboratories should (1B): -Measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology. -Report eGFRcreat in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting eGFRcreat. -Report eGFRcreat in adults using the 2021 CKD-EPI creatinine equation. When reporting serum creatinine: -We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed as standard international units (mmol/l) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dL). When reporting eGFRcreat: -We recommend that eGFRcreat should be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m2 in adults using the units mL/min/1.73 m2. -We recommend eGFRcreat levels less than 60 mL/min/1.73 m2 should be reported as "decreased." 1.4.3.8: We suggest measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact treatment decisions (2B)

Useful For: Diagnosing and monitoring treatment of acute and chronic kidney diseases Adjusting dosage of renally excreted medications Monitoring kidney transplant recipients Estimating glomerular

filtration rate for people with chronic kidney disease (CKD) and those with risk factors for CKD (diabetes, hypertension, cardiovascular disease, and family history of kidney disease)

Interpretation: Because serum creatinine is inversely correlated with glomerular filtration rate (GFR), when kidney function is near normal, absolute changes in serum creatinine reflect larger changes than do similar absolute changes when kidney function is poor. For example, an increase in serum creatinine from 1 to 2 mg/dL may indicate a decrease in GFR of 50 mL/min (from 100 to 50 mL/min), whereas an increase in serum creatinine level from 4 to 5 mg/dL may indicate a decrease of only 5 mL/min (from 25 to 20 mL/min). Because of the imprecision of serum creatinine as an assessment of GFR, there may be clinical situations where a more accurate GFR assessment must be performed, iothalamate or inulin clearance are superior to serum creatinine and eGFR. Several factors may influence serum creatinine independent of changes in GFR. For instance, creatinine generation is dependent upon muscle mass. Thus, young, muscular male patients may have significantly higher serum creatinine levels than older adult female patients, despite having similar GFRs. Also, because some renal clearance of creatinine is due to tubular secretion, drugs that inhibit this secretory component (eg, cimetidine and trimethoprim) may cause small increases in serum creatinine without an actual decrease in GFR. According to the Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group, chronic kidney disease (CKD) is defined as the abnormalities of kidney structure or function, present for more than 3 months, with implications for health.(3) CKD should be classified by cause, GFR category, and albuminuria category.(3) Table. KDIGO guidelines provide the following GFR categories(2,3): Stage Terms GFR mL/min/1.73 m(4) G1* Normal or high 90 G2* Mildly decreased 60 to 89 G3a Mildly to moderately decreased 45 to 59 G3b Moderately to severely decreased 30-44 G4 Severely decreased 15-29 G5 Kidney failure <15 *In the absence of evidence of kidney damage, neither G1 nor G2 fulfill criteria for CKD.

Reference Values:

CREATININE
Males(1)
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL

Females(1)
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL

ESTIMATED Glomerular Filtration Rate (eGFR)
> or =18 years old: > or =60 mL/min/BSA (body surface area)

Note: eGFR results will not be calculated for patients younger than 18 years old.
Estimated GFR calculated using the 2021 CKD-EPI creatinine equation
2021 CKD-EPI creatinine eGFR not valid for patients younger than 18 years old.

Clinical References: 1. Kulasingam V, Jung BP, Blasutig IM, et al: Pediatric reference intervals for 28 chemistries and immunoassays on the Roche cobas 6000 analyzer--a CALIPER pilot study. Clin Biochem. 2010 Sep;43(13-14):1045-1050 2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1-150 3. Inker LA, Astor BC, Fox CH, et al: KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014 May;63(5):713-735 4. Saenger AK, Lockwood C, Snozek CL, et al:

Catecholamine interference in enzymatic creatinine assays. Clin Chem. 2009 Sep;55(9):1732-1736 5. Rifai N, Horvath AR, Wittwer CT, eds: Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics. 8th ed. Elsevier; 2018 6. Miller WG, Kaufman HW, Levey AS, et al: National Kidney Foundation Laboratory Engagement Working Group recommendations for implementing the CKD-EPI 2021 race-free equations for estimated glomerular filtration rate: Practical guidance for clinical laboratories. Clin Chem. 2022 Mar 31;68(4):511-520. doi: 10.1093/clinchem/hvab278 7. Inker LA, Eneanya ND, Coresh J, et al: Chronic Kidney Disease Epidemiology Collaboration. New creatinine- and cystatin C-Based equations to estimate GFR without race. N Engl J Med. 2021 Nov 4;385(19):1737-1749. doi: 10.1056/NEJMoa2102953

CTU
610601

Creatinine, 24 Hour, Urine

Clinical Information: Creatinine is formed from the metabolism of creatine and phosphocreatine, both of which are principally found in muscle. Thus the amount of creatinine produced is, in large part, dependent upon the individual's muscle mass and tends not to fluctuate much from day-to-day. Creatinine is not protein bound and is freely filtered by glomeruli. All of the filtered creatinine is excreted in the urine. Renal tubular secretion of creatinine also contributes to a small proportion of excreted creatinine. Although most excreted creatinine is derived from an individual's muscle, dietary protein intake, particularly of cooked meat, can contribute to urinary creatinine levels. The renal clearance of creatinine provides an estimate of glomerular filtration rate.

Useful For: Calculation of creatinine clearance, a measure of renal function, when used in conjunction with serum creatinine

Interpretation: Twenty-four-hour urinary creatinine determinations are principally used for the calculation of creatinine clearance. Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions such as progressive renal disease or result from adverse effects on renal hemodynamics, which are often reversible, including certain drug usage or from decreases in effective renal perfusion (eg, volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus before diabetic nephropathy has occurred. It also may occur with large dietary protein intake.

Reference Values:

Reference values mg per 24 hours:

Males > or =18 years: 930-2955 mg/24 hours

Females > or =18 years: 603-1783 mg/24 hours

Reference values have not been established for patients who are less than 18 years of age.

For SI unit Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1256-1323 2. Lamb EJ, Jones GRD: Kidney function tests. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:chap32 3. Kasiske BL, Keane WF: Laboratory assessment of renal disease: clearance, urinalysis, and renal biopsy. In: Brenner BM, ed. The kidney. 6th ed. WB Saunders; 2000:1129-1170

CRT24
610597

Creatinine, 24 Hour, Urine

Clinical Information: Creatinine is formed from the metabolism of creatine and phosphocreatine, both of which are principally found in muscle. Thus, the amount of creatinine produced is in large part dependent upon the individual's muscle mass and tends not to fluctuate much from day-to-day. Creatinine is not protein-bound and is freely filtered by glomeruli. All of the filtered creatinine is excreted in the urine. Renal tubular secretion of creatinine also contributes to a small proportion of excreted creatinine. Although most excreted creatinine is derived from an individual's muscle, dietary protein intake, particularly of cooked meat, can contribute to urinary creatinine levels. The renal clearance of creatinine provides an estimate of glomerular filtration rate.

Useful For: Urinary creatinine, in conjunction with serum creatinine, is used to calculate the creatinine clearance, a measure of renal function Normalizing urinary analytes to account for the variation in urinary concentration

Interpretation: Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions such as progressive renal disease, or result from adverse effect on renal hemodynamics that are often reversible including certain drugs or from decreases in effective renal perfusion (eg, volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus, before diabetic nephropathy has occurred. It also may occur with large dietary protein intake.

Reference Values:

Only orderable as part of a profile. For more information see:
-NMH24 / N-Methylhistamine, 24 Hour, Urine
-RB24 / Retinol-Binding Protein, 24 Hour, Urine
-A124 / Alpha-1-Microglobulin, 24 Hour, Urine

Normal values mg per 24 hours:
Males: 930-2955 mg/24 hours
Females: 603-1783 mg/24 hours

Reference values have not been established for patients who are less than 18 years of age.

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1256-1323 2. Meeusen J, Rule A, Voskoboev, N, Baumann N, Lieske J: Performance of cystatin C- and creatinine-based estimated glomerular filtration rate equations depends on patient characteristics. Clin Chem. 2015 Oct;61(10):1265-1272. doi: 10.1373/clinchem.2015.243030 3. Newman DJ, Price CP: Renal function and nitrogen metabolites. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 3rd ed. WB Saunders Company; 1999:1204-1270 4. Kasiske BL, Keane WF: Laboratory assessment of renal disease: clearance, urinalysis, and renal biopsy. In: Brenner BM, ed. The Kidney. 6th ed. WB Saunders Company; 2000:1129-1170

CRT2F
618161

Creatinine, 24 Hour, Urine

Clinical Information: Creatinine is formed from the metabolism of creatine and phosphocreatine, both of which are principally found in muscle. Thus, the amount of creatinine produced is, in large part, dependent upon the individual's muscle mass and tends not to fluctuate much from day-to-day. Creatinine is not protein bound and is freely filtered by glomeruli. All filtered creatinine is excreted in the urine. Renal tubular secretion of creatinine contributes a small proportion of excreted creatinine. Although most excreted creatinine is derived from an individual's muscle mass, dietary protein intake, particularly of

cooked meat, can contribute to urinary creatinine levels. The renal clearance of creatinine provides an estimate of glomerular filtration rate.

Useful For: Normalizing urinary analytes to account for the variation in urinary concentration

Interpretation: Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions, such as progressive kidney disease, or result from adverse effect on renal hemodynamics that are often reversible, including certain drugs or from decreases in effective renal perfusion (eg, volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most frequently seen during pregnancy or in patients with diabetes mellitus before diabetic nephropathy has occurred. It may also occur with large dietary protein intake.

Reference Values:
Only orderable as part of a profile. For more information see:
-TLTE4 / Leukotriene E4, 24 Hour, Urine
-MCM24 / Mast Cell Mediators, 24 Hour, Urine

Normal values mg per 24 hours:
Males: 930-2955 mg/24 hours
Females: 603-1783 mg/24 hours

Reference values have not been established for patients who are younger than 18 years.

Clinical References: 1. Delaney MP, Lamb EJ. Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1256-1323 2. Meeusen JW, Rule AD, Voskoboev N, Baumann NA, Lieske JC. Performance of cystatin C- and creatinine-based estimated glomerular filtration rate equations depends on patient characteristics. Clin Chem. 2015;61(10):1265-1272. doi:10.1373/clinchem.2015.243030 3. Newman DJ, Price CP. Renal function and nitrogen metabolites. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 3rd ed. WB Saunders Company; 1999:1204-1270 4. Kasiske BL, Keane WF. Laboratory assessment of renal disease: clearance, urinalysis, and renal biopsy. In: Brenner BM, ed. The Kidney. 6th ed. WB Saunders Company; 2000:1129-1170

CRBF
606601

Creatinine, Body Fluid

Clinical Information: Byproducts of nitrogen metabolism are present in high concentration in urine compared to blood and serve as a surrogate marker for the identification of urine leakage into a body compartment. Concentrations of creatinine or urea nitrogen that exceed the concentration found in a concurrent sample of blood are suggestive of the presence of urine.(1) Peritoneal, abdominal, pelvic drain fluid: Trauma as well as abdominal or pelvic surgery can lead to bladder perforation or formation of urinary fistula with excessive accumulation of peritoneal fluid or increased surgical drain output caused by intraperitoneal urinary leakage.(1,2) Pleural fluid: Urinoma describes the accumulation of urine in the perirenal and retroperitoneal spaces caused by genitourinary tract injury due to trauma or blockage of the urinary tract due to stones, strictures, tumors, benign prostate hypertrophy, etc.(3) Rarely, this fluid can translocate to the pleural cavity causing pleural effusion via movement of urine through the diaphragm or via lymphatic communication between retroperitoneal and pleural spaces caused by increased pressure due to urinoma. Urinothorax is the term used to describe an accumulation of urine in the pleural space. Patients often develop symptoms of dyspnea, chest pain, abdominal pain, and reduced diuresis.(4) The condition is reversed when treatment is directed to correct the primary cause (trauma in 75% and obstruction in 24% of cases). The pleural fluid to serum creatinine ratio is above 1 in 97.9% of cases (n=48; median ratio=2.9, range=0.95-16). Peritoneal dialysis fluid: Peritoneal dialysis (PD) is a type of ambulatory dialysis in which hyperosmotic fluid is infused into the patient's

peritoneal cavity, with the peritoneum employed as the dialysis membrane promoting the diffusion of small molecules and free water from circulation.(5) The peritoneal equilibration test estimates the rate of small solute transport across the peritoneal membrane and the ultrafiltration capacity. Several analytes may be measured in order to perform this test. Creatinine is measured in PD fluid as well as in plasma or serum in samples taken 2 and/or 4 hours after the dialysate is instilled. The dialysate fluid to serum or plasma creatinine ratio is calculated with larger ratios (approaching 1.0) observed in patients exhibiting faster transport rates.

Useful For: Identifying the presence of urine as a cause for accumulation of fluid in a body compartment Measuring the ultrafiltration capacity of the peritoneal membrane in patients receiving peritoneal dialysis

Interpretation: Peritoneal, pleural, and drain fluid concentrations should be compared to serum or plasma. Fluid to serum ratios above 1.0 suggest the specimen may be contaminated with urine.(1-4) Peritoneal dialysate fluid to serum creatinine ratios can be calculated from timed collections to determine peritoneal membrane transport rates.(5) All other fluids: results should be interpreted in conjunction with serum creatinine and other clinical findings.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Manahan KJ, Fanning J. Peritoneal fluid urea nitrogen and creatinine reference values. Obstet Gynecol. 1999;93:780-782 2. Wong MH, Lim SK, Ng KL, Ng KP. Pseudo-acute kidney injury with recurrent ascites due to intraperitoneal urine leakage. Intern Med J. 2012;42(7):848-849 3. Austin A, Jogani SN, Brasher PB, Argula RG, Huggins JT, Chopra A. The urinothorax: A comprehensive review with case series. Am J Med Sci. 2017;354(1):44-53 4. Toubes ME, Lama A, Ferreiro L, et al. Urinothorax: a systematic review. J Thorac Dis. 2017;9(5):1209-1218 5. Block DR, Florkowski CM. Body fluids. In: Rafai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018: chap 43 6. Saenger AK, Lockwood C, Snozek CL, et al. Catecholamine interference in enzymatic creatinine assays. Clin Chem. 2009;55(9):1732-1736

RCTUR
610603

Creatinine, Random, Urine

Clinical Information: Creatinine is formed from the metabolism of creatine and phosphocreatine, both of which are principally found in muscle. Thus, the amount of creatinine produced is, in large part, dependent upon the individual's muscle mass and tends not to fluctuate much from day-to-day. Creatinine is not protein bound and is freely filtered by glomeruli. All of the filtered creatinine is excreted in the urine. Renal tubular secretion of creatinine also contributes to a small proportion of excreted creatinine. Although most excreted creatinine is derived from an individual's muscle, dietary protein intake, particularly of cooked meat, can contribute to urinary creatinine levels. The renal clearance of creatinine provides an estimate of glomerular filtration rate. Since creatinine, for the most part, in the urine only comes from filtration, the concentration of creatinine reflects overall urinary concentration. Therefore, creatinine can be used to normalize other analytes in a random urine specimen.

Useful For: Calculation of creatinine clearance, a measure of renal function, when used in conjunction with serum creatinine Normalization of urinary analytes by creatinine concentration to account for the variation in urinary concentrations between subjects

Interpretation: Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions such as progressive renal disease, or result from adverse effects on renal hemodynamics, which are often reversible including certain drugs or from decreases in effective renal

perfusion (eg, volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus before diabetic nephropathy has occurred. It also may occur with large dietary protein intake.

Reference Values:
> or =18 years old: 16-326 mg/dL

Reference values have not been established for patients who are <18 years of age.

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds. Textbook of Clinical Chemistry. 6th ed. Elsevier; 2018:1256-1323 2. Lamb EJ, Jones GRD: Kidney function tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:479-517 3. Kasiske BL, Keane WF: Laboratory assessment of renal disease: clearance, urinalysis, and renal biopsy. In: Brenner BM, ed. The Kidney. 6th ed. WB Saunders Company; 2000:1129-1170

CRETR
610598

Creatinine, Random, Urine

Clinical Information: Creatinine is formed from the metabolism of creatine and phosphocreatine, both of which are principally found in muscle. Thus, the amount of creatinine produced is in large part dependent upon the individual's muscle mass and tends not to fluctuate much from day-to-day. Creatinine is not protein-bound and is freely filtered by glomeruli. All of the filtered creatinine is excreted in the urine. Renal tubular secretion of creatinine also contributes to a small proportion of excreted creatinine. Although most excreted creatinine is derived from an individual's muscle, dietary protein intake, particularly of cooked meat, can contribute to urinary creatinine levels. The renal clearance of creatinine provides an estimate of glomerular filtration rate. Since creatinine for the most part in the urine only comes from filtration, the concentration of creatinine reflects overall urinary concentration. Therefore, creatinine can be used to normalize other analytes in a random urine specimen.

Useful For: Normalization of urinary analytes to account for the variation in urinary concentrations between individuals when using random urine collections

Interpretation: Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions such as progressive renal disease, or result from adverse effect on renal hemodynamics that are often reversible including certain drugs or from decreases in effective renal perfusion (eg, volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus, before diabetic nephropathy has occurred. It also may occur with large dietary protein intake.

Reference Values:
Only orderable as part of a profile. For more information see orderable test ID.

> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1256-1323 2. Meeusen JW, Rule AD, Voskoboev N, Baumann NA, Lieske JC: Performance of cystatin C- and creatinine-based estimated glomerular filtration rate equations depends on patient characteristics. Clin Chem. 2015 Oct;61(10):1265-1272. doi: 10.1373/clinchem.2015.243030 3. Newman DJ, Price CP: Renal function and nitrogen metabolites. In: Burtis CA, Ashwood ER, eds. Tietz

Textbook of Clinical Chemistry. 3rd ed. WB Saunders Company; 1999:1204-1270 4. Kasiske BL, Keane WF: Laboratory assessment of renal disease: clearance, urinalysis, and renal biopsy. In: Brenner BM, ed. The Kidney. 6th ed. WB Saunders Company; 2000:1129-1170

CRTFR
618560

Creatinine, Random, Urine

Clinical Information: Creatinine is formed from the metabolism of creatine and phosphocreatine, both of which are principally found in muscle. Thus, the amount of creatinine produced is, in large part, dependent upon the individual's muscle mass and tends not to fluctuate much from day-to-day. Creatinine is not protein bound and is freely filtered by glomeruli. All filtered creatinine is excreted in the urine. Renal tubular secretion of creatinine contributes a small proportion of excreted creatinine. Although most excreted creatinine is derived from an individual's muscle mass, dietary protein intake, particularly of cooked meat, can contribute to urinary creatinine levels. The renal clearance of creatinine provides an estimate of glomerular filtration rate. Since creatinine in the urine only comes mainly from filtration, the concentration of creatinine reflects overall urinary concentration. Therefore, creatinine can be used to normalize other analytes in a random urine specimen.

Useful For: Normalizing urinary analytes to account for the variation in urinary concentrations between individuals when using random urine collections

Interpretation: Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions, such as progressive kidney disease, or result from adverse effect on renal hemodynamics that are often reversible, including certain drugs or from decreases in effective renal perfusion (eg, volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most frequently seen during pregnancy or in patients with diabetes mellitus before diabetic nephropathy has occurred. It may also occur with large dietary protein intake.

Reference Values:
Only orderable as part of a profile. For more information see:
-RLTE4 / Leukotriene E4, Random, Urine.
-TIUCR / Titanium/Creatinine Ratio, Random, Urine

> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Delaney MP, Lamb EJ. Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1256-1323 2. Meeusen JW, Rule AD, Voskoboev N, Baumann NA, Lieske JC. Performance of cystatin C- and creatinine-based estimated glomerular filtration rate equations depends on patient characteristics. Clin Chem. 2015;61(10):1265-1272. doi:10.1373/clinchem.2015.243030 3. Newman DJ, Price CP. Renal function and nitrogen metabolites. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 3rd ed. WB Saunders Company; 1999:1204-1270 4. Kasiske BL, Keane WF: Laboratory assessment of renal disease: clearance, urinalysis, and renal biopsy. In: Brenner BM, ed. The Kidney. 6th ed. WB Saunders Company; 2000:1129-1170

CRE2
614427

Creatinine, Urine

Clinical Information: Creatinine is formed from the metabolism of creatine and phosphocreatine, both of which are principally found in muscle. Thus, the amount of creatinine produced is in large part dependent upon the individual's muscle mass and tends not to fluctuate much from day-to-day. Creatinine is not protein-bound and is freely filtered by glomeruli. All of the filtered creatinine is excreted in the

urine. Renal tubular secretion of creatinine also contributes to a small proportion of excreted creatinine. Although most excreted creatinine is derived from an individual's muscle, dietary protein intake, particularly of cooked meat, can contribute to urinary creatinine levels. The renal clearance of creatinine provides an estimate of glomerular filtration rate (GFR). Since creatinine, for the most part, in the urine only comes from filtration, the concentration of creatinine reflects overall urinary concentration. Therefore, creatinine can be used to normalize other analytes in a random urine specimen.

Useful For: Normalization of urinary analytes to account for the variation in urinary concentrations between individuals when using random urine collections

Interpretation: Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions such as progressive renal disease, or result from adverse effect on renal hemodynamics that are often reversible including certain drugs or from decreases in effective renal perfusion (eg, volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus, before diabetic nephropathy has occurred. It also may occur with large dietary protein intake.

Reference Values:
Only orderable as part of a profile. For more information see:
ALBR / Albumin, Random, Urine
RALB / Albumin, Random, Urine.

Not applicable

Clinical References: 1. Meeusen J, Rule A, Voskoboev N, Baumann N, Lieske J: Performance of cystatin C-creatinine-based estimated glomerular filtration rate equations depends on patient characteristics. Clin Chem. 2015 Oct;61(10):1265-1272. doi:10.1373/clinchem.2015.243030 2. Newman DJ, Price CP: Renal function and nitrogen metabolites. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 3rd ed. WB Saunders Company; 1999:1204-1270 3. Kasiske BL, Keane WF: Laboratory assessment of renal disease: clearance, urinalysis, and renal biopsy. In: Brenner BM, ed. The Kidney. 6th ed. WB Saunders Company; 2000:1129-1170

CJDEI 620375 Creutzfeldt-Jakob Disease Evaluation Interpretation, Spinal Fluid

Clinical Information: This evaluation is intended for use in patients with suspected Creutzfeldt-Jakob disease (CJD) and other human prion diseases. CJD is a rare and fatal neurodegenerative disorder that predominantly affects the brain and is caused by misfolded prion proteins (PrP[Sc]). CJD accounts for more than 90% of human prion diseases. Initial symptom onset is heterogenous but commonly includes rapidly progressive dementia, cerebellar ataxia, and myoclonus. The timeline of symptom progression and the pattern of symptom evolution can be divergent across patients and CJD subtypes, making an accurate diagnosis based on clinical presentation alone challenging. The inclusion of biomarkers with high diagnostic accuracy has improved the differentiation of CJD and related prion diseases from treatable neurological conditions with overlapping phenotypes. The real-time quaking-induced conversion (RT-QuIC) assay in cerebrospinal fluid (CSF) has been established to have strong clinical utility for early and accurate diagnosis of CJD through numerous independent studies. Furthermore, the robustness and reproducibility of the RT-QuIC assay for CJD across laboratories has been demonstrated through international ring trials. The clinical sensitivity and specificity of second-generation RT-QuIC assays in CSF have been consistently reported to be greater than or equal to 92% and greater than or equal to 99%, respectively. Despite the high diagnostic accuracy of the assay, RT-QuIC results should be interpreted in the appropriate clinical context along with other clinical and paraclinical findings. A definitive diagnosis of sporadic prion disease can be established only through

neuropathological assessment of brain tissue. Unexpectedly negative RT-QuIC test results should prompt careful consideration of the differential diagnosis. If there is high suspicion of prion disease, repeat RT-QuIC testing may be warranted. A small subset of cases initially negative by RT-QuIC may become positive as the disease progresses. However, RT-QuIC may be persistently negative in a small proportion of patients with definitive prion disease. False-negative RT-QuIC results are most often encountered in cases of genetic prion disease (eg, fatal familial insomnia and Gerstmann-Straussler-Scheinker disease) and in atypical sporadic prion disease subtypes (eg, MM2 cortical subtype) that have slower indolent disease progression. Other CSF biomarkers have been utilized to support the diagnosis of CJD, including 14-3-3, total Tau measurement, and the ratio of total Tau to phosphorylated Tau at threonine 181. Recent studies have indicated that the Tau ratio (total Tau to pT181-Tau or vice versa) has a very high diagnostic accuracy, which exceeds that provided by total Tau or 14-3-3 enzyme-linked immunosorbent assays (ELISA). In a cohort of probable/definite CJD cases and controls tested utilizing the Roche Total-Tau and p-Tau (threonine 181) Elecsys assays, the optimized cut-off value for total Tau (>393 ng/L) had a clinical sensitivity and specificity of 92.3% and 88.3% for CJD, respectively; and the optimized cut-off value for the total Tau to p-Tau ratio (>18) has a clinical sensitivity and specificity of 97.4% and 95.9% for CJD, respectively. Importantly, total Tau or total Tau to p-Tau ratios utilize assay-dependent cut-off values, and cut-off values from one assay are not transferable to different assay platforms. The National Prion Disease Pathology Surveillance Center (NPDPSC) coordinates autopsies and neuropathologic examinations on suspected prion disease cases. More information about services available at the NPDPSC may be found at https://case.edu/medicine/pathology/divisions/prion-center.

Useful For: Interpretation of the Creutzfeldt-Jakob Disease Evaluation

Interpretation: A positive real-time quaking-induced conversion (RT-QuIC) is supportive of prion disease and, in the correct clinical context, fulfills the Centers for Disease Control and Prevention diagnostic criteria of probable prion disease.(1) An elevated total Tau (t-Tau)/p-Tau (threonine 181) ratio (>18) increases the likelihood of prion disease but can be seen in patients with rapidly progressive dementia due to other causes, including autoimmune encephalitis, central nervous system malignancy, seizure disorder, stroke, and other neurodegenerative diseases. Negative results do not exclude the possibility of prion disease. Elevated t-Tau/p-Tau ratio (>18) Normal t-Tau/p-Tau ratio (< or =18) RT-QuIC positive Prion disease highly likely Prion disease likely RT-QuIC negative or inconclusive Prion disease possible Prion disease unlikely RT-QuIC = Real-time quaking-induced conversion

Reference Values:
Only orderable as part of a profile. For more information see CJDE / Creutzfeldt-Jakob Disease Evaluation, Spinal Fluid.

An interpretive report will be provided.

Clinical References:

CJDE
620374

Creutzfeldt-Jakob Disease Evaluation, Spinal Fluid

Clinical Information: This evaluation is intended for use in patients with suspected Creutzfeldt-Jakob disease (CJD) and other human prion diseases. CJD is a rare and fatal neurodegenerative disorder that predominantly affects the brain and is caused by misfolded prion proteins (PrP[Sc]). CJD accounts for more than 90% of human prion diseases. Initial symptom onset is heterogenous but commonly includes rapidly progressive dementia, cerebellar ataxia, and myoclonus. The timeline of symptom progression and the pattern of symptom evolution can be divergent across patients and CJD subtypes, making an accurate diagnosis based on clinical presentation alone challenging. The inclusion of biomarkers with high diagnostic accuracy has improved the differentiation of CJD and related prion diseases from treatable neurological conditions with overlapping phenotypes. The real-time quaking-

induced conversion (RT-QuIC) assay in cerebrospinal fluid (CSF) has been established to have strong clinical utility for early and accurate diagnosis of CJD through numerous independent studies. Furthermore, the robustness and reproducibility of the RT-QuIC assay for CJD across laboratories has been demonstrated through international ring trials. The clinical sensitivity and specificity of second-generation RT-QuIC assays in CSF have been consistently reported to be greater than or equal to 92% and greater than or equal to 99%, respectively. Despite the high diagnostic accuracy of the assay, RT-QuIC results should be interpreted in the appropriate clinical context along with other clinical and paraclinical findings. A definitive diagnosis of sporadic prion disease can be established only through neuropathological assessment of brain tissue. Unexpectedly negative RT-QuIC test results should prompt careful consideration of the differential diagnosis. If there is high suspicion of prion disease, repeat RT-QuIC testing may be warranted. A small subset of cases initially negative by RT-QuIC may become positive as the disease progresses. However, RT-QuIC may be persistently negative in a small proportion of patients with definitive prion disease. False-negative RT-QuIC results are most often encountered in cases of genetic prion disease (eg, fatal familial insomnia and Gerstmann-Straussler-Scheinker disease) and in atypical sporadic prion disease subtypes (eg, MM2 cortical subtype) that have slower indolent disease progression. Other CSF biomarkers have been utilized to support the diagnosis of CJD, including 14-3-3, total Tau measurement, and the ratio of total Tau to phosphorylated Tau at threonine 181. Recent studies have indicated that the Tau ratio (total Tau to pT181-Tau or vice versa) has a very high diagnostic accuracy, which exceeds that provided by total Tau or 14-3-3 enzyme-linked immunosorbent assays (ELISA). In a cohort of probable/definite CJD cases and controls tested utilizing the Roche Total-Tau and p-Tau (threonine 181) Elecsys assays, the optimized cut-off value for total Tau (>393 ng/L) had a clinical sensitivity and specificity of 92.3% and 88.3% for CJD, respectively; and the optimized cut-off value for the total Tau to p-Tau ratio (>18) has a clinical sensitivity and specificity of 97.4% and 95.9% for CJD, respectively. Importantly, total Tau or total Tau to p-Tau ratios utilize assay-dependent cut-off values, and cut-off values from one assay are not transferable to different assay platforms. The National Prion Disease Pathology Surveillance Center (NPDPSC) coordinates autopsies and neuropathologic examinations on suspected prion disease cases. More information about services available at the NPDPSC may be found at https://case.edu/medicine/pathology/divisions/prion-center.

Useful For: Assessment of Creutzfeldt-Jakob disease or other human prion disease in patients with rapidly progressive dementia

Interpretation: A positive real-time quaking-induced conversion (RT-QuIC) is supportive of prion disease and, in the correct clinical context, fulfills the Centers of Disease Control and Prevention diagnostic criteria of probable prion disease.(1) An elevated total Tau/p-Tau (threonine 181) ratio (>18) increases the likelihood of prion disease but can be seen in patients with rapidly progressive dementia due to other causes, including autoimmune encephalitis, central nervous system malignancy, seizure disorder, stroke, and other neurodegenerative diseases. Negative results do not exclude the possibility of prion disease. Elevated t-Tau/p-Tau ratio (>18) Normal t-Tau/p-Tau ratio (< or =18) RT-QuIC positive Prion disease highly likely Prion disease likely RT-QuIC negative or inconclusive Prion disease possible Prion disease unlikely RT-QuIC = Real-time quaking-induced conversion

Reference Values:

RT-QuIC PRION, CSF:
Negative

t-TAU/p-TAU:
< or =18

TOTAL TAU:
< or =393 pg/mL

Clinical References: 1. Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of High-Consequence Pathogens and

Pathology (DHCPP). Diagnostic criteria: CDC's diagnostic criteria for Creutzfeldt-Jakob disease (CJD), 2018. CDC; Updated October 18, 2021. Accessed July 17, 2024. Available at www.cdc.gov/creutzfeldt-jakob/hcp/clinical-overview/diagnosis.html 2. Hermann P, Appleby B, Brandel JP, et al. Biomarkers and diagnostic guidelines for sporadic Creutzfeldt-Jakob disease. Lancet Neurol. 2021;20(3):235-246 3. Rhoads DD, Wrona A, Foutz A, et al. Diagnosis of prion diseases by RT-QuIC results in improved surveillance. Neurology. 2020;95(8):e1017-e1026 4. Hamlin C, Puoti G, Berri S, et al. A comparison of tau and 14-3-3 protein in the diagnosis of Creutzfeldt-Jakob disease. Neurology. 2012;79(6):547-552 5. Shir D, Lazar EB, Graff-Radford J, et al. Analysis of clinical features, diagnostic tests, and biomarkers in patients with suspected Creutzfeldt-Jakob disease, 2014-2021. JAMA Netw Open. 2022;5(8):e2225098 6. Skillback T, Rosen C, Asztely F, Mattsson N, Blennow K, Zetterberg H. Diagnostic performance of cerebrospinal fluid total tau and phosphorylated tau in Creutzfeldt-Jakob disease: results from the Swedish Mortality Registry. JAMA Neurol. 2014;71(4):476-483 7. Hermann P, Haller P, Goebel S, et al. Total and phosphorylated cerebrospinal fluid Tau in the differential diagnosis of sporadic Creutzfeldt-Jakob disease and rapidly progressive Alzheimer's disease. Viruses. 2022;14(2):276

CRGSP
83659

Cryoglobulin and Cryofibrinogen Panel, Serum and Plasma

Clinical Information: Cryoglobulins are immunoglobulins that precipitate when cooled and dissolve when heated. Because these proteins precipitate when cooled, patients may experience symptoms when exposed to the cold. Cryoglobulins may be associated with a variety of diseases including plasma cell disorders, autoimmune diseases, and infections. Cryoglobulins may also cause erroneous results with some automated hematology instruments. Cryoglobulins may be classified as follows: Type I, Type II, and Type III. Type I is composed of a monoclonal immunoglobulin: IgG or IgM, or rarely IgA or free monoclonal light chains. Type II cryoglobulins consist of a monoclonal component and a polyclonal component. Finally, type III cryoglobulins are composed of only polyclonal immunoglobulins. The majority of patients with cryoglobulins are asymptomatic. The type or quantity of cryoglobulin does not reliably predict whether or which symptoms will be present. The concentration of cryoglobulins tends to vary by type with the majority of cases: of type III, being less than 1 mg/mL; of type II, greater than 1 mg/mL; and of type I, greater than 5 mg/mL. Even though the type I cryoglobulin concentrations tend to be the highest, they are the least likely to cause symptoms. The thermal amplitude (temperature at which the cryoglobulin precipitates) is a better predictor of symptoms than quantity or type. Symptoms of cryoglobulinemia include purpura, Raynaud phenomenon, cyanosis, skin ulceration, gangrene, kidney failure, peripheral neuropathy, fever, and malaise. Type I cryoglobulinemia is associated with monoclonal gammopathy of undetermined significance, macroglobulinemia, or multiple myeloma. Type II cryoglobulinemia is associated with autoimmune disorders such as vasculitis, glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren syndrome. It may be seen in infections such as hepatitis, infectious mononucleosis, cytomegalovirus, and toxoplasmosis. Type II cryoglobulinemia may also be essential, ie, occurring in the absence of underlying disease. Type III cryoglobulinemia usually demonstrates trace levels of cryoprecipitate, may take up to 7 days to appear, and is associated with the same disease spectrum as Type II cryoglobulinemia. A cryoprecipitate that is seen in plasma but not in serum is caused by cryofibrinogen. Cryofibrinogens are extremely rare and can be associated with vasculitis. Patients with cryofibrinogenemia often present asymptomatically, but this disorder can also be secondary to numerous conditions that include, but are not limited to, malignancies, infection, inflammation, or thrombotic disorders. Of those with symptoms, primary or essential cryofibrinogenemia can present with systemic manifestations or with a more specific clinical picture that typically includes cold intolerance and thrombotic/hemorrhagic manifestations, such as purpura, necrosis, ulcers and gangrene. Due to the rarity of clinically significant cryofibrinogenemia, testing for cryoglobulins is usually sufficient for investigation of cryoproteins.

Useful For: Evaluating patients with vasculitis, glomerulonephritis, and lymphoproliferative diseases Evaluating patients with macroglobulinemia or myeloma in whom symptoms occur with cold exposure This test is not useful for general screening of a population without a clinical suspicion of cryoglobulinemia.

Interpretation: An interpretive report will be provided

Reference Values:
CRYOGLOBULIN
Negative (positives reported as percent or trace amount)
If positive after 1 or 7 days, immunotyping of the cryoprecipitate is performed at an additional charge.

CRYOFIBRINOGEN
Negative
Quantitation and immunotyping will not be performed on positive cryofibrinogen.

Clinical References: 1. Kyle RA, Lust JA: Immunoglobulins and laboratory recognition of monoclonal proteins. Section III. Myeloma and related disorders. In: Wiernik PH, Canellos GP, Dutcher JP, Kyle RA, eds. Neoplastic Diseases of the Blood. 3rd ed. Churchill Livingstone; 1996:453-475 2. Desbois AC, Cacoub P, Saadoun D: Cryoglobulinemia: An update in 2019. Joint Bone Spine. 2019 Nov;86(6):707-713. doi: 10.1016/j.jbspin.2019.01.016

CRY_S 80988 Cryoglobulin, Serum

Clinical Information: Cryoglobulins are immunoglobulins that precipitate when cooled and dissolve when heated. Because these proteins precipitate when cooled, patients may experience symptoms when exposed to the cold. Cryoglobulins may be associated with a variety of diseases including plasma cell disorders, autoimmune diseases, and infections. Cryoglobulins may also cause erroneous results with some automated hematology instruments. Cryoglobulins may be classified as follows: Type I, Type II, and Type III. Type I is composed of a monoclonal immunoglobulin: IgG or IgM, or rarely IgA or free monoclonal light chains. Type II cryoglobulins consist of a monoclonal component and a polyclonal component. Finally, type III cryoglobulins are composed of only polyclonal immunoglobulins. The majority of patients with cryoglobulins are asymptomatic. The type or quantity of cryoglobulin does not reliably predict whether or which symptoms will be present. The concentration of cryoglobulins tends to vary by type with the majority of cases: of type III, being less than 1 mg/mL; of type II, greater than 1 mg/mL; and of type I, greater than 5 mg/mL. Even though the type I cryoglobulin concentrations tend to be the highest, they are the least likely to cause symptoms. The thermal amplitude (temperature at which the cryoglobulin precipitates) is a better predictor of symptoms than quantity or type. Symptoms of cryoglobulinemia include purpura, Raynaud phenomenon, cyanosis, skin ulceration, gangrene, kidney failure, peripheral neuropathy, fever, and malaise. Type I cryoglobulinemia is associated with monoclonal gammopathy of undetermined significance, macroglobulinemia, or multiple myeloma. Type II cryoglobulinemia is associated with autoimmune disorders such as vasculitis, glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren syndrome. It may be seen in infections such as hepatitis, infectious mononucleosis, cytomegalovirus, and toxoplasmosis. Type II cryoglobulinemia may also be essential, ie, occurring in the absence of underlying disease. Type III cryoglobulinemia usually demonstrates trace levels of cryoprecipitate, may take up to 7 days to appear, and is associated with the same disease spectrum as Type II cryoglobulinemia.

Useful For: Evaluating cryoglobulins in patients with vasculitis, glomerulonephritis, and lymphoproliferative diseases Evaluating cryoglobulins in patients with macroglobulinemia or myeloma in whom symptoms occur with cold exposure This test is not useful for general screening of a population without a clinical suspicion of cryoglobulinemia.

Interpretation: An interpretive report will be provided

Reference Values:

Negative (positives reported as percent or trace amount)
If positive after 1 or 7 days, immunotyping of the cryoprecipitate is performed at an additional charge.

Clinical References: 1. Kyle RA, Lust JA: Immunoglobulins and laboratory recognition of monoclonal proteins. Section III. Myeloma and related disorders. In: Wiernik PH, Canellos GP, Dutcher JP, Kyle RA, eds. Neoplastic Diseases of the Blood. 3rd ed. Churchill Livingstone; 1996:453-475 2. Desbois AC, Cacoub P, Saadoun D: Cryoglobulinemia: An update in 2019. Joint Bone Spine. 2019 Nov;86(6):707-713. doi: 10.1016/j.jbspin.2019.01.016

SLFA
62075

Cryptococcus Antigen Screen with Titer, Serum

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously only associated with tropical and subtropical regions. More recently, however, this organism has been found to be endemic in British Columbia and the Pacific Northwestern US and is associated with several different tree species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii is has a higher predilection for infection of healthy individuals.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Aiding in the diagnosis of cryptococcosis This test should not be used as a test of cure or to guide treatment decisions. This test should not be used as a screening procedure for the general populations.

Interpretation: The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid) is indicative of cryptococcosis. Specimens that are positive by the lateral flow assay screen are automatically repeated with the same method utilizing dilutions to generate a titer value. Disseminated infection is usually accompanied by a positive serum test. Higher Cryptococcus antigen titers appear to correlate with more severe infections. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions. Low-level titers may persist for extended periods of time following appropriate therapy and the resolution of infection.(3)

Reference Values:
Negative

Clinical References: 1. Speed B, Dunt D: Clinical and host differences between infections with the two varieties of Cryptococcus neoformans. Clin Infect Dis. 1995;21(1):28-34 2. Chen S, Sorrell T, Nimmo G, et al: Epidemiology and host- and variety-dependent characteristics of infection due to Cryptococcus neoformans in Australia and New Zealand. Australasian Cryptococcal Study Group. Clin Infect Dis. 2000;31(2):499-505. doi:10.1086/313992 3. Perfect JR, Dismukes WE, Dromer F, et al: Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(3):291-322 4. Perfect JR: Cryptococcosis (Cryptococcus neoformans and Cryptococcus gattii). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3146-3161 5.

Chang CC, Harrison TS, Bicanic TA, et al. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM [published correction appears in Lancet Infect Dis. 2024 Aug;24(8):e485. doi:10.1016/S1473-3099(24)00426-2]. Lancet Infect Dis. 2024;24(8):e495-e512. doi:10.1016/S1473-3099(23)00731-4 6. Perfect JR, Bicanic T. Cryptococcosis diagnosis and treatment: What do we know now. Fungal Genet Biol. 2015;78:49-54. doi:10.1016/j.fgb.2014.10.003

CLFA
62074

Cryptococcus Antigen Screen with Titer, Spinal Fluid

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously only associated with tropical and subtropical regions. More recently, however, this organism has been found to be endemic in British Columbia and the Pacific Northwestern United States and is associated with several different tree species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a higher predilection for infection of healthy individuals.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Aiding in the diagnosis of cryptococcosis This test should not be performed as a screening procedure for the general population. This test should not be used as a test of cure or to guide treatment decisions.

Interpretation: The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid [CSF]) is indicative of cryptococcosis. Specimens that are positive by the lateral flow assay (LFA) screen are automatically repeated by the same method utilizing dilutions to generate a titer value. CSF specimens submitted for initial diagnosis that test positive by LFA should also be submitted for routine fungal culture. Culture can aid in differentiating between the 2 common Cryptococcus species causing disease (Cryptococcus neoformans and Cryptococcus gattii) and can be used for antifungal susceptibility testing, if necessary. CSF specimens submitted to monitor antigen levels during treatment do not need to be cultured. Disseminated infection is usually accompanied by a positive serum test. Higher Cryptococcus antigen titers appear to correlate with more severe infections. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions. Low-level titers may persist for extended periods of time following appropriate therapy and the resolution of infection.(3)

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Speed B, Dunt D: Clinical and host differences between infections with the two varieties of Cryptococcus neoformans. Clin Infect Dis. 1995;21(1):28-34 2. Chen S, Sorrell T, Nimmo G, et al: Epidemiology and host- and variety-dependent characteristics of infection due to Cryptococcus neoformans in Australia and New Zealand. Australasian Cryptococcal Study Group. Clin Infect Dis. 2000 Aug;31(2):499-505. doi: 10.1086/313992 3. Perfect JR, Dismukes WE, Dromer F, et al: Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the

Infectious Diseases Society of America. Clin Infect Dis. 2010 Feb 1;50(3):291-322 4. Perfect JR. Cryptococcosis (Cryptococcus neoformans and Cryptococcus gattii). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3146-3161 5. Chang CC, Harrison TS, Bicanic TA, et al. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM [published correction appears in Lancet Infect Dis. 2024;24(8):e4856. Perfect JR, Bicanic T. Cryptococcosis diagnosis and treatment: What do we know now. Fungal Genet Biol. 2015;78:49-54. doi:10.1016/j.fgb.2014.10.003

PLFA 42396 Cryptococcus Antigen Screen, Lateral Flow Assay, Pleural Fluid

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously associated with tropical and subtropical regions only; however, more recently this organism has also been found to be endemic in British Columbia, along the Pacific Northwest, and in the Southeastern US. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a higher predilection for infection of healthy individuals. In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Diagnosis of infection with Cryptococcus species

Interpretation: The presence of cryptococcal antigen in pleural fluid is indicative of infection with Cryptococcus species. Monitoring cryptococcal antigen levels to determine response to therapy is discouraged, as antigen levels may persist despite adequate treatment and disease resolution. A negative result indicates lack of infection; however, rare cases of false-negative results have been reported. Fungal culture should always be ordered alongside antigen testing.

Reference Values:
Negative

Clinical References: 1. Binnicker MJ, Jespersen DJ, Bestrom JE, Rollins LO. Comparison of four assays for the detection of cryptococcal antigen. Clin Vaccine Immunol. 2012;19(12):1988-1990 2. Howell SA, Hazen KC, Brandt ME. Candida, cryptococcus, and other yeast of medical importance. In: Manual of Clinical Microbiology. 11th ed. ASM Press; 2015:1984-2014 3. Chang CC, Harrison TS, Bicanic TA, et al. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM. [published correction appears in Lancet Infect Dis. 2024;24(8):e485. doi:10.1016/S1473-3099(24)00426-2]. Lancet Infect Dis. 2024;24(8):e495-e512. doi:10.1016/S1473-3099(23)00731-4 4. Perfect JR, Bicanic T. Cryptococcosis diagnosis and treatment: What do we know now. Fungal Genet Biol. 2015;78:49-54. doi:10.1016/j.fgb.2014.10.003

ULFA 604095 Cryptococcus Antigen Screen, Lateral Flow Assay, Random, Urine

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. The organism has been isolated from several sites in nature, particularly weathered pigeon droppings. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a predilection for infection of healthy individuals. In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality associated with CNS cryptococcosis approaches 25% despite antifungal therapy, while untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Aiding in the diagnosis of infection with Cryptococcus neoformans or Cryptococcus gattii This test should not be used as a test of cure. This test should not be used as a screening procedure for the general population.

Interpretation: The presence of cryptococcal antigen (CrAg) in any body fluid is strongly suggestive of infection with Cryptococcus neoformans or Cryptococcus gattii. Declining titer results are suggestive of clinical response to therapy. However, monitoring CrAg titers should not be used as a test of cure, as low-level titers may persist for extended periods of time following appropriate therapy and disease resolution. In addition to testing for CrAg, patients with presumed disease due to C neoformans or C gattii should have appropriate clinical specimens (eg, blood, bronchoalveolar lavage fluid) submitted for routine smear and fungal culture.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Hazen KC, Howell SA: Candida, Cryptococcus, and other yeasts of medical importance. In: Murray PR, ed. Manual of Clinical Microbiology. 9th ed. ASM Press; 2007:1762-1788 2. Bruner KT, Franco-Paredes C, Henao-Martinez A, et al: Cryptococcus gattii complex infections in HIV-infected patients, Southeastern United States. EID. 2018 Nov;24(11):1998-2002. doi: 10.3201/eid2411.180787

PLFAT
48431

Cryptococcus Antigen Titer, Lateral Flow Assay, Pleural Fluid

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously associated with tropical and subtropical regions only; however, more recently this organism has also been found to be endemic in British Columbia, along the Pacific Northwest and in the Southeastern US. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a higher predilection for infection of healthy individuals. In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Diagnosis of infection with Cryptococcus species

Interpretation: The presence of cryptococcal antigen in pleural fluid is indicative of infection with Cryptococcus species. Monitoring cryptococcal antigen levels to determine response to therapy is discouraged, as antigen levels may persist despite adequate treatment and disease resolution. A negative result indicates lack of infection; however rare cases of false-negative results have been reported. Fungal culture should always be ordered alongside antigen testing.

Reference Values:
Only orderable as a reflex. For more information see PLFA / Cryptococcus Antigen Screen, Lateral Flow Assay, Pleural Fluid.

Clinical References: 1. Binnicker MJ, Jespersen DJ, Bestrom JE, Rollins LO. Comparison of four assays for the detection of cryptococcal antigen. Clin Vaccine Immunol. 2012;19(12):1988-1990. doi:10.1128/CVI.00446-12 2. Howell SA, Hazen KC, Brandt ME. Candida, cryptococcus, and other yeast of medical importance. In: Manual of Clinical Microbiology. 11th ed. ASM Press; 2015:1984-2014 3. Chang CC, Harrison TS, Bicanic TA, et al. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM. [published correction appears in Lancet Infect Dis. 2024;24(8):e485. doi:10.1016/S1473-3099(24)00426-2]. Lancet Infect Dis. 2024;24(8):e495-e512. doi:10.1016/S1473-3099(23)00731-4 4. Perfect JR, Bicanic T. Cryptococcosis diagnosis and treatment: What do we know now. Fungal Genet Biol. 2015;78:49-54. doi:10.1016/j.fgb.2014.10.003

SLFAT
62077

Cryptococcus Antigen Titer, Lateral Flow Assay, Serum

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously only associated with tropical and subtropical regions. More recently, however, this organism has been found to be endemic in British Columbia and the Pacific Northwestern US and is associated with several different tree species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a higher predilection for infection of healthy individuals.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Monitoring Cryptococcus antigen titers in serum Aiding in the diagnosis of cryptococcosis This test should not be used as a test of cure or to guide treatment decisions.

Interpretation: The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid) is indicative of cryptococcosis. Disseminated infection is usually accompanied by a positive serum test. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions. Low-level titers may persist for extended periods of time following appropriate therapy and resolution of infection.(3,4)

Reference Values:
Negative

Reference values apply to all ages.

Clinical References: 1. Speed B, Dunt D. Clinical and host differences between infections with the two varieties of Cryptococcus neoformans. Clin Infect Dis. 1995;21(1):28-34 2. Chen S, Sorrell T, Nimmo G, et al. Epidemiology and host- and variety-dependent characteristics of infection due to Cryptococcus neoformans in Australia and New Zealand. Australasian Cryptococcal Study Group. Clin Infect Dis. 2000;31(2):499-505. doi:10.1086/313992 3. Lu H, Zhou Y, Yin Y, Pan X, Weng X. Cryptococcal antigen test revisited: significance for cryptococcal meningitis therapy monitoring in a tertiary Chinese hospital. J Clin Microbiol. 2005;43(6):2989-2990 4. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010 ;50(3):291-322 5. Binnicker MJ, Jespersen DJ, Bestrom JE, Rollins LO. A comparison of four assays for detection of cryptococcal antigen. Clin Vaccine Immunol. 2012;19(12):1988-1990 6. Perfect JR: Cryptococcosis (Cryptococcus neoformans and Cryptococcus gattii). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3146-3161 7. Chang CC, Harrison TS, Bicanic TA, et al. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM [published correction appears in Lancet Infect Dis. 2024 Aug;24(8):e485. doi:10.1016/S1473-3099(24)00426-2]. Lancet Infect Dis. 2024;24(8):e495-e512. doi:10.1016/S1473-3099(23)00731-4 8. Perfect JR, Bicanic T. Cryptococcosis diagnosis and treatment: What do we know now. Fungal Genet Biol. 2015;78:49-54. doi:10.1016/j.fgb.2014.10.003

CLFAT
62076

Cryptococcus Antigen Titer, Lateral Flow Assay, Spinal Fluid

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously only associated with tropical and subtropical regions. More recently, however, this organism has been found to be endemic in British Columbia and the Pacific Northwestern United States and is associated with several different tree species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii is has a higher predilection for infection of healthy individuals.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Monitoring Cryptococcus antigen titers in cerebrospinal fluid Aiding in the diagnosis of cryptococcosis This test should not be used as a test of cure or to guide treatment decisions.

Interpretation: The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid [CSF]) is indicative of cryptococcosis. Disseminated infection is usually accompanied by a positive serum test. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions. Low-level titers may persist for extended periods of time following appropriate therapy and resolution of infection.(3,4) According to the College of American Pathologists (CAP, IMM.41840), CSF specimens submitted for initial diagnosis that test positive by the lateral flow assay, should also be submitted for routine fungal culture. Culture can aid in differentiating between the 2 common Cryptococcus species

causing disease (Cryptococcus neoformans and Cryptococcus gattii) and can be used for antifungal susceptibility testing, if necessary. CSF specimens submitted to monitor antigen levels during treatment do not need to be cultured.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Speed B, Dunt D: Clinical and host differences between infections with the two varieties of Cryptococcus neoformans. Clin Infect Dis. 1995;21(1):28-34 2. Chen S, Sorrell T, Nimmo G, et al: Epidemiology and host- and variety-dependent characteristics of infection due to Cryptococcus neoformans in Australia and New Zealand. Australasian Cryptococcal Study Group. Clin Infect Dis. 2000 Aug;31(2):499-505.doi: 10.1086/313992 3. Lu H, Zhou Y, Yin Y, Pan X, Weng X: Cryptococcal antigen test revisited: significance for cryptococcal meningitis therapy monitoring in a tertiary Chinese hospital. J Clin Microbiol. 2005 June;43(6):2989-2990 4. Perfect JR, Dismukes WE, Dromer F, et al: Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010 Feb 1;50(3):291-322 5. Perfect JR. Cryptococcosis (Cryptococcus neoformans and Cryptococcus gattii). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3146-3161 6. Chang CC, Harrison TS, Bicanic TA, et al. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM [published correction appears in Lancet Infect Dis. 2024;24(8):e485 7. Perfect JR, Bicanic T. Cryptococcosis diagnosis and treatment: What do we know now. Fungal Genet Biol. 2015;78:49-54. doi:10.1016/j.fgb.2014.10.003

ULFAT
604369

Cryptococcus Antigen Titer, Lateral Flow Assay, Urine

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. The organism has been isolated from several sites in nature, particularly weathered pigeon droppings. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a predilection for infection of healthy individuals. In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality associated with CNS cryptococcosis approaches 25% despite antifungal therapy, while untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Aiding in the diagnosis of infection with Cryptococcus neoformans or Cryptococcus gattii
This test should not be used as a test of cure.

Interpretation: The presence of cryptococcal antigen (CrAg) in any body fluid is strongly suggestive of infection with Cryptococcus neoformans or Cryptococcus gattii. Declining titer results are suggestive of clinical response to therapy. However, monitoring CrAg titers should not be used as a test of cure, as low-level titers may persist for extended periods of time following appropriate therapy and disease resolution. In addition to testing for CrAg, patients with presumed disease due to C neoformans or C gattii should have appropriate clinical specimens (eg, blood, bronchoalveolar lavage fluid) submitted for routine smear and fungal culture.

Reference Values:

Only orderable as a reflex. For more information see ULFA / Cryptococcus Antigen Screen, Lateral Flow Assay, Random, Urine.

Negative

Clinical References: Chang CC, Harrison TS, Bicanic TA, et al. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM [published correction appears in Lancet Infect Dis. 2024 Aug;24(8):e485. doi: 10.1016/S1473-3099(24)00426-2]. Lancet Infect Dis. 2024;24(8):e495-e512. doi:10.1016/S1473-3099(23)00731-4

LFACX
62703

Cryptococcus Antigen with Reflex, Spinal Fluid

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously only associated with tropical and subtropical regions. More recently, however, this organism has been found to be endemic in British Columbia and the Pacific Northwestern United States and is associated with several different tree species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a higher predilection for infection of healthy individuals.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Useful For: Aiding in the diagnosis of cryptococcosis This test should not be used as a test of cure or to guide treatment decisions. This test should not be performed as a screening procedure for the general population.

Interpretation: The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid [CSF]) is indicative of cryptococcosis. Specimens that are positive by the lateral flow assay (LFA) screen are automatically repeated by the same method utilizing dilutions to generate a titer value. CSF specimens submitted for initial diagnosis that test positive by LFA should also be submitted for routine fungal culture. Culture can aid in differentiating between the 2 common Cryptococcus species causing disease (Cryptococcus neoformans and Cryptococcus gattii) and can be used for antifungal susceptibility testing, if necessary. CSF specimens submitted to monitor antigen levels during treatment do not need to be cultured. Disseminated infection is usually accompanied by a positive serum test. Higher Cryptococcus antigen titers appear to correlate with more severe infections. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions, as low-level titers may persist for extended periods of time following appropriate therapy and the resolution of infection.

Reference Values:
CRYPTOCOCCUS ANTIGEN SCREEN WITH TITER
Negative
Reference values apply to all ages.

CRYPTOCOCCUS ANTIGEN TITER, LFA

Negative
Reference values apply to all ages.

FUNGAL CULTURE
Negative
If positive, fungus will be identified.
Reference values apply to all ages.

Clinical References: 1. Speed B, Dunt D: Clinical and host differences between infections with the two varieties of Cryptococcus neoformans. Clin Infect Dis. 1995;21(1):28-34 2. Chen S, Sorrell T, Nimmo G, et al: Epidemiology and host- and variety-dependent characteristics of infection due to Cryptococcus neoformans in Australia and New Zealand. Australasian Cryptococcal Study Group. Clin Infect Dis. 2000 Aug;31(2):499-505. doi: 10.1086/313992 3. Perfect JR: Cryptococcosis (Cryptococcus neoformans and Cryptococcus gattii). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3146-3161 4. Chang CC, Harrison TS, Bicanic TA, et al. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM [published correction appears in Lancet Infect Dis. 2024;24(8):e485 5. Perfect JR, Bicanic T. Cryptococcosis diagnosis and treatment: What do we know now. Fungal Genet Biol. 2015;78:49-54. doi:10.1016/j.fgb.2014.10.003

CRYPS
80335

Cryptosporidium Antigen, Feces

Clinical Information: Cryptosporidia are small apicomplexan protozoan parasites that infect the intestinal tract of humans and animals. They were conventionally categorized as coccidia but are now known to be more closely related to the gregarines. Many species may infect humans, with the most common being Cryptosporidium hominis and Cryptosporidium parvum. Infected humans and animals shed small (4-6 micrometer in diameter) infectious oocysts in their stool, and these can subsequently contaminate and survive in recreational and drinking water supplies. Infection of humans occurs by the fecal-oral route or via ingestion of contaminated water or food. Infection is easily acquired, with an infectious dose of approximately 100 oocysts. Waterborne transmission is a primary mode of transmission and is commonly responsible for human outbreaks. This is because Cryptosporidium species oocysts are resistant to cold temperatures and chlorine and require extensive filtration or water treatment to remove them from drinking water. The incubation period is typically 7 to 10 days following exposure. While most patients have symptoms, approximately 30% of infected individuals are asymptomatic. When symptoms are present, they usually include profuse, watery diarrhea, malaise, anorexia, nausea, crampy abdominal pain, and low-grade fever. Infection is usually self-limited in immunocompetent individuals, with resolution of symptoms in 10 to 14 days. However, diarrhea can be prolonged and life-threatening in immunocompromised patients such as those with AIDS, infants, and older adults, and result in severe dehydration and wasting. The fecal ova and parasite examination is an insensitive method for detecting Cryptosporidium, given the small size of the oocysts and their lack of trichrome staining. Instead, use of this test, or the multiplex gastrointestinal polymerase chain reaction (PCR) panel (GIP / Gastrointestinal Pathogen Panel, PCR, Feces), is recommended for sensitive and specific detection. This antigen test is ideal for situations in which cryptosporidiosis is highly suspected (eg, outbreak scenarios), whereas the PCR panel allows for simultaneous detection of multiple parasitic, viral, and bacterial causes of diarrhea. For more information about diagnostic tests that may be of value in evaluating patients with diarrhea, see the following: -Parasitic Investigation of Stool Specimens Algorithm -Laboratory Testing for Infectious Causes of Diarrhea

Useful For: Establishing the diagnosis of intestinal cryptosporidiosis

Interpretation: A positive enzyme-linked immunosorbent assay result indicates the presence of antigens of cryptosporidium and is interpreted as evidence of infection with that organism. Interpretation

of results should be correlated with patient symptoms and clinical picture.

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention (CDC): Parasites-Cryptosporidium (also known as "Crypto"). CDC; Updated July 1, 2019. Accessed October 31, 2022. Available at www.cdc.gov/parasites/crypto/index.html 2. Garcia LS, Arrowood M, Kokoskin E, et al. Practical guidance for clinical microbiology laboratories: Laboratory diagnosis of parasites from the gastrointestinal tract. Clin Microbiol Rev. 2017;31(1):e00025-17. doi:10.1128/CMR.00025-17

CRSBF
610646

Crystal Identification, Body Fluid

Clinical Information: Birefringent crystals are found in the synovial fluid of more than 90% of patients with acutely inflamed joints. Monosodium urate crystals are seen in gouty fluids and calcium pyrophosphate crystals are seen in chondrocalcinosis. The urates are usually needle-shaped, and the calcium crystals are often rhomboidal. Cholesterol crystals may also be observed.

Useful For: Identifying the presence and type of crystals in body fluid

Interpretation: Positive identification of crystals provides a definitive diagnosis for joint disease.

Reference Values:
None seen

If present, crystals are identified.

Clinical References: Hussong JW, Kjeldsberg CR, eds: Kjeldsberg's Body Fluid Analysis. ASCP Press; 2015

CSTB
616515

CSTB Gene, Repeat Expansion Analysis, Varies

Clinical Information: CSTB-related progressive myoclonic epilepsy (PME), also known as progressive myoclonic epilepsy type 1 (EPM1) or Unverricht-Lundborg disease, is the most common and least severe of the collective progressive myoclonic epilepsies. CSTB-related PME is inherited in an autosomal recessive pattern and is associated with inter- and intrafamilial variability. Individuals with CSTB-related PME have normal early development with onset of symptoms typically in the first or second decade of life. CSTB-related PME is characterized by involuntary myoclonus that is action- or stimulus-precipitated. Individuals with the condition are at increased risk for seizures, including tonic-clonic, absence, psychomotor and focal motor. The condition is progressive, leading to wheelchair dependence in some individuals. Later symptoms may also include ataxia, incoordination, intention tremor, dysarthria, mood disorders, and mild cognitive decline. CSTB-related PME is caused by disease-causing variants in the CSTB gene. An expansion of a dodecamer repeat sequence in the promoter region of the CSTB gene accounts for approximately 90% of disease-causing variants (99% in Finnish individuals). Full penetrance CSTB expansions are greater than or equal to 30 repeats, while normal alleles are typically 2 or 3 repeats. Allele sizes between 5 and 29 repeats are of unclear significance. The remainder of disease-causing variants are sequence variants including missense, nonsense, splice site variants, and small deletions and duplications. Genotype/phenotype correlation suggests that individuals who are homozygous for nonexpansion variants or compound heterozygous for one expansion allele and one nonexpansion allele have earlier onset and more severe symptoms than those individuals with

biallelic expansion alleles. Instability of the repeat expansion has been reported with vertical transmission, including both minimal expansion and contraction of repeat sizes. Alleles in the uncertain range are not associated with symptoms of CSTB-related PME but may demonstrate instability with transmission. Since repeat alleles in this size range have rarely been reported, the risk of repeat expansion into the full penetrance allele range (>29 repeats) is not fully understood. Additionally, correlation of repeat size with onset of symptoms is unclear.

Useful For: Molecular confirmation of clinically suspected CSTB-related progressive myoclonic epilepsy Identifying full penetrance dodecamer repeat expansions within CSTB known to cause CSTB-related progressive myoclonic epilepsy, allowing for predictive testing of at-risk family members Impacting patient treatment and management through the identification of a specific underlying etiology for epilepsy (eg, directing appropriate use of anti-epileptic drugs and other treatment modalities)

Interpretation: An interpretive report will be provided.

Reference Values:
Normal: <5 dodecamer repeats
Repeat Size of Uncertain Significance: 5-29 dodecamer repeats
Full Penetrance Expansion: >29 dodecamer repeats
An interpretive report will be provided.

Clinical References: 1. Lehesjoki AE, Koskimiemi M: Progressive myoclonus epilepsy of Unverricht-Lundborg type. Epilepsia. 1999;40 Suppl 3:23-28 2. Hypponen J, Aikia M, Joensuu T, et al: Refining the phenotype of Unverricht-Lundborg disease (EPM1): a population-wide Finnish study. Neurology. 2015 Apr 14;84(15):1529-1536 3. Canafoglia L, Gennaro E, Capovilla G, et al: Electroclinical presentation and genotype-phenotype relationships in patients with Unverricht-Lundborg disease carrying compound heterozygous CSTB point and indel mutations. Epilepsia. 2012 Dec;53(12):2120-2127

FCUIP 57590 CU (Chronic Urticaria) Index Panel

Reference Values:

FCUIX 57549 CU Index

Clinical Information: Patients with a chronic form of urticaria who are positive (>10) with the CU index have an autoimmune basis for their disease. A positive result does not indicate which autoantibody (anti-IgE, anti-FceRI or anti-FCERII) is present.

Reference Values:
< 10.0

The CU Index test is the second generation Functional Anti-FceR test. Patient with a CU Index greater than or equal to 10 have basophil reactive factors in their serum which supports an autoimmune basis for disease.

FCUKG 57651 Cucumber IgG

Interpretation:

Reference Values:

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

CUKE
82861

Cucumber, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cucumber Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

OATC
82916

Cultivated Oat, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cultivated oat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CRYE
82918

Cultivated Rye, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For:

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

WHTC
82915

Cultivated Wheat, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations.

In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cultivated wheat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CULAF
35244

Culture for Genetic Testing, Amniotic Fluid

Clinical Information: Fetal cells obtained by amniocentesis (amniocytes) are used for a wide range of laboratory tests. Prior to testing, the cells may need to be cultured to obtain adequate numbers of amniocytes.

Useful For: Producing amniocyte cultures that can be used for genetic analysis

Reference Values:
Not applicable

Clinical References: Arsham MS, Barch MJ, Lawce HJ, eds. The AGT Cytogenetics Laboratory Manual. 4th ed. Wiley-Blackwell; 2017

FUNID 8223 Culture Referred for Identification, Fungus

Clinical Information: Organisms are referred for identification or to confirm an identification made elsewhere. This may provide helpful information regarding the significance of the organism, its role in the disease process, and its possible origin.

Useful For: Identification of pure isolates of filamentous fungi and yeast

Interpretation: Genus and species are reported on fungal isolates whenever possible.

Reference Values:
Not applicable

Clinical References: Ashbee HR: General approaches for direction detection and identification of fungi. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. Vol 1. ASM Press; 2019:2035-2055

TBIDS 64714 Culture Referred for Identification, Mycobacterium and Nocardia with Antimicrobial Susceptibility Testing, Varies

Clinical Information: There are approximately 200 recognized species of mycobacteria and more than 100 Nocardia species. Many of these species are human pathogens and, therefore, identification to the species level is important to help guide patient care. In addition, there are other aerobic actinomycete genera that can be human pathogens including, but not limited to, Tsukamurella, Rhodococcus, and Gordonia species. Mycobacteria species, Nocardia species, and other aerobic actinomycete genera are identified using matrix-assisted laser desorption ionization time-of-flight mass spectrometry or nucleic acid sequencing of a 500-base pair region of the 16S ribosomal RNA gene. Mycobacterium tuberculosis complex can also be identified via rapid polymerase chain reaction assay which targets a unique sequence within the katG gene, which is present in members of the M tuberculosis complex and can also detect genotypic resistance to isoniazid mediated by mutations in the katG target, when present. After identification, antimicrobial susceptibility testing is performed following Clinical and Laboratory Standards Institute M24 guidelines using either broth dilution or critical concentration methods as appropriate for the species.

Useful For: Rapid identification to the species level and susceptibility testing for Mycobacterium species, Nocardia species, and other aerobic actinomycete genera and species from pure culture isolates

Interpretation: Organisms growing in pure culture are identified to the species level whenever possible.

Reference Values:
Not applicable

Clinical References: 1. Martin I, Pfyffer GE, Parrish N. Mycobacterium: general characteristics, laboratory detection, and staining procedures. In: Carroll KC, Pfaller MA, eds. Manual of Clinical Microbiology. 13th ed. Vol 1. ASM Press; 2023:594-613 2. Clinical and Laboratory Standards Institute. Susceptibility testing of mycobacteria, nocardiae, and other aerobic actinomycetes. 3rd ed. CLSI

document M24-ED3:2018. CLSI; 2018

CTBID 80278 Culture Referred for Identification, Mycobacterium and Nocardia, Varies

Clinical Information: Approximately 200 recognized species of mycobacteria and more than 100 Nocardia species exist. Many of these species are human pathogens and, therefore, identification to the species level is important to help guide patient care. In addition, other aerobic actinomycete genera can be human pathogens including, but not limited to, Tsukamurella, Rhodococcus, and Gordonia species. Mycobacteria species, Nocardia species and other aerobic actinomycete genera are identified using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry or nucleic acid sequencing of a 500-base pair region of the 16S ribosomal RNA gene.

Useful For: Rapid identification to the species level for Mycobacterium species, Nocardia species, and other aerobic actinomycete genera and species from pure culture isolates

Interpretation: Organisms growing in pure culture are identified to the species level where indicated.

Reference Values:
Not applicable

Clinical References: 1. Martin I, Pfyffer GE, Parrish N. Mycobacterium: General characteristics, laboratory detection and staining procedures. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. Vol 1. ASM Press; 2019:558-575 2. Warshauer DM, Salfinger M, Desmond E, Lin SYG. Mycobacterium tuberculosis complex. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. Vol 1. ASM Press; 2019:576-594 3. Caulfield AJ, Richter E, Brown-Elliott BA, Wallace RJ Jr, Wengenack NL. Mycobacterium: Laboratory characteristics of slowly growing mycobacteria other than Mycobacterium tuberculosis. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. Vol 1. ASM Press; 2019:595-611 4. Brown-Elliott BA, Wallace RJ Jr. Mycobacterium: Clinical and laboratory characteristics of rapidly growing mycobacteria. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. Vol 1. ASM Press; 2019:612-629 5. Conville PS, Brown-Elliott BA, Witebsky FG. Nocarida, rhodococcus, gordonia, actinomadura, streptomyces and other aerobic actinomycetes. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. Vol 1. ASM Press; 2019:525-557

CURL 82852 Curvularia lunata, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Curvularia lunata Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FCURV 57898 Curvularia spicifera/Bipolaris IgE

Interpretation: Class IgE (kU/L) Comment 0 <.10 Negative 0/1 0.10 – 0.34 Equivocal/Borderline 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 49.99 Very High Positive 5 50.00 – 99.9 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

CGPH 605198 Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies

Clinical Information: This test can be used to customize genetic testing panels offered at Mayo Clinic Laboratories. Individual genes can be added or removed to an existing genetic testing panel. Additionally, this test can be used to create your own custom single gene or multi-gene panel or to

combine existing panels within the same disease state. Note: Any genes added to the custom panel must be from the same disease state. Only one Gene List ID may be submitted per Custom Gene Panel, Hereditary order. The Gene List ID can be created using the Custom Gene Ordering tool (see Ordering Guidance).

Useful For: Customization of existing next-generation sequencing panels offered through Mayo Clinic Laboratories Detection single nucleotide and copy number variants in a custom gene panel Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for a hereditary condition

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30

CIB
607602

Cutaneous Direct Immunofluorescence Assay, Varies

Clinical Information: Skin or mucosal tissue from patients with autoimmune bullous diseases, connective tissue disease, vasculitis, lichen planus, and other inflammatory conditions often contains bound immunoglobulin, complement, or fibrinogen. Biopsy specimens are examined for the presence of bound IgG, IgM, IgA, third component of complement (C3), fibrinogen, and IgG4.

Useful For: Confirming a diagnosis of bullous pemphigoid, cicatricial pemphigoid, pemphigoid gestationis and other variants of pemphigoid, all types of pemphigus, including paraneoplastic pemphigus (paraneoplastic multiorgan syndrome), dermatitis herpetiformis, linear IgA bullous dermatosis, chronic bullous disease of childhood, epidermolysis bullosa acquisita, porphyria cutanea tarda, bullous eruption of lupus erythematosus, and atypical or mixed forms of bullous disease, systemic lupus erythematosus, cutaneous lupus erythematosus, or other variants, vasculitis, lichen planus, and other inflammatory diseases This test is not useful for diagnosis of malignancies involving the skin.

Interpretation: A board-certified Dermatopathologist will review and interpret the test results in correlation with other clinical findings as provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Jain S, Basavaraj V, Vimala MG. Utility of direct immunofluorescence studies in subclassification of autoimmune sub-epidermal bullous diseases: A 2-year study in a tertiary care hospital. Turk Patoloji Derg. 2016;32(2):91-98. doi:10.5146/tjpath.2015.01345 2. Diercks GF, Pas HH, Jonkman MF. Immunofluorescence of autoimmune bullous siseases. Surg Pathol Clin. 2017;10(2):505-512. doi:10.1016/j.path.2017.01.011 3. Kershenovich R, Hodak E, Mimouni D. Diagnosis and classification of pemphigus and bullous pemphigoid. Autoimmun Rev. 2014;13(4-5):477-481. doi:10.1016/j.autrev.2014.01.011 4. Buschman KE, Seraly M, Thong HY, Deng JS, Draviam RP,

Abernethy JL. A predominant IgG4 subclass may be responsible for false-negative direct immunofluorescence in bullous pemphigoid. J Cutan Pathol. 2002;29(5):282-286. doi:10.1034/j.1600-0560.2002.290504.x 5. Lamb PM, Patton T, Deng JS. The predominance of IgG4 in prodromal bullous pemphigoid. Int J Dermatol. 2008;47(2):150-153. doi:10.1111/j.1365-4632.2008.03361.x

CIFST
622323

Cutaneous Immunofluorescence Antibodies Titer, IgG, Serum

Clinical Information: Immunoglobulin G (IgG) anti-basement membrane zone (BMZ) antibodies are produced by patients with pemphigoid. In most patients with bullous pemphigoid, serum contains IgG anti-BMZ antibodies, while in cicatricial pemphigoid circulating IgG anti-BMZ antibodies are found in a minority of cases. Circulating IgG anti-BMZ antibodies are also detected in patients with epidermolysis bullosa acquisita and bullous eruption of lupus erythematosus. Immunoglobulin G anti-cell surface (CS) antibodies are produced by patients with pemphigus. The titer of IgG anti-CS antibodies generally correlates with disease activity of pemphigus.

Useful For: Confirmation of positive IgG anti-cell surface (CS) and anti-basement membrane zone (BMZ) antibodies.

Interpretation: Indirect immunofluorescence (IF) testing may be diagnostic when histologic or direct IF studies are only suggestive, nonspecific, or negative. Anti-cell surface antibodies correlate with a diagnosis of pemphigus. Anti-basement membrane zone antibodies correlate with a diagnosis of bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita, or bullous eruption of lupus erythematosus.

Reference Values:
Only orderable as a reflex. For more information see CIFS / Cutaneous Immunofluorescence Antibodies, IgG and IgG4, Serum.

Negative in normal individuals

Clinical References: 1. Beutner EH, Chorzelski TP, Kumar V, eds. Immunopathology of the Skin. 3rd ed. Wiley Medical Publication; 1987 2. Gammon WR, Briggaman RA, Inman AO 3rd, Queen LL, Wheeler CE. Differentiating anti-lamina lucida and anti-sublamina densa anti-BMZ antibodies by indirect immunofluorescence on 1.0 M sodium chloride-separated skin. J Invest Dermatol. 1984;82(2):139-144 3. Tirumalae R, Kalegowda IY. Role of BIOCHIP indirect immunofluorescence test in cutaneous vesiculobullous diseases. Am J Dermatopathol. 2020;42(5):322-328

CIFA
610627

Cutaneous Immunofluorescence Antibodies, IgA, Serum

Clinical Information: Immunoglobulin A anti-basement membrane zone (BMZ) antibodies are produced by patients with pemphigoid. In most patients with bullous pemphigoid, serum contains IgA anti-BMZ antibodies, while in cicatricial pemphigoid circulating IgA anti-BMZ antibodies are found in a minority of cases. Sensitivity of detection of anti-BMZ antibodies is increased when serum is tested using sodium chloride-split primate skin as substrate. Circulating IgA anti-BMZ antibodies are also detected in patients with epidermolysis bullosa acquisita and bullous eruption of lupus erythematosus. IgA anti-cell surface (CS) antibodies are produced by patients with pemphigus. The titer of anti-CS antibodies generally correlates with disease activity of pemphigus.

Useful For: Confirming the presence of IgA antibodies to diagnose pemphigoid, pemphigus, epidermolysis bullosa acquisita, or bullous lupus erythematosus

Interpretation: Indirect immunofluorescence (IF) testing may be diagnostic when histologic or direct IF studies are only suggestive, nonspecific, or negative. Anti-cell surface antibodies correlate with a diagnosis of pemphigus. Anti-basement membrane zone (BMZ) antibodies correlate with a diagnosis of bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita (EBA), or bullous eruption of lupus erythematosus (LE). If serum contains anti-BMZ antibodies, the pattern of fluorescence on sodium chloride (NaCl)-split skin substrate helps distinguish pemphigoid from EBA and bullous LE. Staining of the roof (epidermal side) or both epidermal and dermal sides of NaCl-split skin correlates with the diagnosis of pemphigoid, while fluorescence localized only to the dermal side of the split-skin substrate correlates with either EBA or bullous LE.

Reference Values:

Report includes presence and titer of circulating antibodies. If serum contains basement membrane zone antibodies on split-skin substrate, patterns will be reported as:

1) Epidermal pattern, consistent with pemphigoid
2) Dermal pattern, consistent with epidermolysis bullosa acquisita

Negative in normal individuals

Clinical References: 1. Caux F, Kirtschig G, Lemarchand-Venencie F, et al. IgA-epidermolysis bullosa acquisita in a child resulting in blindness. Br J Dermatol. 1997;137(2):270-275 2. Chorzelski TP, Jablonska S. IgA linear dermatosis of childhood (chronic bullous disease of childhood). Br J Dermatol. 1979;101(5):535-542 3. Guide SV, Marinkovich MP. Linear IgA bullous dermatosis. Clin Dermatol. 2001;19(6):719-727 4. Hashimoto T, Ebihara T, Nishikawa T. Studies of autoantigens recognized by IgA anti-keratinocyte cell surface antibodies. J Dermatol Sci. 1996;12(1):10-17 5. Lally A, Chamberlain A, Allen J, Dean D, Wojnarowska F. Dermal-binding linear IgA disease: an uncommon subset of a rare immunobullous disease. Clin Exp Dermatol. 2007;32(5):493-498 6. Tsuruta D, Ishii N, Hamada T, et al. IgA pemphigus. Clin Dermatol. 2011;29(4):437-442 7. Vodegel RM, de Jong MCJM, Pas HH, Jonkman MF. IgA-mediated epidermolysis bullosa acquisita: two cases and review of the literature. J Am Acad Dermatol. 2002;47(6):919-925 8. Willsteed E, Bhogal BS, Black MM, McKee P, Wojnarowska F. Use of 1M NaCl split skin in the indirect immunofluorescence of the linear IgA bullous dermatoses. J Cutan Pathol. 1990;17(3):144-148 9. Wilson BD, Beutner EH, Kumar V, Chorzelski TP, Jablonska S. Linear IgA bullous dermatosis. An immunologically defined disease. Int J Dermatol. 1985;24(9):569-574 10. Wojnarowska F, Collier PM, Allen J, Millard PR. The localization of the target antigens and antibodies in linear IgA disease is heterogeneous, and dependent on the methods used. Br J Dermatol. 1995;132(5):750-757 11. Tirumalae R, Kalegowda IY. Role of BIOCHIP indirect immunofluorescence test in cutaneous vesiculobullous diseases. Am J Dermatopathol. 2020;42(5):322-328

CIFS
8052

Cutaneous Immunofluorescence Antibodies, IgG and IgG4, Serum

Clinical Information: Immunoglobulin G (IgG) and/or IgG4 anti-basement membrane zone (BMZ) antibodies are produced by patients with pemphigoid, pemphigus, and other rare autoimmune blistering disorders such as epidermolysis bullosa acquisita and bullous lupus erythematosus. In most patients with bullous pemphigoid, serum contains IgG anti-BMZ antibodies, while in cicatricial pemphigoid circulating IgG anti-BMZ antibodies are found in a minority of cases. Circulating IgG4 is also variably present. Sensitivity of detection of anti-BMZ antibodies is increased when serum is tested using both sodium chloride-split primate skin and primate esophagus as substrates and using both IgG and IgG4 reactants.

Useful For: Confirming the presence of IgG and/or IgG4 antibodies to diagnose pemphigoid, pemphigus, epidermolysis bullosa acquisita, or bullous lupus erythematosus

Interpretation: Indirect immunofluorescence (IF) testing may aid in the diagnosis of these conditions

when correlated with histopathologic, direct immunofluorescence, and clinical information. Anti-basement membrane zone (BMZ) antibodies correlate with a diagnosis of bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita (EBA), or bullous eruption of lupus erythematosus (LE). Anti-cell surface antibodies correlate with a diagnosis of pemphigus. If serum contains anti-BMZ antibodies, the pattern of fluorescence on sodium chloride (NaCl)-split skin substrate helps distinguish pemphigoid from EBA and bullous LE. Staining of the roof (epidermal side) or both epidermal and dermal sides of NaCl-split skin correlates with the diagnosis of pemphigoid, while fluorescence localized only to the dermal side of the split-skin substrate correlates with either EBA or bullous LE. The report includes presence and titer of circulating antibodies. If the serum contains BMZ antibodies on the split-skin substrate, patterns will be reported as one of the following: 1. Epidermal pattern, suggestive of pemphigoid 2. Dermal pattern, suggestive of epidermolysis bullosa acquisita, bullous lupus erythematosus, or rare pemphigoid variants 3. Mixed pattern, suggestive of rare pemphigoid variants If serum contains BMZ antibodies on the primate esophagus substrate, patterns will be reported as one of the following: -BMZ (linear) pattern, suggestive of a subepidermal autoimmune mucocutaneous blistering disorder -Intercellular substance (cell-surface) pattern, suggestive of pemphigus

Reference Values:
Negative in normal individuals

Clinical References: 1. Beutner EH, Chorzelski TP, Kumar V, eds. Immunopathology of the Skin. 3rd ed. Wiley Medical Publication; 1987 2. Gammon WR, Briggaman RA, Inman AO 3rd, Queen LL, Wheeler CE. Differentiating anti-lamina lucida and anti-sublamina densa anti-BMZ antibodies by indirect immunofluorescence on 1.0 M sodium chloride-separated skin. J Invest Dermatol. 1984;82(2):139-144 3. Tirumalae R, Kalegowda IY. Role of BIOCHIP indirect immunofluorescence test in cutaneous vesiculobullous diseases. Am J Dermatopathol. 2020;42(5):322-328 4. Lehman JS, Aghazadeh Mohandesi N, Agrawal S, et al. Indirect immunofluorescence testing for immunoglobulin G4 and IgG increases test sensitivity over that of IIF testing for IgG alone for pemphigoid and pemphigus diseases: A retrospective study of 278 cases. J Am Acad Dermatol. 2024:S0190-9622(24)03372-3

CXC13
113163

CXCL13 Immunostain, Technical Component Only

Clinical Information: CXCL13 (CXC motif chemokine ligand 13) is useful in the classification of nodal T-cell lymphomas with T-follicular helper (TFH) phenotype, and the diagnosis of follicular dendritic cell sarcoma.

Useful For: Assessment of CXCL13 (CXC motif chemokine ligand 13) expression

Interpretation: This test does not include pathologist interpretation: only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Basha BM, Bryant SC, Rech KL, et al. Application of a 5 marker panel to the routine diagnosis of peripheral T-cell lymphoma with T-follicular helper phenotype. Am J Surg Pathol. 2019; 43(9):1282-1290 2. Kurita D, Miyoshi H, Yoshida N, et al. A clinicopathologic study of Lennert lymphoma and possible prognostic factors. Am J Surg Pathol. 2016;40(9):1249-1260 3. Park J, Han J, Kang H, Lee ES, Chan Kim Y. Expression of follicular helper T-cell markers in primary

cutaneous T-cell lymphoma. Am J Dermatopathol. 2014;36(6):465-470 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FCXCL
75827

CXCL9

Reference Values:
<=647 pg/mL

CXLPL
64759

CXCR4 Mutation Analysis, Somatic, Lymphoplasmacytic Lymphoma/Waldenstrom Macroglobulinemia, Varies

Clinical Information: Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) is a B-cell lymphoma characterized by an aberrant accumulation of malignant lymphoplasmacytic cells in the bone marrow, lymph nodes, and spleen. It is a B-cell neoplasm that can exhibit excess production of serum IgM symptoms related to hyperviscosity, tissue filtration, and autoimmune-related pathology. CXCR4 mutations are identified in approximately 30% to 40% of patients with LPL/WM and are almost always associated with MYD88 L265P, which is highly prevalent in this neoplasm. The status of CXCR4 mutations in the context of MYD88 L265P is clinically relevant as important determinants of clinical presentation, overall survival, and therapeutic response to ibrutinib. A MYD88-L265P/CXCR4-WHIM (C-terminus nonsense/frameshift mutations) molecular signature is associated with intermediate to high bone marrow disease burden and serum IgM levels, less adenopathy, and intermediate response to ibrutinib in previously treated patients. A MYD88-L265P/CXCR4-WT (wildtype) molecular signature is associated with intermediate bone marrow disease burden and serum IgM levels, more adenopathy, and highest response to ibrutinib in previously treated patients. A MYD88-WT/CXCR4-WT molecular signature is associated with inferior overall survival, lower response to ibrutinib therapy in previously treated patients, and lower bone marrow disease burden in comparison to those harboring a MYD88-L265 mutation.

Useful For: Aiding in the prognosis and clinical management of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia

Interpretation: Mutation present or not detected; an interpretive report will be issued.

Reference Values:
Mutations present or absent in the test region c. 898-1059 (amino acids 300-353) of the CXCR4 gene (NCBI NM_003467.2, GRCh37)

Clinical References: 1. Hunter Z, Xu L, Yang G, et al: The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood. 2014 Mar 13;123(11):1637-1646. doi: 10.1182/blood-2013-09-525808 2. Landgren O, Tageja N: MYD88 and beyond: novel opportunities for diagnosis, prognosis and treatment in Waldenstrom's Macroglobulinemia. Leukemia. 2014 Sep;28(9):1799-1803. doi: 10.1038/leu.2014.88 3. Poulain S, Roumier C, Venet-Caillault A, et al: Genomic Landscape of CXCR4 Mutations in Waldenstrom Macroglobulinemia. Clin Cancer Res. 2016 Mar 15;22(6):1480-1488. doi: 10.1158/1078-0432.CCR-15-0646 4. Roccaro A, Sacco A, Jimenez C, et al: C1013G/CXCR4 acts as a driver mutation of tumor progression and modulator of drug resistance in lymphoplasmacytic lymphoma. Blood. 2014 Jun 26;123(26):4120-4131. doi: 10.1182/blood-2014-03-564583 5. Schmidt J, Federmann B, Schindler N, et al: MYD88 L265P and CXCR4 mutations in lymphoplasmacytic lymphoma identify cases with high disease activity. Br J Haematol. 2015 Jun;169(6):795-803. doi: 10.1111/bjh.13361 6. Treon SP, Cao Y, Xu L, Yang G, Liu X,

Hunter ZR: Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. Blood. 2014 May 1;123(18):2791-2796. doi: 10.1182/blood-2014-01-550905 7. Treon SP, Tripsas CK, Meid K, et al: Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med. 2015 Apr 9;372(15):1430-1440. doi: 10.1056/NEJMoa1501548 8. Xu L, Hunter ZR, Tsakmaklis N, et al: Clonal architecture of CXCR4 WHIM-like mutations in Waldenstrom Macroglobulinaemia. Br J Haematol. 2016 Mar;172(5):735-744. doi: 10.1111/bjh.13897

FCYNB 75370 Cyanide, Blood Test

Reference Values:

Normal: Up to 0.05 mcg/mL
Potentially toxic: 0.50 mcg/mL and greater
Potentially lethal: 2.0 mcg/mL and greater

CARU 609739 Cyclic Adenosine Monophosphate (cAMP), Urinary Excretion, Serum and Urine

Clinical Information: Adenosine cyclic 3',5'-monophosphate (cAMP) functions as an intracellular "second messenger" regulating the activity of intracellular enzymes or proteins in response to a variety of hormones (eg, parathyroid hormone). Urinary cAMP is elevated in about 85% of patients with hyperparathyroidism.

Useful For: Differential diagnosis of hypercalcemia As an adjunct to serum parathyroid hormone measurements, especially in the diagnosis of parathyroid hormone resistance states, such as pseudohypoparathyroidism

Interpretation: Urinary adenosine cyclic 3',5'-monophosphate (cAMP) is elevated in about 85% of patients with hyperparathyroidism and in about 50% of patients with humoral hypercalcemia of malignancy.

Reference Values:

CYCLIC AMP
1.3-3.7 nmol/dL of glomerular filtrate

CREATININE, SERUM
Males
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL

Females
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL

CREATININE, URINE

No reference values apply. Interpret with other clinical data.

Clinical References: 1. Aurbach GD, Marx SJ, Spiegel AM: Parathyroid hormone, calcitonin, and the calciferols. In: Wilson JD, Foster DW, eds. Williams Textbook of Endocrinology. 8th ed. WB Saunders Company; 1992:1413-1415 2. Melmed S, Auchus RJ, Goldfine AB, Koenig RJ, Rosen CJ, eds. Williams Textbook of Endocrinology. 14th ed. Elsevier; 2020

CCP
84182

Cyclic Citrullinated Peptide Antibodies, IgG, Serum

Clinical Information: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by interactions between the environment, specific genetic risk factors, and the human immune system. It affects about 0.6% of the US population with a global prevalence of 0.24%.(1) Clinically, RA is typified by progressive damage of synovial joints, inflammation, production of diverse autoantibodies, and variable extra-articular manifestations.(2-4) Patients with RA may be categorized based on the phase of disease (early versus established), presence or absence of antibodies (seropositive versus seronegative), clinical manifestations (joint erosion, interstitial lung disease, or cardiovascular), or specific risks (genes, gender, or smoking).(2-4) Delayed diagnosis of RA is associated with joint erosion, destruction or deformities, poor response to treatment with an ultimate increase in morbidity, and mortality.(3,4) Although late RA diagnosis may be linked to adverse consequences, early diagnosis has been reported to improve outcomes; notably reduced joint destruction or deformity, delayed radiologic progression, and decreased functional disability.(3-5) To facilitate early diagnosis, the American College of Rheumatology/European League Against Rheumatism 2010 RA classification criteria recommend testing for rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA).(2) RF is an autoantibody directed against the Fc portion of immunoglobulin while ACPA are directed against peptides and proteins containing citrulline, a modified form of the amino acid arginine.(6,7) In addition to the use of RA and ACPA IgG to diagnose RA, RF and ACPA isotype antibodies and other serologic biomarkers have been used to predict if, and when, an individual who has inflammatory arthritis (IA) may develop future clinically apparent IA and access genetic and/or environmental risks.(3,4,8,9) Compared to early serologic tests for RA including RF, several studies have demonstrated that ACPA have much improved specificity for RA.(4,6,10) A systemic review and meta-analysis of 33 studies including patients with RA and healthy or disease controls demonstrated the sensitivity of anti-mutated citrullinated vimentin, anticyclic citrullinated peptide, and RF of 71%, 71%, 77%, with the specificity of 89%, 95%, 73%, and the area under the curve of the summary receiver operating characteristic of 89%, 95%, 82%, respectively.(10) Based on these studies, there exist a subset of patients with RA who are negative for RF and ACPA IgG (seronegative) who must be diagnosed clinically or with use of emerging diagnostic tests.(4,7,9) For more information see Connective Tissue Disease Cascade.

Useful For: Evaluating patients suspected of having rheumatoid arthritis (RA) Differentiating RA from other inflammatory arthritis or connective tissue diseases

Interpretation: A positive result for cyclic citrullinated peptide (CCP) antibodies may be suggestive of rheumatoid arthritis (RA) if compatible clinical features of disease are present. Significantly elevated levels of CCP antibodies may be useful to identify RA patients with erosive joint disease. A Mayo Clinic prospective clinical evaluation of the CCP antibody test showed a diagnostic sensitivity for RA of 78% with fewer than 5% false positive results in healthy controls (see Cautions).

Reference Values:

<20.0 U (negative)
20.0-39.9 U (weak positive)
40.0-59.9 U (positive)
> or =60.0 U (strong positive)
Reference values apply to all ages.

Clinical References: 1. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1316-1322 2. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-2581 3. Burgers LE, Raza K, van der Helm-van Mil AH. Window of opportunity in rheumatoid arthritis - definitions and supporting evidence: from old to new perspectives. RMD Open. 2019;5(1):e000870 4. Deane KD, Holers VM. Rheumatoid arthritis pathogenesis, prediction, and prevention: An emerging paradigm shift. Arthritis Rheumatol. 2021;73(2):181-193 5. Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. Ann Rheum Dis. 2002;61(4):290-297 6. Schellekens GA, Visser H, de Jong BA, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum. 2000;43(1):155-163 7. Derksen VFAM, Huizinga TWJ, van der Woude D. The role of autoantibodies in the pathophysiology of rheumatoid arthritis. Semin Immunopathol. 2017;39(4):437-446 8. Hedstrom AK, Ronnelid J, Klareskog L, Alfredsson L. Complex relationships of smoking, HLA-DRB1 genes, and serologic profiles in patients with early rheumatoid arthritis: Update from a Swedish population-based case-control study. Arthritis Rheumatol. 2019;71(9):1504-1511 9. Verheul MK, Bohringer S, van Delft MAM, et al. Triple positivity for anti-citrullinated protein autoantibodies, rheumatoid factor, and anti-carbamylated protein antibodies conferring high specificity for rheumatoid arthritis: Implications for very early identification of at-risk individuals. Arthritis Rheumatol. 2018;70(11):1721-1731 10. Zhu JN, Nie LY, Lu XY, Wu HX. Meta-analysis: compared with anti-CCP and rheumatoid factor, could anti-MCV be the next biomarker in the rheumatoid arthritis classification criteria? Clin Chem Lab Med. 2019;57(11):1668-1679

CYC1
70411

Cyclin D1 Immunostain, Technical Component Only

Clinical Information: Cyclin D1 is a protein that regulates entry of the cell into cell cycle. It drives the transition between G0 and G1 phase. In normal tissues, basal epithelial cells, endothelial cells, and stromal cells are often cyclin D1 positive. As a result of a translocation involving the cyclin D1 gene and IgH, t(11;14), the vast majority of mantle cell lymphomas overexpress cyclin D1. This is a useful feature in the classification of low-grade B-cell lymphomas.

Useful For: Classification of low-grade B-cell lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Salem Amir M, Elfeky MA, Nawar N, Alattar AZ. Prognostic value of combined; Cox-2, cyclin D1 and P21 expression in colorectal cancer (CRC) patients: An immunohistochemical study. Open J Pathol. 2018;8(3):106-121 2. Parvin T, Das C, Choudhury M, Chattopadhyay BK, Mukhopadhyay M. Prognostic utility of cyclin D1 in invasive breast carcinoma. Indian J Surg Oncol. 2019;10(1):167-173 3. Li Z, Liu J, Zhang X, et al.: Prognostic significance of cyclin D1 expression in renal cell carcinoma: a systematic review and meta-analysis. Pathol Oncol Res. 2020;26(3):1401-1409 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FFLEX
90085

Cyclobenzaprine (Flexeril)

Reference Values:
Reference Range: 10 - 30 ng/mL

CYCL
81506

Cyclospora Stain, Feces

Clinical Information: Cyclospora cayetanensis is an apicomplexan protozoan parasite that causes watery diarrhea, anorexia, malaise, and weight loss.(1) The extent of symptoms depends on the age and health of the host and the infectious dose of oocysts. The infection is usually self-limited, but symptoms can be severe and prolonged, particularly in immunocompromised patients. Cyclosporal diarrheal disease is endemic in many parts of the world, including parts of Asia, India, Southeast Asia, and Latin America. Although most cases of cyclosporiasis have been seen in travelers to developing countries, outbreaks in the United States are now seen each year associated with contaminated fruits and vegetables from Latin America. Transmission is via ingestion of fecally contaminated food or water. If untreated, symptoms may last for several weeks and may follow a relapsing course. The infection usually responds to treatment with a sulfamethoxazole-trimethoprim drug combination. C cayetanensis oocysts are traditionally detected by modified acid-fast staining in which the oocysts stain bright pink red.(1,2) However, the modified safranin stain has been shown to provide increased sensitivity over the modified acid-fast method and produces a more rapid result. It is the method used in the Mayo Clinic Parasitology Laboratory to detect C cayetanensis oocysts in fecal sediment. For more information about diagnostic tests that may be of value in evaluating patients with diarrhea see the following: -Laboratory Testing for Infectious Causes of Diarrhea -Parasitic Investigation of Stool Specimens Algorithm

Useful For: Identifying Cyclospora cayetanensis as a cause of infectious gastroenteritis

Interpretation: A report of "Cyclospora cayetanensis detected" indicates the presence of this parasite in the patient's feces.

Reference Values:
Negative
If positive, reported as Cyclospora cayetanensis detected.

Clinical References:

CYSPR
35143

Cyclosporine, Blood

Clinical Information: Cyclosporine is a lipophilic polypeptide used to prevent rejection after solid organ transplantation; it suppresses T-cell activation by inhibiting calcineurin to decrease interleukin-2 (IL-2) production. There is substantial interpatient variability in absorption, half-life, and other pharmacokinetic parameters. Cyclosporine is extensively metabolized by cytochrome P450 (CYP) 3A4 to at least 30 less-active metabolites, many of which are detected by immunoassays. Cyclosporine is known for many drug interactions, including increased neuro- and nephrotoxicity when coadministered with antibiotics, antifungals, or other immunosuppressants. Cyclosporine has a narrow therapeutic range with frequent adverse effects making therapeutic drug monitoring essential. With 80% of cyclosporine sequestered in erythrocytes, whole blood is the preferred specimen for analysis. Dose is adjusted initially (up to 2 months posttransplant) to maintain concentrations generally between 150 and 400 ng/mL. Target trough concentrations vary according to clinical protocol and depend on type of allograft, risk of rejection, concomitant immunosuppressive drugs, and toxicity. After the first 2 postoperative months, the target range is generally lower, between 75 and 300 ng/mL. Conversion between formulations is generally done at the same dose but with drug monitoring.

Useful For: Monitoring whole blood cyclosporine concentration during therapy, particularly in individuals coadministered cytochrome P450 (CYP) 3A4 substrates, inhibitors, or inducers Adjusting dose to optimize immunosuppression while minimizing toxicity Evaluating patient compliance

Interpretation: Most individuals display optimal response to cyclosporine with trough whole blood levels 100 to 400 ng/mL. Preferred therapeutic ranges may vary by transplant type, protocol, and comedications. Therapeutic ranges are based on specimens collected at trough (ie, immediately before the next scheduled dose). Higher results will be obtained when the blood is drawn at other times. This test may also be used to analyze cyclosporine levels 2 hours after dosing (C2 concentrations); trough therapeutic ranges do not apply to C2 specimens. The assay is specific for cyclosporine; it does not cross-react with cyclosporine metabolites, sirolimus, sirolimus metabolites, tacrolimus, or tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry are approximately 30% less than by immunoassay.

Reference Values:
100-400 ng/mL (trough)

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time posttransplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.

Clinical References: 1. Moyer TP, Post GR, Sterioff S, Anderson CF. Cyclosporine nephrotoxicity is minimized by adjusting dosage on the basis of drug concentration in blood. Mayo Clin Proc. 1988;63(3):241-247 2. Kahan BD, Keown P, Levy GA, Johnston A. Therapeutic drug monitoring of immunosuppressant drugs in clinical practice. Clin Ther. 2002;24(3):330-350 3. Dunn CJ, Wagstaff AJ, Perry CM, Plosker GL, Goa KL: Cyclosporin: an updated review of the pharmacokinetic properties, clinical efficacy, and tolerability of a microemulsion-based formulation (neoral) 1 in organ transplantation. Drugs. 2001;61(13):1957-2016 4. Milone MC, Shaw LM: Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

CYCPK
42427

Cyclosporine, Peak, Blood

Clinical Information: Cyclosporine is a lipophilic polypeptide used to prevent rejection after solid organ transplantation; it suppresses T-cell activation by inhibiting calcineurin to decrease interleukin-2 (IL-2) production. There is substantial interpatient variability in absorption, half-life, and other pharmacokinetic parameters. Cyclosporine is extensively metabolized by cytochrome P450 (CYP) 3A4 to at least 30 less-active metabolites, many of which are detected by immunoassays. Cyclosporine is known for many drug interactions, including increased neuro- and nephrotoxicity when coadministered with antibiotics, antifungals, or other immunosuppressants. Cyclosporine has a narrow therapeutic range with frequent adverse effects making therapeutic drug monitoring essential. With 80% of cyclosporine sequestered in erythrocytes, whole blood is the preferred specimen for analysis.

Useful For: Monitoring whole blood peak cyclosporine concentration during therapy, particularly in individuals coadministered cytochrome P450 (CYP) 3A4 substrates, inhibitors, or inducers Adjusting dose to optimize immunosuppression while minimizing toxicity Evaluating patient compliance

Interpretation: No definitive therapeutic or toxic ranges have been established for postdose peak monitoring. Preferred therapeutic ranges may vary by transplant type, protocol, and comedications. The 2-hour postdose cyclosporine ranges listed for this test are only suggested guidelines. This assay is specific for cyclosporine; it does not cross-react with cyclosporine metabolites, sirolimus, sirolimus

metabolites, tacrolimus, or tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry are approximately 30% less than by immunoassay.

Reference Values:
No definitive therapeutic or toxic ranges have been established.

Optimal blood drug levels are influenced by type of transplant, patient response, time posttransplant, coadministration of other drugs, and drug formulation.

The following 2-hour postdose cyclosporine ranges are only suggested guidelines:
Kidney transplant: 800-1700 ng/mL
Liver transplant: 600-1000 ng/mL

Target steady-state peak concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time posttransplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.

Clinical References: 1. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453 2. Moyer TP, Post GR, Sterioff S, Anderson CF. Cyclosporine nephrotoxicity is minimized by adjusting dosage on the basis of drug concentration in blood. Mayo Clin Proc. 1988;63(3):241-247 3. Kahan BD, Keown P, Levy GA, Johnston A. Therapeutic drug monitoring of immunosuppressant drugs in clinical practice. Clin Ther. 2002;24(3):330-350 4. Dunn CJ, Wagstaff AJ, Perry CM, Plosker GL, Goa KL. Cyclosporin: an updated review of the pharmacokinetic properties, clinical efficacy, and tolerability of a microemulsion-based formulation (neoral) 1 in organ transplantation. Drugs. 2001;61(13):1957-2016

2D66Z
610616

CYP2D6 3' Gene Duplication/Multiplication (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

2D65Z
610615

CYP2D6 5' Gene Duplication/Multiplication (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

2D62Z
610612

CYP2D6 Gene CYP2D6-2D7 Hybrid (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

2D63Z
610613

CYP2D6 Gene CYP2D7-2D6 Hybrid (Bill Only)

Reference Values:
This test is for billing purposes only.

This is not an orderable test.

2D64Z
610614

CYP2D6 Nonduplicated Gene (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

CSTCE
614154

Cystatin C with Estimated Glomerular Filtration Rate (eGFR), Serum

Clinical Information: Cystatin C is a low-molecular weight (13,250 Da) cysteine proteinase inhibitor that is produced by all nucleated cells and found in body fluids, including serum. Since it is formed at a constant rate and freely filtered by the kidneys, its serum concentration is inversely correlated with the glomerular filtration rate (GFR); ie, a high concentration indicates a low GFR, while a lower concentration indicates a higher GFR, similar to creatinine. The renal handling of cystatin C differs from creatinine. While both are freely filtered by glomeruli, once filtered, cystatin C, unlike creatinine, is reabsorbed and metabolized by proximal renal tubules. Therefore, under normal conditions, cystatin C does not enter the final excreted urine to any significant degree. The serum concentration of cystatin C is not greatly affected by body mass, age, sex, or race. Thus, in certain cases, cystatin C may be a more reliable marker of kidney function (ie, GFR) than creatinine. GFR can be estimated (eGFR) from serum cystatin C utilizing an equation that includes the age and sex of the patient. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C equation was developed by Inker et al(1) and demonstrated good correlation with measured iothalamate clearance in patients with all common causes of kidney disease, including kidney transplant recipients. Cystatin C eGFR may have advantages over creatinine eGFR in certain patient groups whose muscle mass is abnormally high or low (for example quadriplegics, much older adults, or malnourished individuals). Blood levels of cystatin C also equilibrate more quickly than creatinine, and therefore, serum cystatin C may be more accurate than serum creatinine when kidney function is rapidly changing (eg, amongst hospitalized individuals).(2) The same group also developed an eGFR equation that uses serum creatinine and cystatin C, in addition to age, sex, and race.(1) This equation may be useful to average out potential confounders of creatinine versus cystatin C.

Useful For: Assessing kidney function in patients suspected of having kidney disease Monitoring treatment response in patients with kidney disease An index of glomerular filtration rate (GFR), especially in patients where serum creatinine may be misleading (eg, very obese, older adults, or malnourished patients) Calculation of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C estimated GFR for patients where serum creatinine may be misleading (eg, very obese, older adults, or malnourished patients)

Interpretation: Cystatin C: Cystatin C inversely correlates with the glomerular filtration rate (GFR), that is, elevated levels of cystatin C indicate decreased GFR. Cystatin C may provide more accurate assessment of GFR for very obese, older adults, or malnourished patients than creatinine. Cystatin C equation does not require patient ethnic data and can be used for those patients with this information unavailable. Due to immaturity of kidney function, cystatin C levels are higher in neonates less than 3 months of age.(3) Estimated GFR: Chronic kidney disease (CKD) is defined as the presence of persistent and usually progressive reduction in GFR (GFR <60 mL/min/1.73 m[2]) and/or albuminuria (>30 mg of urinary albumin per gram of urinary creatinine), regardless of GFR. According to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) classification, among patients with CKD, irrespective of diagnosis, the stage of disease should be assigned based on the level of kidney function.(4) Table. Kidney Disease: Improving Global Outcomes (KDIGO)

guidelines provide the following GFR categories Stage Description GFR mL/min/BSA 1 Kidney damage with normal or increased GFR 90 2 Kidney damage with mild decrease in GFR 60-89 3A Mild to moderate decrease in GFR 45-59 3B Moderate to severe decrease in GFR 30-44 4 Severe decrease in GFR 15-29 5 Kidney failure <15 (or dialysis)

Reference Values:

CYSTATIN C:
18-49 years: 0.63-1.03 mg/L
> or =50 years: 0.67-1.21 mg/L
0-17 years: Reference values have not been established. Refer to estimated glomerular filtration rate (eGFR).

ESTIMATED GFR:
>60 mL/min/BSA (body surface area)
Adult eGFR: Estimated GFR calculated using CKD-EPI Cystatin C equation.(1)
Pediatric eGFR: Estimated GFR calculated using Schwartz Cystatin C equation.(12)

Clinical References: 1. Inker LA, Schmid CH, Tighiouart H, et al; CKD-EPI Investigators: Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012 Jul;367(1):20-29. doi: 10.1056/NEJMoa1114248 2. Frazee E, Rule AD, Lieske JC, et al: Cystatin C-guided vancomycin dosing in critically ill patients: a quality improvement project. Am J Kidney Dis. 2017 May;69(5):658-666. doi: 10.1053/j.ajkd.2016.11.016 3. Buehrig CK, Larson TS, Bergert JH, et al: Cystatin C is superior to serum creatinine for the assessment of renal function. J Am Soc Nephrol. 2001;12:194A 4. Inker LA, Astor BC, Fox CH, et al: KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD. Am J Kidney Dis. 2014 May;63(5):713-735. doi: 10.1053/j.ajkd.2014.01.416 5. Grubb AO: Cystatin C--properties and use as a diagnostic marker. Adv Clin Chem. 2000;35:63-99. doi: 10.1016/s0065-2423(01)35015-1 6. Coll E, Botey A, Alvarez L, et al: Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment. Am J Kidney Dis. 2000 Jul;36(1):29-34. doi: 10.1053/ajkd.2000.8237 7. Larsson A, Hansson LO, Flodin M, Katz R, Shlipak MG: Calibration of the Siemens cystatin C immunoassay has changed over time. Clin Chem. 2011 May;57(5):777-778. doi: 10.1373/clinchem.2010.159848 8. Voskoboev NV, Larson TS, Rule AD, Lieske JC: Importance of cystatin C assay standardization. Clin Chem. 2011 Aug;57(8):1209-1211. doi: 10.1373/clinchem.2011.164798 9. Nitsch D, Sandling JK, Byberg L et al: Fetal, developmental, and parental influences on cystatin C in childhood: the Uppsala Family Study. Am J Kidney Dis. 2011 Jun;57(6):863-872. doi: 10.1053/j.ajkd.2010.12.025 10. Voskoboev NV, Larson TS, Rule AD, Lieske JC: Analytic and clinical validation of a standardized cystatin C particle enhanced turbidimetric assay (PETIA) to estimate glomerular filtration rate. Clin Chem Lab Med. 2012 Mar;50(9):1591-1596. doi: 10.1515/cclm-2012-0063 11. Finney H, Newman DJ, Thakkar H, Fell JM, Price CP: Reference ranges for the plasma cystatin C and creatinine measurements in premature infants, neonates, and older children. Arch Dis Child. 2000 Jan;82(1):71-75. doi: 10.1136/adc.82.1.71 12. Schwartz GJ, Schneider MF, Maier PS, et al: Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int. 2012 Aug;82(4):445-453. doi: 10.1038/ki.2012.169

CFSMN
608349

Cystic Fibrosis and Spinal Muscular Atrophy Carrier Screen Panel, Varies

Clinical Information:

Useful For: Reproductive risk refinement via carrier screening for individuals in the general population for cystic fibrosis (CF) and spinal muscular atrophy (SMA). Reproductive risk refinement via carrier

screening for individuals with a family history of CF and/or SMA when familial variants are not available This test is not useful for clinical diagnosis of an affected individual.

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(4) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Langfelder-Schwind E, Karczeski B, Strecker MN, et al. Molecular testing for cystic fibrosis carrier status practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2014;23(1):5-15. doi:10.1007/s10897-013-9636-9 2. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet. 2012;20(1):27-32. doi:10.1038/ejhg.2011.134 3. Luo M, Liu L, Peter I, et al. An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy. Genet Med. 2014;16:149-156. doi:10.1038/gim.2013.84 4. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30 5. Carrier Testing for Cystic Fibrosis. Cystic Fibrosis Foundation; Accessed April 9, 2025. Available at www.cff.org/What-is-CF/Testing/Carrier-Testing-for-Cystic-Fibrosis/ 6. Deignan JL, Gregg AR, Grody WW, et al. Updated recommendations for CFTR carrier screening: A position statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023;25(8):100867. doi:10.1016/j.gim.2023.100867. 7. Prior TW. Professional Practice and Guidelines Committee: Carrier screening for spinal muscular atrophy. Genet Med. 2008;10:840-842. doi:10.1097/GIM.0b013e318188d069 9: Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol. 2017;129(3):e41-e55. doi:10.1097/AOG.0000000000001952 10: Gregg AR, Aarabi M, Klugman S, et al. ACMG Professional Practice and Guidelines Committee: Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(10):1793-1806. doi:10.1038/s41436-021-01203-z

CFTRN 619774 Cystic Fibrosis Transmembrane Conductance Regulator, CFTR, Full Gene Analysis, Varies

Clinical Information: Cystic fibrosis (CF), in the classic form, is a severe autosomal recessive disorder characterized by a varying degree of chronic obstructive lung disease and pancreatic enzyme insufficiency.(1) Clinical diagnosis is generally made based on these features, combined with a positive sweat chloride test or positive nasal potential difference.(1) CF can also have an atypical presentation (CFTR-related disorder [CFRD] or CFTR-related metabolic syndrome [CRMS]) and may manifest solely as congenital absence of the vas deferens or chronic idiopathic pancreatitis.(2) Several states have implemented newborn screening for CF, which identifies potentially affected individuals by measuring immunoreactive trypsinogen in a dried blood specimen collected on filter paper.(3) To date, over 2000 variants have been described within the cystic fibrosis transmembrane conductance regulator (CFTR) gene that can cause CF.(3) The most common variant, deltaF508, accounts for approximately 67% of the variants worldwide and approximately 70% to 75% in the North American White population.(4) Most of the remaining variants are rare, although some show a relatively higher prevalence in certain ancestries or in some atypical presentations of CF, such as CFRD or CRMS. If a clinical diagnosis of CF has been made or is suspected, full gene analysis of the CFTR gene may be utilized instead to genetically confirm the diagnosis. Full gene and deletion/duplication analysis of the CFTR gene can

identify over 98% of the sequence variants in the coding region and splice junctions. Of note, CFTR potentiator therapies may improve clinical outcomes for patients with a clinical diagnosis of CF and at least one copy of a select subset of variants.(3)

Useful For: Follow-up testing to identify variants in individuals with a clinical diagnosis of cystic fibrosis (CF) Identifying genetic variants in individuals with atypical presentations of CF (eg, congenital bilateral absence of the vas deferens or pancreatitis) Identifying genetic variants in individuals where detection rates by targeted variant analysis are low or unknown for their ancestral background Identifying patients who may respond to cystic fibrosis transmembrane conductance regulator (CFTR) potentiator therapy

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Ong T, Marshall SG, Karczeski BA, et al: Cystic fibrosis and congenital absence of the vas deferens. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2001. Updated November 10, 2022. Accessed January 20, 2023. Available at: www.ncbi.nlm.nih.gov/books/NBK1250/ 2. Bombieri C, Claustres M, De Boeck K, et al: Recommendations for the classification of diseases as CFTR-related disorders. J Cyst Fibros. 2011 Jun;10 Suppl 2:S86-102 3. Link SL, Nayak RP: Review of rapid advances in cystic fibrosis. Mo Med. 2020 Nov-Dec;117(6):548-554 4. Bobadilla JL, Macek M Jr, Fine JP, Farrell PM: Cystic fibrosis: a worldwide analysis of CFTR murations--correlation with incidence data and application to screening. Hum Mutat. 2002 Jun;19(6):575-606 5. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

CFMP
605197

Cystic Fibrosis, CFTR Gene, Variant Panel, Varies

Clinical Information: Cystic fibrosis (CF), in the classic form, is a severe autosomal recessive disorder characterized by a varied degree of chronic obstructive lung disease and pancreatic enzyme insufficiency. The incidence of CF varies markedly among different populations, as does the genetic variant detection rate for the variant screening assay. To date, over 1500 variants have been described within the gene that causes CF, named cystic fibrosis transmembrane conductance regulator (CFTR). The most common variant, deltaF508, accounts for approximately 67% of the variants worldwide and approximately 70% to 75% in the North American White population. Most of the remaining variants are rare, although some show a relatively higher prevalence in certain ethnic groups or in certain atypical presentations of CF, such as congenital bilateral absence of the vas deferens (CBAVD). Genetic variants detected by this assay include the 23 variants recommended by the American College of Medical Genetics and Genomics as well as over 450 other variants. Of note, CFTR potentiator therapies may improve clinical outcomes for patients with a clinical diagnosis of CF and at least one copy of a select subset of variants. See the CF Detection rates table for several ethnic and racial group carrier frequency and variant detection rate. Note that interpretation of test results and risk calculations are also dependent on clinical information and family history. Table. CF Detection Rates Racial or ethnic group Carrier frequency Variant detection rate* European American 1/25 94% Ashkenazi Jewish 1/25 95% African American 1/65 87% Hispanic American 1/46 87% Asian American** 1/90 65% General US population 1/35 86% *Rates are for classic CF. Rates are lower for atypical forms of CF and for CBAVD. **Does not apply to

individuals of Japanese ancestry. A list of CFTR variants included in the panel can be found in Targeted Variants Interrogated by Cystic Fibrosis Variant Panel.

Useful For: Confirmation of a clinical diagnosis of cystic fibrosis Reproductive risk refinement via carrier screening for individuals in the general population Reproductive risk refinement via carrier screening for individuals with a family history when familial variants are not available Identification of patients who may respond to cystic fibrosis transmembrane conductance regulator (CFTR) potentiator therapy

Interpretation: All reported alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi: 10.1038/gim.2015.30 2. Quint A, Lerer I, Sagi M, Abeliovich D. Mutation spectrum in Jewish cystic fibrosis patients in Israel: implication to carrier screening. Am J Med Genet A. 2005;136(3):246-248 3. Bobadilla JL, Macek M Jr, Fine JP, Farrell PM. Cystic fibrosis: a worldwide analysis of CFTR mutations-correlation with incidence data and application to screening. Hum Mutat. 2002;19(6):575-606 4. Sugarman EA, Rohlfs EM, Silverman LM, Alitto BA. CFTR mutation distribution among U.S. Hispanic and African American individuals: evaluation in cystic fibrosis patient and carrier screening populations. Genet Med. 2004;6(5):392-399 5. Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med. 2004;6(5):387-391 6. Heim RA, Sugarman EA, Allitto BA. Improved detection of cystic fibrosis mutations in the heterozygous U.S. population using an expanded, pan-ethnic mutation panel. Genet Med. 2001;3(3):168-176 7. De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. J Cyst Fibros. 2014;13(6):674-680 8. Carrier Testing for Cystic Fibrosis. Cystic Fibrosis Foundation; Accessed November 14, 2024. Available at www.cff.org/What-is-CF/Testing/Carrier-Testing-for-Cystic-Fibrosis/

CKDGP
618072

Cystic Kidney Disease Gene Panel, Varies

Clinical Information: Hereditary forms of cystic kidney disease have several underlying genetic etiologies and may present in childhood or adulthood, with or without extrarenal features. The two most common categories of hereditary cystic kidney disease are the ciliopathic disorders and the phakomatoses.(1) Ciliopathic disorders causing cystic kidney disease include polycystic kidney disease (PKD), nephronophthisis (NPHP), and medullary cystic kidney disease (MCKD). The PKD1 and PKD2 genes cause the majority of autosomal dominant PKD (ADPKD), while the GANAB and DNAJB11 genes are implicated in a minority of cases.(2,3) The PKHD1 gene is the major gene associated with autosomal recessive PKD (ARPKD), while DZIP1L has been more recently identified as a secondary cause.(4) ARPKD is often diagnosed in utero due to oligohydramnios. NPHP is an autosomal recessive condition characterized by cystic kidney disease, inflammation, fibrosis, and progression to kidney failure. MCKD is an autosomal dominant condition characterized by cysts in the medullary region of the kidney, kidney tubule fibrosis, hyperuricemia, and slowly worsening kidney function. Genes included on this panel for MCKD include HNF1B, UMOD, and SEC61A1 (note the MUC1 gene is not included on this panel). Phakomatoses, also known as neurocutaneous syndromes, are a broad group of hereditary disorders characterized by involvement of structures that arise from the embryonic ectoderm

(central nervous system, skin, and eyes). Cystic renal lesions are common in these disorders. Phakomatoses genes included on this panel are the TSC1 and TSC2 tumor suppressor genes associated with tuberous sclerosis complex (TSC) and the VHL gene associated with von Hippel-Lindau syndrome.

Useful For: Providing a genetic evaluation for patients with a personal or family history of cystic kidney disease Establishing a diagnosis of hereditary cystic kidney disease

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Dillman JR, Trout AT, Smith EA, Towbin AJ: Hereditary renal cystic disorders: Imaging of the kidneys and beyond. Radiographics. May-Jun 2017;37(3):924-946. doi: 10.1148/rg.2017160148 2. Porath B, Gainullin VG, Cornec-Le Gall E, et al: Mutations in GANAB, encoding the glucosidase IIa subunit, cause autosomal-dominant polycystic kidney and liver disease. Am J Hum Genet. 2016 Jun 2;98(6):1193-1207. doi: 10.1016/j.ajhg.2016.05.004 3. Cornec-Le Gall E, Olson RJ, Besse W, et al: Monoallelic mutations to DNAJB11 cause atypical autosomal-dominant polycystic kidney disease. Am J Hum Genet. 2018 May 3;102(5):832-844. doi: 10.1016/j.ajhg.2018.03.013 4. Lu H, Rondon Galeano M, Ott E, et al: Mutations in DZIP1L, which encodes a ciliary-transition-zone protein, cause autosomal recessive polycystic kidney disease. Nat Genet. 2017 Jul;49(7):1025-1034. doi: 10.1038/ng.3871 5. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424. doi: 10.1038/gim.2015.30

CYSTG
616730

Cysticercosis (Taenia solium), IgG, Serum

Clinical Information: Cysticercosis is caused by infection with Taenia solium, a tapeworm (cestode). In this form of infection, humans and pigs serve as the intermediate host and have the cystic larval form in their tissues. Humans can also serve as the definitive host for T solium and have the adult form in their intestine (known as taeniasis). Humans acquire cysticercosis by ingesting microscopic T solium eggs in contaminated food, water, or on fomites. The eggs enter the environment when they are shed in stool from a person with the intestinal form of infection; this could be the same patient (autoinfection) or a different patient. Once ingested, the eggs hatch in the intestine to release oncospheres, which invade the intestinal wall and disseminate via the blood to muscles, liver, brain, and other tissues where they form cysts (cysticerci). Taeniasis occurs when cysticerci are ingested in the undercooked flesh of an infected intermediate host (eg, pig). In the small intestine, cysticerci will evaginate and attach via a scolex to the intestinal wall. They then grow to become mature adult tapeworms. Adults can reside in the intestine for years and grow from 2 to 7 meters with over 500 proglottids, each filled with 50,000 eggs. While cysticercosis and taeniasis occur globally, in the United States, infections are predominantly encountered in immigrants from Latin and Central America who acquired the infection locally. The symptoms associated with cysticercosis depend on where the cysticerci localize, their size, number, and stage (degenerating, calcified, etc). The time between initial infection and symptom onset may vary from several months to years. The presence of cysts in the brain or spinal cord, referred to as neurocysticercosis, is the most serious form of disease and, while some individuals may be asymptomatic, many present with seizures (70%-90%), headache, confusion, and difficulty with balance. Cysts present in striated muscle are typically asymptomatic. Diagnosis of cysticercosis relies on both imaging studies and serologic testing results. Importantly, detection of T solium eggs or proglottids in stool by an ova and

parasite exam is diagnostic for taeniasis, not cysticercosis. Individuals with taeniasis should be evaluated for cysticercosis by serology since autoinfection can occur. Due to imperfect sensitivity and specificity of commercially available enzyme-linked immunosorbent assays (ELISA) for cysticercosis, it is recommended that both positive and negative results by commercial ELISA be confirmed by a cysticercosis immunoblot offered through the Centers for Disease Control and Prevention (www.cdc.gov/dpdx/cysticercosis/index.html) for patients strongly suspected of having cysticercosis. Currently available antibody detection assays are unable to distinguish between active and inactive infections.

Useful For: Aid for the diagnosis of cysticercosis caused by infection with Taenia solium

Interpretation: Positive: Antibodies to Taenia solium (cysticercosis) detected. Confirmatory testing through the Centers for Disease Control and Prevention is recommended. False-positive results may occur in patients with other helminth infections. Negative: No antibodies to T solium (cysticercosis) detected. A negative result may not rule-out infection as the sample may have been collected prior to the development of a detectable level of antibodies. Sensitivity is negatively impacted by the presence of few cysticerci or location in areas less accessible to the immune system. Repeat testing on a new sample is recommended for patients at high risk of cysticercosis.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Garvey BT, Moyano LM, Ayvar V, et al: Neurocysticercosis among people living near pigs heavily infected with cysticercosis in rural endemic Peru. Am J Trop Med Hyg. 2018;98(2):558-564 2. Garcia HH, Gonzalez AE, Gilman RH. Taenia solium cysticercosis and its impact in neurological disease. Clin Microbiol Rev. 2020;33(3):e00085-19. doi:10.1128/CMR.00085-19

FCAEC
75587

Cysticercus Antibody (IgG), ELISA, CSF

Clinical Information:

Reference Values:
Reference Range: <0.75

Interpretive Criteria:
<0.75 Antibody Not Detected
> or =0.75 Antibody Detected

Diagnosis of central nervous system infections can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpretation of results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps. Antibodies to other parasitic infections, particularly echinococcosis, may crossreact in the cysticercus IgG ELISA. Confirmation of positive ELISA results by the cysticercus IgG antibody Western blot is thus recommended.

CYSGP
608027

Cystinuria Gene Panel, Varies

Clinical Information: Cystinuria is an inborn error of metabolism resulting from poor absorption and reabsorption of the amino acid cystine in the intestines and kidneys. This leads to an accumulation

of poorly soluble cystine and dibasic amino acids (lysine, arginine, and ornithine) in the urine and results in the production of kidney stones (urolithiasis). Symptoms may include acute episodes of abdominal or lower back pain, presence of blood in the urine (hematuria), and recurrent episodes of kidney stones may result in frequent urinary tract infections, which may ultimately result in renal insufficiency. The combined incidence of cystinuria has been estimated to be 1 in 7000. Cystinuria is an autosomal recessive disease, but some heterozygous carriers have an autosomal dominant, incomplete penetrance appearance with elevated, but typically benign, urinary cystine and dibasic amino acid excretion. Some heterozygotes do tend to have higher levels of lysine and cystine versus arginine and ornithine as compared to patients with homozygous variants, who excrete large amounts of cysteine and all 3 dibasic amino acids. Cystinuria is caused by variants in genes, SLC3A1 and PREPL on chromosome 2p and SLC7A9 on chromosome 19q. Initially, the disease was classified into subtypes I, II, and III (type II and III are also referred as nontype I) based on the amount of urinary cystine excreted in heterozygous parental specimens. A new classification system has been proposed to distinguish the various forms of cystinuria: type A, due to variants in the SLC3A1 gene; type B, due to variants in the SLC7A9 gene; and type AB, due to 1 variant in each SLC3A1 and SLC7A9 gene. A contiguous gene deletion involving both SLC3A1 and PREPL gene is associated with an autosomal recessive hypotonia-cystinuria syndrome, presenting with dysmorphic features, severe neonatal hypotonia, myasthenic syndrome, failure to thrive in infancy with transition to hyperphagia in late childhood, and nephrolithiasis with excretion of cystine, lysine, arginine, and ornithine. Variants in the PREPL gene are associated with autosomal recessive congenital myasthenic syndrome 22 (CMS22), which does not present with cystinuria. Urinary measurement of cystine, lysine, ornithine, and arginine (CYSQN / Cystinuria Profile, Quantitative, 24 Hour, Urine or CYSR / Cystinuria Profile, Quantitative, Random, Urine) is recommended as a first-tier test to screen for cystinuria prior to molecular genetics testing. Treatment/management options for cystinuria include a high fluid intake, alkali and dietary modifications, and administration of oral tiopronin to prevent formation of cystine stones.

Useful For: Follow up for abnormal biochemical results suggestive of cystinuria Establishing a molecular diagnosis for patients with cystinuria Identifying variants within genes known to be associated with cystinuria, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

CYSQN
8376

Cystinuria Profile, Quantitative, 24 Hour, Urine

Clinical Information: Cystinuria is an inborn error of metabolism resulting from poor absorption and reabsorption of the amino acid cystine in the intestines and kidneys. This leads to an accumulation of poorly soluble cystine in the urine and results in the production of kidney stones (urolithiasis). Symptoms may include acute episodes of abdominal or lower back pain and the presence of blood in the urine (hematuria). Recurrent episodes of kidney stones may result in frequent urinary tract infections, which may ultimately result in renal insufficiency. The combined incidence of cystinuria has been estimated to be 1 in 7000. Cystinuria is an autosomal recessive disease, but some heterozygous carriers have an autosomal dominant, incomplete penetrance appearance with elevated, but typically nondisease-causing, urinary cystine excretion. Cystinuria is caused by variants in genes, SLC3A1 on the short arm of chromosome 2 and SLC7A9 on the long arm of chromosome 19. Initially, the disease was classified into

subtypes I, II, and III (type II and III are also referred as non-type I) based on the amount of urinary cystine excreted in heterozygous parental specimens. A new classification system has been proposed to distinguish the various forms of cystinuria: type A, due to variants in the SLC3A1 gene; type B, due to variants in the SLC7A9 gene; and type AB, due to 1 variant in each SLC3A1 and SLC7A9 gene.

Useful For: Diagnosis of cystinuria using 24-hour urine collections

Interpretation: Individuals who are homozygous or compound heterozygous for cystinuria excrete large amounts of cystine in urine, but the amount varies markedly. Urinary excretion of other dibasic amino acids (arginine, lysine, and ornithine) is also typically elevated. Plasma concentrations are generally normal or slightly decreased. Individuals who are homozygous and heterozygous for non-type I cystinuria can be distinguished by the pattern of urinary amino acids excretion: homozygous individuals secrete large amounts of cystine and all 3 dibasic amino acids, whereas heterozygous individuals secrete more lysine and cystine than arginine and ornithine.

Reference Values:

Cystine
3-15 years: < or =53 mcmol/24 h
> or =16 years: < or =115 mcmol/24 h

Lysine
3-15 years: < or =140 mcmol/24 h
> or =16 years: < or =290 mcmol/24 h

Ornithine
3-15 years: < or =16 mcmol/24 h
> or =16 years: < or =70 mcmol/24 h

Arginine
3-15 years: < or =25 mcmol/24 h
> or =16 years: < or =64 mcmol/24 h

Conversion Formulas:
Result in mcmol/24 hours x 0.24 =result in mg/24 h
Result in mg/24 hours x 4.17 =result in mcmol/24 h

Clinical References: 1. Servais A, Thomas K, Strologo LD, et al. Cystinuria: clinical practice recommendation. Kidney Int. 2021;99(1):48-58 2. Palacin M, Goodyer P, Nunes V, Gasparini P. Cystinuria. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed October 24, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225555540

CYSR
81067

Cystinuria Profile, Quantitative, Random, Urine

Clinical Information: Cystinuria is an inborn error of metabolism resulting from poor absorption and reabsorption of the amino acid cystine in the intestines and kidneys. This leads to an accumulation of poorly soluble cystine in the urine and results in the production of kidney stones (urolithiasis). Symptoms may include acute episodes of abdominal or lower back pain and the presence of blood in the urine (hematuria). Recurrent episodes of kidney stones may result in frequent urinary tract infections, which may ultimately result in renal insufficiency. The combined incidence of cystinuria has been estimated to be 1 in 7000. Cystinuria is an autosomal recessive disease, but some heterozygous carriers have an autosomal dominant, incomplete penetrance appearance with elevated, but typically nondisease-

causing, urinary cystine excretion. Cystinuria is caused by variants in genes, SLC3A1 on the short arm of chromosome 2 and SLC7A9 on the long arm of chromosome 19. Initially, the disease was classified into subtypes I, II, and III (type II and III are also referred as non-type I) based on the amount of urinary cystine excreted in heterozygous parental specimens. A new classification system has been proposed to distinguish the various forms of cystinuria: type A, due to variants in the SLC3A1 gene; type B, due to variants in the SLC7A9 gene; and type AB, due to 1 variant in each SLC3A1 and SLC7A9 gene.

Useful For: Biochemical diagnosis of cystinuria using random urine specimens

Interpretation: Individuals who are homozygous or compound heterozygous for cystinuria excrete large amounts of cystine in urine, but the amount varies markedly. Urinary excretion of other dibasic amino acids (arginine, lysine, and ornithine) is also typically elevated. Plasma concentrations are generally normal or slightly decreased. Individuals who are homozygous and heterozygous for non-type I cystinuria can be distinguished by the pattern of urinary amino acids excretion: homozygous individuals secrete large amounts of cystine and all 3 dibasic amino acids, whereas heterozygous individuals secrete more lysine and cystine than arginine and ornithine.

Reference Values:

Amino Acid	Age groups
	2-35 months
Arginine	Arg
Ornithine	Orn
Cystine	Cys
Lysine	Lys

Clinical References: 1. Servais A, Thomas K, Strologo LD, et al. Cystinuria: clinical practice recommendation. Kidney Int. 2021;99(1):48-58 2. Palacin M, Goodyer P, Nunes V, Gasparini P: Cystinuria. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed October 24, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225555540

METR1
65609

Cytochrome b5 Reductase Enzyme Activity, Blood

Clinical Information: Cytochrome b5 reductase (CYB5R), also called methemoglobin reductase, is the enzyme within the erythrocyte that maintains hemoglobin in the reduced (non-methemoglobin) state. A deficiency of CYB5R in erythrocytes is an autosomal recessive disorder resulting from variants in the CYB5R3 or the CYB5A genes. Persons who are heterozygous for CYB5R genetic variants have no clinical or laboratory abnormalities, are not cyanotic, and have normal methemoglobin concentrations in their blood. However, they hold an increased risk for more severely symptomatic acute episodes of methemoglobinemia with exposure to inducing agents. Persons who are homozygous for CYB5R genetic variants have normal arterial oxygen saturation but have varying quantities of methemoglobin in their blood, generally 15% to 20%, and are quite cyanotic. Paradoxically, homozygous individuals typically have normal blood counts; the condition only rarely causes polycythemia. The presence of methemoglobin shifts the hemoglobin-oxygen dissociation curve to the right, so although the transport of oxygen is diminished, the delivery of oxygen to tissues is normal. Because of the chronicity, the homozygous condition is usually compensated and, therefore, quite benign, but it may cause concern to

parents of affected children, be a cosmetic embarrassment to the children, and alarm the attending physician. The cyanosis may be treated with methylene blue.

Useful For: Evaluation of patients with cyanosis Confirming cases of suspected cytochrome b5 reductase (methemoglobin reductase) deficiency Functional studies in families with cytochrome b5 reductase deficiency

Interpretation: Cytochrome b5 reductase (methemoglobin reductase) activity in neonates (0-6 weeks of age) is normally 60% of the normal adult value. Adult values are attained by 2 to 3 months of age. Heterozygotes have results slightly lower than the reference range. Homozygotes demonstrate little to no cytochrome b5 reductase activity and increased levels of methemoglobin.

Reference Values:
> or =12 months of age: 7.8-13.1 U/g Hb
Reference values have not been established for patients who are younger than 12 months.

Clinical References: 1. Agarwal AM, Prchal JT. Methemoglobinemia and other dyshemoglobinemias. In: Kaushansky K, Lichtman MA, Prchal JT, et al, eds. Williams Hematology. 9th ed. McGraw-Hill; 2016:789-800 2. Percy MJ, Barnes C, Crighton G, et al. Methemoglobin reductase deficiency: Novel mutation is associated with a disease phenotype of intermediate severity. J Pediatr Haematol Oncol. 2012;34:457-460

1A2Q
610041

Cytochrome P450 1A2 Genotype, Varies

Clinical Information: The cytochrome P450 (CYP) family is involved in the primary metabolism of many drugs. The CYPs are a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP enzymes, CYP1A2, is wholly or partially responsible for the hydroxylation or dealkylation of many commonly prescribed drugs. CYP1A2-mediated drug metabolism is highly variable. A number of variants have been identified in the CYP1A2 gene that results in increased, diminished, or abolished catalytic activity and substrate metabolism. The frequency of these variants varies by ethnicity. Dosing of drugs that are metabolized through CYP1A2 may require adjustment based on the CYP1A2 genotype. Individuals who are poor metabolizers may require lower than usual doses to achieve optimal response, whereas individuals who are ultrarapid metabolizers may benefit from increased doses. CYP1A2 phenotype is predicted based upon the number of functional, partially functional, nonfunctional, and inducible alleles present in a sample. In the absence of clear guidance on dosing for various metabolizer phenotypes, patients with either rapid or poor metabolism also may benefit by switching to another comparable drug that is not primarily metabolized by CYP1A2 or by therapeutic drug monitoring where applicable. The following table outlines the relationship between the variations (star alleles) detected in this assay and the effect on the activity of the enzyme produced by that allele. CYP1A2 allele Nucleotide change (legacy nomenclature) cDNA nucleotide change (NM_000761.4) Effect on enzyme metabolism(a) *1 None (wild type) None (wild type) Normal (extensive) activity *1F -163C>A c.-9-154C>A Increased inducibility *1K -729C>T c.-10+113C>T Decreased activity and decreased inducibility *6 5090C>T c.1291C>T No activity *7 3533G>A c.1253+1G>A No activity a. Effect of a specific allele on the activity of the CYP1A2 enzyme can only be estimated since the literature does not provide precise data.(1-5) A complicating factor in correlating CYP1A2 genotype to CYP1A2 phenotype is that some drugs or their metabolites are inhibitors of CYP1A2 catalytic activity. These drugs may reduce CYP1A2 catalytic activity. Consequently, an individual may require a dose decrease greater than predicted based upon genotype alone. Another complicating factor is that CYP1A2 is inducible by several drugs and environmental agents (eg, cigarette smoke) and the degree of inducibility is under genetic control. It is important to interpret the results of testing in the context of other coadministered drugs and environmental factors.

Useful For: Identifying individuals who are poor, intermediate, normal (extensive) or rapid metabolizers of drugs metabolized by cytochrome P450 1A2 to assist drug therapy decision making

Interpretation: An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(6) CYP1A2 activity is also dependent upon hepatic function status, as well as age. Renal function may be important for drugs that are excreted in urine. Patients may develop drug toxicity if hepatic or renal function is decreased. Drug metabolism is known to decrease with age. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and age. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Ito M, Katono Y, Oda A, Hirasawa N, Hiratsuka M: Functional characterization of 20 allelic variants of CYP1A2. Drug Metab Pharmacokinet. 2015 Jun;30(3):247-252. doi: 10.1016/j.dmpk.2015.03.001 2. Zhou H, Josephy PD, Kim D, Guengerich FP: Functional characterization of four allelic variants of human cytochrome P450 1A2. Arch Biochem Biophys. 2004 Feb;422(1):23-30. doi: 10.1016/j.abb.2003.11.019 3. Murayama N, Soyama A, Saito Y, et al: Six novel nonsynonymous CYP1A2 gene polymorphisms: catalytic activities of the naturally occurring variant enzymes. J Pharmacol Exp Ther. 2004 Mar;308(3):1219 4. Murayama N, Soyama A, Saito Y, et al: J Pharmacol Exp Ther. 2004;308(1):300-306. doi: 10.1124/jpet.103.055798 5. Saito Y, Hanioka N, Maekawa K, et al. Functional analysis of three CYP1A2 variants found in a Japanese population. Drug Metab Dispos. 2005;33(12):1905-1910. doi: 10.1124/dmd.105.005819 6. PharmVar. Pharmacogene Variation Consortium. Updated March 3, 2021. Accessed March 22, 2021. Available at www.pharmvar.org/

2B6Q
610042

Cytochrome P450 2B6 Genotype, Varies

Clinical Information:

Useful For: Aiding in determining therapeutic strategies for drugs that are metabolized by cytochrome P450 (CYP) 2B6 Providing information relevant to bupropion, efavirenz, ketamine, methadone, and nevirapine, as well as other medications metabolized by CYP2B6 Determining the genotype if genotype-phenotype discord is encountered clinically after testing with a less comprehensive genotyping method has occurred Identifying genotype when required for drug trials and research protocols

Interpretation: An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(1) For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. PharmVar. Pharmacogene Variation Consortium. Updated March 3, 2021. Accessed March 22, 2021. Available at www.pharmvar.org/ 2. Clinical Pharmacogenetics Implementation Consortium (CPIC). Accessed October 14, 2020. Available at https://cpicpgx.org/ 3. Desta Z, Gammal RS, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2B6

and Efavirenz-Containing Antiretroviral Therapy. Clin Pharmacol Ther. 2019;106(4):726-733. doi:10.1002/cpt.1477 4. U.S National Library of Medicine: DailyMed. National Institutes of Health. Accessed October 14, 2020. Available at https://dailymed.nlm.nih.gov/dailymed/index.cfm

2C19R
610043

Cytochrome P450 2C19 Genotype, Varies

Clinical Information: Primary metabolism of many drugs is performed by the cytochrome P450 (CYP) enzymes, a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP enzymes, CYP2C19, participates in the metabolism of a wide variety of drugs, including the activation of the anticoagulant clopidogrel and the inactivation of citalopram. CYP2C19 drug metabolism is variable among individuals. Some individuals have CYP2C19 genetic variants that lead to severely diminished or absent CYP2C19 catalytic activity (ie, poor metabolizers). The frequency of CYP2C19 variants (formerly known as polymorphisms) depends on ethnicity. CYP2C19 variants that produce poor metabolizers are found with frequencies of 2% to 5% in the White population, 4% in African Americans, 13% to 23% in Asians, and 38% to 79% in Polynesians and Micronesians. The following table displays the CYP2C19 variants detected by this assay, the corresponding star allele, and the effect on CYP2C19 enzyme activity. Table. Enzyme Activity of Individual Star Alleles CYP2C19 allele cDNA nucleotide change (NM_000769.1) Effect on enzyme activity *1 None (wild type) Normal (extensive) activity *2 c.681G>A No activity *3 c.636G>A No activity *4 c.1A>G No activity *5 c.1297C>T No activity *6 c.395G>A No activity *7 c.819+2T>A No activity *8 c.358T>C No activity *9 c.431G>A Decreased activity *10 c.680C>T Decreased activity *17 c.-806C>T Enhanced activity *35 c.332-23A>G in the absence of c.681G>A No activity CYP2C19 drug metabolism is dependent on the specific genotype detected and also on the number and type of drugs administered to the patient. Phenotyping is derived from the Pharmacogene Variation Consortium website(1), the Clinical Pharmacogenetics Implementation Consortium website(2), published guidelines(3-8), and an exhaustive review of the CYP2C19 literature(9-10). Individuals without a detectable CYP2C19 variant will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2C19*1/*1. If an individual is homozygous or compound heterozygous for alleles with no activity, the individual is predicted to be a poor metabolizer. If an individual is heterozygous for an allele with no activity, the individual is predicted to be an intermediate metabolizer. Individuals with the CYP2C19*17 allele (in the absence of any inactive or decreased activity alleles) may have enhanced metabolism of drugs. In some cases, a range of potential phenotypes may be given, depending on the combination of alleles identified. Patients who are poor metabolizers may benefit from dose alteration or selection of a comparable drug that is not primarily metabolized by CYP2C19. It is important to interpret the results of testing in the context of other coadministered drugs.

Useful For: Identifying patients who may be at risk for altered metabolism of drugs that are modified by cytochrome P450 2C19 Predicting anticoagulation response to clopidogrel

Interpretation: An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(1) For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Drug-drug interactions and drug-metabolite inhibition must be considered when treating intermediate metabolizers. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. PharmVar: Pharmacogene Variation Consortium. Updated November 5, 2024. Accessed November 14, 2024. Available at www.pharmvar.org/ 2. Clinical Pharmacogenetics Implementation Consortium (CPIC). Updated September 23, 2022. Accessed November 14, 2024. Available at https://cpicpgx.org/ 3. Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther. 2013;94(3):317-323. doi:10.1038/clpt.2013.105 4. Lima JJ, Thomas CD, Barbarino J, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C19 and proton pump inhibitor dosing. Clin Pharmacol Ther. 2021;109(6):1417-1423. doi:10.1002/cpt.2015 5. Moriyama B, Obeng AO, Barbarino J, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP2C19 and voriconazole therapy. Clin Pharmacol Ther. 2017;102(1):45-51. doi:10.1002/cpt.583. Erratum in: Clin Pharmacol Ther. 2018 Feb;103(2):349 6. Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147 7. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597 8. Blaisdell J, Mohrenweiser H, Jackson J, et al. Identification and functional characterization of new potentially defective alleles of human CYP2C19. Pharmacogenetics. 2002;12(9):703-711. doi:10.1097/00008571-200212000-00004 9. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009;360(4):354-362. doi:10.1056/NEJMoa0809171

2C9QT
610044

Cytochrome P450 2C9 Genotype, Varies

Clinical Information: Primary metabolism of many drugs is performed by the cytochrome P450 (CYP) enzymes, a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues, but primarily in the intestines and liver. One of these CYP enzymes, CYP2C9, participates in the metabolism of a wide variety of drugs including warfarin and phenytoin. CYP2C9-mediated drug metabolism is variable among individuals. Some individuals have CYP2C9 genetic variants that lead to severely diminished or absent CYP2C9 catalytic activity (ie, poor metabolizers). These individuals may metabolize various drugs at a slower rate than normal and may require dosing adjustments to prevent adverse drug reactions. A number of specific CYP2C9 variants have been identified that result in enzymatic deficiencies. The following information outlines the relationship between the variants detected in the assay and their effect on enzyme activity: Table. Enzyme Activity of Individual Star Alleles CYP2C9 allele cDNA nucleotide change (NM_000771.3) Effect on enzyme metabolism *1 None (wild type) Normal activity *2 c.430C>T Reduced activity *3 c.1075A>C No activity *4 c.1076T>C Reduced activity *5 c.1080C>G Reduced activity *6 c.818delA No activity *8 c.449G>A Reduced activity *9 c.752A>G Normal activity *11 c.1003C>T Reduced activity *12 c.1465C>T Reduced activity *13 c.269C>T No activity *14 c.374G>A Reduced activity *15 c.485C>A No activity *16 c.895A>G Reduced activity *17 c.1144C>T Reduced activity *18 c.1190A>C No activity *25 c.353_362del No activity *26 c.389C>G Reduced activity *28 c.641A>T Reduced activity *30 c.1429G>A Reduced activity *33 c.395G>A No activity *35 c.374G>T;430C>T No activity CYP2C9 drug metabolism is dependent on the specific genotype detected and also on the number and type of drugs administered to the patient. Phenotyping is derived from the Pharmacogene Variation Consortium website(1), the Clinical Pharmacogenetics Implementation Consortium website (2), published guidelines (3-5), and an exhaustive review of the CYP2C9 literature (6-7). Individuals without a detectable CYP2C9 variant will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2C9 *1/*1. If an individual is homozygous or compound heterozygous for an allele with no activity, the individual is predicted to be a poor metabolizer. If an individual is heterozygous for an allele with no activity, the individual is predicted to be an intermediate metabolizer. In some cases, a range of potential phenotypes may be given, depending on the combination of alleles identified. Patients who are poor metabolizers may benefit from dose alteration or selection of a comparable drug that is not primarily metabolized by CYP2C9. It is important to interpret the results of testing in the context of other coadministered drugs.

Useful For: Identifying individuals who may be at risk for altered metabolism of drugs that are modified by cytochrome P450 2C9

Interpretation: An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(1) For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Drug-drug interactions and drug/metabolite inhibition must be considered in the case of all metabolizer categories except poor metabolizer. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. PharmVar: Pharmacogene Variation Consortium. Updated March 3, 2021. Accessed March 22, 2021. Available at www.pharmvar.org/ 2. Clinical Pharmacogenetics Implementation Consortium (CPIC). Accessed October 14, 2020. Available at https://cpicpgx.org/ 3. Karnes JH, Rettie AE, Somogyi AA, et al: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing: 2020 Update. Clin Pharmacol Ther. 2021 Feb;109(2):302-309. doi: 10.1002/cpt.2008 4. Johnson JA, Caudle KE, Gong L, et al: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther. 2017 Sep;102(3):397-404. doi: 10.1002/cpt.668 5. Theken KN, Lee CR, Gong L, et al: Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther. 2020 Aug;108(2):191-200. doi: 10.1002/cpt.1830 6. Niemi M, Cascorbi I, Timm R, Kroemer HK, Neuvonen PJ, Kivisto KT: Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Clin Pharmacol Ther. 2002;72(3):326-332. doi: 10.1067/mcp.2002.127495 7. Blaisdell J, Jorge-Nebert LF, Coulter S, et al: Discovery of new potentially defective alleles of human CYP2C9. Pharmacogenetics. 2004;14(8):527-537. doi: 10.1097/01.fpc.0000114759.08559.51

2D6Q
610045

Cytochrome P450 2D6 Comprehensive Cascade, Varies

Clinical Information: The cytochrome P450 (CYP) family of enzymes is a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of the CYP enzymes, CYP2D6, is wholly or partially responsible for the metabolism of many commonly prescribed drugs. The CYP2D6 gene is highly variable with over 100 named alleles. The gene may be deleted, duplicated, and multiplied and can have multiple sequence variations. In addition, some individuals have genes that are hybrids of CYP2D6 and the CYP2D7 pseudogene. Some individuals have CYP2D6 variants that result in synthesis of an enzyme with decreased or absent catalytic activity. These individuals may process CYP2D6-metabolized medications more slowly. CYP2D6 duplications and multiplications involving active alleles may result in ultrarapid metabolism of CYP2D6-metabolized drugs. CYP2D6 genotype results are used to predict metabolizer phenotypes.(See Table 1) Table 1. Enzyme Activity of Individual Star Alleles Enzyme activity Examples of CYP2D6 star alleles Normal (extensive) metabolism *1, *2, *35 Decreased activity *9, *10, *14, *17, *29, and *41, *59 No or null activity *3, *4, *4N, *5, *6, *7, *8, *11, *12, *13, *15, *36, *68, *114 CYP2D6 phenotype is predicted based upon the number of functional, partially functional, and nonfunctional alleles present in a sample. Phenotyping is derived from the Pharmacogene Variation Consortium website (1), the Clinical Pharmacogenetics Implementation Consortium website (2), published guidelines (3-8), and an exhaustive review of the CYP2D6 literature (9-10). There are instances where a precise phenotype prediction is not possible, and in these instances, a range of possible phenotypes will be given. Individuals without a detectable gene alteration will have

the predicted phenotype of an extensive drug metabolizer and are designated as CYP2D6*1/*1. Drugs that are metabolized through CYP2D6 may require dosage adjustment based on the individual patient's genotype. Patients who are poor metabolizers may require lower than usual doses to achieve optimal response in the case of drugs that are inactivated by the CYP2D6 enzyme and higher than usual doses in the case of drugs that are activated by CYP2D6 enzyme. Alternatively, patients who are ultrarapid metabolizers may benefit from increased doses in the case of drugs that are inactivated by CYP2D6 enzyme and lower doses in the case of drugs that are activated by CYP2D6. In the absence of clear guidance from the U.S. Food and Drug Administration on dosing for various metabolizer phenotypes, patients with either ultrarapid or poor metabolism may benefit by switching to comparable alternate medications not primarily metabolized by CYP2D6 or by therapeutic drug monitoring where applicable. Overall, this test provides a comprehensive CYP2D6 genotype result for patients, ensuring a more accurate phenotype prediction. This assay has clinical significance for patients taking or considering medications activated (eg, codeine, tramadol, and tamoxifen) or inactivated (eg, antidepressants and antipsychotics) by the CYP2D6 enzyme. Sequential tier testing associated with this test will be initiated until the least ambiguous phenotype possible is determined.

Useful For: Providing information relevant to tamoxifen, codeine, and tramadol, as well as other medications metabolized by cytochrome P450 2D6 Determining the exact genotype when other methods fail to generate this information or if genotype-phenotype discord is encountered clinically Identifying precise genotype when required (eg, drug trials, research protocols) Identifying novel variants that may interfere with drug metabolism (when reflex to sequencing is performed)

Interpretation: A comprehensive interpretive report will be provided, which combines the results of all tier testing utilized to obtain the final genotype. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(1) For the CYP2D6 copy number variation assay, the reportable copy number range is 0 to 4 copies for each of the CYP2D6 region assessed. Novel variants will be classified based on known, predicted, or possible effect on gene function and reported with interpretive comments detailing their potential or known significance. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
A comprehensive interpretive report will be provided.

Clinical References: 1. PharmVar: Pharmacogene Variation Consortium. Updated November 5, 2024. Accessed November 14, 2024. Available at www.pharmvar.org/ 2. Clinical Pharmacogenetics Implementation Consortium (CPIC). Accessed November 14, 2024. https://cpicpgx.org/ 3. Brown JT, Bishop JR, Sangkuhl K, et al. Clinical pharmacogenetics implementation consortium guideline for cytochrome P450 (CYP)2D6 genotype and atomoxetine therapy. Clin Pharmacol Ther. 2019;106(1):94-102. doi:10.1002/cpt.1409 4. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014;95(4):376-382. doi:10.1038/clpt.2013.254 5. Bell GC, Caudle KE, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther. 2017;102(2):213-218. doi:10.1002/cpt.598 6. Goetz MP, Sangkuhl K, Guchelaar HJ, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2D6 and tamoxifen therapy. Clin Pharmacol Ther. 2018;103(5):770-777. doi:10.1002/cpt.1007 7. Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther. 2015;98(2):127-134. doi:10.1002/cpt.147 8. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597 9. Black JL 3rd, Walker DL, O'Kane DJ, Harmandayan M. Frequency of undetected

CYP2D6 hybrid genes in clinical samples: impact on phenotype prediction [published correction appears in Drug Metab Dispos. 2012 Jun;40(6):1238]. Drug Metab Dispos. 2012;40(1):111-119. doi:10.1124/dmd.111.040832 10. Kirchheiner J, Nickchen K, Bauer M, et al. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. Mol Psychiatry. 2004;9(5):442-473. doi:10.1038/sj.mp.4001494 11. Crews KR, Monte AA, Huddart R, et al: Clinical pharmacogenetics implementation consortium guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. Clin Pharmacol Ther. 2021 Jan 2. doi:10.1002/cpt.2149

3A4Q
610046

Cytochrome P450 3A4 Genotype, Varies

Clinical Information: CYP3A4 is a member of the CYP3A family of genes located on chromosome 7. The cytochrome P450 (CYP) 3A subfamily of enzymes is responsible for the metabolism of more than 50% of medications that undergo hepatic metabolism and first-pass metabolism in intestinal epithelial cells, including some lipid-lowering drugs. The CYP3A4 enzyme activity is highly variable. Interindividual differences in enzyme expression may be due to several factors including: variable homeostatic control mechanisms, disease states that alter homeostasis, up- or down-regulation by environmental stimuli, and genetic variation.(1) One variant, CYP3A4*22 (NM_017460.6: c.522-191C>T, rs35599367), has been studied extensively. This variant affects hepatic expression of CYP3A4 and is associated with reduced CYP3A4 activity. Studies show that in livers with the reference (wild-type) genotype (homozygous C or CC) the CYP3A4 mRNA level and enzyme activity were 1.7- and 2.5-fold greater than in CYP3A4*22 heterozygotes (CT) and homozygotes (TT), respectively. The Dutch Pharmacogenetics Working Group published a guideline related to pharmacogenomic interactions with antipsychotic medications. This guideline recommends avoiding quetiapine in favor of an alternate medication to treat depression, or a dose reduction for other indications; however, the guideline indicates that the evidence is limited. Of note, there is currently no standardized method for translation of CYP3A4 genotype to CYP3A4 phenotype, and the method used in this guideline differs slightly from that used in this genotyping test. The reported allele frequency of CYP3A4*22 is 5% to 8% in the white population and 4.3% in African American and Chinese populations. Other alleles have not been as extensively studied in clinical trials but are expected to have similar impacts on statin metabolism and the metabolism of other drugs primarily metabolized by CYP3A4. The following table displays the CYP3A4 variants detected by this assay, the corresponding star allele, and the effect on CYP3A4 enzyme activity. Individuals without a detectable CYP3A4 variant are designated as CYP3A4*1/*1. CYP3A4 allele cDNA nucleotide change (NM_017460.5) Effect on enzyme activity *1 None (wild type) Normal activity *8 c.389G>A No activity *11 c.1088C>T Reduced activity *12 c.1117C>T Reduced activity *13 c.1247C>T No activity *16 c.554C>G Minimal activity *17 c.566T>C No activity *18 c.878T>C Reduced activity *22 c.522-191C>T Reduced activity *26 c.802C>T No activity Genotype to phenotype predictions are based on a review of the CYP3A4 literature.

Useful For: Aids in determining therapeutic strategies for drugs that are metabolized by cytochrome P450 3A4, including quetiapine This test is not useful for managing patients receiving fluvastatin, rosuvastatin, or pravastatin since these drugs are not metabolized appreciably by CYP3A4.

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(3) For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:

An interpretive report will be provided.

Clinical References: 1. Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. Science. 1999;286(5439):487-491. doi: 10.1126/science.286.5439.487 2. Wang D, Guo Y, Wrighton SA, Cooke GE, Sadee W. Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs. Pharmacogenomics J. 2011;11(4):274-286. doi:10.1038/tpj.2010.28 3. PharmVar: Pharmacogene Variation Consortium. Updated April 29, 2025. Accessed May 15, 2025. Available at www.pharmvar.org/ 4. Lamba JK, Lin YS, Schuetz EG, Thummel KE. Genetic contribution to variable human CYP3A-mediated metabolism. Adv Drug Deliv Rev. 2002;54(10):1271-1294. doi: 10.1016/s0169-409x(02)00066-2 5. Elens L, Becker ML, Haufroid V, et al. Novel CYP3A4 intron 6 single nucleotide polymorphism is associated with simvastatin-mediated cholesterol reduction in the Rotterdam Study. Pharmacogenet Genomics. 2011;21(12):861-866. doi: 10.1097/FPC.0b013e32834c6edb 6. Elens L, van Schaik RH, Panin N, et al. Effect of a new functional CYP3A4 polymorphism on calcineurin inhibitors' dose requirements and trough blood levels in stable renal transplant patients. Pharmacogenomics. 2011;12(10):1383-1396. doi: 10.2217/pgs.11.90 7. Clinical Pharmacogenetics Implementation Consortium (CPIC). Accessed May 15. 2025. https://cpicpgx.org/ 8. Beunk L, Marga N, Bianca S, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6, CYP3A4, and CYP1A2 and antipsychotics. Eur J Hum Genet. 2024;32(3):278-285. doi:10.1038/s41431-023-01347-3

3A5Q
610047

Cytochrome P450 3A5 Genotype, Varies

Clinical Information:

Useful For: Aids in optimizing treatment with tacrolimus and other drugs metabolized by cytochrome P450 3A5

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by Pharmacogene Variation (PharmVar) Consortium.(5) For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Birdwell KA, Decker B, Barbarino JM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther. 2015;98(1):19-24. doi:10.1002/cpt.113 2. Thervet E, Loriot MA, Barbier S, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. Clin Pharmacol Ther. 2010;87(6):721-726. doi:10.1038/clpt.2010.17 3. Lamba J, Hebert JM, Schuetz EG, Klein TE, Altman RB. PharmGKB summary: very important pharmacogene information for CYP3A5. Pharmacogenet Genomics. 2012;22(7):555-558. doi:10.1097/FPC.0b013e328351d47f 4. Clinical Pharmacogenetics Implementation Consortium (CPIC). Accessed May 15, 2025. https://cpicpgx.org/ 5. PharmVar: Pharmacogene Variation Consortium. Updated April 29, 2025. Accessed May 15, 2025. Available at www.pharmvar.org/ 6. Lee SJ, Usmani KA, Chanas B, et al. Genetic findings and functional studies of human CYP3A5 single nucleotide polymorphisms in different ethnic groups. Pharmacogenetics. 2003;13(8):461-472. doi:10.1097/00008571-200308000-00004

FCYTP
75139

Cytokine Panel 13, Serum

Interpretation:

Reference Values:

Tumor Necrosis Factor-alpha:	**< or =7.2 pg/mL**
Interleukin 2:	< or =2.1 pg/mL
Interleukin 2 Receptor Soluble:	175.3 to 858.2 pg/mL
Interleukin 12:	< or =1.9 pg/mL
Interferon gamma:	< or =4.2 pg/mL
Interleukin 4:	< or =2.2 pg/mL
Interleukin 5:	< or =2.1 pg/mL
Interleukin 10:	< or =2.8 pg/mL
Interleukin 13:	< or =2.3 pg/mL
Interleukin 17:	< or =1.4 pg/mL
Interleukin 1 beta:	< or =6.7 pg/mL
Interleukin 6:	< or =2.0 pg/mL
Interleukin 8:	< or =3.0 pg/mL

CYPAN
610259

Cytokine Panel, Plasma

Clinical Information: Cytokines are important mediators of cell-to-cell communication within the innate and adaptive immune systems. The expression of most cytokines is highly regulated and generally occurs in response to foreign or self-antigenic stimulation. The functions of cytokines are extremely varied, with many cytokines also displaying pleiotropic effects, depending on their cellular target. Some cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1 beta, IL-6, interferon (IFN)-alpha and beta, IL-10, and IL-18 are particularly important in the innate immune response. For example, TNF, IL-1 beta, and IL-6 induce expression of acute phase proteins in the liver. TNF and IL-1 beta also lead to endothelial activation and are critical regulators of the hypothalamus, which can result in elevated body temperature. IL-6, in comparison, is a bridge to the adaptive immune response, by acting on B cells to induce proliferation. In contrast, IFN-alpha and IFN-beta (members of the type I IFN family) are key components of the innate immune response to viral infections. IFN-gamma, which is a type II IFN, has roles in both the innate and adaptive immune responses, including macrophage activation, induction of B-cell isotype switching, and T helper type 1 cell differentiation. Other cytokines, such as monocyte chemoattractant protein-1 and macrophage inflammatory protein-1 alpha, are categorized as chemokines because they function primarily to attract leukocytes to the site of inflammation. Further, some cytokines act on hematopoietic stem cells to induce differentiation of various leukocytes. For example, granulocyte-monocyte colony stimulating factor induces myeloid progenitor cells to differentiate into neutrophils and monocytes. Lastly, for some cytokines, soluble forms of the receptor can be found in the peripheral circulation. The IL-2 soluble receptor is produced from proteolytic cleavage of the membrane-bound receptor, which occurs during T-cell activation. As a group, cytokines and their receptors represent a highly complex and critical regulator of a normal immune response.

Useful For: Understanding the etiology of infectious or chronic inflammatory diseases, when used in conjunction with clinical information and other laboratory testing Research studies in which an assessment of cytokine responses is needed

Interpretation: Elevated cytokine concentrations could be consistent with the presence of infection or other inflammatory process.

Reference Values:
Tumor necrosis factor: <10.0 pg/mL
Interleukin (IL)-6: <5.0 pg/mL
Interferon (IFN)-beta: <20.0 pg/mL
IL-10: <7.0 pg/mL
Monocyte chemoattractant protein-1: < or =198 pg/mL
IL-1 beta: <20.0 pg/mL
IFN-gamma: <60.0 pg/mL
Macrophage inflammatory protein-1 alpha: <220 pg/mL
Granulocyte-monocyte colony stimulating factor: <15.0 pg/mL
IL-2 receptor alpha soluble: < or =959 pg/mL
IFN-alpha: <20.0 pg/mL
IL-18: < or =468 pg/mL

Clinical References: 1. Bozza FA, Salluh JI, Japiassu AM, et al. Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis. Crit Care. 2007;11(2):R49. doi:10.1186/cc5783 2. Milman N, Karsh J, Booth RA. Correlation of a multi-cytokine panel with clinical disease activity in patients with rheumatoid arthritis. Clin Biochem. 2010;43(16-17):1309-1314. doi:10.1016/j.clinbiochem.2010.07.012 3. Teijara JR. Type I interferons in viral control and immune regulation. Curr Opin Virol. 2016;16:31-40. doi:10.1016/j.coviro.2016.01.001 4. Tisoncki JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Rev. 2010;76(1):16-32. doi:10.1128/MMBR.05015-11 5. Garcia Borrega J, Godel P, Ruger MA, et al. In the eye of the storm: Immune-mediated toxicities associated with CAR-T cell therapy. Hemasphere. 2019;3(2):e191. doi:10.1097/HS9.0000000000000191

CTFNA
70334

Cytology Fine-Needle Aspiration, Varies

Clinical Information: Aspiration cytology from a variety of organ sites is useful in the determination of pathologic states, particularly neoplasms. Commonly examined sites include lung, liver, lymph nodes, pancreas, kidney, thyroid, retroperitoneum, breast, salivary glands, and soft tissue. In many cases, an open biopsy is no longer required to make a diagnosis.

Useful For: Detection of malignancy Detection of certain inflammatory conditions

Interpretation: Aspiration therapy is highly specific with rare false-positives. A positive diagnosis should be definitive for malignancy. Precise cell typing is variably possible depending on circumstances.

Reference Values:
Negative for malignant cells

Clinical References: Mody DR, Thrall MJ, Krishnamurthy S, eds. Diagnostic Pathology: Cytopathology, 2nd ed. Elsevier, 2019

CFNPC
113344

Cytology FNA (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

CYTNG
70330

Cytology Non-Gynecologic, Varies

Clinical Information: This test is used for the identification of malignant cells by cytopathology interpretation from nongynecological body sites.

Useful For: Detecting malignant and premalignant changes

Interpretation: Suspicious or atypical results need further confirmation: clinical observation, repeat cytology, or perhaps appropriate biopsy. Positive results should be confirmed by histologic examination of tissue before definitive therapy is instituted.

Reference Values:
Negative for malignant cells

Clinical References: Mody DR, Thrall MJ, Krishnamurthy S, eds. Diagnostic Pathology: Cytopathology, 2nd ed. Elsevier; 2019

CTPPC
113340

Cytology Touch Prep (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

CTAPC
113341

Cytology Touch Prep Additional (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

CMVG
34970

Cytomegalovirus (CMV) Antibodies, IgG, Serum

Clinical Information: Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow-derived cells.(1) Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise, and lymphadenopathy. Cytomegalovirus is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS, and other immunosuppressed patients due to virus reactivation or from a newly acquired infection.(2,3) Infection in these patient populations can affect almost any organ and lead to multiorgan failure. CMV is also responsible for congenital disease among newborns and is one of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus). Cytomegalovirus seroprevalence increases with age. In the United States, the prevalence of CMV

specific antibodies increases from approximately 36% in children from 6 to 11 years old to over 91% in adults over 80 years old.(4)

Useful For: Determining whether a patient (especially transplant recipients and organ and blood donors) has had a recent infection or previous exposure to cytomegalovirus

Interpretation: Positive cytomegalovirus (CMV) IgG results indicate past or recent CMV infection. These individuals may transmit CMV to susceptible individuals through blood and tissue products. Equivocal CMV IgG results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional sample for testing if clinically indicated. Individuals with negative CMV IgG results are presumed to not have had prior exposure or infection with CMV and are, therefore, considered susceptible to primary infection.

Reference Values:
Negative (reported as positive, negative, or equivocal)

Clinical References: 1. Soderberg-Naucler C, Fish KN, Nelson JA. Reactivation of latent human cytomegalovirus by allogeneic stimulation of blood cells from healthy donors. 1997;91(1):119-126 2. Kusne S, Shapiro R, Fung J. Prevention and treatment of cytomegalovirus infection in organ transplant recipients. Transpl Infect Dis. 1999;1(3):187-203 3. Rubin RH. Importance of CMV in the transplant population. Transpl Infect Dis. 1999;1 Suppl 1:3-7 4. Staras SA, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1998-1994. Clin Infect Dis. 2006;143(9):1143-1151 5. Bruminhent J, Thongprayoon C, Dierkhising RA, Kremers WK, Theel ES, Razonable RR. Risk factors for cytomegalovirus reactivation after liver transplantation: can pre-transplant cytomegalovirus antibody titers predict outcome? Liver Transpl. 2015;21(4):539-546 6. Dioverti MV, Razonable RR. Cytomegalovirus. Microbiol Spectr. 2016;4(4). doi:10.1128/microbiolspec.DMIH2-0022-2015

CMVP
62067

Cytomegalovirus (CMV) Antibodies, IgM and IgG, Serum

Clinical Information: Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow derived cells. Primary CMV infection in immunocompetent individuals may manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise and lymphadenopathy. Cytomegalovirus is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS, and other immunosuppressed patients due to virus reactivation or from a newly acquired infection. Infection in these patient populations can affect almost any organ and lead to multiorgan failure. CMV is also responsible for congenital disease among newborns and is one of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus). Cytomegalovirus seroprevalence increases with age. In the United States, the prevalence of CMV-specific antibodies increases from approximately 36% in children from 6 to 11 years old to over 91% in adults over 80 years old.

Useful For: Aiding in the diagnosis of acute or past infection with cytomegalovirus (CMV) Determining prior exposure to CMV This test should not be used for screening blood or plasma donors.

Interpretation: IgM: A negative cytomegalovirus (CMV) IgM result suggests that the patient is not experiencing acute or active infection. However, a negative result does not rule-out primary CMV infection. It has been reported that CMV-specific IgM antibodies were not detectable in 10% to 30% of cord blood sera from infants demonstrating infection in the first week of life. In addition, up to 23% (3/13) of pregnant women with primary CMV infection did not demonstrate detectable CMV IgM responses within 8 weeks postinfection. In cases of primary infection where the time of seroconversion is

not well defined, as high as 28% (10/36) of pregnant women did not demonstrate CMV IgM antibody. Positive CMV IgM results indicate a recent infection (primary, reactivation, or reinfection). IgM antibody responses in secondary (reactivation) CMV infections have been demonstrated in some CMV mononucleosis patients, a few pregnant women, and kidney and cardiac transplant patients. Levels of antibody may be lower in transplant patients with secondary rather than primary infections. IgG: Positive CMV IgG results indicate past or recent CMV infection. These individuals may transmit CMV to susceptible individuals through blood and tissue products. Individuals with negative CMV IgG results are presumed to not have had prior exposure or infection with CMV and are, therefore, considered susceptible to primary infection. Equivocal CMV IgM or IgG results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional specimen for testing if clinically indicated.

Reference Values:

CYTOMEGALOVIRUS IgM:
Negative

CYTOMEGALOVIRUS IgG:
Negative

Reference values apply to all ages.

Clinical References: 1. Soderberg-Naucler C, Fish NK, Nelson JA. Reactivation of latent human cytomegalovirus by allogeneic stimulation of blood cells from healthy donors. Cell. 1997;91(1):119-126 2. Bruminhent J, Thongprayoon C, Dierkhising RA, Kremers WK, Theel ES, Razonable RR. Risk factors for cytomegalovirus reactivation after liver transplantation: can pre-transplant cytomegalovirus antibody titers predict outcome? Liver Transpl. 2015;21(4):539-546 3. Dioverti MV, Razonable RR. Cytomegalovirus. Microbiol Spectr. 2016;4(4) 4. Staras SA, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1998-1994. Clin Infect Dis. 2006;43(9):1143-1151

CMVM
34971

Cytomegalovirus (CMV) Antibodies, IgM, Serum

Clinical Information: Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection, after which it remains latent in patients, primarily within bone marrow-derived cells. Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise, and lymphadenopathy. Cytomegalovirus is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS, and other immunosuppressed patients due to virus reactivation or from a newly acquired infection. Infection in these patient populations can affect almost any organ and lead to multiorgan failure. CMV is also responsible for congenital disease among newborns and is 1 of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus). Cytomegalovirus seroprevalence increases with age. In the United States, the prevalence of CMV specific antibodies increases from approximately 36% in children from 6 to 11 years old to over 91% in adults over 80 years old.

Useful For: Aiding in the diagnosis of acute infection with cytomegalovirus This test should not be used for screening blood or plasma donors.

Interpretation: A negative cytomegalovirus (CMV) IgM result suggests that the patient is not experiencing acute or active infection. However, a negative result does not rule-out primary CMV infection. It has been reported that CMV-specific IgM antibodies were not detectable in 10% to 30% of cord blood sera from infants demonstrating infection in the first week of life. In addition, up to 23%

(3/13) of pregnant women with primary CMV infection did not demonstrate detectable CMV IgM responses within 8 weeks postinfection. In cases of primary infection where the time of seroconversion is not well defined, as high as 28% (10/36) of pregnant women did not demonstrate CMV-IgM antibody. Positive CMV IgM results indicate a recent infection (primary, reactivation, or reinfection). IgM antibody responses in secondary (reactivation) CMV infections have been demonstrated in some CMV mononucleosis patients, a few pregnant women, and kidney and cardiac transplant patients. Levels of antibody may be lower in transplant patients with secondary, rather than primary, infections. Equivocal CMV IgM results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional sample for testing if clinically indicated.

Reference Values:

Negative
Reference values apply to all ages.

Clinical References: 1. Soderberg-Naucler C, Fish KN, Nelson JA. Reactivation of latent human cytomegalovirus by allogeneic stimulation of blood cells from healthy donors. 1997;91(1):119-126 2. Bruminhent J, Thongprayoon C, Dierkhising RA, Kremers WK, Theel ES, Razonable RR. Risk factors for cytomegalovirus reactivation after liver transplantation: can pre-transplant cytomegalovirus antibody titers predict outcome? Liver Transpl. 2015;21(4):539-546 3. Dioverti MV, Razonable RR. Cytomegalovirus. Microbiol Spectr. 2016;4(4). doi:10.1128/microbiolspec.DMIH2-0022-2015. 4. Staras SA, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1998-1994. Clin Infect Dis 2006;43(9):1143-1151

CMVC8
88826

Cytomegalovirus (CMV) CD8 T-Cell Immune Competence, Quantitative Assessment by Flow Cytometry, Blood

Clinical Information: Cytomegalovirus (CMV), a double-stranded DNA virus, belongs to the Herpesviridae family of viruses and is structurally similar to other herpes viruses. Although many human strains of CMV exist, there is little genetic homology between human CMV and CMV of other species. The reported seroprevalence rates of CMV range from 40% to 100% in the general population. In the urban United States, the seroprevalence of CMV has been reported to be 60% to 70%.(1) However, data from Mayo Clinic's laboratory indicate that the seroprevalence in the Midwestern US population is closer to 30% (unpublished observations). Once CMV infection occurs, the virus spreads hematogenously to almost every organ. After acute infection, the virus enters a latent phase. Activation from this phase can be seen after acute illness, immunosuppression in allogeneic hematopoietic stem cell transplantation (HSCT) or solid organ transplantation, or use of chemotherapy agents. CMV infection or reactivation has been implicated in allograft rejection in renal (2) and cardiac transplantation.(1) In cardiac transplants, CMV infection has been shown to contribute to accelerated development of transplant atherosclerosis (cardiac allograft vasculopathy). CMV remains a significant cause of morbidity and mortality after HSCT. Of allogeneic HSCT patients who are CMV-seropositive, 60% to 70% will experience reactivation and, without ganciclovir or other preemptive therapy, 20% to 30% will develop end-organ disease.(3) CD8 T cells play a critical role in viral immunity, and CD8 T-cell effector functions include cytotoxicity and cytokine production. Cytotoxicity occurs after CD8 T-cell activation, causing target cell apoptosis. Cytotoxic T-cell responses mediate killing of target cells via 2 major pathways, granule-dependent (perforin and granzymes) and granule-independent (Fas and Fas ligand [FasL]) mechanisms. The granule-dependent pathway does not require the de novo synthesis of proteins by effector CD8 T cells, but rather it utilizes preformed lytic granules located within the cytoplasm. Among the proteins in these preformed lytic granules are the lysosomal-associated membrane proteins (LAMP), including LAMP-1 (CD107a) and LAMP-2 (CD107b). These proteins are not normally found on the surface of T cells. Degranulation of activated CD8 T cells occurs rapidly after T-cell receptor (TCR) stimulation, exposing CD107a and CD107b. The cytokines produced by activated T cells include interferon-gamma (IFN-gamma), tumor necrosis factor alpha (TNF-alpha), macrophage inflammatory protein 1 alpha (MIP-1 alpha), macrophage

inflammatory protein 1 beta (MIP-1 beta), and interleukin-2 (IL-2). Several studies have shown the importance of cytotoxic T-cell responses to CMV in conferring protection from subsequent CMV disease. Antiviral drugs have helped reduce the incidence of early CMV infection, and acyclovir and ganciclovir have been the mainstay of antiviral treatment for a number of years, although these drugs have poor bioavailability.(4) The development of the new antiviral drugs valacyclovir and valganciclovir (by the addition of a valine ester) has increased the bioavailability of these drugs by 10-fold.(4) There is some data to suggest valganciclovir prophylaxis may be considered for HSCT patients who are at high risk for infection and disease, though there is a need for further study in this area.(5) Two main strategies have been used for the prevention of early CMV infection and disease in CMV-seropositive patients and in seronegative recipients who receive a seropositive graft-preemptive therapy: -Patient monitoring for CMV infection and treatment only when CMV viremia is present. -Prophylactic management-where all patients receive treatment after transplantation with the goal of preventing CMV disease.(5) The disadvantage of prophylactic therapy is that it requires monitoring for myelosuppression and infections-side effects of antiviral drug therapy. Despite this disadvantage, there are several reasons to consider prophylaxis, including the fact that the incidence of recurrent infections after treatment is 30% to 40%,(5) patients receiving preemptive therapy have a 5% CMV disease break-through, and prophylaxis reduces the risk of viral reactivation. Late CMV infection occurs 3 months after transplantation and is now recognized as a significant cause of morbidity after allogeneic HSCT.(6) These complications usually occur in the setting of continued immunosuppression for chronic graft-versus-host disease (GVHD). The clinical manifestations of late CMV disease differ slightly from those seen early after transplantation. Within the first 100 days after HSCT, almost all patients with CMV disease have CMV pneumonia or gastrointestinal disease. In late CMV disease, the more unusual manifestations of CMV infection (eg, CMV retinitis, CMV-associated bone marrow failure, or CMV encephalitis) tend to occur.(7) These late manifestations occur in a setting of continued CMV-specific T-cell immunodeficiency. Therefore, it is necessary to monitor CMV-specific CD8 T-cell responses, in addition to viral load, to effectively identify patients at higher risk of CMV disease. It has been shown that ganciclovir may delay the recovery of the protective CMV-specific T-cell response, which may contribute to the occurrence of late CMV disease.(8) The use of ganciclovir as early treatment after detection of CMV in blood or other body fluid and as a prophylaxis for CMV infection in bone marrow transplant (BMT) and heart transplant recipients has dramatically reduced the incidence of CMV in these immunocompromised hosts. Yet, early treatment and prophylaxis have not been uniformly successful, with up to 15% of BMT recipients developing CMV disease after discontinuation of antiviral therapy. Similarly, patients undergoing lung transplantation have been shown to be only transiently protected with antiviral agents. These data suggest that the CMV-specific responses necessary for protection may not recover during the time the host is receiving antiviral therapy. Ganciclovir exerts its antiviral effects at the stage of viral DNA replication and, therefore, in the presence of the drug, infected cells may express some of the immediate early and early gene products, but not the full complement of CMV genes required for replication and virion formation. In latently infected CMV-seropositive individuals, the human leukocyte antigen (HLA) class I-restricted cytotoxic T lymphocyte response to CMV is predominantly specific for epitopes derived from structural virion proteins. Therefore, in patients receiving ganciclovir, the viral antigens may be inadequate to activate host T-cell responses, resulting in the failure to reconstitute CMV-specific immunity. In fact, a prospective, randomized placebo-controlled study of ganciclovir prophylaxis revealed that when ganciclovir therapy is discontinued, a larger fraction of patients (who received the drug) are deficient in CMV-specific T-cell immunity at day 100 than in the placebo group.(8) That study also showed that bone marrow donor serology has an important influence on the early detection of virus-specific T-cell responses.(8) Not all medical centers use ganciclovir for prophylaxis; some use acyclovir and the same findings may apply in this case as well. In a more recent study, it was shown that impaired CD8 function was associated with the use of high-dose steroids, bone marrow as a source of stem cells, and CD8 T-cell lymphopenia.(3) In the absence of high-dose steroids, low-level subclinical CMV antigenemia was found to stimulate both CD4 and CD8 functional recovery in recipients of ganciclovir prophylaxis, suggesting that subclinical CMV reactivation while on antiviral therapy can be a potent stimulator of T-cell function.(3) Regardless of antiviral therapy, immunologic reconstitution remains the key element in protection from late-onset CMV disease. This test assesses the number of CMV-specific

CD8 T cells and their function (activation via production of the cytokine IFN-gamma and cytotoxic potential via CD107a and CD107b as markers of degranulation) using a panel of 5 major histocompatibility complex (MHC) class I alleles (HLA A1, A2, B7, B8, and B35) along with their respective immunodominant CMV epitopes. This 3-part assay allows a comprehensive assessment of CMV-specific CD8 T cell immunity and, when combined with evaluation of viremia using molecular analyses, provides a more accurate picture of the nature of CMV reactivation and the corresponding immune response than evaluating viremia alone (9). Assessment of Global CD8 T-Cell Function: CD8 T cell activation occurs either through the TCR-peptide-MHC or by use of a mitogen (eg, phorbol myristate acetate and the calcium ionophore ionomycin). Mitogen-mediated activation is antigen nonspecific. Impairment of global CD8 T cell activation (due to inherent cellular immunodeficiency or as a consequence of immunosuppression by therapeutic agents) results in reduced production of interferon-gamma and other cytokines, reduced cytotoxic function, and increased risk for developing infectious complications. Agents associated with over-immunosuppression include the calcineurin inhibitors (eg, cyclosporine A, FK506 [Prograf/tacrolimus], and rapamycin [sirolimus]), antimetabolites (eg, mycophenolate mofetil), and thymoglobulin. The incorporation of global CD8 T cell function in this assay is helpful in determining if the lack of CMV-specific (antigen-specific) response is due to a global impairment in CD8 T cell function, due to immunosuppression or other causes, or whether the lack of CMV CD8 T cell immunity is unrelated to overall CD8 T cell function. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day.(10) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(11-13) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(11) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening(13), and during summer compared to winter.(14) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Assessing cytomegalovirus (CMV)-specific immune competence in allo-hematopoietic stem cell transplantation patients who are at risk for developing late CMV disease (beyond day 100 after transplant) Assessing CMV-specific immune competence in solid organ transplant patients who are at high risk for CMV reactivation posttransplant Monitoring immune competence in patients post-primary CMV infection after transplant who are at risk for CMV reactivation after the cessation of antiviral prophylaxis Identifying individuals who are likely to be protected from posttransplant CMV infection and those who are at higher risk of CMV reactivation The global CD8 T cell immune competence assay is useful for determining over immunosuppression within the CD8 T cell compartment, when used on transplant recipients and patients with autoimmune disorders receiving therapy with immunosuppressant agents

Interpretation: For allogeneic hematopoietic stem cell transplantation (HSCT) and solid organ transplant patients who are cytomegalovirus (CMV)-seropositive and at risk for CMV reactivation, posttransplant results should be compared to pretransplant (preconditioning/baseline) results. The report includes absolute CD3 and CD8 T-cell counts as well as a derived CMV-specific CD8 T-cell count (derived from CD3 and CD8 T-cell counts). The absolute count of CMV-CD8 T cells that are activated and have cytotoxic function in response to specific CMV peptide is also provided. The data from the 3 components of this assay should be interpreted together and not individually.(15) In the setting of CMV viremia, frequent monitoring of CMV-immune competence helps define the evolution of the CMV-immune response. In this clinical context, CMV-immune competence should be measured as frequently as viral load to determine correlation between the 2 parameters. CMV-specific CD8 T-cell counts may show a decline in numbers over time in the absence of active infection or antigenemia. The absence of CMV-specific CD8 T cells may be a risk factor in the immune-compromised or immune-incompetent transplant patient, who is at risk for CMV reactivation. The presence of CMV-specific CD8 T cells may not be

protective in itself. If the CMV-specific CD8 T cells do not show appropriate cytotoxic function (due to the fact that they recognize CMV epitopes that do not effectively induce a cytotoxic response), these patients may be at higher risk of an inadequate immune response to CMV infection. While the reference values provide a guideline of CMV-specific CD8 T-cell numbers and function in a cohort of healthy individuals, baseline (pretransplant/preconditioning) assessments should be taken into consideration when determining CMV-specific immune competence posttransplant. Correlation between data from multiple post-transplant specimens (if available) and the presence or absence of viremia (or active CMV disease) also are useful in the interpretation of results. CD8 T cell counts are elevated when the immune system is initially reconstituted post-HSCT, and the CD4 to CD8 ratio can be inverted for about 12 months post-HSCT. Interferon-gamma (IFN-gamma) and CD107a/b expression below the defined reference range are consistent with a global impairment in CD8 T cell function, most likely due to over-immunosuppression. IFN-gamma and CD107a/b levels greater than the defined reference range are unlikely to have any clinical significance.

Reference Values:

Total CD3 T cells: 884-5830 x 10(3)/mL
Total CD8 T cells: 168-1847 x 10(3)/mL
Total CMV CD8 T cells: 0-115 x 10(3)/mL

The adult reference values were determined for healthy adult controls ages 20 to 80 years (n=94), for HLA A1, A2, B7, B8, and B35 alleles.

Reference values for cytomegalovirus (CMV) specific T cells that are functional (interferon-gamma+, IFN-g+) and have cytotoxic activity (CD107a and CD107b expression, CD107 a/b+):
Total CMV CD8 T-cells IFN-g: 0.028-52.200 x 10(3)/mL
Total CMV CD8 T-cells CD107a/b: 0.252-50.760 x 10(3)/mL

The 95% confidence interval reference values were determined from 102 healthy adult donors:
Interferon-gamma (IFN-gamma) expression (as % CD8 T cells): 10.3-56.0%
CD107a/b expression (as % CD8 T cells): 8.5-49.1%

The reference values were developed for each of the following 4 major histocompatibility complex class I alleles: A1, A2, B7, and B8 (n=45). We were unable to develop ranges for the B35 allele due to a lack of matching donors. The data is expressed as the absolute number of CMV-specific CD8 T cells that are IFN-gamma+ or CD107a/b+.

Clinical References:

1. Melnick JL, Adam E, Debakey ME. Cytomegalovirus and atherosclerosis. Eur Heart J. 1993;14 Suppl K:30-38 2. von Willebrand E, Petterson E, Ahnonen J, Hayry P. CMV infection, class II antigen expression, and human kidney allograft rejection. Transplantation. 1986;42(4):364-367 3. Hakki M, Riddell SR, Storek J, et al. Immune reconstitution to CMV after allogeneic hematopoietic stem cell transplantation: impact of host factors, drug therapy, and subclinical reactivation. Blood. 2003;102(8):3060-3067 4. Baden LR. Pharmacokinetics of valganciclovir in HSCT patients with gastrointestinal GVHD. Biol Blood Marrow Transplant. 2005;15(2):5-7 5. Bachier C, Shaughnessy P, Wall D, et al. Valganciclovir for the prophylaxis of early cytomegalovirus (CMV) infection after allogeneic stem cell transplantation,. Biol Blood Marrow Transplant. 2005;11(2):90-91 6. Annaloro C, Serpenti F, Saporiti G, et al. Viral infections in HSCT: Detection, monitoring, clinical management, and immunologic implications. Front Immunol. 2021;11:569381. doi:10.3389/fimmu.2020.569381 7. Boeckh M. Prevention of late CMV infection in HSCT. Biol Blood Marrow Transplant. 2005;15(2):9-11 8. Li CR, Greenberg PD, Gilbert MJ, et al. Recovery of HLA-restricted CMV-specific T cell responses after allogeneic bone marrow transplant: correlation with CMV disease and effect of ganciclovir prophylaxis. Blood. 1994;83(7):1971-1979 9. Meesing A, Abraham RS, Razonable RR. Clinical correlation of cytomegalovirus infection with CMV-specific CD8+ T-cell Immune competence score and lymphocyte subsets in solid organ transplant recipients. transplantation. 2019;103(4):832-838. doi:10.1097/TP.0000000000002396 10. Carmichael KF,

Abayomi A. Analysis of diurnal variation of lymphocyte subsets in healthy subjects in the Caribbean, and its implication in HIV monitoring and treatment. Afr J Med Med Sci. 2006;35(1):53-57 11. Dimitrov S, Benedict C, Heutling D, et al. Cortisol and epinephrine control opposing circadian rhythms in T-cell subsets. Blood. 2009;113(21):5134-5143 12. Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating antigen presenting cells regulated by sleep. Sleep. 2007;30(4):401-411 13. Kronfol Z, Nair M, Zhang Q, et al. Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Pyschosom Med. 1997;59(1):42-50 14. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994;34(6):512-516 15. Meesing A, Abraham RS, Razonable RR. Clinical correlation of cytomegalovirus infection with CMV-specific CD8+ T-cell immune competence score and lymphocyte subsets in solid organ transplant recipients. Transplantation. 2019;103(4):832-838 16. Malone JL, Simms TE, Gray GC, et al. Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J Acquir Immune Defic Syndr (1988). 1990;3(2):144-151 17. Prakash K, Chandorkar A, Saharia KK. Utility of CMV-specific immune monitoring for the management of CMV in solid organ transplant recipients: a clinical update. Diagnostics (Basel) 2021;11(5):875

CMVQN 601954 Cytomegalovirus (CMV) DNA Detection and Quantification by Real-Time PCR, Plasma

Clinical Information: Cytomegalovirus (CMV) is a common and major cause of opportunistic infection in organ transplant recipients, causing significant morbidity and mortality. CMV infection and disease typically occur during the first year after organ transplantation after cessation of antiviral prophylaxis. Such infection usually manifests as fever, leukopenia, hepatitis, colitis, or retinitis. Other manifestations of CMV infection in this population may be more subtle and include allograft injury and loss, increased susceptibility to infections with other organisms, and decreased patient survival (ie, indirect effects). The risk of CMV disease is highest among organ recipients who are CMV seronegative prior to transplantation and receive allografts from CMV-seropositive donors (ie, CMV D+/R- mismatch). The infection is transmitted via latent CMV present in the transplanted organ donor and the virus subsequently reactivates, causing a primary CMV infection in the recipient. CMV disease may also occur from reactivation of the virus already present within the recipients. Factors, such as the type of organ transplanted, intensity of the antirejection immunosuppressive therapy, advanced age, and presence of comorbidities in the recipient, are also associated with increased risk for CMV disease after allograft transplantation. Lung, heart, small intestine, pancreas, and kidney-pancreas transplant recipients are at greater risk for CMV infection than kidney and liver transplant recipients. Among the various clinical laboratory diagnostic tests currently available to detect CMV infection, nucleic acid amplification tests (eg, polymerase chain reaction) are the most sensitive and specific detection methods. In addition, quantification of CMV DNA level in peripheral blood (ie, CMV viral load) is used routinely to determine when to initiate preemptive antiviral therapy, diagnose active CMV disease, and monitor response to antiviral therapy. A number of factors can affect CMV viral load results, including the specimen type (whole blood versus plasma), biologic properties of CMV, performance characteristics of the quantitative assay (eg, limit of detection, limits of quantification, linearity, and reproducibility), degree of immunosuppression, and intensity of antiviral therapy. In general, higher CMV viral loads are associated with tissue-invasive disease, while lower levels are associated with asymptomatic infection. However, the viral load in the peripheral blood compartment may be low or undetectable in some cases of tissue-invasive disease. Since a wide degree of overlap exists in CMV viral load and disease, a rise in viral load over time is more important in predicting CMV disease than a single viral load result at a given time point. Therefore, serial monitoring (eg, weekly intervals) of organ transplant recipients with quantitative CMV PCR is recommended in such patients at risk for CMV disease. Since changes in viral load may be delayed by several days in response to antiviral therapy and immunosuppression, viral load should not be monitored more frequently than a weekly basis. Typically, CMV viral load changes of greater than 0.5 log IU/mL are considered biologically significant changes in viral replication. Patients with suppression of CMV replication (ie, viral load of <35 or <1.54 log IU/mL at days 7, 14, and 21 of treatment) had shorter

times to resolution of clinical disease than those without viral suppression. No degree of relative viral load reduction from pretreatment level was associated with faster resolution of CMV disease.

Useful For: Detection and quantification of cytomegalovirus (CMV) viremia Monitoring CMV disease progression and response to antiviral therapy

Interpretation: The quantification range of this assay is 35 to 10,000,000 IU/mL (1.54 log to 7.00 log IU/mL), with a 95% or higher limit of detection at 35 IU/mL. A result of "Undetected" indicates the absence of cytomegalovirus (CMV) DNA in the plasma (see Cautions below). A result of "<35 IU/mL (<1.54 log IU/mL)" indicates that CMV DNA is detected in the plasma, but the assay cannot accurately quantify the CMV DNA present below this level. A quantitative value (reported in IU/mL and log IU/mL) indicates the level of CMV DNA (ie, viral load) present in the plasma. A result of ">10,000,000 IU/mL (>7.00 log IU/mL)" indicates that CMV DNA level present in plasma is above 10,000,000 IU/mL (7.00 log IU/mL), and the assay cannot accurately quantify CMV DNA present above this level.

Reference Values:
Undetected

Clinical References:

CMVI
70406

Cytomegalovirus (CMV) Immunostain, Technical Component Only

Clinical Information: Cytomegalovirus (CMV) stain visualizes the intranuclear and cytoplasmic viral inclusions of CMV-infected cells. CMV can cause severe systemic infection (primary or reactivated infection) in patients who are immunocompromised. Antibodies to cytomegalovirus fail to react with any normal human tissue.

Useful For: Identification of cytomegalovirus infection

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Johnson J, Affolter K, Boynton K, Chen X, Valentine J, Peterson K. CMV Disease in IBD: Comparison of Diagnostic Tests and Correlation with Disease Outcome. Inflamm Bowel Dis. 2018;24(7):1539-1546. doi:10.1093/ibd/izy045 2. Agnarsdottir M, Popova S, Alafuzoff I. Expression of CMV protein pp65 in cutaneous malignant melanoma. PLoS One. 2019;14(10):e0223854. doi:10.1371/journal.pone.0223854 3. Jung KH, Kim J, Lee HS, et al. Clinical implications of the CMV-specific T-cell response and local or systemic CMV viral replication in patients with moderate to severe ulcerative colitis. Open Forum Infect Dis. 2019;6(12):ofz526. doi:10.1093/ofid/ofz526 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CMVLR
621770

Cytomegalovirus (CMV) Molecular Detection, PCR, Lower Respiratory

Clinical Information: Cytomegalovirus (CMV) is a double-stranded DNA virus of the Herpesviridae family. CMV is transmitted through infected body fluids, as well as through sexual contact, organ transplantation, and intrauterine transmission during pregnancy. CMV infection may be asymptomatic but can cause a wide range of symptoms in immunocompromised individuals. Detection of CMV DNA in lower respiratory specimens may support the clinical diagnosis of CMV pneumonitis. Infection with CMV is a significant cause of morbidity and mortality in transplant recipients and other immunocompromised hosts.

Useful For: Rapid qualitative detection of cytomegalovirus (CMV) DNA in lower respiratory specimens This test is not intended for the monitoring of CMV disease progression or response to therapy.

CMVPV
618968

Cytomegalovirus (CMV) Molecular Detection, PCR, Varies

Clinical Information: Infection with cytomegalovirus (CMV) is a significant cause of morbidity and mortality in transplant recipients and other immunocompromised hosts. Specific neurologic syndromes associated with CMV infection include subacute radiculomyelopathy, peripheral neuropathy, and encephalitis. Cytomegalovirus-associated central nervous system disease occurs most commonly in immunocompromised patients. Histologic evidence of CMV infections in autopsy brain tissue was identified in 20% to 40% of patients with AIDS. In 2 separate studies, CMV (DNA) was the most common herpesvirus (29/181, 16/49) detected from the cerebrospinal fluid of patients with AIDS. Central nervous system infections with CMV can also occur in immunocompetent patients, and infection can result in a mono-like illness. A significant percentage of adults are positive for IgG antibodies against CMV, suggesting prior infection with the virus.

Useful For: Rapid qualitative detection of cytomegalovirus (CMV) DNA This test is not intended for the monitoring of CMV disease progression.

Interpretation: Detection of cytomegalovirus (CMV) DNA in a specimen supports the clinical diagnosis of infection due to this virus. Studies indicate that CMV DNA is not detected by polymerase chain reaction in cerebrospinal fluid from patients without central nervous system disease caused by this virus.

Reference Values:
Negative

Reference values apply to all ages.

Clinical References: 1. Binnicker MJ, Espy M. Comparison of six real-time PCR assays for the qualitative detection of cytomegalovirus in clinical specimens. J Clin Microbiol. 2013:51(11):3749-3752 2. Petito CK, Cho ES, Lemann W, Navia BA, Price RW. Neuropathy of acquired immunodeficiency syndrome (AIDS): an autopsy review. J Neuropathol Exp Neurol. 1986;45(6):635-646 3. Cinque P, Vago L, Dahl H, et al. Polymerase chain reaction on cerebrospinal fluid for diagnosis of virus-associated opportunistic diseases of the central nervous system in HIV-infected patients. AIDS. 1996;10(9):951-958 4. Broccolo F, Iulioano R, Careddu AM, et al. Detection of lymphotropic herpesvirus DNA by polymerase chain reaction in cerebrospinal fluid of AIDS patients with neurological disease. Acta Virol. 2000;44(3):137-143 5. Prosch S, Schielke E, Reip A, et al. Human cytomegalovirus (HCMV) encephalitis in an immunocompetent young person and diagnostic reliability of HCMV DNA PCR using cerebrospinal fluid of nonimmunosuppressed patients. J Clin Microbiol. 1998;36(12):3636-3640 6. Sia IG, Patel R. New strategies for prevention and therapy of cytomegalovirus infection and disease in solid-organ transplant recipients. Clin Microbiol Rev. 2000;13(1):83-121 7. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13512. doi:10.1111/ctr.13512 8. Febbo J, Revels J, Revels L. Viral pneumonias. Infect Dis Clin North Am. 2024;38(1):167-182. doi:10.1016/j.idc.2023.12.009

LCMV
800145

Cytomegalovirus (CMV), Molecular Detection, PCR, Varies

Clinical Information: Infection with cytomegalovirus (CMV) is a significant cause of morbidity and

mortality in transplant recipients and other immunocompromised hosts. Specific neurologic syndromes associated with CMV infection include subacute radiculomyelopathy, peripheral neuropathy, and encephalitis. Cytomegalovirus-associated central nervous system disease occurs most commonly in immunocompromised patients. Histologic evidence of CMV infections in autopsy brain tissue was identified in 20% to 40% of patients with AIDS. In 2 separate studies, CMV (DNA) was the most common herpesvirus (29/181, 16/49) detected from cerebrospinal fluid of patients with AIDS. Central nervous system infections with CMV can also occur in immunocompetent patients. CMV is a leading cause of congenital viral infections worldwide, and laboratory testing by real-time polymerase chain reaction is useful in the diagnosis of neonatal CMV disease.

Useful For: Rapid qualitative detection of cytomegalovirus (CMV) DNA This test is not intended for the monitoring of CMV disease progression. This test should not be used to screen asymptomatic patients.

Interpretation: Detection of cytomegalovirus (CMV) DNA in a specimen supports the clinical diagnosis of infection due to this virus. Studies indicate that CMV DNA is not detected by polymerase chain reaction assays in cerebrospinal fluid from patients without central nervous system disease caused by this virus.

Reference Values:
Negative

Reference values apply to all ages.

Clinical References: 1. Binnicker MJ, Espy ME. Comparison of six real-time PCR assays for the qualitative detection of cytomegalovirus in clinical specimens. J Clin Microbiol. 2013:51(11):3749-3752 2. Petito CK, Cho ES, Lemann W, Navia BA, Price RW. Neuropathy of acquired immunodeficiency syndrome (AIDS): an autopsy review. J Neuropathol Exp Neurol. 1986;45(6):635-646 3. Cinque P, Vago L, Dahl H, et al. Polymerase chain reaction on cerebrospinal fluid for diagnosis of virus-associated opportunistic diseases of the central nervous system in HIV-infected patients. AIDS. 1996;10(9):951-958 4. Broccolo F, Iulioano R, Careddu AM, et al. Detection of lymphotropic herpesvirus DNA by polymerase chain reaction in cerebrospinal fluid of AIDS patients with neurological disease. Acta Virol. 2000;44(3):137-143 5. Prosch S, Schielke E, Reip A, et al. Human cytomegalovirus (HCMV) encephalitis in an immunocompetent young person and diagnostic reliability of HCMV DNA PCR using cerebrospinal fluid of nonimmunosuppressed patients. J Clin Microbiol. 1998;36(12):3636-3640 6. Sia IG, Patel R. New strategies for prevention and therapy of cytomegalovirus infection and disease in solid-organ transplant recipients. Clin Microbiol Rev. 2000;13(1):83-121

FCYTG
75445

Cytomegalovirus IgG Avidity

Clinical Information: Discrimination between recent (primary) and past cytomegalovirus (CMV) infection can be an important tool in the clinical management of pregnant women. Although nearly all individuals with recent CMV infection are positive for CMV IgM, individuals with past CMV may also express CMV IgM due to long-term IgM persistence or viral reactivation; thus, detection of CMV IgM is not a reliable indicator of recent CMV infection. Measurement of CMV IgG avidity can assist in discriminating recent from past CMV infection. A low avidity index is a reliable indicator of CMV infection within the previous 6 months, a high avidity index essentially excludes the possibility that infection occurred within the previous 4 months. Avidity index values should be considered within the context of other laboratory findings and clinical signs.

Interpretation:

Reference Values:
>0.70

ANCA2
610030

Cytoplasmic Neutrophil Antibodies, Inflammatory Bowel Disease Panel, Serum

Clinical Information: Inflammatory bowel disease (IBD) refers to 2 diseases-ulcerative colitis (UC) and Crohn disease (CD), both of which result from chronic inflammation in the gastrointestinal (GI) tract.(1) CD is characterized by chronic diarrhea, abdominal pain, and fatigue.(2) In comparison, UC frequently presents with bloody diarrhea that is of an urgent nature.(3) Inflammation in UC most frequently affects the rectum and proximal colon and presents with continue mucosal involvement. In CD, inflammation can affect almost any area of the GI tract and is usually evidenced as patchy, transmural lesions. Diagnosis of IBD is primarily based on clinical evaluation, endoscopy with biopsy, and imaging studies.(4) Because CD and UC are characterized by GI inflammation, fecal calprotectin can be used to differentiate IBD from noninflammatory conditions such as irritable bowel syndrome (IBS). Fecal calprotectin is useful in excluding IBD as a diagnosis and avoiding unnecessary endoscopic or imaging procedures. CD and UC are associated with the presence of various antimicrobial and autoantibodies.(5) Patients with UC often have measurable antineutrophil cytoplasmic antibodies (ANCA), which react with as yet uncharacterized target antigens in human neutrophils; in contrast, patients with CD often have measurable IgA and/or IgG antibodies, which react with cell wall mannan of Saccharomyces cerevisiae. Despite these associations, current guidelines indicate that testing for these antibodies is not sufficiently sensitive for use in the diagnosis of IBD.(2,3) Rather, these antibodies should be limited to distinguishing between CD and UC in cases where the specific diagnosis is unclear based on pathologic and imaging studies.

Useful For: Measurement of antineutrophil cytoplastic antibodies as a part of a profile to aid in distinguishing between ulcerative colitis and Crohn disease in patients for whom the specific diagnosis is unclear based on endoscopic, pathologic, and imaging evaluations This test is not useful for determining the extent of disease in patients with inflammatory bowel disease or determining the response to disease-specific therapy including surgical resection of diseased intestine.

Interpretation: The presence of antineutrophil cytoplasmic antibodies (ANCA) in the absence of IgA and IgG anti-Saccharomyces cerevisiae antibodies (ASCA) is consistent with the diagnosis of ulcerative colitis; the presence of IgA and IgG ASCA in the absence of ANCA is consistent with Crohn disease.

Reference Values:
Only orderable as part of a profile. For more information see IBDP2 / Inflammatory Bowel Disease Serology Panel, Serum.

Clinical References: 1. Rose NR, Mackay IR, eds. Inflammatory bowel diseases. In: The Autoimmune Diseases. Elsevier; 2008 2. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE: ACG Clinical Guideline: Management of Crohn's disease in adults. Am J Gastroenterol. 2018 Apr;113(4):481-517 3. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD: ACG Clinical Guideline: Ulcerative colitis in adults. Am J Gastroenterol. 2019 Mar;114(3):384-413 4. Clark C, Turner J: Diagnostic modalities for inflammatory bowel disease: Serologic markers and endoscopy. Surg Clin North Am. 2015 Dec;95(6):1123-1141 5. Zhou G, Song Y, Yang W, et al: ASCA, ANCA, ALCA and many more: Are they useful in the diagnosis of inflammatory bowel disease? Dig Dis. 2016;34(1-2):90-97

ANCA
9441

Cytoplasmic Neutrophil Antibodies, Serum

Clinical Information: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides are characterized by a pauci-immune inflammation within the walls of small blood vessels (1). There are 3 specific diseases which are identified as ANCA-associated vasculitides: microscopic polyangiitis (MPA), granulomatosus with polyangiitis (GPA), and eosinophilic granulomatosus with polyangiitis (EGPA). The serological hallmark of these disorders is the presence of ANCA, which are antibodies that bind to cytoplasmic antigens found in the granules of neutrophils (2). Patients with GPA frequently have antibodies specific for proteinase 3 (PR3), while individuals with MPA or EGPA are more likely to have antibodies that bind to myeloperoxidase (MPO). The presence of PR3-ANCA and MPO-ANCA can be detected using antigen-specific immunoassays or indirect immunofluorescence (IIF). IIF is performed most commonly using ethanol-fixed neutrophils. Using this substrate, anti-PR3 antibodies produce a granular cytoplasmic staining pattern, which is referred to as cANCA. In comparison, due to an artefact that is a result of the fixation process, anti-MPO antibodies display a perinuclear pattern, or pANCA. Patients with suspected ANCA-associated vasculitis should be evaluated for the presence of PR3-ANCA, MPO-ANCA and ANCA by IIF. A consensus guideline published in 2017 recommends that patients with possible GPA or MPA be tested for PR3-ANCA and MPO-ANCA using antigen-specific immunoassays (3). ANCA by IIF should then be used in cases where there is a high degree of suspicion for GPA or MPA but the PR3-ANCA and MPO-ANCA testing is negative. This guideline also suggests that ANCA may be used in situations where a low positive PR3-ANCA or MPO-ANCA is detected, to improve specificity of the testing. The classification criteria for MPA, GPA and EGPA published by the American College of Rheumatology and the European Alliance of Associations for Rheumatology include PR3-ANCA and MPO-ANCA detected by either antigen-specific immunoassay or IIF (4-6). These classification criteria incorporate serological ANCA testing along with clinical symptoms, imaging, and biopsy results to determine a score which allows for the classification of the various ANCA-associated vasculitides.

Useful For: Evaluating patients with clinical features of ANCA-associated vasculitis, specifically granulomatosus with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosus with polyangiitis

Interpretation: Positive results for proteinase 3 (PR3) antineutrophil cytoplasmic antibodies (ANCA) by antigen-specific immunoassay and cANCA by indirect immunofluorescence are consistent with the diagnosis of granulomatosus with polyangiitis, in patients with the appropriate clinical presentation. Positive results for myeloperoxidase-ANCA by antigen-specific immunoassay and pANCA by indirect immunofluorescence are consistent with the diagnosis of microscopic polyangiitis or eosinophilic granulomatosus with polyangiitis, in patients with the appropriate clinical presentation.

Reference Values:
<1:4 (Negative)

Clinical References: 1. Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. Nat Rev Dis Primers. 2020:6(1):71 2. Ramponi G, Folci M, De Santis M, et al. The biology, pathogenetic role, clinical implications, and open issues of serum anti-neutrophil cytoplasmic antibodies. Autoimmun Rev. 2021:20(3):102759 3. Bossuyt X, Cohen Tervaert W, Arimura Y, et al. Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol. 2017:13(11):683-692 4. Suppiah R, Robson JC, Grayson PC, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. Ann Rheum Dis. 2022;81(3):321-326. doi:10.1136/annrheumdis-2021-221796 5. Robson JC, Grayson PC, Ponte C, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. Ann Rheum Dis. 2022;81(3):315-320. doi:10.1136/annrheumdis-2021-221795 6. Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. Ann Rheum Dis. 2022;81(3):309-314. doi:10.1136/annrheumdis-2021-221794

DDITT
40936

D-Dimer, Plasma

Clinical Information: The specific degradation of fibrin (ie, fibrinolysis) is the reactive mechanism responding to the formation of fibrin. Plasmin is the fibrinolytic enzyme derived from inactive plasminogen. Plasminogen is converted into plasmin by plasminogen activators. The main plasminogen activators are tissue plasminogen activator (tPA) and pro-urokinase, which is activated into urokinase (UK) by, among others, the contact system of coagulation. In the bloodstream, plasmin is rapidly and specifically neutralized by alpha-2-antiplasmin, thereby restricting its fibrinogenolytic activity and localizes the fibrinolysis on the fibrin clot. On the fibrin clot, plasmin degrades fibrin into various products (ie, D-dimers). Antibodies specific for these products, which do not recognize fibrinogen, have been developed. The presence of these various fibrin degradation products, among which D-dimer is the terminal product, is the proof that the fibrinolytic system is in action in response to coagulation activation. Elevated D-dimer levels are found in association with disseminated intravascular coagulation (DIC), pulmonary embolism (PE), deep vein thrombosis (DVT), trauma, and bleeding. D-dimer may also be increased in association with pregnancy, liver disease, malignancy, inflammation, or a chronic hypercoagulable state.

Useful For: Excluding the diagnosis of acute pulmonary embolism or deep vein thrombosis, particularly when results of a sensitive D-dimer assay are combined with clinical information, including pretest disease probability(1-4) Diagnosis of intravascular coagulation and fibrinolysis, also known as disseminated intravascular coagulation, especially when combined with clinical information and other laboratory test data (eg, platelet count, assays of clottable fibrinogen and soluble fibrin monomer complex, and clotting time assays-prothrombin time and activated partial thromboplastin time)(5)

Interpretation: A normal D-dimer result of 500 ng/mL or less fibrinogen equivalent units (FEU) on the IL D-Dimer HS500 kit has a negative predictive value of approximately 100% (range 97%-100%) and is FDA approved for the exclusion of acute pulmonary embolism (PE) and deep vein thrombosis (DVT) when there is low or moderate pretest probability for PE or DVT. D-dimer concentrations increase with age and, therefore, the specificity for DVT and PE exclusion decreases with age. For DVT or PE exclusion, in addition to clinical pretest probability, age-adjusted D-dimer cutoffs are suggested for patients older than 50 years of age. Recent evidence suggests using clinical pretest probability and age-adjusted cutoffs to improve the performance of D-dimer testing in patients older than 50 years of age. In recent studies, when compared to a fixed D-dimer cutoff, age-adjusted D-dimer cutoff values (calculated as follows: age [years] x 10 ng/mL) resulted in equivalent outcomes and no additional false negative findings.(6-7) Increased D-dimer values are abnormal but do not indicate a specific disease state. D-dimer values may be increased as a result of: -Clinical or subclinical disseminated intravascular coagulation/intravascular coagulation and fibrinolysis -Other conditions associated with increased activation of the procoagulant and fibrinolytic mechanisms such as recent surgery, active or recent bleeding, hematomas, trauma, or thromboembolism -Association with pregnancy, liver disease, inflammation, malignancy, or hypercoagulable (procoagulant) states The degree of D-dimer increase does not definitely correlate with the clinical severity of associated disease states.

Reference Values:
< or =500 ng/mL Fibrinogen Equivalent Units (FEU)
D-dimer values < or =500 ng/mL FEU may be used in conjunction with clinical pretest probability to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE).

Clinical References: 1. Brill-Edward P, Lee A: D-dimer testing in the diagnosis of acute venous thromboembolism. Thromb Haemost. 1999 August;82(2):688-694 2. Heit JA, Minor TA, Andrews JC, Larson DR, Li H, Nichols WL: Determinants of plasma fibrin D-dimer sensitivity for acute pulmonary embolism as defined by pulmonary angiography. Arch Pathol Lab Med. 1999 March;123(3):235-240. doi: 10.1043/0003-9985(1999)123. 3. Heit JA, Meyers BJ, Plumhoff EA, Larson DR, Nichols WL: Operating characteristics of automated latex immunoassay tests in the diagnosis of angiographically-defined acute pulmonary embolism. Thromb Haemost. 2000 June;83(6):970 4. Bates SM, Grand'Maison A, Johnston M,

Naguit I, Kovacs MJ, Ginsberg JS: A latex D-dimer reliably excludes venous thromboembolism. Arch Intern Med. 2001 February;161(3):447-453. doi: 10.1001/archinte.161.3.447. 5. Levi M, Ten Cate H: Disseminated intravascular coagulation. N Engl J Med. 1999 Aug 19;341(8):586-592. doi: 10.1056/NEJM199908193410807. 6. Righini M, Van Es J, Den Exter PL, et al: Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA. 2014 Mar 19;311(11):1117-1124. doi:10.1001/jama.2014.2135 7. Schouten HJ, Geersing GJ, Koek HL, et al: Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. BMJ. 2012;346:f2492. doi: 10.1136/bmj.f2492. 8. Feinstein DI, Marder VJ, Colman RW: Consumptive thrombohemorrhagic disorders. In: Colman RW, Hirsh J, Marder VJ, et al. eds. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. 3rd ed. JB Lippincott Co.; 2001;1197-1234

DIMER
602174

D-Dimer, Plasma

Clinical Information: Thrombin, the terminal enzyme of the plasma procoagulant cascade, cleaves fibrinopeptides A and B from fibrinogen, generating fibrin monomer. Fibrin monomer contains D domains on each end of the molecule and a central E domain. Most of the fibrin monomers polymerize to form insoluble fibrin, or the fibrin clot, by repetitive end-to-end alignment of the D domains of 2 adjacent molecules in lateral contact with the E domain of a third molecule. The fibrin clot is subsequently stabilized by thrombin-activated factor XIII, which covalently cross-links fibrin monomers by transamidation, including dimerization of the D domains of adjacently polymerized fibrin monomers. The fibrin clot promotes activation of fibrinolysis by catalyzing the activation of plasminogen (by plasminogen activators) to form plasmin enzyme. Plasmin proteolytically degrades cross-linked fibrin, ultimately producing soluble fibrin degradation products of various sizes that include cross-linked fragments containing neoantigenic D-dimer (DD) epitopes. Plasmin also degrades fibrinogen to form fragments X, Y, D, and E. D-dimer immunoassays use monoclonal antibodies to DD neoantigen and mainly detect cross-linked fibrin degradation products, whereas the fibrino(geno)lytic degradation products-X, Y, D, and E, and their polymers may be derived from fibrinogen or fibrin. Therefore, the blood content of D-dimer indirectly reflects the generation of thrombin and plasmin, roughly indicating the turnover or activation state of the coupled blood procoagulant and fibrinolytic mechanisms.

Useful For: Diagnosis of intravascular coagulation and fibrinolysis, also known as disseminated intravascular coagulation, especially when combined with clinical information and other laboratory test data (eg, platelet count, assays of clottable fibrinogen and soluble fibrin monomer complex, and clotting time assays-prothrombin time and activated partial thromboplastin time) Exclusion of the diagnosis of acute pulmonary embolism or deep vein thrombosis, particularly when results of a sensitive D-dimer assay are combined with clinical information, including pretest disease probability

Interpretation: D-dimer values less than or equal to500 ng/mL fibrinogen-equivalent units (FEU) are normal. Within the reportable normal range (220-500 ng/mL FEU), measured values may reflect the activation state of the procoagulant and fibrinolytic systems, but the clinical utility of such quantitation is not established. A normal D-dimer result (< or =500 ng/mL FEU) has a negative predictive value of approximately 95% for the exclusion of acute pulmonary embolism (PE) or deep vein thrombosis when there is low or moderate pretest PE probability. Increased D-dimer values are abnormal but do not indicate a specific disease state. D-dimer values may be increased as a result of: -Clinical or subclinical intravascular coagulation and fibrinolysis (ICF)/disseminated intravascular coagulopathy (DIC). -Other conditions associated with increased activation of the procoagulant and fibrinolytic mechanisms such as recent surgery, active or recent bleeding, hematomas, trauma, or thromboembolism. -Association with pregnancy, liver disease, inflammation, malignancy or hypercoagulable (procoagulant) states. The degree of D-dimer increase does not definitely correlate with the clinical severity of associated disease states.

Reference Values:
Only orderable as part of a profile or reflex. For more information see:
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
AATHR / Thrombophilia Profile, Plasma and Whole Blood
APROL / Prolonged Clot Time Profile, Plasma
ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma
ALUPP / Lupus Anticoagulant Profile, Plasma

< or =500 ng/mL Fibrinogen Equivalent Units (FEU)
D-dimer values < or =500 ng/mL FEU may be used in conjunction with clinical pretest probability to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE).

Clinical References: Favaloro EJ, Lippi G. eds. Hemostasis and Thrombosis: Methods and Protocols. 1st ed. Humana Press; 2017

DLAC
8878

D-Lactate, Plasma

Clinical Information: D-lactate is produced by bacteria residing in the colon when carbohydrates are not completely absorbed in the small intestine. When large amounts of D-lactate are present, individuals can experience metabolic acidosis, altered mental status (from drowsiness to coma), and a variety of other neurologic symptoms, in particular dysarthria and ataxia. Although a temporal relationship has been described between elevations of plasma and urine D-lactate and the accompanying encephalopathy, the mechanism of neurologic manifestations has not been elucidated. D-lactic acidosis is typically observed in patients with a malabsorptive disorder, such as short-bowel syndrome, or following a jejunoileal bypass. In addition, healthy children presenting with gastroenteritis may also develop the clinical presentation of D-lactic acidosis. Routine lactic acid determinations in blood will not reveal abnormalities because most lactic acid assays measure only L-lactate. Accordingly, D-lactate analysis must be specifically requested (eg, this test). However, as D-lactate is readily excreted in urine, it is the preferred specimen for D-lactate determinations; see DLAU / D-Lactate, Urine.

Useful For: As an adjunct to urine D-lactate (preferred) for the diagnosis of D-lactate acidosis

Interpretation: Increased levels are consistent with D-lactic acidosis. However, because D-lactate is readily excreted, urine determinations are preferred.

Reference Values:
0.0-0.25 mmol/L

Clinical References: 1. Khrais A, Ali H, Choi S, Ahmed A, Ahlawat S. D-Lactic acidosis in short bowel syndrome. Cureus. 2022;14(5):e25471. doi:10.7759/cureus.25471 2. Bianchetti DGAM, Amelio GS, Lava SAG, et al. D-lactic acidosis in humans: systematic literature review. Pediatr Nephrol. 2018;33(4):673-681. doi:10.1007/s00467-017-3844-8

DLAU
8873

D-Lactate, Urine

Clinical Information: D-lactate is produced by bacteria residing in the colon when carbohydrates are not completely absorbed in the small intestine. When large amounts of D-lactate are present, individuals can experience metabolic acidosis, altered mental status (from drowsiness to coma) and a variety of other neurologic symptoms, in particular dysarthria and ataxia. Although a temporal relationship has been described between elevations of plasma and urine D-lactate and the accompanying encephalopathy, the

mechanism of neurologic manifestations has not been elucidated. D-lactic acidosis is typically observed in patients with a malabsorptive disorder, such as short-bowel syndrome, or following jejunoileal bypass. In addition, healthy children presenting with gastroenteritis may also develop the clinical presentation of D-lactic acidosis. Routine lactic acid determinations in blood will not reveal abnormalities because most lactic acid assays measure only L-lactate. Accordingly, D-lactate analysis must be specifically requested (eg, DLAC / D-Lactate, Plasma). However, as D-lactate is readily excreted in urine, this is the preferred specimen for D-lactate determinations.

Useful For: Preferred test for diagnosing D-lactate acidosis, especially in patients with jejunoileal bypass and short-bowel syndrome

Interpretation: Increased levels are diagnostic.

Reference Values:
0.0-0.25 mmol/L

Clinical References: 1. Brandt RB, Siegel SA, Waters MG, Bloch MH. Spectrophotometric assay for D-(-)-lactate in plasma. Anal Biochem. 1980;102(1):39-46 2. Khrais A, Ali H, Choi S, Ahmed A, Ahlawat S. D-Lactic Acidosis in Short Bowel Syndrome. Cureus. 2022;14(5):e25471. doi:10.7759/cureus.25471 3. Bianchetti DGAM, Amelio GS, Lava SAG, et al. D-lactic acidosis in humans: systematic literature review. Pediatr Nephrol. 2018;33(4):673-681. doi:10.1007/s00467-017-3844-8

DAGR
31768

Dairy and Grain Allergen Profile, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to dairy and grain Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In. McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070

DAND
82694

Dandelion, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to dandelion Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

DATE
82358

Date, Fruit, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to date, fruit Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

DATRE
82481

Date, Tree, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to date, tree Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

DCALP
622511

Decalcification (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

DOCK8
608112

Dedicator of Cytokinesis 8 (DOCK8) Deficiency, Blood

Clinical Information: Dedicator of cytokinesis 8 (DOCK8) is an atypical guanine exchange factor that plays a role in regulating actin polymerization and cytoskeletal rearrangement. DOCK8 is important in both innate and adaptive immunity by contributing to cellular migration, cytotoxicity, antibody production, and immunological memory. DOCK8 deficiency is a rare, combined immunodeficiency with an autosomal recessive inheritance that typically presents in childhood. Its clinical features include atopic disease, recurrent sinopulmonary infections, cutaneous viral infection, Staphylococcus aureus skin infections, and cancer. DOCK8 deficiency is diagnosed based on clinical phenotype, immunologic findings, and molecular analysis. Diseases in the differential diagnosis include Job syndrome (AD-HIES), ZNF341 deficiency, and severe atopic dermatitis. Assessment of DOCK8 expression on immune cells is an important component and facilitates the diagnosis of this condition and the timely treatment of the patient.

Useful For: Aiding in the diagnosis of dedicator of cytokinesis 8 (DOCK8) deficiency This test is not useful for assessing DOCK8 carrier status.

Interpretation: The results will be reported as the percentage of dedicator of cytokinesis 8 (DOCK8) expression on T cells, B cells, natural killer (NK) cells, and monocytes. The absence of DOCK8 expression on all cell types will be consistent with DOCK8 deficiency. In this case, genetic analysis of DOCK8 to confirm the diagnosis and to identify the underlying alteration will be recommended. The expression of DOCK8 on a subset of T cells and/or NK cells could suggest somatic reversion in a patient with DOCK8 deficiency, which can modulate disease phenotype over time.

Reference Values:
The appropriate reference values will be provided on the report.

Clinical References: 1. Engelhardt KR, McGhee S, Winkler S, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. J Allergy Clin Immunol. 2009; 124(6):1289-302 e4. doi:10.1016/j.jaci.2009.10.038 2. Jing H, Zhang Q, Zhang Y, et al. Somatic reversion in dedicator of cytokinesis 8 immunodeficiency modulates disease phenotype. J Allergy Clin Immunol. 2014;133(6):1667-1675. doi:10.1016/j.jaci.2014.03.025 3. Pai SY, de Boer H, Massaad MJ, et al. Flow cytometry diagnosis of dedicator of cytokinesis 8 (DOCK8) deficiency. J Allergy Clin Immunol. 2014;134(1):221-223. doi:10.1016/j.jaci.2014.02.023 4. Engelhardt KR, Gertz ME, Keles S, et al. The extended clinical phenotype of 64 patients with dedicator of cytokinesis 8 deficiency. J Allergy Clin Immunol. 2015;136(2):402-412. doi:10.1016/j.jaci.2014.12.1945 5. Su HC, Jing H, Angelus P, Freeman AF. Insights into immunity from clinical and basic science studies of DOCK8 immunodeficiency syndrome. Immunol Rev. 2019;287(1):9-19. doi:10.1111/imr.12723 6. Aydin SE, Freeman AF, Al-Herz W, et al. Hematopoietic stem cell transplantation as treatment for patients with DOCK8 deficiency. J Allergy Clin Immunol Pract. 2019;7(3):848-855. doi:10.1016/j.jaip.2018.10.035

DHEA_
81405

Dehydroepiandrosterone (DHEA), Serum

Clinical Information: Dehydroepiandrosterone (DHEA) is the principal human C-19 steroid. DHEA has very low androgenic potency but serves as the major direct or indirect precursor for most sex steroids. DHEA is secreted by the adrenal gland and production is at least partly controlled by adrenocorticotropic hormone (ACTH). The bulk of DHEA is secreted as a 3-sulfoconjugate dehydroepiandrosterone sulfate (DHEAS). Both hormones are albumin bound, but DHEAS binding is much tighter. As a result, circulating concentrations of DHEAS are much higher (>100-fold) compared to DHEA. In most clinical situations, DHEA and DHEAS results can be used interchangeably. In gonads and several other tissues, most notably skin, steroid sulfatases can convert DHEAS back to DHEA, which can then be metabolized to stronger androgens and to estrogens. During pregnancy, DHEA/DHEAS and their 16-hydroxylated metabolites are secreted by the fetal adrenal gland in large quantities. They serve as precursors for placental production of the dominant pregnancy estrogen, estriol. Within weeks after birth, DHEA/DHEAS levels fall by 80% or more and remain low until the onset of adrenarche at age 7 or 8 in girls and age 8 or 9 in boys. Adrenarche is a poorly understood phenomenon, peculiar to higher primates, that is characterized by a gradual rise in adrenal androgen production. It precedes puberty but is not casually linked to it. Early adrenarche is not associated with early puberty or with any reduction in final height or overt androgenization. However, girls with early adrenarche may be at increased risk of polycystic ovarian syndrome as adults and some boys may develop early penile enlargement. Following adrenarche, DHEA/DHEAS levels increase until the age of 20 to a maximum roughly comparable to that observed at birth. Levels then decline over the next 40 to 60 years to around 20% of peak levels. The clinical significance of this age-related drop is unknown, and trials of DHEA/DHEAS replacement in older individuals have not produced convincing benefits. However, in younger and older patients with primary adrenal failure, the addition of DHEA/DHEAS to corticosteroid replacement has been shown in some studies to improve mood, energy, and sex drive. Elevated DHEA/DHEAS levels can cause signs or symptoms of hyperandrogenism in women. Men are usually asymptomatic but, through peripheral conversion of androgens to estrogens, can occasionally experience mild estrogen excess. Most mild-to-moderate elevations in DHEAS levels are idiopathic. However, pronounced elevations of DHEA/DHEAS may be indicative of androgen-producing adrenal tumors. In small children, congenital adrenal hyperplasia (CAH) due to 3 beta-hydroxysteroid dehydrogenase deficiency is associated with excessive DHEA/DHEAS production. Lesser elevations may be observed in 21-hydroxylase deficiency (the most common form of CAH) and 11 beta-hydroxylase deficiency. By contrast, steroidogenic acute regulatory protein or 17 alpha-hydroxylase deficiency is characterized by low DHEA/DHEAS levels. For more information see Steroid Pathways.

Useful For: Diagnosing and differential diagnosis of hyperandrogenism (in conjunction with measurements of other sex steroids) As an initial screen in adults with bioavailable testosterone measurement that may be supplemented with measurements of sex hormone-binding globulin and occasionally other androgenic steroids (eg, 17-hydroxyprogesterone), depending on results An adjunct in the diagnosis of congenital adrenal hyperplasia (CAH); DHEA/DHEAS measurements play a secondary role to the measurements of cortisol/cortisone, 17 alpha-hydroxyprogesterone, and androstenedione Diagnosing and differential diagnosis of premature adrenarche

Interpretation: Elevated dehydroepiandrosterone (DHEA)/dehydroepiandrosterone sulfate (DHEAS) levels indicate increased adrenal androgen production. Mild elevations in adults are usually idiopathic, but levels 5-fold or more of the upper limit of normal can suggest the presence of an androgen-secreting adrenal tumor. DHEA/DHEAS levels are elevated in greater than 90% of patients with such tumors. This is particularly true for androgen-secreting adrenal carcinomas, as they have typically lost the ability to produce downstream androgens, such as testosterone. By contrast, androgen-secreting adrenal adenomas may also produce excess testosterone and secrete lesser amounts of DHEA/DHEAS. Patients with congenital adrenal hyperplasia (CAH) may show very high levels of DHEA/DHEAS, often 5-fold to 10-fold elevations. However, with the possible exception of 3 beta-hydroxysteroid dehydrogenase deficiency, other steroid analytes offer better diagnostic accuracy than DHEA/DHEAS measurements. Consequently, DHEA/DHEAS testing should not be used as the primary tool for CAH diagnosis. Similarly, discovering a high DHEA/DHEAS level in an infant or child with symptoms or signs of possible CAH should prompt additional testing, as should the discovery of very high DHEA/DHEAS levels in an adult. In the latter case, adrenal tumors need to be excluded, and additional adrenal steroid profile testing may assist in diagnosing nonclassical CAH. For more information see Steroid Pathways.

Reference Values:

Premature: <40 ng/mL*
0-1 day: <11 ng/mL*
2-6 days: <8.7 ng/mL*
7 days-1 month: <5.8 ng/mL*
>1-23 months: <2.9 ng/mL*
2-5 years: <2.3 ng/mL
6-10 years: <3.4 ng/mL
11-14 years: <5.0 ng/mL
15-18 years: <6.6 ng/mL
19-30 years: <13 ng/mL
31-40 years: <10 ng/mL
41-50 years: <8.0 ng/mL
51-60 years: <6.0 ng/mL
> or =61 years: <5.0 ng/mL

*Source: Dehydroepiandrosterone. In: Soldin SJ, Brugnara C, Wong Ed, eds. Pediatric Reference Ranges. 5th ed. AACC Press; 2005:75

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References:

DHES1 Dehydroepiandrosterone Sulfate, Serum

113595

Clinical Information: Dehydroepiandrosterone (DHEA) is the principal human C-19 steroid.

DHEA has very low androgenic potency but serves as the major direct or indirect precursor for most sex steroids. DHEA is secreted by the adrenal gland and production is at least partly controlled by adrenocorticotropic hormone. The bulk of DHEA is secreted as a 3-sulfoconjugate (DHEA-S). Both hormones are albumin bound, but binding of DHEA-S is much tighter. In gonads and several other tissues, most notably skin, steroid sulfatases can convert DHEA-S back to DHEA, which can then be metabolized to stronger androgens and to estrogens. During pregnancy, DHEA-S and its 16-hydroxylated metabolites are secreted by the fetal adrenal gland in large quantities. They serve as precursors for placental production of the dominant pregnancy-related estrogen, estriol. Within weeks after birth, DHEA-S levels fall by 80% or more and remain low until the onset of adrenarche. Adrenarche is a poorly understood phenomenon peculiar to higher primates, which is characterized by a gradual rise in adrenal androgen production. It precedes puberty but is not causally linked to it. Early adrenarche is not associated with early puberty or with any reduction in final height or overt androgenization and is generally regarded as a benign condition, not needing intervention. However, girls with early adrenarche may be at increased risk of polycystic ovarian syndrome as adults, and some boys may develop early penile enlargement. Following adrenarche, DHEA-S levels increase until the age of 20, up to maximum levels roughly comparable to that observed at birth. Levels then decline over the next 40 to 60 years to around 20% of peak levels. The clinical significance of this age-related drop is unknown and trials of DHEA-S replacement in the elderly have not produced convincing benefits. However, in young and old patients with primary adrenal failure, the addition of DHEA-S to corticosteroid replacement has been shown in some studies to improve mood, energy, and sex drive. Elevated DHEA-S levels can cause symptoms or signs of hyperandrogenism in women. Men are usually asymptomatic, but through peripheral conversion of androgens to estrogens can occasionally experience mild estrogen excess. Most mild to moderate elevations in DHEA-S levels are idiopathic. However, pronounced elevations of DHEA-S may be indicative of androgen-producing adrenal tumors. In small children, congenital adrenal hyperplasia (CAH) due to 3 beta-hydroxysteroid deficiency is associated with excessive DHEA-S production. Lesser elevations may be observed in 21-hydroxylase deficiency (the most common form of CAH) and 11 beta-hydroxylase deficiency. By contrast, steroidogenic acute regulatory protein or 17 alpha-hydroxylase deficiencies are characterized by low DHEA-S levels. An initial workup in adults might also include total and bioavailable testosterone (TTBS / Testosterone, Total and Bioavailable, Serum) measurements. Depending on results, this may be supplemented with measurements of sex hormone-binding globulin (SHBG /Sex Hormone-Binding Globulin [SHBG], Serum) and occasionally other androgenic steroids (eg, 17-hydroxyprogesterone).

Useful For: Diagnosis and differential diagnosis of hyperandrogenism (in conjunction with measurements of other sex steroids) An adjunct in the diagnosis of congenital adrenal hyperplasia Diagnosis and differential diagnosis of premature adrenarche

Interpretation: Elevated dehydroepiandrosterone sulfate (DHEA-S) levels indicate increased adrenal androgen production. Mild elevations in adults are usually idiopathic, but levels of 600 mcg/dL or more can suggest the presence of an androgen-secreting adrenal tumor. DHEA-S levels are elevated in more than 90% of patients with such tumors, usually well above 600 mcg/dL. This is particularly true for androgen-secreting adrenal carcinomas, as they have typically lost the ability to produce down-stream androgens, such as testosterone. By contrast, androgen-secreting adrenal adenomas may also produce excess testosterone and secrete lesser amounts of DHEA-S. Patients with congenital adrenal hyperplasia (CAH) may show very high levels of DHEA-S, often 5- to 10-fold elevations. However, with the possible exception of 3 beta-hydroxysteroid dehydrogenase deficiency, other steroid analytes offer better diagnostic accuracy than DHEA-S measurements. Consequently, DHEA-S testing should not be used as the primary tool for CAH diagnosis. Similarly, discovering a high DHEA-S level in an infant or child with symptoms or signs of possible CAH should prompt additional testing, as should the discovery of very high DHEA-S levels in an adult. In the latter case, adrenal tumors need to be excluded and additional adrenal steroid profile testing may assist in diagnosing nonclassical CAH. Girls below the age of 7 to 8 and boys before age 8 to 9, who present with early development of pubic hair, or, in boys, penile enlargement, may be suffering from either premature adrenarche or premature puberty or both. Measurement of DHEA-S (DHES / Dehydroepiandrosterone Sulfate [DHEA-S], Serum),

dehydroepiandrosterone (DHEA_ / Dehydroepiandrosterone [DHEA], Serum), and androstenedione (ANST / Androstenedione, Serum), alongside determination of sensitive estradiol (EEST / Estradiol, Serum), testosterone and bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum), or free testosterone (TGRP / Testosterone, Total and Free, Serum), sex hormone-binding globulin (SHBG / Sex Hormone-Binding Globulin [SHBG], Serum), and luteinizing hormone (LH / Luteinizing Hormone [LH], Serum)/follicle-stimulating hormone (FSH / Follicle-Stimulating Hormone [FSH], Serum) levels will allow correct diagnosis in most cases. In premature adrenarche, only the adrenal androgens, chiefly DHEA-S, will be above prepubertal levels, whereas early puberty will also show a fall in SHBG levels and variable elevations of gonadotropins and gonadal sex-steroids above the prepuberty reference range. Levels of DHEA-S do not show significant diurnal variation. Many drugs and hormones can result in changes in DHEA-S levels. Whether any of these secondary changes in DHEA-S levels are of clinical significance and how they should be related to the established normal reference ranges is unknown. In most cases, the drug-induced changes are not large enough to cause diagnostic confusion, but when interpreting mild abnormalities in DHEA-S levels, drug and hormone interactions should be taken into account. Examples of drugs and hormones that can reduce DHEA-S levels include: insulin, oral contraceptive drugs, corticosteroids, central nervous system agents that induce hepatic enzymes (eg, carbamazepine, clomipramine, imipramine, phenytoin), many antilipemic drugs (eg, statins, cholestyramine), dopaminergic drugs (eg, levodopa/dopamine, bromocriptine), fish oil, and vitamin E. Drugs that may increase DHEA-S levels include metformin, troglitazone, prolactin, many neuroleptic drugs (by indirect implication)), danazol, calcium channel blockers (eg, diltiazem, amlodipine), and nicotine.

Reference Values:

Clinical References:

THCCR 616333 Delta 9-Carboxy-Tetrahydrocannabinol (THC-COOH) Confirmation and Creatinine Ratio, Random, Urine

Clinical Information: Delta-9-tetrahydrocannabinol (THC) is the active agent of the popularly abused/used drug, cannabis/marijuana. Following consumption of the drug, either by inhalation or ingestion, it is metabolized to a variety of inactive chemicals, one of them being delta-9-tetrahydrocannabinol carboxylic acid (delta-9-THC-COOH). For confirmation of abstinence, urine analysis is a useful tool. The presence of delta-9-THC-COOH is a strong indicator that a patient has used cannabis/marijuana. However, increases in urine delta-9-THC-COOH concentrations resulting from changes in urinary output may be mistakenly interpreted as new drug use rather than carryover from previous drug exposure. Individuals continue to excrete THC-COOH days after abstinence, and although concentrations generally decrease with time, the concentrations can fluctuate with levels of hydration. As a result, the division of urinary delta-9-THC-COOH concentrations by creatinine produces a metabolite/creatinine ratio that should decrease until a new episode of drug use occurs. Delta-9-THC-COOH/creatinine ratios of specimens collected over time can be compared to determine if new cannabis/marijuana use has occurred.

Useful For: Measuring the delta-9 carboxy-tetrahydrocannabinol to creatinine ratio to detect use of tetrahydrocannabinol

Interpretation: Delta-9 carboxy-tetrahydrocannabinol (delta-9-THC-COOH) and creatinine concentrations must be obtained for at least 2 urine specimens with a known time interval (1-7 days) between collections. Using these creatinine-normalized delta-9-THC-COOH concentrations, a ratio is

calculated between the concentration of any urine specimen (U2) divided by the concentration in a previously collected urine specimen (U1). The most conservative method for reporting new cannabis/marijuana use between collections would apply a U2/U1 decision ratio equal to the maxima listed in the Table. A more realistic decision ratio with reasonable certainty would be to use the 95% below limits in the same table. U2/U1 ratios above these limits would indicate new usage between those collection time points. Table. Adapted from Smith ML et al. for less than daily users of cannabis/marijuana.(1) Time interval between urine collections (hours) Maximum ratio (U2/U1) 95% Below (U2/U1) 0-23.9 6.29 1.42 24-47.9 2.27 1.01 48-71.9 1.47 0.853 72-95.9 1.63 0.595 96-119.9 0.555 0.347 120-143.9 0.197 0.146 144-167.9 0.080 0.073

Reference Values:

Carboxy-Tetrahydrocannabinol (THC):
Not Detected

Cutoff concentration:
Delta-9 Carboxy-tetrahydrocannabinol by liquid chromatography tandem mass spectrometry: <5.0 ng/mL

Creatinine:
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years.

Clinical References: 1. Smith ML, Barnes AJ, Huestis MA. Identifying new cannabis use with urine creatinine normalized THCCOOH concentrations and time intervals between specimen collections. J Anal Toxicol. 2009;33(4):185-9. doi:10.1093/jat/33.4.185 2. Huestis MA, Cone EJ. Differentiating new marijuana use from residual drug excretion in occasional marijuana users. J Anal Toxicol. 1998;22(6):445-54. doi:10.1093/jat/22.6.445 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 4. Delaney MP, Lamb EJ. Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1256-1323 5. Meeusen J, Rule A, Voskoboev N, Baumann N, Lieske J. Performance of cystatin C- and creatinine-based estimated glomerular filtration rate equations depends on patient characteristics. Clin Chem. 2015;61(10):1265-1272. doi:10.1373/clinchem.2015.243030 6. Newman DJ, Price CP. Renal function and nitrogen metabolites. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 3rd ed. WB Saunders Company; 1999:1204-1270 7. Kasiske BL, Keane WF. Laboratory assessment of renal disease: clearance, urinalysis, and renal biopsy. In: Brenner BM, ed. The Kidney. 6th ed. WB Saunders Company; 2000:1129-1170

THCX
62743

Delta-8 and Delta-9-Carboxy-Tetrahydrocannabinol (THC) Confirmation, Chain of Custody, Random, Urine

Clinical Information: There are over 100 different cannabinoids in cannabis/marijuana. The main psychoactive cannabinoid is delta-9- tetrahydrocannabinol (delta-9-THC), which is the active agent of the popularly abused street drug, cannabis/marijuana. Delta-8 tetrahydrocannabinol (delta-8-THC) is another psychoactive substance found in the Cannabis sativa plant, of which cannabis/marijuana and hemp are 2 varieties. Delta-8 THC is one of over 100 cannabinoids produced naturally by the cannabis plant but is not typically found in significant amounts in the plant itself. As a result, concentrated amounts of delta-8 THC are typically manufactured from hemp-derived cannabidiol. Following consumption of cannabis/marijuana, delta-9-THC metabolizes to a variety of inactive products, one of them being the carboxy metabolite (delta-9-THC-COOH). In almost all medico-legal cases or when the patient adamantly denies cannabis/marijuana use and the immunoassay test is positive, confirmation of the result by a definitive test is required. This test is a definitive, confirmatory test using liquid chromatography tandem

mass spectrometry to identify and quantify delta-8-THC-COOH and delta-9-THC-COOH. Chain of custody is a record of the disposition of a specimen to document the personnel who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detection and confirmation of drug use of cannabis/marijuana and to specifically identify and quantify delta-8 carboxy tetrahydrocannabinol (THC-COOH) and delta-9-THC-COOH Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of delta-8 and/or delta-9 carboxy tetrahydrocannabinol (THC-COOH) in urine is a strong indicator that the patient has used cannabis/marijuana. THC-COOH has a long half-life and can be detected in urine for more than 7 days after a single use. Chronic use causes accumulation of THC and THC-COOH in adipose tissue, such that it is excreted into the urine for as long as 30 to 60 days from the time chronic use is halted.

Reference Values:
Not detected
Positive results are reported with a quantitative result.

Cutoff concentrations:

Immunoassay Screen: 50 ng/mL

Liquid chromatography tandem mass spectrometry:
Delta8- tetrahydrocannabinol (THC): 5.0 ng/mL
Delta-9-THC: 5.0 ng/mL

Clinical References: 1. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 12th ed. Biomedical Publications; 2020 2.Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

THCU
8898

Delta-8 and Delta-9-Carboxy-Tetrahydrocannabinol (THC) Confirmation, Random, Urine

Clinical Information: There are over 100 different cannabinoids in cannabis/marijuana. The main psychoactive cannabinoid is delta-9-tetrahydrocannabinol (delta-9-THC), which is the active agent of the popularly abused street drug, cannabis/marijuana. Delta-8 tetrahydrocannabinol (delta-8 THC) is another psychoactive substance found in the Cannabis sativa plant, of which cannabis/marijuana and hemp are 2 varieties. Delta-8 THC is one of over 100 cannabinoids produced naturally by the cannabis plant but is not typically found in significant amounts in the plant itself. As a result, concentrated amounts of delta-8 THC are typically manufactured from hemp-derived cannabidiol. Following consumption of cannabis/marijuana, delta-9-THC metabolizes to a variety of inactive products, one of them being the carboxy metabolite (delta-9-THC-COOH). In almost all medico-legal cases or when the patient adamantly denies cannabis/marijuana use and the immunoassay test is positive, confirmation of the result by a definitive test is required. This test is a definitive, confirmatory test using liquid chromatography tandem mass spectrometry to identify and quantify delta-8-THC-COOH and delta-9 THC-COOH.

Useful For: Detection and confirmation of drug use of cannabis/marijuana and to specifically identify and quantify delta-8-carboxy tetrahydrocannabinol (THC-COOH) and delta-9-THC-COOH

Interpretation: The presence of delta-8 and/or delta-9 carboxy tetrahydrocannabinol (THC-COOH) in urine is a strong indicator that the patient has used cannabis/marijuana. THC-COOH has a long half-life and can be detected in urine for more than 7 days after a single use. Chronic use causes accumulation of THC and THC-COOH in adipose tissue, such that it is excreted into the urine for as long as 30 to 60 days from the time chronic use is halted.

Reference Values:
Not Detected (Positive results are reported with a quantitative result.)

Cutoff concentration by liquid chromatography tandem mass spectrometry:
Delta-8-Carboxy-Tetrahydrocannabinol (THC): 5.0 ng/mL
Delta-9-Carboxy-Tetrahydrocannabinol (THC): 5.0 ng/mL

Clinical References: 1. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 12th ed. Biomedical Publications; 2020 2. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

THCCU
616334

Delta-9-Carboxy-Tetrahydrocannabinol Confirmation and Creatinine Ratio, Random, Urine

Clinical Information: Delta-9-tetrahydrocannabinol (THC) is the active agent of the popularly abused/used drug, cannabis/marijuana. Following consumption of the drug, either by inhalation or ingestion, it is metabolized to a variety of inactive chemicals, one of them being delta-9-tetrahydrocannabinol carboxylic acid (delta-9-THC-COOH). For confirmation of abstinence, urine analysis is a useful tool. The presence of delta-9-THC-COOH is a strong indicator that a patient has used cannabis/marijuana. However, increases in urine delta-9-THC-COOH concentrations resulting from changes in urinary output may be mistakenly interpreted as new drug use rather than carryover from previous drug exposure. Individuals continue to excrete THC-COOH for days after abstinence, and although concentrations generally decrease with time, the concentrations can fluctuate with levels of hydration. As a result, the division of urinary delta-9-THC-COOH concentrations by creatinine produces a metabolite/creatinine ratio that should decrease until a new episode of drug use occurs. Delta-9-THC-COOH/creatinine ratios of specimens collected over time can be compared to determine if new cannabis/marijuana use has occurred.

Useful For: Measuring the delta-9 carboxy-tetrahydrocannabinol to creatinine ratio as a part of a profile

Interpretation: Delta-9 carboxy-tetrahydrocannabinol (delta-9-THC-COOH) and creatinine concentrations must be obtained for at least 2 urine specimens with a known time interval (1-7 days) between collections. Using these creatinine-normalized delta-9-THC-COOH concentrations, a ratio is calculated between the concentration of any urine specimen (U2) divided by the concentration in a previously collected urine specimen (U1). The most conservative method for reporting new cannabis/marijuana use between collections would apply a U2/U1 decision ratio equal to the maxima listed in the Table. A more realistic decision ratio with reasonable certainty would be to use the 95% below limits in the same table. U2/U1 ratios above these limits would indicate new usage between those collection time points. Table. Adapted from Smith ML et al. for less than daily users of cannabis/marijuana.(1) Time interval between urine collections (hours) Maximum ratio (U2/U1) 95% Below (U2/U1) 0-23.9 6.29 1.42 24-47.9 2.27 1.01 48-71.9 1.47 0.853 72-95.9 1.63 0.595 96-119.9 0.555

0.347 120-143.9 0.197 0.146 144-167.9 0.080 0.073

Reference Values:
Only orderable as part of a profile. For more information see THCCR / Delta 9-Carboxy-Tetrahydrocannabinol (THC-COOH) Confirmation and Creatinine Ratio, Random, Urine

Not detected (Positive result is reported with a quantitative result)

Cutoff concentration by liquid chromatography tandem mass spectrometry:
Delta-9 Carboxy-Tetrahydrocannabinol: 5.0 ng/mL

Clinical References: 1. Smith ML, Barnes AJ, Huestis MA. Identifying new cannabis use with urine creatinine normalized THCCOOH concentrations and time intervals between specimen collections. J Anal Toxicol. 2009;33(4):185-189. doi:10.1093/jat/33.4.185 2. Huestis MA, Cone EJ. Differentiating new marijuana use from residual drug excretion in occasional marijuana users. J Anal Toxicol. 1998;22(6):445-454. doi:10.1093/jat/22.6.445 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

DLL3
603332

Delta-Like 3 Protein (SP347), Semi-Quantitative Immunohistochemistry, Manual, Tissue

Clinical Information: Delta-like 3 protein (DLL3) is an atypical Notch ligand induced by the neuroendocrine transcription factor, ASCL-1. DLL3 is expressed on the cell membrane and in the cytoplasm of tumor cells.

Useful For: Diagnosis of small cell lung carcinoma (SCLC), large cell neuroendocrine carcinoma (LCNEC), amongst other tumors

Interpretation: Positivity for delta-like 3 protein is determined by immunoreactivity of any tumor cells within a specimen with an intensity ranging from 1 to 3+.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Saunders LR, Bankovich AJ, Anderson WC, et al. A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo. Sci Transl Med. 2015;7(302):302ra136 2. Xie H, Boland JM, Maleszewski JJ, et al. Expression of delta-like protein 3 is reproducibly present in a subset of small cell lung carcinomas and pulmonary carcinoid tumors. Lung Cancer. 2019;135:73-79. doi:10.1016/j.lungcan.2019.07.016 3. Xie H, Kaye FJ, Isse K, et al. Delta-like protein 3 expression and targeting in merkel cell carcinoma. Oncologist. 2020;10:810-817. doi:10.1634/theoncologist.2019-0877 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

DMS2
92114

Dementia, Autoimmune/Paraneoplastic Evaluation, Serum

Clinical Information: The rapid identification of subacute cognitive decline as autoimmune dementia facilitates optimum treatment with immunotherapy and an expedited search for a limited stage of cancer in some patients. Traditionally, neurologists have been reluctant to consider a diagnosis of an

autoimmune cognitive disorder in the absence of delirium. However, some recent case series and clinical-serologic observations have suggested a growing appreciation for autoimmune neurologic disorders presenting with features of a rapidly progressive dementia rather than delirium. These disorders can affect all age groups. Unfortunately, these potentially reversible conditions may be misdiagnosed as being progressive neurodegenerative (currently irreversible) disorders with devastating consequences for the patient. In the evaluation of a patient with cognitive decline, clinicians should consider the possibility of an autoimmune etiology on their list of differential diagnoses. The importance of not overlooking this possibility rests in the experience that these patients have a potentially immunotherapy-responsive, reversible disorder. The development and widespread availability of neural antibody marker testing has changed this perspective so that other presenting symptoms, such as personality change, executive dysfunction, and psychiatric symptoms, are increasingly recognized in an autoimmune context. Clues that are helpful in identifying patients with an autoimmune dementia can be summarized as a triad of: -Suspicious clinical features (a subacute onset of symptoms, a rapidly progressive course, and fluctuating symptoms) and radiological findings -Detection of cerebrospinal fluid (CSF) or serological biomarkers of autoimmunity -Response to immunotherapy Detection of neural autoantibodies in serum or CSF serves 2 purposes: to inform the physician of a likely autoimmune etiology and to raise suspicion for a paraneoplastic cause. The neurological associations of neural autoantibodies tend to be diverse and multifocal, although certain syndromic associations may apply. For example, LGI1 (leucine-rich, glioma inactivated 1) antibody was initially considered to be specific for autoimmune limbic encephalitis but, over time, other presentations have been reported, including rapidly progressive course of cognitive decline mimicking neurodegenerative dementia. Since neurological presentations are often multifocal and diverse, comprehensive antibody testing is usually more informative than testing for 1 or 2 selected antibodies. Some of the antibodies are highly predictive of an unsuspected underlying cancer. For example, small-cell lung carcinoma (antineuronal nuclear antibody-type 1 [ANNA-1]; collapsin response-mediator protein-5 neuronal [CRMP-5-IgG]), ovarian teratoma (N-methyl-D-aspartate receptor: NMDA-R), and thymoma (CRMP-5 IgG). Also, a profile of seropositivity for multiple autoantibodies may be informative for cancer type. For example, in a patient presenting with a rapidly progressive dementia who has CRMP-5-IgG, and subsequent testing reveals muscle acetylcholine receptor (AChR) binding antibody, the findings should raise a high suspicion for thymoma. If an associated tumor is found, its resection or ablation optimizes the neurological outcome. Antibody testing on CSF is additionally helpful, particularly when serum testing is negative, although, in some circumstances, testing both serum and CSF simultaneously is pertinent. Testing of CSF is recommended for some antibodies (eg, NMDA-R antibody and glial fibrillary acidic protein [GFAP]-IgG) because CSF testing is more sensitive and specific.

Useful For: Investigating new onset dementia and cognitive impairment plus 1 or more of the following using serum specimens: -Rapid onset and progression -Fluctuating course -Psychiatric accompaniments (psychosis, hallucinations) -Movement disorder (myoclonus, tremor, dyskinesias) -Headache -Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) -Smoking history (20 or more pack-years) or other cancer risk factors -History of cancer -Inflammatory cerebrospinal fluid -Neuroimaging findings atypical for degenerative etiology

Interpretation: Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune dementia: -Plasma membrane antibodies (N-methyl-D-aspartate [NMDA] receptor; 2-amino-3-[5-methyl-3-oxo-1,2-oxazol-4-yl] propanoic acid [AMPA] receptor; gamma-amino butyric acid [GABA-B] receptor). These autoantibodies are all potential effectors of dysfunction. -Neuronal nuclear autoantibody, type 1 (ANNA-1) or type 3 (ANNA-3). -Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2 [PCA-2], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG], or glutamic acid decarboxylase [GAD65] antibody).

Reference Values:

Clinical References: 1. Sechi E, Flanagan EP. Diagnosis and management of autoimmune dementia. Curr Treat Options Neurol. 2019;21(3):11. Published 2019 Feb 27. doi:10.1007/s11940-019-0550-9 2. Bastiaansen AEM, van Steenhoven RW, de Bruijn MAAM, et al. Autoimmune encephalitis resembling dementia syndromes. Neurol Neuroimmunol Neuroinflamm. 2021;8(5):e1039. Published 2021 Aug 2. doi:10.1212/NXI.0000000000001039 3. Flanagan EP, Geschwind MD, Lopez-Chiriboga AS, et al. Autoimmune encephalitis misdiagnosis in adults. JAMA Neurol. 2023;80(1):30-39. doi:10.1001/jamaneurol.2022.4251 4. Orozco E, Valencia-Sanchez C, Britton J, et al. Autoimmune encephalitis criteria in clinical practice. Neurol Clin Pract. 2023;13(3):e200151. doi:10.1212/CPJ.0000000000200151 5. Bastiaansen AEM, van Steenhoven RW, Te Vaarwerk ES, et al. Antibodies associated with autoimmune encephalitis in patients with presumed neurodegenerative dementia. Neurol Neuroimmunol Neuroinflamm. 2023;10(5):e200137. Published 2023 Jun 13. doi:10.1212/NXI.0000000000200137

DMC2 92115 Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

Clinical Information: The rapid identification of subacute cognitive decline as autoimmune dementia facilitates optimum treatment with immunotherapy and an expedited search for a limited stage of cancer in some patients. Traditionally, neurologists have been reluctant to consider a diagnosis of an autoimmune cognitive disorder in the absence of delirium. However, some recent case series and clinical-serologic observations have suggested a growing appreciation for autoimmune neurologic disorders presenting with features of a rapidly progressive dementia rather than delirium. These disorders can affect all age groups. Unfortunately, these potentially reversible conditions may be misdiagnosed as being progressive neurodegenerative (currently irreversible) disorders with devastating consequences for the patient. In the evaluation of a patient with cognitive decline, clinicians should consider the possibility of an autoimmune etiology on their list of differential diagnoses. The importance of not overlooking this possibility rests in the experience that these patients have a potentially immunotherapy-responsive, reversible disorder. The development and widespread availability of neural antibody marker testing has changed this perspective so that other presenting symptoms, such as personality change, executive dysfunction, and psychiatric symptoms, are increasingly recognized in an autoimmune context. Clues that are helpful in identifying patients with an autoimmune dementia can be summarized as a triad of: -Suspicious clinical features (a subacute onset of symptoms, a rapidly progressive course, and fluctuating symptoms) and radiological findings -Detection of cerebrospinal fluid (CSF) or serological biomarkers of autoimmunity -Response to immunotherapy Detection of neural autoantibodies in serum or CSF serves 2 purposes: to inform the physician of a likely autoimmune etiology and to raise suspicion for a paraneoplastic cause. The neurological associations of neural autoantibodies tend to be diverse and multifocal, although certain syndromic associations may apply. For example, LGI1 (leucine-rich, glioma inactivated 1) antibody was initially considered to be specific for autoimmune limbic encephalitis but, over time, other presentations have been reported, including rapidly progressive course of cognitive decline mimicking neurodegenerative dementia. Since neurological presentations are often multifocal and diverse, comprehensive antibody testing is usually more informative than testing for 1 or 2 selected antibodies. Some of the antibodies are highly predictive of an unsuspected underlying cancer. For example, small-cell lung carcinoma (antineuronal nuclear antibody-type 1 [ANNA-1]; collapsin response-mediator protein-5 neuronal [CRMP-5-IgG]), ovarian teratoma (N-methyl-D-aspartate receptor: NMDA-R), and thymoma (CRMP-5 IgG). Also, a profile of seropositivity for multiple autoantibodies may be informative for cancer type. For example, in a patient presenting with a rapidly progressive dementia who has CRMP-5-IgG, and subsequent testing reveals muscle acetylcholine receptor (AChR) binding antibody, the findings should raise a high suspicion for thymoma. If an associated tumor is found, its

resection or ablation optimizes the neurological outcome. Antibody testing on CSF is additionally helpful particularly when serum testing is negative, although, in some circumstances, testing both serum and CSF simultaneously is pertinent. Testing of CSF is recommended for some antibodies (eg, NMDA-R antibody and glial fibrillary acidic protein [GFAP]-IgG) because CSF testing is more sensitive and specific.

Useful For: Investigating new onset dementia and cognitive impairment plus 1 or more of the following accompaniments using cerebrospinal fluid specimens: -Rapid onset and progression -Fluctuating course -Psychiatric accompaniments (psychosis, hallucinations) -Movement disorder (myoclonus, tremor, dyskinesias) -Headache -Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) -Smoking history (20 or more pack-years) or other cancer risk factors -History of cancer -Inflammatory cerebrospinal fluid -Neuroimaging findings atypical for degenerative etiology

Interpretation: Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune dementia: -Plasma membrane antibodies (N-methyl-D-aspartate [NMDA] receptor; 2-amino-3-[5-methyl-3-oxo-1,2- oxazol-4-yl] propanoic acid [AMPA] receptor; gamma-amino butyric acid [GABA]-B receptor). These autoantibodies are all potential effectors of dysfunction. -Neuronal nuclear autoantibody type 1 (ANNA-1) or type 3 (ANNA-3) -Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2 [PCA-2], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG], or glutamic acid decarboxylase [GAD65] antibody).

Reference Values:

Test ID	Reporting name	Methodology*	Reference value
ADMCI	Dementia, Interpretation, CSF	Medical interpretation	Interpretive report
AMPCC	AMPA-R Ab CBA, CSF	CBA	Negative
AMPHC	Amphiphysin Ab, CSF	IFA	Negative
AGN1C	Anti-Glial Nuclear Ab, Type 1	IFA	Negative
ANN1C	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2C	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3C	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
CS2CC	CASPR2-IgG CBA, CSF	CBA	Negative
CRMC	CRMP-5-IgG, CSF	IFA	Negative
DPPCC	DPPX Ab CBA, CSF	CBA	Negative
GABCC	GABA-B-R Ab CBA, CSF	CBA	Negative
GD65C	GAD65 Ab Assay, CSF	RIA	< or =0.02 nmol/L Reference values apply to all ages.

GFAIC	GFAP IFA, CSF	IFA	Negative
IG5CC	IgLON5 CBA, CSF	CBA	Negative
LG1CC	LGI1-IgG CBA, CSF	CBA	Negative
NCDIC	Neurochondrin IFA, CSF	IFA	Negative
GL1IC	mGluR1 Ab IFA, CSF	IFA	Negative
NIFIC	NIF IFA, CSF	IFA	Negative
NMDCC	NMDA-R Ab CBA, CSF	CBA	Negative
PCTRC	Purkinje Cell Cytoplasmc Ab Type Tr	IFA	Negative
PCA2C	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
PDEIC	PDE10A Ab IFA, CSF	IFA	Negative
T46IC	TRIM46 IFA, CSF	IFA	Negative
Reflex Information: Test ID	Reporting name	Methodology*	Reference value
AGNBC	AGNA-1 Immunoblot, CSF	IB	Negative
AGNTC	AGNA-1 Titer, CSF	IFA	
AINCC	Alpha Internexin CBA, CSF	CBA	Negative
AMPIC	AMPA-R Ab IF Titer Assay, CSF	IFA	
AMIBC	Amphiphysin Immunoblot, CSF	IB	Negative
AN1BC	ANNA-1 Immunoblot, CSF	IB	Negative
AN1TC	ANNA-1 Titer, CSF	IFA	
AN2BC	ANNA-2 Immunoblot, CSF	IB	Negative
AN2TC	ANNA-2 Titer, CSF	IFA	
AN3TC	ANNA-3 Titer, CSF	IFA	
APHTC	Amphiphysin Ab Titer, CSF	IFA	
CRMTC	CRMP-5-IgG Titer, CSF	IFA	
CRMWC	CRMP-5 Western Blot, CSF	WB	Negative
DPPTC	DPPX Ab IFA Titer, CSF	IFA	
GABIC	GABA-B-R Ab IF Titer Assay, CSF	IFA	
GFACC	GFAP CBA, CSF	CBA	Negative

GFATC	GFAP IFA Titer, CSF	IFA	
IG5TC	IgLON5 IFA Titer, CSF	IFA	
GL1CC	mGluR1 Ab CBA, CSF	CBA	Negative
GL1TC	mGluR1 Ab IFA Titer, CSF	IFA	
NCDCC	Neurochondrin CBA, CSF	CBA	Negative
NCDTC	Neurochondrin IFA Titer, CSF	IFA	
NFHCC	NIF Heavy Chain CBA, CSF	CBA	Negative
NIFTC	NIF IFA Titer, CSF	IFA	
NFLCC	NIF Light Chain CBA, CSF	CBA	Negative
NMDIC	NMDA-R Ab IF Titer Assay, CSF	IFA	
PC2TC	PCA-2 Titer, CSF	IFA	
PCTBC	PCA-Tr Immunoblot, CSF	IB	Negative
PCTTC	PCA-Tr Titer, CSF	IFA	
PDETC	PDE10A Ab IFA Titer, CSF	IFA	
T46CC	TRIM46 CBA, CSF	CBA	Negative
T46TC	TRIM46 IFA Titer, CSF	IFA	

Clinical References: 1. Sechi E, Flanagan EP. Diagnosis and management of autoimmune dementia. Curr Treat Options Neurol. 2019;21(3):11. Published 2019 Feb 27. doi:10.1007/s11940-019-0550-9 2. Bastiaansen AEM, van Steenhoven RW, de Bruijn MAAM, et al. Autoimmune encephalitis resembling dementia syndromes. Neurol Neuroimmunol Neuroinflamm. 2021;8(5):e1039. Published 2021 Aug 2. doi:10.1212/NXI.0000000000001039 3. Flanagan EP, Geschwind MD, Lopez-Chiriboga AS, et al. Autoimmune encephalitis misdiagnosis in adults. JAMA Neurol. 2023;80(1):30-39. doi:10.1001/jamaneurol.2022.4251 4. Orozco E, Valencia-Sanchez C, Britton J, et al. Autoimmune encephalitis criteria in clinical practice. Neurol Clin Pract. 2023;13(3):e200151. doi:10.1212/CPJ.0000000000200151 5. Bastiaansen AEM, van Steenhoven RW, Te Vaarwerk ES, et al. Antibodies associated with autoimmune encephalitis in patients with presumed neurodegenerative dementia. Neurol Neuroimmunol Neuroinflamm. 2023;10(5):e200137. Published 2023 Jun 13. doi:10.1212/NXI.0000000000200137

DCME
609795

Dendritic Cell and Monocyte Enumeration, Blood

Clinical Information: Dendritic cells (DC) play a critical role in both innate and adaptive immune responses. DC include 2 major subsets: myeloid (or conventional) dendritic cells and plasmacytoid dendritic cells. Myeloid DC can capture and present antigens to CD4+ T cells and cross-present them to CD8+ T cells. They are also a source of inflammatory cytokines. Plasmacytoid DC take part in priming of antiviral T cells and are the major source of type I interferons; as such they act as a primary defense against viremia. Monocytes are the archetypal myeloid mononuclear cells. Although human monocytes do

have phenotypic heterogeneity, the majority are CD14+ and are classified as classical or inflammatory monocytes. The list of conditions where this test can be used as part of the assessment include, but are not limited to, GATA-binding protein 2 deficiency, IKZF1 deficiency, IRF8 deficiency, STAT3 gain-of-function disease, HYOU1 deficiency, reticular dysgenesis due to AK2 variants, WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis), dedicator of cytokinesis 8 (DOCK8) deficiency, IRF7 deficiency, and Hermansky-Pudlak syndrome type II. In addition, unexplained monocytopenia can be a relevant clue in detecting DC deficiency.

Useful For: Aiding in the diagnosis of patients suspected of defects in innate immunity, particularly those involving monocyte and dendritic cell development This test has not been validated for the diagnosis of hematologic malignancies.

Interpretation: Interpretive comments will be provided, where applicable, to complement the reported plasmacytoid dendritic cells, myeloid (or conventional) dendritic cells, and monocyte counts, and their respective reference ranges.

Reference Values:
The appropriate reference values will be provided on the report.

Clinical References: 1. Bigley V, Cytlak U, Collin M. Human dendritic cell immunodeficiencies. Semin Cell Dev Biol. 2019;86:50-61 2. Ciancanelli MJ, Huang SX, Luthra P, et al. Infectious disease. Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. Science. 2015;348(6233):448-453 3. Cytlak U, Resteu A, Bogaert D, et al. Ikaros family zinc finger 1 regulates dendritic cell development and function in humans. Nat Commun. 2018;9(1):1239 4. Dickinson RE, Griffin H, Bigley V, et al. Exome sequencing identifies GATA-2 mutation as the cause of dendritic cell, monocyte, B and NK lymphoid deficiency. Blood. 2011;118(10):2656-2658 5. Haapaniemi EM, Fogarty CL, Keskitalo S, et al. Combined immunodeficiency and hypoglycemia associated with mutations in hypoxia upregulated 1. J Allergy Clin Immunol. 2017;139(4):1391-1393 6. Haapaniemi EM, Kaustio M, Rajala HL, et al. Autoimmunity, hypogammaglobulinemia, lymphoproliferation, and mycobacterial disease in patients with activating mutations in STAT3. Blood. 2015;125(4):639-648 7. Hambleton S, Salem S, Bustamante J, et al. IRF8 mutations and human dendritic-cell immunodeficiency. N Engl J Med. 2011;365(2):127-138 8. Keles S, Jabara HH, Reisli I, et al. Plasmacytoid dendritic cell depletion in DOCK8 deficiency: rescue of severe herpetic infections with IFN-alpha 2b therapy. J Allergy Clin Immunol. 2014;133(6):1753-1755 9. Pannicke U, Honig M, Hess I, et al. Reticular dysgenesis (aleukocytosis) is caused by mutations in the gene encoding mitochondrial adenylate kinase 2. Nat Genet. 2009;41(1):101-105 10. Prandini A, Salvi V, Colombo F, et al. Impairment of dendritic cell functions in patients with adaptor protein-3 complex deficiency. Blood. 2016;127(26):3382-3386 11. Reizis B. Plasmacytoid dendritic cells: Development, regulation, and function. Immunity. 2019;50(1):37-50 12. Tassone L, Moratto D, Vermi W, et al. Defect of plasmacytoid dendritic cells in warts, hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome patients. Blood. 2010;116(23):4870-4873 13. Vuckovic S, Gardiner D, Field K, et al. Monitoring dendritic cells in clinical practice using a new whole blood single-platform TruCOUNT assay. J Immunol Methods. 2004;284(1-2):73-87

DENGM
83865

Dengue Virus Antibody, IgG and IgM, Serum

Clinical Information: Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4). It is primarily transmitted by the Aedes aegypti mosquito, which is found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected, and approximately 30,000 patients will succumb to the disease, annually. Following dengue infection, the incubation period varies from 3 to 7 days, and

while some infections remain asymptomatic, the majority of individuals will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of dengue-specific IgM and IgG-class antibodies remains the most commonly utilized diagnostic method. Seroconversion occurs approximately 3 to 7 days following exposure, and therefore, testing of acute and convalescent sera may be necessary to make the diagnosis. As an adjunct to serologic testing, identification of early DV infection may be made by detection of the DV nonstructural protein 1 (NS1) antigen. NS1 antigenemia is detectable within 24 hours of infection and up to 9 days following symptom onset. The DV NS1 antigen can be detected by ordering DNSAG / Dengue Virus NS1 Antigen, Serum.

Useful For: Aiding in the diagnosis of dengue virus infection

Interpretation: The presence of IgG-class antibodies to dengue virus (DV) is consistent with exposure to this virus sometime in the past. By 3 weeks following exposure, nearly all immunocompetent individuals should have developed IgG antibodies to DV. The presence of IgM-class antibodies to DV is consistent with acute-phase infection. IgM antibodies become detectable 3 to 7 days following infection and may remain detectable for up to 6 months or longer following disease resolution. The absence of IgM-class antibodies to DV is consistent with lack of infection. However, specimens collected too soon following exposure may be negative for IgM antibodies to DV. If DV remains suspected, a second specimen collected approximately 10 to 12 days following exposure should be tested.

Reference Values:
Dengue virus antibody, IgG: Negative
Dengue virus antibody, IgM: Negative
Reference values apply to all ages.

Clinical References: 1. Centers for Disease Control and Prevention (CDC). Clinical Testing Guidance for Dengue. Updated August 26, 2024. Accessed December 11, 2024, Available at www.cdc.gov/dengue/hcp/diagnosis-testing/index.html 2. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: World Health Organization; 2009 3. Khan MB, Yang ZS, Lin CY, et al. Dengue overview: An updated systemic review. J Infect Public Health. 2023;16(10):1625-1642. doi:10.1016/j.jiph.2023.08.001

DENVP
62869

Dengue Virus Antibody/Antigen Panel, Serum

Clinical Information: Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4). It is primarily transmitted by the Aedes aegypti mosquito, which is found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected, and approximately 30,000 patients will succumb to the disease, annually. Following dengue infection, the incubation period varies from 3 to 7 days, and while some infections remain asymptomatic, the majority of individuals will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of dengue-specific IgM and IgG-class antibodies remains the most commonly utilized diagnostic method. Seroconversion occurs approximately 3 to 7 days following exposure, and therefore, testing of acute and convalescent sera may be necessary to make the diagnosis.

Detection of the DV nonstructural protein 1 (NS1) has emerged as an alternative biomarker to both serologic- and molecular-based techniques for diagnosis of acute DV infection. NS1 antigenemia is detectable within 24 hours and up to 9 days following symptoms onset. This overlaps with the DV viremic phase, and NS1 is often detectable prior to IgM seroconversion. Concurrent evaluation (as performed in this profile) for the NS1 antigen alongside testing for IgM- and IgG-class antibodies to DV provides optimal diagnostic potential for both early and late dengue disease.

Useful For: Aiding in the diagnosis of dengue virus infection by detection of IgM and IgG antibodies and the nonstructural protein 1 (NS1)

Interpretation: The presence of IgG-class antibodies to dengue virus (DV) is consistent with exposure to this virus sometime in the past. By 3 weeks following exposure, nearly all immunocompetent individuals should have developed IgG antibodies to DV. The presence of IgM-class antibodies to DV is consistent with acute-phase infection. IgM antibodies become detectable 3 to 7 days following infection and may remain detectable for up to 6 months or longer following disease resolution. The absence of IgM-class antibodies to DV is consistent with lack of infection. However, specimens collected too soon following exposure may be negative for IgM antibodies to DV. If DV remains suspected, a second specimen, collected approximately 10 to 12 days following exposure should be tested. The presence of dengue nonstructural protein 1 (NS1) antigen is consistent with acute-phase infection with dengue virus. The NS1 antigen is typically detectable within 1 to 2 days following infection and up to 9 days following symptom onset. NS1 antigen may also be detectable during secondary dengue virus infection, but for a shorter duration of time (1-4 days following symptom onset). The absence of dengue NS1 antigen is consistent with the lack of acute-phase infection. The NS1 antigen may be negative is samples collected immediately following dengue virus infection (<24-48 hours) and is rarely detectable following 9 to 10 days of symptoms.

Reference Values:
IgG: Negative
IgM: Negative
NS1: Negative
Reference values apply to all ages.

Clinical References: 1. Centers for Disease Control and Prevention (CDC). Clinical Testing Guidance for Dengue. Updated August 26, 2024. Accessed December 11, 2024, Available at www.cdc.gov/dengue/hcp/diagnosis-testing/index.html 2. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: World Health Organization; 2009 3. Khan MB, Yang ZS, Lin CY, et al. Dengue overview: An updated systemic review. J Infect Public Health. 2023;16(10):1625-1642. doi:10.1016/j.jiph.2023.08.001

DNSAG
36781

Dengue Virus NS1 Antigen, Serum

Clinical Information: Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4). It is primarily transmitted by the Aedes aegypti mosquito, which is found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected, and approximately 30,000 patients will succumb to the disease, annually. Following dengue infection, the incubation period varies from 3 to 7 days, and while some infections remain asymptomatic, the majority of individuals will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome,

particularly during repeat infection with a new DV serotype. Detection of the DV nonstructural protein 1 (NS1) has emerged as an alternative biomarker to both serologic and molecular based techniques for diagnosis of acute DV infection. NS1 antigenemia is detectable within 24 hours and up to 9 days following symptoms onset. This overlaps with the DV viremic phase, and NS1 is often detectable prior to IgM seroconversion. Concurrent evaluation for the NS1 antigen alongside testing for IgM- and IgG-class antibodies to DV (DENGM / Dengue Virus Antibody, IgG and IgM, Serum) provides optimal diagnostic potential for both early and late dengue disease.

Useful For: Aiding in the diagnosis of dengue virus infection

Interpretation: Positive: The presence of dengue nonstructural protein 1 (NS1) antigen is consistent with acute-phase infection with dengue virus. The NS1 antigen is typically detectable within 1 to 2 days following infection and up to 9 days following symptom onset. NS1 antigen may also be detectable during secondary dengue virus infection, but for a shorter duration of time (1-4 days following symptom onset). Negative: The absence of dengue NS1 antigen is consistent with the lack of acute-phase infection. The NS1 antigen may be negative if specimen is collected immediately following dengue virus infection (<24-48 hours) and is rarely detectable following 9 to 10 days of symptoms.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Centers for Disease Control and Prevention (CDC). Clinical Testing Guidance for Dengue. Updated August 26, 2024. Accessed December 11, 2024, Available at www.cdc.gov/dengue/hcp/diagnosis-testing/index.html 2. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: World Health Organization; 2009 3. Khan MB, Yang ZS, Lin CY, et al. Dengue overview: An updated systemic review. J Infect Public Health. 2023;16(10):1625-1642. doi:10.1016/j.jiph.2023.08.001

DENGS
606372

Dengue Virus, Molecular Detection, PCR, Serum

Clinical Information: Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4) primarily transmitted by the Aedes aegypti mosquito, which is found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected and approximately 30,000 patients will succumb to the disease annually. Following dengue infection, the incubation period varies from 3 to 7 days. While some individuals remain asymptomatic, the majority will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of DV nucleic acid in serum is a marker of acute infection with this virus. Importantly, the period of time that the virus can be detected in serum is brief and, therefore, molecular testing should be performed within the first week following onset of symptoms. After this time, serologic testing is the preferred method for diagnosis of DV infection.

Useful For: Aiding in the diagnosis of acute infection caused by dengue virus

Interpretation: Positive: The detection of dengue virus nucleic acid in serum is consistent with acute-phase infection. Dengue virus nucleic acid may be detectable during the first 1 to 7 days following the onset of symptoms. Negative: The absence of dengue nucleic acid in serum is consistent with the lack of

acute-phase infection. Dengue virus nucleic acid may not be detected if the serum specimen is collected immediately following dengue virus infection (<24-48 hours) and is rarely detectable following 7 days of symptoms.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504-507 2. Dengue-an infectious disease of staggering proportions. Lancet. 2013;381(9884):2136 3. Rigau-Perez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ, Vorndam AV. Dengue and dengue haemorrhagic fever. Lancet. 1998;352(9132):971-977 4. Tang KF, Ooi EE. Diagnosis of dengue: an update. Expert Rev Anti Infect Ther. 2012;10(8):895-907 5. Guzman MG, Kouri G. Dengue diagnosis, advances and challenges. Int J Infect Dis. 2004;8(2):69-80

DENGC
606371

Dengue Virus, Molecular Detection, PCR, Spinal Fluid

Clinical Information: Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4) primarily transmitted by the Aedes aegypti mosquito, which is found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected and approximately 30,000 patients will succumb to the disease annually. Following dengue infection, the incubation period varies from 3 to 7 days. While some individuals remain asymptomatic, the majority will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of DV nucleic acid in cerebrospinal fluid (CSF) is a marker for central nervous system infection caused by this virus. Importantly, the period of time that the virus can be detected in serum and CSF is brief and, therefore, molecular testing should be performed within the first week following onset of symptoms. After this time, serologic testing is the preferred method for diagnosis of DV infection.

Useful For: Aiding in the diagnosis of central nervous system infection caused by dengue virus

Interpretation: Positive: The detection of dengue virus nucleic acid in cerebrospinal fluid (CSF) is consistent with acute-phase infection of the central nervous system. Dengue virus nucleic acid may be detectable during the first 1 to 7 days following the onset of symptoms. Negative: The absence of dengue nucleic acid in CSF is consistent with the lack of acute-phase infection. Dengue virus nucleic acid may not be detected if the CSF specimen is collected immediately following dengue virus infection (<24-48 hours) and is rarely detectable following 7 days of symptoms.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504-507 2. Dengue--an infectious disease of staggering proportions. Lancet. 2013;381(9884):2136 3. Rigau-Perez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ, Vorndam AV. Dengue and dengue haemorrhagic fever. Lancet. 1998;352(9132):971-977 4. Tang KF, Ooi EE. Diagnosis of dengue: an update. Expert Rev Anti Infect Ther. 2012;10(8):895-907 5. Guzman MG,

Kouri G. Dengue diagnosis, advances and challenges. Int J Infect Dis. 2004;8(2):69-80

DRPL
35402

Dentatorubral-Pallidoluysian Atrophy (DRPLA) Gene Analysis, Varies

Clinical Information: Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare autosomal dominant neurodegenerative disorder characterized by ataxia, choreoathetosis, dementia, and psychiatric disturbance in adults and ataxia, myoclonus, seizures, and progressive intellectual deterioration in children. Characteristic neuropathologic observations include degeneration of the dentatorubral and pallidoluysian systems of the central nervous system. The prevalence of DRPLA depends on the geographic and ethnic origin of the population being studied. DRPLA was first described in a European individual without a family history of the disorder; however, it is predominantly found as an inherited condition and is most prevalent in Japan (0.2-0.7 per 100,000). Although rare, DRPLA has been identified in other populations, including Europe and North America. Dentatorubral-pallidoluysian atrophy is caused by an expansion of a CAG trinucleotide repeat in the ATN1 gene. This trinucleotide repeat is polymorphic in the general population, with the number of repeats ranging from 6 to 35. Affected individuals, have 48 or greater CAG repeats. Repeat sizes between 35 and 47 are associated with incomplete penetrance and a milder clinical phenotype. As with other trinucleotide repeat disorders, anticipation is frequently observed, and larger CAG expansions are associated with earlier onset and a more severe and rapid clinical course. More marked expansion may occur with paternal transmission.

Useful For: Confirming the diagnosis of dentatorubral-pallidoluysian atrophy (DRPLA) for symptomatic patients Predictive testing for individuals with a family history of DRPLA and a documented expansion in the ATN1 gene in an affected family member

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
Normal alleles: 7-35 CAG repeats
Abnormal alleles: 49-93 CAG repeats

An interpretive report will be provided.

Clinical References: 1. Ikeuchi T, Onodera O, Oyake M, Koide R, Tanaka H, Tsuji S. Dentatorubral-pallidoluysian atrophy (DRPLA): close correlation of CAG repeat expansions with the wide spectrum of clinical presentations and prominent anticipation. Semin Cell Biol. 1995;6(1):37-44 2. Tsuji S. Dentatorubral-pallidoluysian atrophy: clinical aspects and molecular genetics. Ad Neurol. 2002;89:231-239 3. Carroll LS, Massey TH, Wardle M, Peall KJ. Dentatorubral-pallidoluysian atrophy: An update. Tremor Other Hyperkinet Mov (N Y). 2018;8:577 4. Prades S, Melo de Gusmao C, Grimaldi S, Shiloh-Malawsky Y, Felton T, Houlden H. DRPLA. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated September 21, 2023. Accessed November 14, 2024. Available at https://www.ncbi.nlm.nih.gov/books/NBK1491/

FDCU
58048

Deoxypyridinoline Crosslinks, Urine

Reference Values:
Deoxypyridinoline Urine-ratio to CRT Adult Male: 2.3 – 8.7 nmol/mmol
Premenopausal Adult Female: 3.1 – 8.7 nmol/mmol

Creatinine, Urine – per volume No reference interval

The target value for treated post-menopausal adult females is the same as the Premenopausal reference interval.

DEXT
70596

Dermatopathology Consultation, Wet Tissue

Clinical Information: Dermatopathology involves histologic examination of skin biopsy and oral mucosal specimens.

Useful For: Histologic diagnosis and differential diagnosis of cutaneous diseases

Interpretation: Histologic diagnosis is based primarily on interpretation of hematoxylin and eosin-stained sections. Special histochemical stains, such as alcian blue, Giemsa, or periodic acid-Schiff, may be necessary in some cases. Interpretation is based on evaluation of patterns including architectural and cytologic details, which are included in a microscopic description.

Reference Values:
Diagnosis and description of microscopic findings

Clinical References: 1. Lever WF, Schaumburg-Lever G. Histopathology of the Skin. 7th ed. JB Lippincott; 1990 2. Elder D, Elenitsas R, Ioffreda M, et al, eds. Atlas of Dermatopathology: Synopsis and Atlas of Lever's Histopathology of the Skin. 4th ed. Lippincott Williams and Wilkins; 2020

DMIC
82828

Dermatophagoides microceras, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Dermatophagoides microceras Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with

the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

DCP
61844

Des-Gamma-Carboxy Prothrombin, Serum

Clinical Information: Des-gamma-carboxy prothrombin (DCP), also known as the protein induced by vitamin K absence or antagonist II (PIVKA-II), is an abnormal form of the coagulation protein, prothrombin. DCP is a nonfunctional prothrombin resulting from a lack of carboxylation of 10 glutamic acid residues in the N-terminal portion of the molecule. In normal liver, prothrombin undergoes post-translational carboxylation before release into the peripheral blood. The carboxylation converts specific amino-terminal glutamic acid residues to gamma-carboxyglutamic acid. The vitamin K dependent carboxylase responsible for the carboxylation is absent in many hepatocellular carcinoma (HCC) cells, and an abnormal prothrombin with all or some unconverted glutamic acid is secreted. Therefore, this non-carboxylated form (DCP) has been used as an HCC biomarker. DCP is considered a complementary biomarker to alpha fetoprotein (AFP) and third electrophoretic form of lentil lectin-reactive AFP% (AFP-L3%) for assessing the risk of developing HCC. The elevation of both AFP-L3 and DCP indicate progression of HCC, albeit reflecting different features of the progression. In a prospective study of patients in the United States with an established diagnosis of HCC, the sensitivities for AFP, AFP-L3%, and DCP were 68%, 62%, and 73%, respectively. When the 3 markers were combined, the sensitivity was 86%. In another study, DCP levels were shown to correlate with tumor size and metastatic HCC. In this study, compared to AFP and AFP-L3%, DCP had the highest sensitivity (87%) and the highest positive predictive value (87%) in patients with HCC due to chronic hepatitis B and C infections. A number of studies have shown that elevated serum DCP is significantly related to portal vein invasion and/or intrahepatic metastasis, which significantly affect prognosis for patients with HCC. DCP can be elevated in other conditions besides HCC. Conditions such as obstructive jaundice, intrahepatic cholestasis causing chronic decrease in vitamin K, and ingestion of drugs such as warfarin or wide-spectrum antibiotics can result in high concentrations of DCP. In addition, 25% to 50% of patients with HCC will have a DCP value within the reference range. Because of this, a normal DCP value does not rule out HCC.

Useful For: Risk assessment of patients with chronic liver disease for development of hepatocellular carcinoma (HCC) Aiding in the monitoring of HCC patients post therapy if the des-gamma-carboxy

prothrombin level was elevated prior to therapy

Interpretation: In patients with an elevated des-gamma-carboxy prothrombin (DCP) result (> or =7.5 ng/mL), the risk of developing hepatocellular carcinoma (HCC) is 36.5% (95% CI: 23.5%-49.6%). The risk of developing HCC with a negative DCP result (<7.5 ng/mL) is 7.6% (95% CI: 4.4%-10.8%). For patients with HCC and an elevated DCP level prior to therapy, an elevated DCP level posttherapy is associated with an increased risk of HCC recurring.

Reference Values:
<7.5 ng/mL

Clinical References: 1. Lai Q, Iesari S, Levi Sandri GB, Lerut J. Des-gamma-carboxy prothrombin in hepatocellular cancer patients waiting for liver transplant: a systematic review and meta-analysis. Int J Biol Markers. 2017;32(4):e370-e374. doi:10.5301/ijbm.5000276 2. Zhu R, Yang J, Xu L, et al. Diagnostic performance of des-gamma-carboxy prothrombin for hepatocellular carcinoma: A meta-analysis. Gastroenterol Res Pract. 2014;2014:529314. doi:10.1155/2014/529314 3. De J, Shen Y, Qin J, Feng L, Wang Y, Yang L. A systematic review of des-gamma-carboxy prothrombin for the diagnosis of primary hepatocellular carcinoma. Medicine (Baltimore). 2016;95(17):e3448. doi:10.1097/MD.0000000000003448

DESPR
37123

Desipramine, Serum

Clinical Information: Desipramine is a tricyclic antidepressant and a metabolite of imipramine. These drugs have also been employed in the treatment of enuresis (involuntary urination) in childhood and severe obsessive-compulsive neurosis. Desipramine is the antidepressant of choice in patients where maximal stimulation is indicated. The therapeutic concentration of desipramine is 100 to 300 ng/mL. About 1 to 3 weeks of treatment are required before therapeutic effectiveness becomes apparent. The most frequent side effects are those attributable to anticholinergic effects: dry mouth, constipation, dizziness, tachycardia, palpitations, blurred vision, and urinary retention. These occur at blood concentrations more than 400 ng/mL, although they may occur at therapeutic concentrations in the early stage of therapy. Cardiac toxicity (first-degree heart block) is usually associated with blood concentrations more than 400 ng/mL.

Useful For: Monitoring serum concentration of desipramine during therapy Evaluating potential desipramine toxicity May aid in evaluating patient compliance

Interpretation: Most individuals display optimal response to desipramine with serum levels of 100 to 300 ng/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Risk of toxicity is increased with levels above 400 ng/mL.

Reference Values:
Therapeutic concentration: 100-300 ng/mL

Note: Therapeutic ranges are for specimens collected at trough (ie, immediately before next scheduled dose).
Levels may be elevated in non-trough specimens.

Clinical References: 1. Wille SM, Cooreman SG, Neels HM, Lambert WE. Relevant issues in the monitoring and toxicology of antidepressants. Crit Rev Clin Lab Sci. 2008;45(1):25-89 2. Thanacoody HK, Thomas SH. Antidepressant poisoning. Clin Med. 2003;3(2):114-118 3. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in

neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62 4. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453.

DESMN
70421

Desmin Immunostain, Technical Component Only

Clinical Information: Desmin is an intermediate filament protein in striated and smooth muscle cells. In neoplastic tissues, the antibody reacts with tumors of myogenic origin such as those arising from smooth muscle (leiomyosarcomas) and those derived from striated muscle (rhabdomyosarcomas).

Useful For: Identification of striated and smooth muscle cells and tumors derived from this cell type

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Pawlak A, Rejmak-Kozicka E, Gil KE, Ziemba A, Kaczmarek L, Gil RJ. Patterns of desmin expression in idiopathic dilated cardiomyopathy are related to the desmin mRNA and ubiquitin expression. J Investig Med. 2019;67(1):11-19. doi:10.1136/jim-2017-000707 2. Bermudez-Jimenez FJ, Carriel V, Brodehl A, et al. Novel desmin mutation p.Glu401Asp impairs filament formation, disrupts cell membrane integrity, and causes severe arrhythmogenic left ventricular cardiomyopathy/dysplasia. Circulation. 2018;137(15):1595-1610. doi:10.1161/CIRCULATIONAHA.117.028719 3. Ekinci O, Ogut B, Celik B, Dursun A. Compared with elastin stains, h-caldesmon and desmin offer superior detection of vessel invasion in gastric, pancreatic, and colorectal adenocarcinomas. Int J Surg Pathol. 2018;26(4):318-326. doi:10.1177/1066896917752442 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

DSGAB
606818

Desmoglein 1 (DSG1) and Desmoglein 3 (DSG3), IgG Antibodies, Serum

Clinical Information: Pemphigus includes a group of often fatal autoimmune blistering diseases characterized by intraepithelial lesions. Pemphigus vulgaris and its variants may present with oral or mucosal lesions alone or with mucosal plus skin lesions. Pemphigus foliaceous and variants present with skin lesions alone. Indirect immunofluorescence studies reveal that both forms of pemphigus are caused by autoantibodies to cell surface antigens of stratified epithelia or mucous membranes and skin. These antibodies bind to calcium-dependent adhesion molecules in cell surface desmosomes, notably desmoglein 1 (DSG1) in pemphigus foliaceus and desmoglein 3 (DSG3) and/or DSG1 in pemphigus vulgaris. Desmogleins are protein substances located in and on the surface of keratinocytes. These proteins have been shown to be a critical factor in cell-to-cell adhesion. Antibodies to desmogleins can result in loss of cell adhesion, the primary cause of blister formation in pemphigus. The diagnosis of pemphigus depends on biopsy and serum studies that characterize lesions and detect the autoantibodies that cause them. Originally, the serum studies were performed by IIF using primate esophagus and other tissue substrates. The identification of the reactive antigens as DSG1 and DSG3 has made it possible to develop highly specific and sensitive enzyme-linked immunosorbent assay methods.

Useful For: Preferred screening test for patients suspected to have an autoimmune blistering disorder of the skin or mucous membranes (pemphigus) Aiding in the diagnosis of pemphigus

Interpretation: Antibodies to desmoglein 1 (DSG1) and desmoglein 3 (DSG3) have been shown to be present in patients with pemphigus. Many patients with pemphigus foliaceus, a superficial form of pemphigus have antibodies to DSG1. Patients with pemphigus vulgaris, a deeper form of pemphigus, have antibodies to DSG3 and sometimes DSG1 as well. Antibody titer correlates in a semiquantitative manner with disease activity in many patients. Patients with severe disease can usually be expected to have high titers of antibodies to DSG. Titers are expected to decrease with clinical improvement. Our experience demonstrates a very good correlation between DSG1 and DSG3 results and the presence of pemphigus. Adequate sensitivities and specificity for disease are documented. However, in those patients strongly suspected to have pemphigus either by clinical findings or by routine biopsy, and in whom the DSG assay is negative, indirect immunofluorescence testing is recommended. For more information see CIFS / Cutaneous Immunofluorescence Antibodies (IgG), Serum.

Reference Values:

DESMOGLEIN 1:
<20 RU/mL (negative)
> or =20 RU/mL (positive)

DESMOGLEIN 3:
<20 RU/mL (negative)
> or =20 RU/mL (positive)

Clinical References: 1. Amagai M, Tsunoda K, Zillikens D, Nagai T, Nishikawa T. The clinical phenotype of pemphigus is defined by the anti-desmoglein autoantibody profile. J Am Acad Dermatol. 1999;40(2 Pt 1):167-170 2. Amagai M, Komai A, Hashimoto T, et al. Usefulness of enzyme-linked immunoabsorbent assay using recombinant desmogleins 1 and 3 for sero-diagnosis of pemphigus. Brit J Dermatol. 1999;140(2):351-357 3. Harman KE, Gratian MJ, Bhogal BS, Challacombe SJ, Black M. The clinical significance of autoantibodies to desmoglein 1 in 78 cases of pemphigus vulgaris. J Invest Derm. 1999;112(4):568. Abstract 273 4. Harman KE, Gratian MJ, Seed PT, Bhogal BS, Challacombe SJ, Black MM. Diagnosis of pemphigus by ELISA: a critical evaluation of two ELISAs for the detection of antibodies to the major pemphigus antigens, desmoglein 1 and 3. Clin Exp Dermatol. 2000;25(3):236-240 5. Prussmann W, Prussmann J, Koga H, et al. Prevalence of pemphigus and pemphigoid autoantibodies in the general population. Orphanet J Rare Dis. 2015;10:63 6. Toosi S, Collins JW, Lohse CM, et al. Clinicopathologic features of IgG/IgA pemphigus in comparison with classic (IgG) and IgA pemphigus. Int J Dermatol. 2016;55(4):e184-e190 7. Montagnon CM, Tolkachjov SN, Murrell DF, Camilleri MJ, Lehman JS. Intraepithelial autoimmune blistering dermatoses: Clinical features and diagnosis. J Am Acad Dermatol. 2021;84(6):1507-1519

DESG3
70420

Desmoglein 3 (DSG3) Immunostain, Technical Component Only

Clinical Information: Desmoglein 3 (DSG3) is a calcium-binding transmembrane glycoprotein component of desmosomes in vertebrate epithelial cells. Currently, three desmoglein subfamily members have been identified and all are members of the cadherin cell adhesion molecule superfamily. Positivity for DSG3 in a non-small cell lung carcinoma supports a diagnosis of squamous cell carcinoma.

Useful For: Classification of squamous cell carcinomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the

patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Funahashi SI, Kawai S, Fujii E, et al. Generation of an anti-desmoglein 3 antibody without pathogenic activity of pemphigus vulgaris for therapeutic application to squamous cell carcinoma. J Biochem. 2018;164(6):471-481. doi:10.1093/jb/mvy074 2. Xiao J, Lu X, Chen X, et al. Eight potential biomarkers for distinguishing between lung adenocarcinoma and squamous cell carcinoma. Oncotarget. 2017;8(42):71759-71771. doi:10.18632/oncotarget.17606 3. Brown L, Wan H. Desmoglein 3: a help or a hindrance in cancer progression?. Cancers (Basel). 2015;7(1):266-286. doi:10.3390/cancers7010266 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

DEXA
609439

Dexamethasone, Serum

Clinical Information: Synthetic glucocorticoids are widely used and have an important clinical utility both as antiinflammatory and immunosuppressive agents. The medical use of these agents, as well as their surreptitious use, can sometimes lead to a confusing clinical presentation. Patients exposed to these steroids may present with clinical features of Cushing syndrome but with suppressed cortisol levels and evidence of hypothalamus-pituitary-adrenal axis suppression.

Useful For: Confirming the presence of dexamethasone in serum Confirming the cause of secondary adrenal insufficiency This test is not useful as the sole basis for a diagnosis or treatment decisions.

Interpretation: This test will screen for, and quantitate if present, the synthetic glucocorticoid, dexamethasone. The presence of this synthetic glucocorticoid in serum indicates the current or recent use of this compound.

Reference Values:
Baseline: <30 ng/dL
8:00 a.m. following 1 mg Dexamethasone, previous evening: >100 ng/dL
8:00 a.m. following 8 mg Dexamethasone, (4 x 2 mg doses) previous day: >800 ng/dL

Clinical References: 1. Genere N, Kaur RJ, Athimulam S, et al. Interpretation of abnormal dexamethasone suppression test is enhanced with use of synchronous free cortisol assessment. J Clin Endocrinol Metab. 2021;107(3):e1221-e1230 doi:10.1210/clinem/dgab724 2. Cave A, Arlett P, Lee E. Inhaled and nasal corticosteroids: factors affecting the risks of systemic adverse effects. Pharmacol Ther. 1999;83(3):153 3. Bijlsma JW, van Everdingen AA, Huisman M, et al. Glucocorticoids in rheumatoid arthritis: effects on erosions and bone. Ann N Y Acad Sci. 2002;966:82-90. doi:10.1111/j.1749-6632.2022.tb04205.x 4. Genere N, Kaur RJ, Athimulam S, et al. Interpretation of abnormal dexamethasone suppression test is enhanced with use of synchronous free cortisol assessment. J Clin Endocrinol Metab. 2022;107(3):e1221-e1230. doi:10.1210/clinem/dgab724

FDXAP
57720

Dexedrine (Dextroamphetamine)

Reference Values:
Reference Range: 10 – 100 ng/mL

FCDU8
75783

Dextro/Levo Methorphan, Umbilical Cord Tissue

Reference Values:
Reporting limit determined each analysis.

Units: ng/g

Only orderable as part of a profile-see FCDSU.

FDM
90117

Dextromethorphan (DM), Serum

Reference Values:
Reference Range: 2.0 - 6.0 ng/mL

DBS1
48400

Diabetes Mellitus Type 1 Evaluation, Serum

Clinical Information: Islet cell autoantibodies have been known to be associated with type 1 diabetes mellitus since the 1970s. Since 1988, several autoantigens, against which islet antibodies are directed, have been identified. These include the insulinoma-associated protein 2 (IA-2), glutamic acid decarboxylase 65 (GAD65), insulin and, most recently, the zinc transporter ZnT8.(1) Only 4% to 7% of patients with type 1 diabetes are autoantibody negative, fewer than 10% have only 1 marker, and around 70% have 3 or 4 markers. These findings have been confirmed in multiple specialty laboratories internationally. One or more of these autoantibodies are detected in 93% to 96% of patients with type 1 diabetes, both adults and children. These antibodies are also detectable in relatives of type 1 diabetic patients at risk for developing diabetes, before clinical onset.(2) Some patients with type 1 diabetes are initially diagnosed as having type 2 diabetes because of symptom-onset in adulthood, societal obesity, and initial insulin-independence. These patients with either "latent autoimmune diabetes in adulthood" or type 1 diabetes mellitus may be distinguished from those patients with type 2 diabetes by detection of 1 or more islet autoantibodies (including ZnT8 antibody). Patients with gestational diabetes can also be stratified for future diabetes risk by detection of 1 or more islet autoantibodies.

Useful For: Distinguishing type 1 from type 2 diabetes mellitus Identifying individuals at risk of type 1 diabetes (including high-risk relatives of patients with diabetes) Predicting future insulin requirement treatment in patients with adult-onset diabetes

Interpretation: Seropositivity for 1 or more islet cell autoantibodies is supportive of: -A diagnosis of type 1 diabetes. Only 2% to 4% of patients with type 1 diabetes are antibody negative; 90% have more than 1 antibody marker, and 70% have 3 or 4 markers.(1) Patients with gestational diabetes who are antibody seropositive are at high risk for diabetes postpartum. Rarely, diabetic children test seronegative, which may indicate a diagnosis of maturity-onset diabetes of the young in clinically suspicious cases. -A high risk for future development of diabetes. Among 44 first-degree relatives of patients with type 1 diabetes, those with 3 antibodies had a 70% risk of developing type 1 diabetes within 5 years.(2) -A current or future need for insulin therapy in patients with diabetes. In the UK Prospective Diabetes Study, 84% of those classified clinically as having type 2 diabetes and seropositive for glutamic acid decarboxylase 65 (GAD65) required insulin within 6 years, compared to 14% that were antibody negative.(3)

Reference Values:
GLUTAMIC ACID DECARBOXYLASE (GAD65) ANTIBODY
< or =0.02 nmol/L
Reference values apply to all ages.

INSULIN ANTIBODIES

< or =0.02 nmol/L
Reference values apply to all ages.

ISLET ANTIGEN 2 (IA-2) ANTIBODY
< or =0.02 nmol/L
Reference values apply to all ages.

ZINC TRANSPORTER 8 (ZnT8) ANTIBODY
< 15.0 U/mL
Reference values apply to all ages.

Clinical References: 1. Bingley PJ. Clinical applications of diabetes antibody testing. J Clin Endocrinol Metab. 2010;95(1):25-33 2. Bingley PJ, Gale EA. Progression to type 1 diabetes in islet cell antibody-positive relatives in the European Nicotinamide Diabetes Intervention Trial: the role of additional immune, genetic and metabolic markers of risk. Diabetologia. 2006;49(5):881-890 3. Turner R, Stratton I, Horton V, et al. UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group. Lancet. 1997;350(9087):1288-1293 4. Thomas NJ, Jones AG. The challenges of identifying and studying type 1 diabetes in adults [published online ahead of print, 2023 Sep 20]. Diabetologia. 2023;10.1007/s00125-023-06004-4. doi:10.1007/s00125-023-06004-4

DIA
8629

Diazepam and Nordiazepam, Serum

Clinical Information: Diazepam, a benzodiazepine derivative, is an anxiolytic agent that reduces neuronal depolarization resulting in decreased action potentials. It enhances the action of gamma-aminobutyric acid (GABA) by tightly binding to A-type GABA receptors, thus opening the membrane channels, and allowing the entry of chloride ions. It is also used as a muscle relaxant, procedural sedation agent, and sedative-hypnotic agent to treat withdrawal states (ie, ethanol), along with other conditions (seizures). Diazepam is metabolized to several metabolites in the liver, including temazepam, oxazepam, and nordiazepam (desmethyldiazepam), and the clearance of the drug is reduced considerably in older individuals and in patients with hepatic disease. Therapeutic assessment typically includes measurement of both the parent drug (diazepam) and the active metabolite (nordiazepam).

Useful For: Assessing compliance Monitoring for appropriate therapeutic level Assessing diazepam toxicity

Interpretation: For seizures: Serum concentrations are not usually monitored during early therapy because response to the drug can be monitored clinically as seizure control. If seizures resume despite adequate therapy, another anticonvulsant must be considered. Toxicity is commonly seen when diazepam plus nordiazepam concentrations exceed 3000 ng/mL. Adverse effects of benzodiazepines in therapeutic doses usually reflect the drug's pharmacology and include sedation, slurred speech, and ataxia. Respiratory depression/arrest may occur with large overdoses or following rapid intravenous injection with short-acting benzodiazepines.

Reference Values:
Therapeutic concentrations
Diazepam and Nordiazepam: 200-2,500 ng/mL

Clinical References: 1. Langman LJ, Bechtel LK, Meier BM, Holstege C. Clinical toxicology. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:832-887 2. Burtis CA, Ashwood ER, Bruns DE, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. WB Saunders Company; 2011:Table 60.2

DICET
619667

DICER1 Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information: This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for somatic mutations involving the DICER1 gene known to be associated with multiple tumor types. DICER1 mutations are a diagnostic marker of embryonal rhabdomyosarcoma and Sertoli-Leydig cell tumors.(1) In central nervous system (CNS) tumors, DICER1 mutations are a diagnostic molecular biomarker for primary intracranial sarcoma, DICER1-mutant, embryonal tumor with multilayered rosettes and pituitary blastoma.(2) DICER1 mutations also occur in a subset of pineoblastoma, typically in the context of DICER1 tumor-predisposition syndrome. DICER1 tumor-predisposition syndrome is an inherited predisposition to pleuropulmonary blastoma, cystic nephroma, Wilms' Tumor, anaplastic sarcoma of the kidney, ovarian Sertoli-Leydig cell tumor, and cervical embryonal rhabdomyosarcoma.

Useful For: Identifying specific mutations within the DICER1 gene to assist in tumor diagnosis/classification

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board. Female genital tumours. 5th ed. World Health Organization; 2020. WHO Classification of Tumours. Vol 4 2. WHO Classification of Tumours Editorial Board: Central nervous system tumours. 5th ed. World Health Organization; 2021. WHO Classification of Tumours. Vol 6 3. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 4. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 5. Caroleo AM, De loris MA, Boccuto L, et al: DICER1 syndrome and cancer predisposition: From a rare pediatric tumor to lifetime risk. Front Oncol. 2021 Jan 21;10:614541 6. Li BK, Vasiljevic A, Dufour C, et al: Pineoblastoma segregates into molecular sub-groups with distinct clinico-pathologic features: a rare brain tumor consortium registry study. Acta Neuropathol. 2020 Feb;139(2):223-241 7. Koelsche C, Mynarek M, Schrimpf D, et al: Primary intracranial spindle cell sarcoma with rhabdomyosarcoma-like features share a highly distinct methylation profile and DICER1 mutations. Acta Neuropathol. 2018 Aug;136(2):327-337 8. de Kock L, Yoon JY, Apellaniz-Ruiz M, et al: Significantly greater prevalence of DICER1 alterations in uterine embryonal rhabdomyosarcoma compared to adenosarcoma. Mod Pathol. 2020 Jun;33:1207-1219 9. McCluggage WG, Apellaniz-Ruiz M, Chong AL, et al: Embryonal rhabdomyosarcoma of the ovary and fallopian tube: Rare neoplasms associated with germline and somatic DICER1 mutations. Am J Surg Pathol. 2020 Jun;44:738-747 10. de Kock L, Terzic T, McCluggage WG, et al: DICER1 mutations are consistently present in moderately and poorly differentiated sertoli-leydig cell tumors. Am J Surg Pathol. 2017 Sep;41:1178-1187

FDGTX
75374

Digitoxin, Serum

Reference Values:

FRDIG
82130

Digoxin, Free, Serum

Clinical Information: Digoxin, a widely prescribed cardiac drug, has a narrow therapeutic window (a very small difference exists between therapeutic and toxic tissue concentrations). While excess digoxin can have serious side effects (eg, cardiac dysrhythmias, heart failure, seizures, death), it is one of the few therapeutic drugs for which antidotal therapy is available.(1) In toxic situations, antibody fragment therapy, which involves the administration of antibodies to digoxin (eg, Digibind, Digoxin Immune Fab), is indicated. In manufacturing of Digibind, papain cleaves digoxin-specific IgG antibody into 2 antigen binding-site fragments (Fab fragments). These fragments bind to digoxin, block the active site of the digoxin molecule, and make it unavailable to its receptor molecule and biologically inactive. The Fab fragment-digoxin complex is then excreted by the kidney. Total digoxin concentration in blood increases approximately 10 to 30 fold after administration of Fab fragments. On the other hand, the unbound (free) fraction, which is responsible for its pharmacological activity, decreases. Traditional digoxin assays performed by immunoassay (eg, DIG / Digoxin, Serum) measure both Fab fragment-bound (inactive) digoxin and free (active) digoxin (ie, total digoxin), and are unsuitable for managing patients when digoxin-specific Fab fragment therapy has been administered. Assays for measurement of free digoxin levels only are necessary in such situations. The kidneys provide the main route of Fab fragment elimination from the body. In patients with normal renal function, digoxin-specific Fab fragments are excreted in the urine with a biological half-life of 15 to 20 hours. Ordinarily, improvement in signs or symptoms of digoxin intoxication begins within a half hour or less after initiation of Fab fragment therapy. Clearance may be delayed in patients with renal failure. In such patients, toxicity may recur if previously bound drug is released from the Fab fragments, resulting in increased levels of free digoxin. Digoxin-like immunoreactive factors (DLIFs) are endogenous substances that can cross-react with testing antibodies used in some digoxin immunoassays, causing erroneous results. DLIFs may be seen in certain volume-expanded patients such as neonates, patients with renal or liver disease, and in women in the third trimester of pregnancy being treated with digoxin.(2) DLIFs are strongly bound to proteins and, in this assay, are removed prior to testing. The following ordering guidelines are offered: -When creatinine clearance is less than 30 mL/min/surface area: order free digoxin levels daily for 12 days (or until dismissal) -When creatinine clearance is equal to or above 30 mL/min/surface area (and the patient is not on renal-replacement therapy): order free levels daily for 72 hours, as long as the last level is not supratherapeutic (these patients are expected to have good clearance and a lower risk for reintoxication) -Also order total digoxin levels every other day during the time periods above, with a goal of determining whether there is correlation between changes in free and total levels.

Useful For: Evaluating recrudescent (breakthrough) digoxin toxicity in renal-failure patients Assessing the need for more antidigoxin Fab to be administered Deciding when to reintroduce digoxin therapy Monitoring patients with possible digoxin-like immunoreactive factors (DLIFs)

Interpretation: The target therapeutic level is 0.4 to 0.9 ng/mL. Toxicity may be seen when free digoxin concentrations are 3.0 ng/mL or higher. Pediatric patients may tolerate higher concentrations. Therapeutic concentrations for free digoxin are 25% lower than therapeutic values for total digoxin due to the separation of protein-bound digoxin in the assay.

Reference Values:

<16 years:

Therapeutic ranges have not been established for patients who are under 16 years of age. In adults, the suggested serum free digoxin therapeutic range is 0.4-0.9 ng/mL.

Toxic concentration: > or =3.0

> or =16 years:

0.4-0.9 ng/mL

Toxic concentration: > or =3.0 ng/ mL

Clinical References: 1. Jortani SA, Pinar A, Johnson NA, Valdes R Jr: Validity of unbound digoxin measurements by immunoassays in presence of antidote (Digibind). Clin Chim Acta. 1999;283:159-169 2. DIGIBIND Digoxin Immune FAB (Ovine). Package insert. GlaxoSmithKline; 2003 3. Moyer TP,

Boeckx RL, eds: Applied Therapeutic Drug Monitoring. Vol 2. American Association for Clinical Chemistry Press; 1984 4. Jortani SA, Voldes R Jr: Digoxin and its related endogenous factors. Crit Rev Clin Lab Sci. 1997;34:225-274 5. Datta P, Hinz V, Klee G: Comparison four digoxin immunoassays with respect to interference from digoxin-like immunoreactive factors. Clin Biochem. 1996;29(6):541-547 6. Soldin SJ: Free drug measurements. When and why? An overview. Arch Pathol Lab Med. 1999;123:822-823 7. Dickstein K, Cohen-Solal A, Filippatos G, et al: ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Eur Heart J. 2008;29:2388-2442 8. Milone MC, Shaw LM: Therapeutic drugs and their management. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 6th ed. Elsevier; 2018800-831

DIG
8674

Digoxin, Serum

Clinical Information: Compounds in the digitalis family of glycosides consist of a steroid nucleus, a lactone ring, and a sugar. Digoxin is widely prescribed for the treatment of congestive heart failure and various disturbances of cardiac rhythm. Digoxin improves the strength of myocardial contraction, and results in the beneficial effects of increased cardiac output, decreased heart size, decreased venous pressure, and decreased blood volume. Digoxin therapy also results in stabilized and slowed ventricular pulse rate. These therapeutic effects are produced through a network of direct and indirect interactions upon the myocardium, blood vessels, and the autonomic nervous system. Digoxin is well absorbed after oral administration and is widely distributed to tissues, especially the heart, kidney, and liver. A number of factors can alter normal absorption, distribution, and bioavailability of the drug, including naturally occurring enteric bacteria in the bowel, presence of food in the gut, strenuous physical activity, ingestion of quinine or quinidine, and concomitant use of a wide range of drugs. Children generally require higher concentrations of digoxin. After oral administration, there is an early rise in serum concentration. Equilibration of serum and tissue levels occurs at approximately 6 to 8 hours. For this reason, blood specimens for digoxin analysis should be drawn at least 6 to 8 hours after drug administration. Digoxin is excreted primarily in the urine. The average elimination half-life is 36 to 40 hours but may be considerably prolonged in those with renal disease, causing digoxin accumulation and toxicity. Symptoms of digoxin toxicity often mimic the cardiac arrhythmia's for which the drug was originally prescribed (eg, heart block and heart failure). Other typical symptoms of toxicity include gastrointestinal effects, such as anorexia, nausea, vomiting, abdominal pain and diarrhea, and neuropsychologic symptoms, such as fatigue, malaise, dizziness, clouded or blurred vision, visual and auditory hallucination, paranoid ideation, and depression. Toxicity of digoxin may reflect several factors: the drug has a narrow therapeutic window (a very small difference exists between therapeutic and toxic tissue levels); individuals vary in their ability to metabolize and respond to digoxin; absorption of various oral forms of digoxin may vary over a 2-fold range; susceptibility to digitalis toxicity apparently increases with age.

Useful For: Monitoring digoxin therapy

Interpretation: The therapeutic range is 0.6 to 1.2 ng/mL. Levels of 4.0 ng/mL and above may be potentially life-threatening.

Reference Values:
<16 years:
Therapeutic ranges have not been established for patients who are less than 16 years of age.

> or =16 years:
Therapeutic range: 0.6-1.2 ng/mL
Toxic concentration: > or =4.0 ng/mL

Clinical References:

DPYDQ
610052

Dihydropyrimidine Dehydrogenase Genotype, Varies

Clinical Information: 5-Fluorouracil (5-FU) and its orally administered prodrug, capecitabine, are fluoropyrimidine-based chemotherapeutic agents that are widely used for the treatment of colorectal cancer and other solid tumors. The dihydropyrimidine dehydrogenase (DPYD) gene encodes the rate-limiting enzyme for fluoropyrimidine catabolism and eliminates over 80% of administered 5-FU. Dihydropyrimidine dehydrogenase (DPD) activity is subject to wide variability, mainly due to genetic variation. This results in a broad range of enzymatic deficiency from partial (3%-5% of population) to complete loss (0.2% of population) of enzyme activity.(2-5) Patients who are deficient in DPD are at an increased risk for side effects and toxicity when undergoing 5-FU treatment.(6) In addition, pathogenic homozygous or compound heterozygous variants within DPYD are associated with DPD deficiency. DPD deficiency shows large phenotypic variability, ranging from no symptoms to a convulsive disorder with motor and intellectual disabilities. The following table displays the DPYD variants detected by this assay, the corresponding star allele, and the effect on DPD enzyme activity. Other or novel variants, besides those listed here, may also impact fluoropyrimidine-related adverse effects and tumor response. Table. Enzyme Activity of Individual Star Alleles DPYD allele cDNA nucleotide change Effect on enzyme activity *1 None (wild type) Normal activity *2A c.1905+1G>A No activity *7 c.299_302del No activity *8 c.703C>T No activity *10 c.2983G>T No activity *13 c.1679T>G No activity rs67376798 c.2846A>T Decreased activity rs75017182 c.1129-5923C>G Decreased activity rs115232898 c.557A>G Decreased activity

Useful For: Identifying individuals with genetic variants in DPYD who are at increased risk of toxicity when prescribed 5-fluorouracil (5-FU) or capecitabine chemotherapy treatment

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
DPYD Phenotype: Normal metabolizer
DPYD Activity Score: 2.00
DPYD Genotype: No variants were detected in the DPYD gene.

An interpretive report will be provided.

Clinical References: 1. OMIM: Dihydropyrimidine dehydrogenase; DPYD. 2009. Updated December 13, 2023. Accessed April 1,2025. Available at www.omim.org/entry/612779 2. Clinical Pharmacogenetics Implementation Consortium (CPIC): Guideline for Fluoropyrimidines and DPYD. Updated March 2024. Accessed December 23, 2024. Available at https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/ 3. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 Update. Clin Pharmacol Ther. 2018;103(2):210-216. doi:10.1002/cpt.911 4. Lunenburg CATC, van der Wouden CH, Nijenhuis M, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines. Eur J Hum Genet. 2020;28(4):508-517. doi:10.1038/s41431-019-0540-0 5. Morel A, Boisdron-Celle M, Fey L, et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. Mol Cancer Ther. 2006;5(11):2895-2904. doi:10.1158/1535-7163.MCT-06-0327 6. Offer SM, Fossum CC, Wegner NJ, Stuflesser AJ, Butterfield GL, Diasio RB. Comparative functional analysis of DPYD variants of potential clinical relevance to

dihydropyrimidine dehydrogenase activity. Cancer Res. 2014;74(9):2545-2554. doi:10.1158/0008-5472.CAN-13-24826 7. U.S. Food and Drug Administration: Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated September 23, 2024. Accessed April 1, 2025. Available at www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

DPYDZ
610051

Dihydropyrimidine Dehydrogenase, DPYD Full Gene Sequencing, Varies

Clinical Information: 5-Fluorouracil (5-FU) and its orally administered prodrug, capecitabine, are fluoropyrimidine-based chemotherapeutic agents that are widely used for the treatment of colorectal cancer and other solid tumors. The DPYD gene encodes dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme for fluoropyrimidine catabolism, which eliminates over 80% of administered 5-FU. Genetic variation in DYPD is the main cause for variability in DPD activity and can lead to partial or complete enzymatic deficiency (3-5% or 0.2% of the population, respectively).(2,3) Patients who are deficient in DPD are at an increased risk for adverse effects and toxicity when undergoing 5-FU treatment.(4) In addition, disease-causing homozygous or compound heterozygous variants within DPYD are associated with DPD deficiency. DPD deficiency shows a wide range of severity, from asymptomatic (albeit at risk for drug toxicity) to neurological problems, including seizures and intellectual disability, delayed motor development, and microcephaly. DPYD variants impacting the metabolic pathway of fluoropyrimidines have been shown to contribute to the differences in clinical outcomes, including toxicity and tumor response. Common DPYD variants that result in no activity include c.1905+1G>A (*2A), c.299_302del (*7), c.703C>T (*8), c.2983G>T (*10), and c.1679T>G (*13). Common DPYD variants resulting in reduced activity include c.2846A>T (rs67376798), c.1129-5923C>G (rs75017182, also part of the HapB3 haplotype), and c.557A>G (rs115232898). In addition to these common variants, this sequencing test may also detect rare variants that impact DPD activity.

Useful For: Identifying individuals at increased risk of toxicity when considering 5-fluorouracil and capecitabine chemotherapy treatment Identifying common and rare variants associated with decreased or absent dihydropyrimidine dehydrogenase (DPD) enzyme activity in individuals with suspected DPD deficiency

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics recommendations as a guideline.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Additionally variant functional status and activity score are assigned using the most recent published Clinical Pharmacogenetics Implementation Consortium (CPIC) recommendations as a guideline.(2) For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Association Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
DPYD Total Activity Score: 2

DPYD Phenotype: Normal metabolizer

An interpretive report will be provided.

Clinical References: 1. OMIM. 274270 Dihydropyrimidine dehydrogenase deficiency. Johns Hopkins University; 1986. Updated October 4, 2023. Accessed June 4, 2024. Available from

www.omim.org/entry/274270 2. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin Pharmacol Ther. 2018;103(2):210-216 3. Morel A, Boisdron-Celle M, Fey L, et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. Mol Cancer Ther. 2006;5(11):2895-2904 4. U.S. Food and Drug Administration (FDA). Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated February 2, 2024. Accessed June 4, 2024. Available at: www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm 5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 6. Offer SM, Fossum CC, Wegner NJ, et al. Comparative functional analysis of DPYD variants of potential clinical relevance to dihydropyrimidine dehydrogenase activity. Cancer Res. 2014;74(9):2545-2554

DHRF
62766

Dihydrorhodamine Flow Cytometric N-Formyl-Methionyl-Leucyl-Phenylalanine Test, Blood

Clinical Information: This assay can be used for the diagnostic evaluation of Rac2 deficiency, which is a neutrophil defect that causes profound neutrophil dysfunction with decreased chemotaxis, polarization, superoxide anion production, azurophilic granule secretion. This disease is caused by inhibitory variants in the RAC2 gene, which encodes a Rho family GTPase essential to neutrophil activation and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) function.(1) Patients with Rac2 deficiency have been shown to have normal neutrophil oxidative burst when stimulated with phorbol myristate acetate (PMA), indicating normal NOX activity but abnormal neutrophil responses to N-formyl-methionyl-leucyl-phenylalanine (fMLP), which is a physiological activator of neutrophils. The defective oxidative burst to fMLP, but not to PMA, is consistent with Rac2 deficiency.(2) By contrast, gain of function variants in RAC2 would lead to an exaggerated response to fMLP.(3)

Useful For: Evaluation of Rac2 deficiency and RAC2 gain of function

Interpretation: An interpretive report will be provided, in addition to the quantitative values described in Clinical Information. Interpretation of the results of the quantitative dihydrorhodamine (DHR) flow cytometric assay must include both the proportion of positive neutrophils for DHR after N-formyl-methionyl-leucyl-phenylalanine stimulation and the mean fluorescence intensity.

Reference Values:

Result name	Unit	Cutoff for defining normal
% fMLP ox-DHR+	%	> or =10%
MFI fMLP ox-DHR+	MFI	> or =2
Control % fMLP ox-DHR+	%	> or =10%
Control MFI fMLP ox-DHR+	MFI	> or =2

Clinical References: 1. Ambruso DR, Knall C, Abell AN, et al. Human neutrophil immunodeficiency syndrome is associated with an inhibitory Rac2 mutation. Proc Natl Acad Sci U S A. 2000;97(9):4654-4659 2. Accetta D, Syverson G, Bonacci B, et al. Human phagocyte defect caused by a RAC2 mutation detected by means of neonatal screening for T cell lymphopenia. J Allergy Clin Immunol. 2011;127(2):535-538 3. Hsu AP, Donko A, Arrington ME, et al. Dominant activating RAC2 mutation with lymphopenia, immunodeficiency, and cytoskeletal defects. Blood. 2019;133(18):1977-1988

DHRP 62765 Dihydrorhodamine Flow Cytometric Phorbol Myristate Acetate Test, Blood

Clinical Information: Chronic granulomatous disease (CGD) is caused by genetic alterations in the gene components that encode the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) enzyme complex. These alterations result in an inability to produce superoxide anions required for killing of bacterial and fungal organisms. Other clinical features include a predisposition to systemic granulomatous complications and autoimmunity.(1) There are 6 known genes associated with the clinical phenotype of CGD.(2) The gene defects include disease-causing variants in the CYBB gene, encoding the gp91phox protein, which is X-linked and accounts for approximately 70% of CGD cases. Other genetic causes are autosomal recessive in inheritance and occur in one of the following genes: NCF1 (p47phox), NCF2 (p67phox), CYBA (p22phox), NCF4 (p40phox) and CYBC1.(3) Typically, patients with X-linked CGD have the most severe disease, while patients with p47phox defects tend to have the best outcomes. Disease-causing variants in NCF4 and CYBC1 have been the most recently described rare causes of disease.(3,4) There is significant clinical variability even among individuals with similar variants, in terms of NOX function, indicating that there can be several modulating factors including the genetic alteration, infection history, and granulomatous and autoimmune complications. There appears to be a correlation between very low NADPH superoxide production and worse outcomes. CGD can be treated with hematopoietic cell transplantation, which can be effective for the inflammatory and autoimmune manifestations. It has been shown that survival of patients with CGD was strongly associated with residual reactive oxygen intermediate (ROI) production, independent of the specific gene alteration.(5) Measurement of NOX activity through the dihydrorhodamine (DHR) flow cytometry assay contributed to the assessment of ROI. The diagnostic laboratory assessment for CGD includes evaluation of NOX function in neutrophils, using historically the nitroblue tetrazolium test or currently the more analytically sensitive DHR test as described here. Activation of neutrophils with phorbol myristate acetate (PMA) results in oxidation of DHR to a fluorescent compound, rhodamine 123, which can be measured by flow cytometry. Flow cytometry can distinguish between the some genetic forms of CGD.(6,7) DHR test may be normal or mildly impaired in patients who are NCF4 (p40phox) deficient.(4) Complete myeloperoxidase (MPO) deficiency can cause a false-positive result for CGD in the DHR flow cytometric assay;(8) however, there is a difference between the percent of DHR positive neutrophils and the mean fluorescence intensity after PMA stimulation that allows discrimination between true X-linked CGD and complete MPO deficiency. Further, the addition of recombinant human MPO enhances the DHR signal in MPO-deficient neutrophils but not in CGD neutrophils.(8) It is important to have quantitative measures in the DHR flow cytometry assay to effectively use the test for diagnosis of the different forms of CGD as well as for monitoring chimerism and NOX activity post-hematopoietic cell transplantation. These quantitative measures include assessment of the relative proportion (%) of neutrophils that are positive for DHR fluorescence after PMA stimulation and the relative fluorescence intensity of DHR on neutrophils after activation. Female carriers of X-linked CGD can become symptomatic for CGD due to skewed lyonization (X chromosome inactivation).(9) Age-related acquired skewing of lyonization can also cause increased susceptibility to infections in carriers of X-linked CGD.(10) While inherited disease-causing variants are more common in CGD, there have been reports of de novo variants in the CYBB gene, causing X-linked CGD in male patients whose mothers are not carriers for the affected allele. Additionally, somatic mosaicism has been reported in patients with X-linked CGD who have small populations of normal cells.(11) There are also reports of triple somatic mosaicism in female carriers (12,13) as well as

late-onset disease in an adult female who was a somatic mosaic for a novel variant in the CYBB gene.(14) Therefore, the clinical, genetic, and age spectrum of CGD is varied and laboratory assessment of NOX activity after neutrophil stimulation, coupled with appropriate interpretation, is critical to achieving an accurate diagnosis or for monitoring patients posttransplant.

Useful For: Evaluating chronic granulomatous disease (CGD), X-linked and autosomal recessive forms, complete myeloperoxidase deficiency Monitoring chimerism and nicotinamide adenine dinucleotide phosphate oxidase (NOX) function post-hematopoietic cell transplantation Assessing residual NOX activity pretransplant Identifying of female carriers for X-linked CGD Assessing changes in lyonization with age in female carriers

Interpretation: An interpretive report will be provided, in addition to the quantitative values. Interpretation of the results of the quantitative dihydrorhodamine (DHR) flow cytometric assay must include both the proportion of positive neutrophils for DHR after phorbol myristate acetate stimulation, and the mean fluorescence intensity. Additionally, visual assessment of the pattern of DHR fluorescence is helpful in discriminating between the various genetic defects associated with chronic granulomatous disease and complete myeloperoxidase deficiency.

Reference Values:

Result Name	Unit	Cutoff for defining normal
% PMA ox-DHR+	%	> or =95%
MFI PMA ox-DHR+	MFI	> or =60
Control % PMA ox-DHR+	%	> or =95%
Control MFI PMA ox-DHR+	MFI	> or =60

Clinical References: 1. Kang EM, Marciano BE, DeRavin SS, et al. Chronic granulomatous disease: overview and hematopoietic stem cell transplantation. J Allergy Clin Immunol. 2011;127(6):1319-1326 2. Segal BH, DeCarlo ES, Kwon-Chung KJ, et al. Aspergillus nidulans infection in chronic granulomatous disease. Medicine. 1998;77(5):345-354 3. Arnadottir GA, Norddahl GL, Gudmundsdottir S, et al. A homozygous loss-of-function mutation leading to CYBC1 deficiency causes chronic granulomatous disease. Nat Commun. 2018;9(1):4447 4. van de Geer A, Nieto-Patlan A, Kuhns DB, et al. Inherited p40phox deficiency differs from classic chronic granulomatous disease. J Clin Invest. 2018;128(9):3957-3975. doi:10.1172/JCI97116 5. Kuhns DB, Alvord WG, Heller T, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. N Engl J Med. 2010;363:2600-2610 6. Vowells SJ, Fleisher TA, Sekhsaria S, et al. Genotype-dependent variability in flow cytometric evaluation of reduced NADPH oxidase function in patients with chronic granulomatous disease. J Pediatr. 1996;128:104(1)-107 7. Vowells SJ, Sekhsaria S, Malech H, et al. Flow cytometric analysis of the granulocyte respiratory burst: a comparison study of fluorescent probes. J Immunol Methods. 1995;178(1):89-97 8. Mauch L, Lun A, O'Gorman MRG, et al. Chronic granulomatous disease (CGD) and complete myeloperoxidase deficiency both yield strongly reduced DHR 123 test signals but can be easily discerned in routine testing for CGD. Clin Chem. 2007;53(5):890-896 9. Roesler J. Carriers of X-linked chronic granulomatous disease at risk. Clin Immunol. 2009;130(2):233; author reply 234. doi:10.1016/j.clim.2008.09.013 10. Rosen-Wolff A, Soldan W, Heyne K, et al. Increased susceptibility of a carrier of X-linked chronic granulomatous disease (CGD) to Aspergillus fumigatus infection associated with age-related skewing of lyonization. Ann Hematol. 2001;80(2):113-115 11. Yamada M, Okura Y,

Suzuki Y, et al. Somatic mosaicism in two unrelated patients with X-linked chronic granulomatous disease characterized by the presence of a small population of normal cells. Gene. 2012;497(1):110-115 12. de Boer M, Bakker E, Van Lierde S, Roos D. Somatic triple mosaicism in a carrier of X-linked chronic granulomatous disease. Blood. 1998;91(1):252-257 13. Noack D, Heyworth PG, Kyono W, et al. A second case of somatic triple mosaicism in the CYBB gene causing chronic granulomatous disease. Hum Genet. 2001;109(2):234-238 14. Wolach B, Scharf Y, Gavrieli R, et al. Unusual late presentation of X-linked chronic granulomatous disease in an adult female with a somatic mosaic for a novel mutation in CYBB. Blood. 2005;105(1):61-66 15. Siler U, Romao S, Tejera E, et al. Severe glucose-6-phosphate dehydrogenase deficiency leads to susceptibility to infection and absent NETosis. J Allergy Clin Immunol. 2017;139(1):212-219.e3 16. Kuhns DB. Diagnostic testing for chronic granulomatous disease. Methods Mol Biol. 2019;1982:543-571 17. Delmonte OM, Fleisher TA. Flow cytometry: Surface markers and beyond. J Allergy Clin Immunol. 2019;143(2):528-537 18. Knight V, Heimall JR, Chong H, et al. A toolkit and framework for optimal laboratory evaluation of individuals with suspected primary immunodeficiency. J Allergy Clin Immunol Pract. 2021;9(9):3293-3307.e6

DHR
62764

Dihydrorhodamine Flow Cytometric Test, Blood

Clinical Information:

Useful For: Evaluation of chronic granulomatous disease (CGD), X-linked and autosomal recessive forms, Rac2 deficiency, complete myeloperoxidase deficiency Monitoring chimerism and nicotinamide adenine dinucleotide phosphate oxidase (NOX) function post-hematopoietic cell transplantation Assessing residual NOX activity pretransplant Identifying female carriers for X-linked CGD Assessing changes in lyonization with age in female carriers

Interpretation: An interpretive report will be provided, in addition to the quantitative values. Interpretation of the results of the quantitative dihydrorhodamine (DHR) flow cytometric assay must include both the proportion of positive neutrophils for DHR after phorbol myristate acetate and/or N-formyl-methionyl-leucyl-phenylalanine stimulation and the mean fluorescence intensity. Additionally, visual assessment of the pattern of DHR fluorescence is helpful in discriminating between the various genetic defects associated with chronic granulomatous disease and complete myeloperoxidase deficiency.

Reference Values:

Result name	Unit	Cutoff for defining normal
% PMA ox-DHR+	%	> or =95%
MFI PMA ox-DHR+	MFI	> or =60
% fMLP ox-DHR+	%	> or =10%
MFI fMLP ox-DHR+	MFI	> or =2
Control % PMA ox-DHR+	%	> or =95%
Control MFI PMA ox-DHR+	MFI	> or =60
Control % fMLP ox-DHR+	%	> or =10%
Control MFI fMLP ox-DHR+	MFI	> or =2

Clinical References: 1. Kang EM, Marciano BE, DeRavin SS, et al. Chronic granulomatous disease: Overview and hematopoietic stem cell transplantation. J Allergy Clin Immunol. 2011;127(6):1319-1326 2. Segal BH, DeCarlo ES, Kwon-Chung KJ, et al. Aspergillus nidulans infection in chronic granulomatous disease. Medicine. 1998;77(5):345-354 3. Arnadottir GA, Norddahl GL, Gudmundsdottir S, et al. A homozygous loss-of-function mutation leading to CYBC1 deficiency causes chronic granulomatous disease. Nat Commun. 2018;9(1):4447 4. van de Geer A, Nieto-Patlan A, Kuhns DB, et al. Inherited p40phox deficiency differs from classic chronic granulomatous disease. J Clin Invest. 2018;128(9):3957-3975. doi:10.1172/JCI97116 5. Kuhns DB, Alvord WG, Heller T, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. N Engl J Med. 2010;363(27):2600-2610 6. Vowells SJ, Fleisher TA, Sekhsaria S, et al. Genotype-dependent variability in flow cytometric evaluation of reduced NADPH oxidase function in patients with chronic granulomatous disease. J Pediatr. 1996;128(1):104-107 7. Vowells SJ, Sekhsaria S, Malech H, et al. Flow cytometric analysis of the granulocyte respiratory burst: a comparison study of fluorescent probes. J Immunol Methods. 1995;178(1):89-97 8. Mauch L, Lun A, O'Gorman MRG, et al. Chronic granulomatous disease (CGD)and complete myeloperoxidase deficiency both yield strongly reduced DHR 123 test signals but can be easily discerned in routine testing for CGD. Clin Chem. 2007;53(5):890-896 9. Ambruso DR, Knall C, Abell AN, et al. Human neutrophil immunodeficiency syndrome is associated with an inhibitory Rac2 mutation. Proc Natl Acad Sci U S A 2000;97(9):4654-4659 10. Accetta D, Syverson G, Bonacci B, et al. Human phagocyte defect caused by a RAC2 mutation detected by means of neonatal screening for T cell lymphopenia. J Allergy Clin Immunol. 2011;127(2):535-538 11. Hsu AP, Donko A, Arrington ME, et al. Dominant activating RAC2 mutation with lymphopenia, immunodeficiency, and cytoskeletal defects. Blood. 2019;133(18):1977-1988 12. Roesler J. Carriers of X-linked chronic granulomatous disease at risk. Clin Immunol. 2009;130(2):233. doi:10.1016/j.clim.2008.09.013 13. Rosen-Wolff A, Soldan W, Heyne K, et al. Increased susceptibility of a carrier of X-linked chronic granulomatous disease (CGD) to Aspergillus fumigatus infection associated with age-related skewing of lyonization. Ann Hematol. 2001;80(2):113-115 14. Yamada M, Okura Y, Suzuki Y, et al. Somatic mosaicism in two unrelated patients with X-linked chronic granulomatous disease characterized by the presence of a small population of normal cells. Gene. 2012;:497(1):110-115 15. de Boer M, Bakker E, Van Lierde S, et al. Somatic triple mosaicism in a carrier of X-linked chronic granulomatous disease. Blood. 1998;91(1):252-257 16. Noack D, Heyworth PG, Kyono W, Cross AR. A second case of somatic triple mosaicism in the CYBB gene causing chronic granulomatous disease. Hum Genet. 2001;109(2):234-238 17. Wolach B, Scharf Y, Gavrieli R, et al. Unusual late presentation of X-linked chronic granulomatous disease in an adult female with a somatic mosaic for a novel mutation in CYBB. Blood. 2005;105:61-66 18. Siler U, Romao S, Tejera E, et al. Severe glucose-6-phosphate dehydrogenase deficiency leads to susceptibility to infection and absent NETosis. J Allergy Clin Immunol. 2017;139(1):212-219 19. Kuhns DB. Diagnostic testing for chronic granulomatous disease. Methods Mol Biol. 2019;1982:543-571 20. Delmonte OM, Fleisher TA. Flow cytometry: Surface markers and beyond. J Allergy Clin Immunol. 2019;143(2):528-537 21. Knight V, Heimall JR, Chong H, et al. A toolkit and framework for optimal laboratory evaluation of individuals with suspected primary immunodeficiency. J Allergy Clin Immunol Pract. 2021;9(9):3293-3307.e6

DHTS
81479

Dihydrotestosterone, Serum

Clinical Information: The principal prostatic androgen is dihydrotestosterone (DHT). Levels of DHT remain normal with aging, despite a decrease in the plasma testosterone, and are not elevated in benign prostatic hyperplasia.(1) Dihydrotestosterone is generated by reduction of testosterone by 5-alpha reductase. Two isoenzymes of 5-alpha reductase have been discovered. Type 1 is present in most tissues in the body where 5-alpha reductase is expressed and is the dominant form in sebaceous glands. Type 2 is the dominant isoenzyme in genital tissues, including the prostate. Androgenetic alopecia (AGA; male-pattern baldness) is a hereditary and androgen-dependent progressive thinning of the scalp hair that follows a defined pattern.(2) While the genetic involvement is pronounced, but poorly understood, major advances have been achieved in understanding the principal elements of androgen metabolism that are involved. DHT may be related to baldness. High concentrations of 5-alpha reductase have been found in frontal scalp and genital skin and androgen-dependent processes are predominantly due to the binding of

DHT to the androgen receptor. Since the clinical success of treatment of AGA with modulators of androgen metabolism or hair growth promoters is limited, sustained microscopic follicular inflammation with connective tissue remodeling, eventually resulting in permanent hair loss, is considered a possible cofactor in the complex etiology of AGA. Available AGA treatment modalities with proven efficacy are oral finasteride, a competitive inhibitor of 5-alpha reductase type 2, and topical minoxidil, an adenosine triphosphate-sensitive potassium channel opener that has been reported to stimulate the production of vascular endothelial growth factor in cultured dermal papilla cells. Currently, many patients with prostate disease receive treatment with a 5-alpha reductase inhibitor such as finasteride (Proscar) to diminish conversion of DHT from testosterone. For more information see Steroid Pathways.

Useful For: Monitoring patients receiving 5-alpha reductase inhibitor therapy or chemotherapy
Evaluating patients with possible 5-alpha reductase deficiency

Interpretation: Patients taking 5-alpha reductase inhibitor have decreased dihydrotestosterone (DHT) serum levels. Patients with genetic 5-alpha reductase deficiency (a rare disease) also have reduced DHT serum levels. Dihydrotestosterone should serve as the primary marker of peripheral androgen production. However, because it is metabolized rapidly and has a very high affinity for sex hormone-binding globulin, DHT does not reflect peripheral androgen action. Instead, its distal metabolite, 3-alpha, 17-beta-androstanediol glucuronide, serves as a better marker of peripheral androgen action. For more information see Steroid Pathways.

Reference Values:

Males Cord blood: < or =100 pg/mL < or =6 months: < or =1,200 pg/mL Tanner Stages Mean	**Age**	**Reference range (pg/mL)**
Stage I (>6 months and prepubertal)	7.1 years	< or =50
Stage II	12.1 years	< or =200
Stage III	13.6 years	80-330
Stage IV	15.1 years	220-520
Stage V	18 years	240-650
>19 years: 112-955 pg/mL Females Cord blood: < or =50 pg/mL < or =6 months: < or =1,200 pg/mL Tanner Stages Mean	Age	Reference range (pg/mL)
Stage I (>6 months and prepubertal)	7.1 years	< or =50
Stage II	10.5 years	< or =300
Stage III	11.6 years	< or =300
Stage IV	12.3 years	< or =300
Stage V	14.5 years	< or =300

Clinical References: 1. Bartsch G, Rittmaster RS, Klocker H. Dihydrotestosterone and the concept of 5 alpha-reductase inhibition in human benign prostatic hyperplasia. World J Urol 2002;19(6):413-425 2. Trueb RM. Molecular mechanisms of androgenetic alopecia. Exp Gerontol. 2002;37(8-9):981-990 3. Singh SM, Gauthier S, Labrie F. Androgen receptor antagonists (antiandrogens): structure-activity relationships. Curr Med Chem 2000;7(2):211-247 4. Rhodes L, Harper J, Uno H, et al. The effects of finasteride (Proscar) on hair growth, hair cycle stage, and serum testosterone and dihydrotestosterone in adult male and female stumptail macaques (Macaca arctoides). J Clin Endocrinol Metab. 1994;79:991-996 5. Gustafsson O, Norming U, Gustafsson S, et al. Dihydrotestosterone and testosterone levels in men screened for prostate cancer: a study of a randomized population. Br J Urol. 1996;77:433-440 6. van der Veen A, van Faassen M, de Jong WHA, van Beek AP, Dijck-Brouwer DAJ, Kema IP. Development and validation of a LC-MS/MS method for the establishment of reference intervals and biological variation for five plasma steroid hormones. Clin Biochem. 2019;68:15-23. doi:10.1016/j.clinbiochem.2019.03.013 7. Kinter KJ, Amraei R, Anekar AA. Biochemistry, Dihydrotestosterone. In: StatPearls [Internet]. StatPearls Publishing. Last updated July 30, 2023. Accessed April 14, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK557634

DCLNG
617239

Dilated Cardiomyopathy and Left Ventricular Noncompaction Cardiomyopathy Gene Panel, Varies

Clinical Information: The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors or by nongenetic (acquired) causes such as infection and inflammation.(1) When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Hereditary forms of dilated cardiomyopathy (DCM) are characterized by ventricular dilation with reduced cardiac performance in the absence of other cardiac or systemic causes that may cause dilation of the heart muscle, such as hypertension and ischemic heart disease. The incidence of DCM in the general population is approximately 1 in 2500 (1), and it is estimated that approximately 50% of cases can be attributed to a genetic etiology.(1) Hereditary forms of DCM are most often caused by genes encoding proteins of the cardiac cytoskeleton and sarcomere. Left ventricular noncompaction (LVNC) is characterized by prominent trabeculations of the left ventricle with trabecular recesses extending into the ventricular cavity. The incidence of LVNC in the general population is estimated to be 1 in 5000.(2) It is currently unclear if LVNC represents a genetically distinct form of cardiomyopathy, as many familial cases of LVNC have been linked to the same genes associated with other forms of hereditary cardiomyopathies, and many affected individuals also meet diagnostic criteria for DCM or hypertrophic cardiomyopathy.(2,3) The clinical presentation of DCM and LVNC can be variable, even within the same family. DCM and LVNC can be apparently asymptomatic in some individuals but can cause sudden, life-threatening arrhythmias, increasing the risk of sudden cardiac death. In addition, some patients with primary hypertrophic cardiomyopathy or arrhythmogenic cardiomyopathy may eventually develop dilated ventricles, resembling DCM in later stages of disease progression.(1) DCM may also be a feature of an underlying systemic disorder such as amyloidoses and musculoskeletal conditions.(1) Hereditary forms of DCM and LVNC can follow an autosomal dominant, autosomal recessive, and X-linked patterns of inheritance. Mitochondrial inheritance is also possible, however, genes associated with mitochondrial inheritance of DCM and LNVC are not assessed on this panel.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of a hereditary form of dilated cardiomyopathy or left ventricular noncompaction Establishing a diagnosis of a hereditary form dilated cardiomyopathy or left ventricular noncompaction

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(4) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known

significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Bozkurt B, Colvin M, Cook J, et al; American Heart Association Committee on Heart Failure and Transplantation of the Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; and Council on Quality of Care and Outcomes Research: Current diagnostic and treatment strategies for specific dilated cardiomyopathies: A scientific statement from the American Heart Association Circulation. 2016 Dec 6;134(23):e579-e646. doi: 10.1161/CIR.0000000000000455. Erratum in: Circulation. 2016 Dec 6;134(23):e652 2. Ichida F: Left ventricular noncompaction-Risk stratification and genetic consideration. J Cardiol. 2020 Jan;75(1):1-9. doi: 10.1016/j.jjcc.2019.09.011 3. Aung N, Doimo S, Ricci F, et al: Prognostic significance of left ventricular noncompaction: Systematic review and meta-analysis of observational studies. Circ Cardiovasc Imaging. 2020 Jan;13(1):e009712. doi: 10.1161/CIRCIMAGING.119.009712 4. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

DILL
82602

Dill, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to dill Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FDILT
91118

Diltiazem (Cardizem, Dilacor)

Reference Values:
Reference Range: 50 - 200 ng/mL

DRVI3
602181

Dilute Russell's Viper Venom Time (DRVVT) Confirmation Ratio, Plasma

Clinical Information:

Useful For: Confirming the presence or helping to exclude the presence of lupus anticoagulants (LA) Identifying LA that do not prolong the activated partial thromboplastin time (APTT) Evaluating unexplained prolongation of the APTT or prothrombin time clotting tests Distinguishing LA from a specific coagulation factor inhibitor or coagulation factor deficiencies

Interpretation: Dilute Russell's viper venom time screen ratio (<1.20): A normal dilute Russell's viper venom time (DRVVT) screen ratio (<1.20) indicates that lupus anticoagulant (LA) is not present or not detectable by this method (but might be detected with other methods). An abnormal DRVVT screen ratio (DRVVT screen ratio > or =1.20) may suggest presence of LA, however, other possibilities include: -Deficiencies or dysfunction of factors I (fibrinogen), II, V, or X, congenital or acquired -Inhibitors of factor V, or occasionally by inhibitors of factor VIII, or other specific or nonspecific inhibitors -Anticoagulation therapy effects (see Cautions) Further evaluation consists of performing mixing studies with an equal volume of normal pooled plasma (DRVVT 1:1 mix) to investigate the possibility of coagulation factor deficiency (suggested by DRVVT mix ratio <1.20) and to evaluate inhibition (suggested by DRVVT mix ratio > or =1.20) and mixing patient plasma with DRVVT reagent enriched in phospholipid (DRVVT confirmatory reagent) (DRVVT mix and DRVVT confirmation ratios). Possible combinations of results include the following: -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio <1.20: No evidence of LA. These data may reflect anticoagulation therapy effects or other (congenital or acquired) coagulopathy. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio <1.20: The prolonged and inhibited DRVVT

(DRVVT screen and mix ratios) may reflect presence of a specific factor inhibitor (eg, factor V inhibitor), anticoagulation therapy effects or other nonspecific inhibitors as can be seen with monoclonal protein disorders, lymphoproliferative disease etc. Although LA cannot be conclusively excluded, the DRVVT confirmation ratio of < or =1.20 makes this less likely. -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio > or =1.20: Although mixing study of the prolonged DRVVT screen and mix ratios provides no evidence of inhibition, additional phospholipid shortens the clotting time (DRVVT confirmation ratio), suggesting presence of LA. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio > or =1.20: The data are consistent with presence of LA, provided anticoagulant effect can be excluded (see Cautions) DRVVT assays ordered as a single, stand-alone test should be interpreted within patient clinical context and close attention to medication use by patient (see Cautions).

Reference Values:

Only orderable as part of a reflex. For more information see DRVI1 / Dilute Russell's Viper Venom Time (DRVVT), with Reflex, Plasma.

<1.20

Normal ranges for children: not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months.

Clinical References: 1. Proven A, Bartlett RP, Moder KG, et al. Clinical importance of positive test results for lupus anticoagulant and anticardiolipin antibodies. Mayo Clin Proc. 2004;79(4):467-475 2. Gastineau DA, Kazmier FJ, Nichols WL, Bowie EJ. Lupus anticoagulant: an analysis of the clinical and laboratory features of 219 cases. Am J Hematol. 1985;19(3):265-275 3. Brandt JT, Triplett DA, Alving B, Sharrer I. Criteria for the diagnosis of lupus anticoagulant: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardization Committee of the ISTH. Thromb Haemost. 1995;74(4);1185-1190 4. Arnout J, Vermylen J. Current status and implications of autoimmune antiphospholipid antibodies in relation to thrombotic disease. J Thromb Haemost. 2003;1(5):931-942 5. Pengo V, Tripodi A, Reber G, Rand JH, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2009;7:1737-1740. doi:10.1111/j.1538-7836.2009.03555.x 6. Clinical and Laboratory Standards Institute (CLSI). Laboratory Testing for Lupus Anticoagulant; Approved Guideline. CLSI document H60-A. CLSI; 2014

DRV3
602178

Dilute Russell's Viper Venom Time (DRVVT) Confirmation, Plasma

Clinical Information: Lupus anticoagulants (LA) are immunoglobulins (IgG, IgM, IgA, or a combination of these) of autoimmune type that are specifically directed against antigenic complexes of negatively charged phospholipids (such as phosphatidylserine or phosphatidylethanolamine) and coagulation-related proteins (such as beta-2-glycoprotein I) or clotting factors (including prothrombin [factor II] or factor X), and which cause prolongation of phospholipid-dependent clotting time tests due to inhibition. LA are functionally and clinically distinct members of a broader group of antiphospholipid autoantibodies that includes immunologically detectable anticardiolipin antibodies or antibodies against other phospholipid-protein complexes. LA interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of 1 or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time: APTT, dilute Russell's viper venom time: DRVVT) due to inhibition. This characteristic in vitro inhibition can be overcome by addition of excess phospholipid. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LA. Currently, the International Society on Thrombosis and Haemostasis and the Clinical and Laboratory Standards Institute (CLSI) recommend testing for LA with at least 2 phospholipid-

dependent clotting time assays based on different coagulation pathways and principles (eg, lupus-sensitive APTT and DRVVT). In addition, given the potential for false-positive results in patients on anticoagulants, a profile or panel of coagulation tests is performed, including the prothrombin time (PT), APTT, thrombin time (TT), and DRVVT. If the PT, APTT, and/or DRVVT are prolonged, additional testing may include mixing tests with normal plasma (to evaluate for inhibition) and the use of excess phospholipid in appropriate assay systems to evaluate for phospholipid-dependent inhibition. Additional reflexive testing helps determine presence or absence of anticoagulants and/or inhibitors to other factors. The diagnosis of LA requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information, including evidence of persistence of LA over time (> or =12 weeks). The venom obtained from Russell's viper (Vipera russelli) contains enzymes that directly activate coagulation factors V and X, bypassing the activation of factors VII, VIII, IX, XI, and XII, and therefore, the effect of deficiencies or inhibitors of these factors. Diluting the phospholipid necessary for the clotting factor interactions increases the sensitivity to LA and the likelihood of identifying a phospholipid-dependent inhibitor that may not be detected by other coagulation tests with a higher phospholipid content (eg, LA-insensitive APTT reagents). The DRVVT screen ratio test is one of several available in vitro tests that may be used to screen and confirm for presence of LA or to help exclude LA. DRVVT testing is used in conjunction with other appropriate coagulation tests (reflexive testing panels) to assist in detection and confirmation of LA, or help exclude their presence. The DRVVT may be abnormally prolonged (DRVVT screen ratio > or =1.20) by LA as well as coagulation factor deficiencies, anticoagulant effects, or other types of coagulation factor inhibitors. Specimens with abnormal results (DRVVT screen ratio > or =1.20) are subjected to reflexive testing (see Testing Algorithm). With the reflexive testing algorithm, the sensitivity of DRVVT testing for LA diagnosis is approximately 65% to 70% and the specificity is 95% or higher. Although LA cause prolonged clotting times in vitro, there is a strong association with thrombosis risk. However, not all patients with persisting LA develop thrombosis.

DRVI4
603310

Dilute Russell's Viper Venom Time (DRVVT) Interpretation

Clinical Information:

Useful For: Interpreting mixing and confirmation assays for lupus anticoagulants

Interpretation: Dilute Russell's viper venom time screen ratio (<1.20): A normal dilute Russell's viper venom time (DRVVT) screen ratio (<1.20) indicates that lupus anticoagulant (LA) is not present or not detectable by this method (but might be detected with other methods). An abnormal DRVVT screen ratio (DRVVT screen ratio > or =1.20) may suggest presence of LA, however, other possibilities include: -Deficiencies or dysfunction of factors I (fibrinogen), II, V, or X, congenital or acquired -Inhibitors of factor V, or occasionally by inhibitors of factor VIII, or other specific or nonspecific inhibitors -Anticoagulation therapy effects (see Cautions) Further evaluation consists of performing mixing studies with an equal volume of normal pooled plasma (DRVVT 1:1 mix) to investigate the possibility of coagulation factor deficiency (suggested by DRVVT mix ratio <1.20) and to evaluate inhibition (suggested by DRVVT mix ratio > or =1.20) and mixing patient plasma with DRVVT reagent enriched in phospholipid (DRVVT confirmatory reagent) (DRVVT mix and DRVVT confirmation ratios). Possible combination of results includes the following: -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio <1.20: No evidence of LA. These data may reflect anticoagulation therapy effects or other (congenital or acquired) coagulopathy. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio <1.20: The prolonged and inhibited DRVVT (DRVVT screen and mix ratios) may reflect presence of a specific factor inhibitor (eg, factor V inhibitor), anticoagulation therapy effects or other nonspecific inhibitors as can be seen with monoclonal protein disorders, lymphoproliferative disease etc. Although LA cannot be conclusively excluded, the DRVVT confirmation ratio of < or =1.20 makes this less likely. -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio > or =1.20: Although mixing study of the prolonged DRVVT screen and mix ratios provides no evidence of inhibition, additional phospholipid shortens the clotting time (DRVVT confirm ratio), suggesting presence of LA. -DRVVT screen ratio > or =1.20, DRVVT mix

ratio > or =1.20, and DRVVT confirmation ratio > or =1.20: The data are consistent with presence of LA, provided anticoagulant effect can be excluded (see Cautions) Because no single coagulation test can identify or exclude all LAs, and because of the complexity of testing LA, one of the following Coagulation Consultation reflexive panel procedures is recommended if clinically indicated: ALUPP / Lupus Anticoagulant Profile, Plasma AATHR / Thrombophilia Profile, Plasma and Whole Blood APROL / Prolonged Clot Time Profile, Plasma DRVVT assays ordered as a single, stand-alone test should be interpreted within patient clinical context and close attention to medication use by patient (see Cautions).

Reference Values:

Only orderable as a part of a profile. For more information see DRVI1 / Dilute Russell's Viper Venom Time (DRVVT), with Reflex, Plasma.

An interpretive comment will be provided.

Clinical References: 1. Proven A, Bartlett RP, Moder KG, et al. Clinical importance of positive test results for lupus anticoagulant and anticardiolipin antibodies. Mayo Clin Proc. 2004;79(4):467-475 2. Gastineau DA, Kazmier FJ, Nichols WL, Bowie EJ. Lupus anticoagulant: an analysis of the clinical and laboratory features of 219 cases. Am J Hematol. 1985;19(3):265-275 3. Brandt JT, Triplett DA, Alving B, Sharrer I. Criteria for the diagnosis of lupus anticoagulant: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost. 1995;74(4);1185-1190 4. Arnout J, Vermylen J. Current status and implications of autoimmune antiphospholipid antibodies in relation to thrombotic disease. J Thromb Haemost. 2003;1(5):931-942 5. Pengo V, Tripodi A, Reber G, Rand JH, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2009;7:1737-1740. doi:10.1111/j.1538-7836.2009.03555.x 6. Clinical and Laboratory Standards Institute (CLSI). Laboratory Testing for Lupus Anticoagulant; Approved Guideline. CLSI document H60-A. CLSI; 2014

DRVI2
602180

Dilute Russell's Viper Venom Time (DRVVT) Mix Ratio, Plasma

Clinical Information: Lupus anticoagulants (LA) are immunoglobulins (IgG, IgM, IgA, or a combination of these) of autoimmune type that are specifically directed against antigenic complexes of negatively charged phospholipids (such as phosphatidylserine or phosphatidylethanolamine) and coagulation-related proteins (such as beta-2-glycoprotein I) or clotting factors (including prothrombin [factor II] or factor X), and which cause prolongation of phospholipid-dependent clotting time tests due to inhibition. LA are functionally and clinically distinct members of a broader group of antiphospholipid autoantibodies that includes immunologically detectable anticardiolipin antibodies or antibodies against other phospholipid-protein complexes. LA interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of 1 or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time [APTT], dilute Russell's viper venom time [DRVVT]) due to inhibition. This characteristic in vitro inhibition can be overcome by addition of excess phospholipid. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LA. Currently, the International Society on Thrombosis and Haemostasis and the Clinical and Laboratory Standards Institute recommend testing for LA with at least 2 phospholipid-dependent clotting time assays based on different coagulation pathways and principles (eg, lupus-sensitive APTT and DRVVT). In addition, given the potential for false-positive results in patients on anticoagulants, a profile or panel of coagulation tests is performed, including prothrombin time (PT), APTT, thrombin time (TT), and DRVVT. If the PT, APTT, and/or DRVVT are prolonged, additional testing may include mixing tests with normal plasma (to evaluate for inhibition) and the use of excess phospholipid in appropriate assay systems to evaluate for phospholipid-dependent inhibition. Additional reflexive testing helps determine presence or absence of anticoagulants and/or inhibitors to other factors. The

diagnosis of LA requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information, including evidence of persistence of LA over time (> or =12 weeks). The venom obtained from Russell's viper (Vipera russelli) contains enzymes that directly activate coagulation factors V and X, bypassing the activation of factors VII, VIII, IX, XI, and XII, and therefore, the effect of deficiencies or inhibitors of these factors. Diluting the phospholipid necessary for the clotting factor interactions increases the sensitivity to LA and the likelihood of identifying a phospholipid-dependent inhibitor that may not be detected by other coagulation tests with higher phospholipid content (eg, LA-insensitive APTT reagents). The DRVVT screen ratio test is one of several available in vitro tests that may be used to screen and confirm for presence of LA or to help exclude LA. DRVVT testing is used in conjunction with other appropriate coagulation tests (reflexive testing panels) to assist in detection and confirmation of LA or help exclude their presence. The DRVVT may be abnormally prolonged (DRVVT screen ratio > or =1.20) by LA as well as coagulation factor deficiencies, anticoagulant effects, or other types of coagulation factor inhibitors. Specimens with abnormal results (DRVVT screen ratio > or =1.20) are subjected to reflexive testing. With the reflexive testing, the sensitivity of DRVVT testing for LA diagnosis is approximately 65% to 70%, and the specificity is 95% or higher. It is advisable to use the DRVVT screen, mix and confirm ratio results in conjunction with other appropriate coagulation tests (reflexive testing panels) to diagnose or exclude LA. Although LA cause prolonged clotting times in vitro, there is a strong association with thrombosis risk. However, not all patients with persisting LA develop thrombosis.

Useful For: Detecting the presence or helping to exclude the presence of lupus anticoagulants (LA) Identifying LA that do not prolong the activated partial thromboplastin time (APTT) Evaluating unexplained prolongation of the APTT or prothrombin time clotting tests Distinguishing LA from a specific coagulation factor inhibitor or coagulation factor deficiencies

Interpretation: Dilute Russell's viper venom time screen ratio (<1.20): A normal dilute Russell's viper venom time (DRVVT) screen ratio (<1.20) indicates that lupus anticoagulant (LA) is not present or not detectable by this method (but might be detected with other methods). An abnormal DRVVT screen ratio (DRVVT screen ratio > or =1.20) may suggest presence of LA, however, other possibilities include: -Deficiencies or dysfunction of factors I (fibrinogen), II, V, or X, congenital or acquired -Inhibitors of factor V, or occasionally by inhibitors of factor VIII, or other specific or nonspecific inhibitors -Anticoagulation therapy effects (see Cautions) Further evaluation consists of performing mixing studies with an equal volume of normal pooled plasma (DRVVT 1:1 mix) to investigate the possibility of coagulation factor deficiency (suggested by DRVVT mix ratio <1.20) and to evaluate inhibition (suggested by DRVVT mix ratio > or =1.20) and mixing patient plasma with DRVVT reagent enriched in phospholipid (DRVVT confirmatory reagent) (DRVVT mix and DRVVT confirmation ratios). Possible combinations of results include the following: -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio <1.20: No evidence of LA. These data may reflect anticoagulation therapy effects or other (congenital or acquired) coagulopathy. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio <1.20: The prolonged and inhibited DRVVT (DRVVT screen and mix ratios) may reflect presence of a specific factor inhibitor (eg, factor V inhibitor), anticoagulation therapy effects or other nonspecific inhibitors as can be seen with monoclonal protein disorders, lymphoproliferative disease etc. Although LA cannot be conclusively excluded, the DRVVT confirmation ratio of < or =1.20 makes this less likely. -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio > or =1.20: Although mixing study of the prolonged DRVVT screen and mix ratios provides no evidence of inhibition, additional phospholipid shortens the clotting time (DRVVT confirmation ratio), suggesting presence of LA. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio > or =1.20: The data are consistent with presence of LA, provided anticoagulant effect can be excluded (see Cautions) Because no single coagulation test can identify or exclude all LAs, and because of the complexity of testing LA, one of the following Coagulation Consultation reflexive panel procedures are recommended if clinically indicated: ALUPP / Lupus Anticoagulant Profile, Plasma AATHR / Thrombophilia Profile, Plasma and Whole Blood APROL / Prolonged Clot Time Profile, Plasma DRVVT assays ordered as a single, stand-alone test should be interpreted within patient clinical context and close attention to medication use by patient (see Cautions).

Reference Values:
Only orderable as part of a reflex. For more information see DRVI1 / Dilute Russell's Viper Venom Time (DRVVT), with Reflex, Plasma.

<1.20
Normal ranges for children: not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.

Clinical References: 1. Proven A, Bartlett RP, Moder KG, et al. Clinical importance of positive test results for lupus anticoagulant and anticardiolipin antibodies. Mayo Clin Proc. 2004;79(4):467-475 2. Gastineau DA, Kazmier FJ, Nichols WL, Bowie EJ. Lupus anticoagulant: an analysis of the clinical and laboratory features of 219 cases. Am J Hematol. 1985;19(3):265-275 3. Brandt JT, Triplett DA, Alving B, Sharrer I: Criteria for the diagnosis of lupus anticoagulant: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost. 1995;74(4);1185-1190 4. Arnout J, Vermylen J. Current status and implications of autoimmune antiphospholipid antibodies in relation to thrombotic disease. J Thromb Haemost. 2003;1(5):931-942 5. Pengo V, Tripodi A, Reber G, Rand JH, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2009;7:1737-1740. doi:10.1111/j.1538-7836.2009.03555.x 6. CLSI document H60-A

DRV2
602177

Dilute Russell's Viper Venom Time (DRVVT) Mix, Plasma

Clinical Information: Lupus anticoagulants (LA) are immunoglobulins (IgG, IgM, IgA, or a combination of these) of autoimmune type that are specifically directed against antigenic complexes of negatively charged phospholipids (such as phosphatidylserine or phosphatidylethanolamine) and coagulation-related proteins (such as beta-2-glycoprotein I or clotting factors including prothrombin [factor II] or factor X), and which cause prolongation of phospholipid-dependent clotting time tests due to inhibition. LA are functionally and clinically distinct members of a broader group of antiphospholipid autoantibodies that includes immunologically detectable anticardiolipin antibodies or antibodies against other phospholipid-protein complexes. LA interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of 1or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time: APTT, dilute Russell's viper venom time: DRVVT) due to inhibition. This characteristic in vitro inhibition can be overcome by addition of excess phospholipid. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LA. Currently, the International Society on Thrombosis and Haemostasis and the Clinical and Laboratory Standards Institute (CLSI) recommend testing for LA with at least 2 phospholipid-dependent clotting time assays based on different coagulation pathways and principles (eg, lupus-sensitive APTT and DRVVT). In addition, given the potential for false-positive results in patients on anticoagulants, a profile or panel of coagulation tests is performed, including the prothrombin time (PT), APTT, thrombin time (TT) and DRVVT. If the PT, APTT, and/or DRVVT are prolonged, additional testing may include mixing tests with normal plasma (to evaluate for inhibition) and the use of excess phospholipid in appropriate assay systems to evaluate for phospholipid-dependent inhibition. Additional reflexive testing helps determine presence or absence of anticoagulants and/or inhibitors to other factors. The diagnosis of LA requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information, including evidence of persistence of LA over time (> or =12 weeks). The venom obtained from Russell's viper (Vipera russelli) contains enzymes that directly activate coagulation factors V and X, bypassing the activation of factors VII, VIII, IX, XI, and XII, and, therefore, the effect of deficiencies or inhibitors of these factors. Diluting the phospholipid necessary for the clotting factor interactions increases the sensitivity to LA and the likelihood of identifying a phospholipid-dependent inhibitor that may not be detected by other coagulation tests with a higher phospholipid content (eg, LA-insensitive APTT reagents). The DRVVT

screen ratio test is one of several available in vitro tests that may be used to screen and confirm for presence of LA or to help exclude LA. DRVVT testing is used in conjunction with other appropriate coagulation tests (reflexive testing panels) to assist in detection and confirmation of LA, or help exclude their presence. The DRVVT may be abnormally prolonged (DRVVT screen ratio > or =1.20) by LA as well as coagulation factor deficiencies, anticoagulant effects, or other types of coagulation factor inhibitors. Specimens with abnormal results (DRVVT screen ratio > or =1.20) are subjected to reflexive testing. With the reflexive testing algorithm, the sensitivity of DRVVT testing for LA diagnosis is approximately 65% to 70% and the specificity is 95% or higher. Although LA cause prolonged clotting times in vitro, there is a strong association with thrombosis risk. However, not all patients with persisting LA develop thrombosis.

Useful For: Detecting the presence or helping to exclude the presence of lupus anticoagulants (LA) Identifying LA that do not prolong the activated partial thromboplastin time (APTT) Evaluating unexplained prolongation of the APTT or prothrombin time clotting tests Distinguishing LA from a specific coagulation factor inhibitor or coagulation factor deficiencies Confirmation of abnormal dilute Russell's viper venom time ratios

Interpretation: Dilute Russell's viper venom time (DRVVT) screen ratio (<1.20): A normal DRVVT screen ratio (<1.20) indicates that lupus anticoagulant (LA) is not present or not detectable by this method (but might be detected with other methods). An abnormal DRVVT screen ratio (DRVVT screen ratio >1.20) may suggest presence of LA, however, other possibilities include: -Deficiencies or dysfunction of factors I (fibrinogen), II, V, or X, congenital or acquired -Inhibitors of factor V, or occasionally by inhibitors of factor VIII, or other specific or nonspecific inhibitors -Anticoagulation therapy effects (see Cautions) Further evaluation consists of performing mixing studies with an equal volume of normal pooled plasma (DRVVT 1:1 mix) to investigate the possibility of coagulation factor deficiency (suggested by DRVVT mix ratio <1.20) and to evaluate inhibition (suggested by DRVVT mix ratio > or =1.20) and mixing patient plasma with DRVVT reagent enriched in phospholipid (DRVVT confirmatory reagent) (DRVVT mix and DRVVT confirmation ratios). Possible combination of results include the following: -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio <1.20: No evidence of LA. These data may reflect anticoagulation therapy effects or other (congenital or acquired) coagulopathy. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio <1.20: The prolonged and inhibited DRVVT (DRVVT screen and mix ratios) may reflect presence of a specific factor inhibitor (eg, factor V inhibitor), anticoagulation therapy effects or other nonspecific inhibitors as can be seen with monoclonal protein disorders, lymphoproliferative disease etc. Although LA cannot be conclusively excluded, the DRVVT confirmation ratio of < or =1.20 makes this less likely. -DRVVT screen ratio > or =1.20, DRVVT mix ratio <1.20, and DRVVT confirmation ratio > or =1.20: Although mixing study of the prolonged DRVVT screen and mix ratios provides no evidence of inhibition, additional phospholipid shortens the clotting time (DRVVT confirmation ratio), suggesting presence of LA. -DRVVT screen ratio > or =1.20, DRVVT mix ratio > or =1.20, and DRVVT confirmation ratio > or =1.20: The data are consistent with presence of LA, provided anticoagulant effect can be excluded (see Cautions) Additional tests to evaluate abnormal DRVVT results include activated partial thromboplastin time (APTT), prothrombin time (PT), and thrombin time. Abnormalities observed with these tests may be further evaluated with normal plasma mixing studies, the platelet neutralization procedure (for APTT), and coagulation factor assays may sometimes be needed. All of these reflexive testing procedures, together with Coagulation Consultant interpretation, are included in Mayo Clinic's Coagulation Consultation test panels: ALUPP / Lupus Anticoagulant Profile, Plasma ALBLD / Bleeding Diathesis Profile, Limited, Plasma AATHR / Thrombophilia Profile, Plasma and Whole Blood APROL / Prolonged Clot Time Profile, Plasma ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma DRVVT assays ordered as a single, stand-alone test should be interpreted within patient clinical context and close attention to medication use by patient (see Cautions).

Reference Values:
Only orderable as part of a reflex. For more information see:

ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
AATHR / Thrombophilia Profile, Plasma and Whole Blood
APROL / Prolonged Clot Time Profile, Plasma
ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

<1.20
Normal ranges for children: not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.

Clinical References: 1. Proven A, Bartlett RP, Moder KG, et al. Clinical importance of positive test results for lupus anticoagulant and anticardiolipin antibodies. Mayo Clin Proc. 2004l;79(4):467-475 2. Gastineau DA, Kazmier FJ, Nichols WL, Bowie EJ. Lupus anticoagulant: an analysis of the clinical and laboratory features of 219 cases. Am J Hematol. 1985;19(3):265-275 3. Brandt JT, Triplett DA, Alving B, Sharrer I. Criteria for the diagnosis of lupus anticoagulant: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost. 1995;74(4);1185-1190 4. Arnout J, Vermylen J. Current status and implications of autoimmune antiphospholipid antibodies in relation to thrombotic disease. J Thromb Haemost. 2003;1(5):931-942 5. Pengo V, Tripodi A, Reber G, Rand JH, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2009;7:1737-1740. doi:10.1111/j.1538-7836.2009.03555.x 6. CLSI Laboratory Testing for Lupus Anticoagulant; Approved Guideline. CLSI document H60-A. Clinical and Laboratory Standards Institute; 2014

DRV1
602176

Dilute Russell's Viper Venom Time (DRVVT), Plasma

Clinical Information: Lupus anticoagulants (LA) are immunoglobulins (IgG, IgM, IgA, or a combination of these) of autoimmune type that are specifically directed against antigenic complexes of negatively charged phospholipids (such as phosphatidylserine or phosphatidylethanolamine) and coagulation-related proteins (such as beta-2-glycoprotein I) or clotting factors (including prothrombin [factor II] or factor X), and which cause prolongation of phospholipid-dependent clotting time tests due to inhibition. LA are functionally and clinically distinct members of a broader group of antiphospholipid autoantibodies that includes immunologically detectable anticardiolipin antibodies or antibodies against other phospholipid-protein complexes. LA interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of 1 or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time: APTT, dilute Russell's viper venom time: DRVVT) due to inhibition. This characteristic in vitro inhibition can be overcome by addition of excess phospholipid. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LA. Currently, the International Society on Thrombosis and Haemostasis and the Clinical and Laboratory Standards Institute (CLSI) recommend testing for LA with at least 2 phospholipid-dependent clotting time assays based on different coagulation pathways and principles (eg, lupus-sensitive APTT and DRVVT). In addition, given the potential for false-positive results in patients on anticoagulants, a profile or panel of coagulation tests is performed, including the prothrombin time (PT), APTT, thrombin time (TT), and DRVVT. If the PT, APTT, and/or DRVVT are prolonged, additional testing may include mixing tests with normal plasma (to evaluate for inhibition) and the use of excess phospholipid in appropriate assay systems to evaluate for phospholipid-dependent inhibition. Additional reflexive testing helps determine presence or absence of anticoagulants and/or inhibitors to other factors. The diagnosis of LA requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information, including evidence of persistence of LA over time (> or =12 weeks). The venom obtained from Russell's viper (Vipera russelli) contains enzymes that directly activate coagulation factors V and X, bypassing the activation of factors VII, VIII,

IX, XI, and XII, and therefore, the effect of deficiencies or inhibitors of these factors. Diluting the phospholipid necessary for the clotting factor interactions increases the sensitivity to LA and the likelihood of identifying a phospholipid-dependent inhibitor that may not be detected by other coagulation tests with a higher phospholipid content (eg, LA-insensitive APTT reagents). The DRVVT screen ratio test is one of several available in vitro tests that may be used to screen and confirm for presence of LA or to help exclude LA. DRVVT testing is used in conjunction with other appropriate coagulation tests (reflexive testing panels) to assist in detection and confirmation of LA, or help exclude their presence. The DRVVT may be abnormally prolonged (DRVVT screen ratio > or =1.20) by LA as well as coagulation factor deficiencies, anticoagulant effects, or other types of coagulation factor inhibitors. Specimens with abnormal results (DRVVT screen ratio > or =1.20) are subjected to reflexive testing (see Testing Algorithm). With the reflexive testing algorithm, the sensitivity of DRVVT testing for LA diagnosis is approximately 65% to 70% and the specificity is 95% or higher. Although LA cause prolonged clotting times in vitro, there is a strong association with thrombosis risk. However, not all patients with persisting LA develop thrombosis.

Useful For: Detecting and confirming or helping to exclude the presence of lupus anticoagulants (LA) Identifying LA that do not prolong the activated partial thromboplastin time (APTT) Evaluating unexplained prolongation of the APTT or prothrombin time clotting tests Distinguishing LA from a specific coagulation factor inhibitor or coagulation factor deficiencies

Interpretation:

Reference Values:

Only orderable as part of a profile or reflex. For more information see:
ALUPP / Lupus Anticoagulant Profile, Plasma
AATHR / Thrombophilia Profile, Plasma and Whole Blood
APROL / Prolonged Clot Time Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

< 1.20
Normal ranges for children: not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.

Clinical References: 1. Proven A, Bartlett RP, Moder KG, et al. Clinical importance of positive test results for lupus anticoagulant and anticardiolipin antibodies. Mayo Clin Proc. 2004;79(4):467-475 2. Gastineau DA, Kazmier FJ, Nichols WL, Bowie EJ. Lupus anticoagulant: an analysis of the clinical and laboratory features of 219 cases. Am J Hematol. 1985;19(3):265-275 3. Brandt JT, Triplett DA, Alving B, Sharrer I. Criteria for the diagnosis of lupus anticoagulant: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost. 1995;74(4);1185-1190 4. Arnout J, Vermylen J. Current status and implications of autoimmune antiphospholipid antibodies in relation to thrombotic disease. J Thromb Haemost. 2003;1(5):931-942 5. Pengo V, Tripodi A, Reber G, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2009;7:1737-1740. doi:10.1111/j.1538-7836.2009.03555.x 6. CLSI Laboratory Testing for Lupus Anticoagulant; Approved Guideline. CLSI document H60-A. Clinical and Laboratory Standards Institute; 2014

DRVI1 602179 Dilute Russell's Viper Venom Time (DRVVT), with Reflex, Plasma

Clinical Information: Lupus anticoagulants (LA) are immunoglobulins (IgG, IgM, IgA, or a combination of these) of autoimmune type that are specifically directed against antigenic complexes of negatively charged phospholipids (such as phosphatidylserine or phosphatidylethanolamine) and coagulation-related proteins (such as beta-2-glycoprotein I) or clotting factors (including prothrombin [factor II] or factor X) and cause prolongation of phospholipid-dependent clotting time tests due to inhibition. LA are functionally and clinically distinct members of a broader group of antiphospholipid autoantibodies that includes immunologically-detectable anticardiolipin antibodies or antibodies against other phospholipid-protein complexes. LA interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of 1 or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time [APTT], dilute Russell's viper venom time [DRVVT]) due to inhibition. This characteristic in vitro inhibition can be overcome by addition of excess phospholipid. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LA. Currently, the International Society on Thrombosis and Haemostasis and the Clinical and Laboratory Standards Institute (CLSI) recommend testing for LA with at least 2 phospholipid-dependent clotting time assays based on different coagulation pathways and principles (eg, lupus sensitive APTT and DRVVT). In addition, given the potential for false-positive results in patients on anticoagulants, a profile or panel of coagulation testing is recommended, including prothrombin time (PT), APTT, thrombin time (TT), and DRVVT. If the PT, APTT, or DRVVT are prolonged, additional testing may include mixing tests with normal plasma (to evaluate for inhibition) and the use of excess phospholipid in appropriate assay systems to evaluate for phospholipid-dependent inhibition. Additional reflexive testing helps determine the presence or absence of anticoagulants or inhibitors to other factors. The diagnosis of LA requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information, including evidence of persistence of LA over time (> or =12 weeks). The venom obtained from the Russell's viper (Vipera russelli) contains enzymes that directly activate coagulation factors V and X, bypassing the activation of factors VII, VIII, IX, XI, and XII, and, therefore, the effect of deficiencies or inhibitors of these factors. Diluting the phospholipid necessary for the clotting factor interactions increases the sensitivity to LA and the likelihood of identifying a phospholipid-dependent inhibitor that may not be detected by other coagulation tests that have a higher phospholipid content (eg, LA-insensitive APTT reagents). The DRVVT screen ratio test is one of several available in vitro tests that may be used to screen and confirm the presence of LA or to help exclude LA. DRVVT testing is used in conjunction with other appropriate coagulation tests (reflexive testing panels) to assist in detection and confirmation of LA or help exclude their presence. The DRVVT may be abnormally prolonged (DRVVT screen ratio > or =1.20) by LA as well as coagulation factor deficiencies, anticoagulant effects, or other types of coagulation factor inhibitors. Specimens with abnormal results (DRVVT screen ratio > or =1.20) are subjected to reflexive testing (see Testing Algorithm). With the reflexive testing algorithm, the sensitivity of DRVVT testing for LA diagnosis is approximately 65% to 70%, and the specificity is 95% or higher. It is advisable to use the DRVVT screen, mix and confirm ratio results in conjunction with other appropriate coagulation tests (reflexive testing panels) to diagnose or exclude LA. Although LA cause prolonged clotting times in vitro, there is a strong association with thrombosis risk. However, not all patients with persisting LA develop thrombosis.

Useful For: Detecting and confirming or helping to exclude the presence of lupus anticoagulants (LA) Identifying LA that do not prolong the activated partial thromboplastin time (APTT) Evaluating unexplained prolongation of the APTT or prothrombin time clotting tests Distinguishing LA from a specific coagulation factor inhibitor or coagulation factor deficiencies

Interpretation:

Reference Values:

Dilute Russell's viper venom time screen ratio: <1.20

Normal ranges for children: Not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.

Clinical References: 1. Proven A, Bartlett RP, Moder KG, et al. Clinical importance of positive test results for lupus anticoagulant and anticardiolipin antibodies. Mayo Clin Proc. 2004;79(4):467-475 2. Gastineau DA, Kazmier FJ, Nichols WL, Bowie EJ. Lupus anticoagulant: an analysis of the clinical and laboratory features of 219 cases. Am J Hematol. 1985;19(3):265-275 3. Brandt JT, Triplett DA, Alving B, Sharrer I. Criteria for the diagnosis of lupus anticoagulant: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost. 1995;74(4);1185-1190 4. Arnout J, Vermylen J. Current status and implications of autoimmune antiphospholipid antibodies in relation to thrombotic disease. J Thromb Haemost. 2003;1(5):931-942 5. Pengo V, Tripodi A, Reber G, Rand JH, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2009;7:1737-1740. doi:10.1111/j.1538-7836.2009.03555.x 6. Clinical and Laboratory Standards Institute (CLSI). Laboratory Testing for Lupus Anticoagulant; Approved Guideline. CLSI document H60-A. CLSI; 2014

DIPGS
36664

Diphtheria Toxoid IgG Antibody, Serum

Clinical Information: Diphtheria is an acute, contagious, febrile illness caused by the bacterium Corynebacterium diphtheriae. The disease is classically characterized by a combination of localized inflammation in the upper respiratory tract with the formation of a diphtheric pseudomembrane over the oropharynx, including the tonsils, pharynx, larynx, and posterior nasal passages. C diphtheriae produces a potent diphtheria exotoxin that is absorbed systemically and can lead to cardiac failure and paralysis of the diaphragm. The disease is preventable by vaccination with diphtheria toxoid, which stimulates antidiphtheria toxoid antibodies. In the United States, diphtheria toxoid is administered to children as part of the combined diphtheria, tetanus, and acellular pertussis (TDaP) vaccine. A patient's immunological response to diphtheria toxoid vaccination can be determined by measuring antidiphtheria toxoid IgG antibody using this enzyme immunoassay technique. An absence of antibody formation postvaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs.

Useful For: Determining a patient's immunological response to diphtheria toxoid vaccination Aiding in the evaluation of immunodeficiency

Interpretation: Results of 0.01 IU/mL or more suggest a vaccine response. A diphtheria toxoid booster should be considered for patients with antidiphtheria toxoid IgG values between 0.01 and less than 0.1 IU/mL.

Reference Values:
Vaccinated: Positive (> or =0.01 IU/mL)
Unvaccinated: Negative (<0.01 IU/mL)
Reference values apply to all ages.

Clinical References: 1. Centers for Disease Control and Prevention (CDC); National Center for Immunization and Respiratory Diseases, Division of Bacterial Diseases. Diphtheria. CDC; Updated September 9, 2022. Accessed September 5, 2024. Available at www.cdc.gov/diphtheria/index.html 2. Truelove SA, Keegan LT, Moss WJ, et al. Clinical and epidemiological aspects of diphtheria: a systematic review and pooled analysis. Clin Infect Dis. 2020;71(1):89-97

DTABS
36670

Diphtheria/Tetanus Antibody Panel, Serum

Clinical Information: Diphtheria is an acute, contagious, febrile illness caused by the bacterium

Corynebacterium diphtheriae. The disease is classically characterized by a combination of localized inflammation in the upper respiratory tract with the formation of a diphtheric pseudomembrane over the oropharynx, including the tonsils, pharynx, larynx, and posterior nasal passages. C diphtheriae produces a potent diphtheria exotoxin that is absorbed systemically and can lead to cardiac failure and paralysis of the diaphragm. Tetanus results from contamination of wounds or lacerations with Clostridium tetani spores from the environment. The spores germinate to actively replicating bacterial cells localized within the wound and produce the heat-labile toxin tetanospasmin. Tetanospasmin attaches to peripheral nerve endings and travels to the central nervous system where it blocks inhibitory impulses to motor neurons and leads to severe, spastic muscle contractions, a classic characteristic of tetanus. Both diseases are preventable by vaccination with diphtheria toxoid, which stimulates antidiphtheria toxoid antibodies, and tetanus toxoid (formaldehyde-treated tetanospasmin), which stimulates development of antitetanus toxoid antibodies. In the United States, these toxoids are administered to children as part of the combined diphtheria, tetanus, and acellular pertussis (TDaP) vaccine. Two to 3 weeks following vaccination, a patient's immunological response may be assessed by measuring the antidiphtheria toxoid IgG antibody and total antitetanus toxoid IgG antibody levels in serum. An absence of either antibody formation postvaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs.

Useful For: Assessing antibody response to tetanus and diphtheria toxoid vaccines, which should be performed at least 3 weeks after immunization Aiding in the evaluation of immunodeficiency This test should not be used to diagnose tetanus infection

Interpretation: Diphtheria: Results of 0.01 IU/mL or more suggest a vaccine response. A diphtheria toxoid booster should be considered for patients with antidiphtheria toxoid IgG values between 0.01 and less than 0.1 IU/mL. Tetanus: Results of 0.01 IU/mL or more suggest a vaccine response. A tetanus toxoid booster should be strongly considered for patients with antitetanus toxoid IgG values between 0.01 and 0.5 IU/mL. Some cases of tetanus, usually mild, have occasionally been observed in patients with a measurable serum level of 0.01 to 1.0 IU/mL.

Reference Values:

DIPHTHERIA TOXOID IgG ANTIBODY
Vaccinated: Positive (> or =0.01 IU/mL)
Unvaccinated: Negative (<0.01 IU/mL)
Reference values apply to all ages.

TETANUS TOXOID IgG ANTIBODY
Vaccinated: Positive (> or =0.01 IU/mL)
Unvaccinated: Negative (<0.01 IU/mL)
Reference values apply to all ages.

Clinical References: 1. Bleck TP: Clostridium tetani (tetanus). In: Mandell GL, Bennett JE, Dolin R, eds. Principals and Practice of Infectious Disease. 5th ed. Churchill Livingstone; 2000:2537-2543 2. Gergen PJ, McQuillan GM, Kiely M, Ezzati-Rice TM, Sutter RW, Virella G: A population-based serologic survey of immunity to tetanus in the United States. N Engl J Med. 1995 Mar;332(12):761-766 3. Bjorkholm B, Wahl M, Granstrom M, Hagberg L: Immune status and booster effects of low doses of tetanus toxoid in Swedish medical personnel. Scand J Infect Dis. 1994;26(4):471-475 4. Ramsay ME, Corbel MJ, Redhead K, Ashworth LA, Begg NT: Persistence of antibody after accelerated immunization with diphtheria/tetanus/pertussis vaccine. Br Med J. 1991 Jun;302(6791):1489-1491 5. Centers for Disease Control and Prevention (CDC); National Center for Immunization and Respiratory Diseases, Division of Bacterial Diseases. Diphtheria. CDC; Updated September 9, 2022. Accessed October 27, 2022. Available at www.cdc.gov/diphtheria/index.html 6. Truelove SA, Keegan LT, Moss WJ, et al: Clinical and epidemiological aspects of diphtheria: a systematic review and pooled analysis. Clin Infect Dis. 2020 Jun;71(1):89-97

DCTR
113489

Direct Antiglobulin Test (Polyspecific), Blood

Clinical Information: IgG antibody or complement components secondary to the action of IgM antibody may be present on the patient's own red blood cells (RBC) or on transfused RBC.

Useful For: Demonstrating in vivo coating of red blood cells with IgG or the complement component C3d in the following settings: -Autoimmune hemolytic anemia -Hemolytic transfusion reactions -Drug-induced hemolytic anemia

Interpretation: Negative: No IgG antibody or complement (C3d) detected on the surface of the red cell. Positive: Test polyspecific direct antiglobulin testing will be ordered and performed.

Reference Values:
Negative

Clinical References: Cohn CS, Delaney DO, Johnson ST, Katz LM, Schwartz J, eds. Technical Manual. 21st ed. AABB; 2023

DSAC
608236

Disaccharidase Activity Panel, Tissue

Clinical Information: Disaccharidases in the small intestines are responsible for the breakdown of disaccharides (double sugars) into monosaccharides (simple sugars). Patients with a deficiency of one or more disaccharidase can experience intolerance to foods containing complex sugars resulting in a range of gastrointestinal symptoms, including diarrhea or constipation, abdominal pain and cramping, gas, bloating, and nausea. In addition, patients may experience malnutrition, weight loss, or failure to thrive. Given the nonspecificity and frequency of abdominal symptoms, misdiagnosis or a diagnostic delay of disaccharide deficiencies may occur. Primary and secondary causes of disaccharidase deficiencies exist, and age of onset may vary from birth through adulthood. Primary causes are rare and result from genetic alterations in a variety of genes. Secondary deficiencies typically result from small intestinal mucosal damage. Treatment of both primary and secondary disaccharidase deficiencies involves dietary management. While primary deficiencies require lifelong treatment, secondary disaccharidase deficiencies may require treatment only until the intestinal lining recovers.

Useful For: Evaluation of patients who present with signs or symptoms suggestive of disaccharidase disorders This test is not intended for carrier detection.

Interpretation: Quantitative values of lactase, sucrase, maltase, palatinase, and glucoamylase are reported. Clinical interpretation of results is provided.

Reference Values:
Lactase: > or =14.0 nmol/min/mg protein
Sucrase: > or =19.0 nmol/min/mg protein
Maltase: > or =70.0 nmol/min/mg protein
Palatinase: > or =6.0 nmol/min/mg protein
Glucoamylase: > or =8.0 nmol/min/mg protein

Clinical References: 1. Cohen SA, Oloyede H, Gold BD, Mohammed A, Elser HE. Clinical characteristics of disaccharidase deficiencies among children undergoing upper endoscopy. J Pediatr Gastroenterol Nutr. 2018;66 Suppl 3:S56-S60 2. Semenza G, Auricchio S, Mantei N. Small-intestinal disaccharidases. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed November 18, 2024.

ADICI 603182 Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile Interpretation

Clinical Information: Disseminated intravascular coagulation (DIC)/intravascular coagulation and fibrinolysis (ICF), collectively termed DIC/ICF is a consumptive hemorrhagic and microthrombotic disorder that manifests as clinical bleeding or thrombosis. Conditions associated with DIC/ICF can include; sepsis, trauma (head injury, severe tissue injury), obstetric complications (amniotic fluid embolism, abruptio placentae), malignancies, vascular disorders (hemangiomas, aortic aneurysm), and immunologic disorders. These disorders can cause formation of thrombin and fibrin intravascularly, which can result in widespread fibrin deposition contributing to thrombosis and organ failure or, conversely, can result in bleeding due to consumption of coagulation proteins and platelets. DIC/ICF is not a disease; rather it is a syndrome that is secondary to an underlying disorder.

Useful For: Interpretation of testing performed as part of a profile to evaluate laboratory evidence of disseminated intravascular coagulation

Interpretation: An interpretive report will be provided when testing is completed, noting presence or absence of disseminated intravascular coagulation/intravascular coagulation and fibrinolysis.

Reference Values:
Only orderable as part of a profile. For more information see ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma.

An interpretive report will be provided.

Clinical References: Boender J: A Diagnostic Approach to Mild Bleeding Disorders Journal of Thrombosis and Haemostasis 2016;14:1507-1516

ADIC 603306 Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

Clinical Information: Disseminated intravascular coagulation (DIC) and intravascular coagulation and fibrinolysis (ICF), collectively termed DIC/ICF, is a consumptive hemorrhagic and microthrombotic disorder that manifests as clinical bleeding or thrombosis. Conditions associated with DIC/ICF can include sepsis, trauma (eg, head injury, severe tissue injury), obstetric complications (eg, amniotic fluid embolism, abruptio placentae), malignancies, vascular disorders (eg, hemangiomas, aortic aneurysm), and immunologic disorders. These disorders can cause thrombin and fibrin intravascular formation, which can result in widespread fibrin deposition contributing to thrombosis and organ failure or, conversely, can result in bleeding due to consumption of coagulation proteins and platelets. DIC/ICF is not a disease, rather it is a syndrome that is secondary to an underlying disorder.

Useful For: Establishing laboratory evidence of disseminated intravascular coagulation

Interpretation: An interpretive report will be provided when testing is completed, noting presence or absence of disseminated intravascular coagulation and intravascular coagulation and fibrinolysis.

Reference Values:

An interpretive report is provided.

Clinical References: Boender J, Kruip MJ, Leebeek FWG. A diagnostic approach to mild bleeding disorders. J Thromb Haemost.. 2016;14(8):1507-1516. doi: 10.1111/jth.13368

FDIRU
57280

Diuretic Screen, Urine

Reference Values:
Qualitative diuretic screen includes: benzthiazide, bumetanide, chlorothiazide, chlorthalidone, furosemide, hydrochlorothiazide, hydroflumethiazide, and metolazone.

DMDZ
617532

DMD Gene, Full Gene Analysis, Varies

Clinical Information: Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder characterized initially by proximal muscle weakness beginning before age 5 years. Affected individuals typically have pseudohypertrophy of the calf muscles and exhibit toe-walking, waddling gait, and the Gower sign (climbing up the legs when rising from a seated position on the floor). Not only is skeletal muscle affected in DMD but also the smooth muscle of the gastrointestinal tract and possibly bladder as well as cardiac muscle. Initial symptoms are followed by dramatic progression of weakness leading to loss of ambulation by age 11 or 12 years. Death is often caused by cardiac failure or by respiratory failure before age 30 years unless ventilator support is provided. The allelic Becker muscular dystrophy (BMD) has a similar presentation, although age of onset is later, and the clinical course is much milder. Cardiac involvement can be the only sign and patients are often ambulatory into their thirties. Duchenne muscular dystrophy and BMD are caused by mutations in the DMD gene, which encodes for dystrophin. Approximately 50% to 65% of patients have intragenic deletions and approximately 5% to 10% have intragenic duplications. Less frequently, DMD and BMD result from nondeletion and nonduplication mutations. Approximately one-third of sporadic cases of DMD/BMD occur due to new variants. In sporadic cases, it is possible for the mother of an affected individual to have germline mosaicism. This means that the germ cells may contain a variant even if the variant is not detected in peripheral blood. In cases of germline mosaicism, which occurs with a frequency of up to 15%, further offspring are at risk of inheriting a dystrophin variant.

Useful For: Establishing a molecular diagnosis for patients with Duchenne muscular dystrophy and Becker muscular dystrophy Identifying variants within DMD known to be associated with Duchenne muscular dystrophy or Becker muscular dystrophy, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Aartsma-Rus A, Ginjaar IB, Bushby K. The importance of genetic diagnosis for Duchenne muscular dystrophy. J Med Genet. 2016;53(3):145-151

FDM1
91592

DMPK DNA Test (DM1)

Clinical Information: Detects CTG repeat expansions in the muscle protein kinase (DMPK) gene. Typical presentation: Adults may present with a range of symptoms from cataracts to significant muscle wasting, cardiac complications, ptosis and myotonia, infants may present with severe hypotonia, skeletal deformities, developmental delay and mental retardation.

Reference Values:
A final report will be attached in MayoAccess.

CRITH
62925

DNA Double-Stranded (dsDNA) Antibodies by Crithidia luciliae IFA, IgG, Serum

Clinical Information: Double-stranded DNA (dsDNA) antibodies are systemic lupus erythematosus (SLE)-specific antibodies and are part of the immunology domain of the 2019 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for SLE (1) as well as a previous guidance on SLE diagnosis.(2) The Crithidia luciliae indirect immunofluorescence test (CLIFT) is widely used as a confirmatory test following a positive dsDNA IgG result obtained by a solid-phase immunoassay due to its structural or analytical specificity.(3-5) The CLIFT (dsDNA) test is indicated in patients who are positive for anti-cellular antibody (also known as antinuclear antibody [ANA]) homogeneous pattern (6) using HEp-2 substrate by indirect immunofluorescence assay (IFA) following a positive result for dsDNA IgG using a solid-phase immunoassay (eg, enzyme-linked immunosorbent assay or multiplex bead assay).(3,4) A positive CLIFT result is usually associated with the presence of moderate-to-high affinity dsDNA IgG antibodies. The CLIFT result may be negative and the immunoassay positive for dsDNA IgG in SLE patients with inactive (remission) disease or in patients with early disease.(3,4,7) Discordant results between CLIFT and solid-phase immunoassays may also be due to differences in the structural specificities of DNA analytes as well as the absence reliable reagents to harmonize available clinical tests.(3,5,8) A minority of SLE patients may test negative using HEp-2 by IFA for nuclear antibodies.(9) Testing antibodies associated with the HEp-2 IFA cytoplasmic pattern such as ribosomal P IgG autoantibodies may be useful if features of neuropsychiatric disease are present.(9) Alternatively, patients may be tested for Smith, ribonuclear protein (RNP), SSA-52 and SSA-60 antibodies.(6,9)

Useful For: Confirmation testing for dsDNA IgG antibodies in patients with clinical features of systemic lupus erythematosus or at-risk for disease This test should not be used independently for monitoring treatment response or establishing remission.

Interpretation: A positive result for double-stranded DNA (dsDNA) IgG antibodies in the appropriate clinical context is highly suggestive of systemic lupus erythematosus (SLE). The presence of dsDNA IgG antibodies detected using the Crithidia luciliae indirect immunofluorescence test is highly specific for SLE with moderate sensitivity. A negative result does not exclude a diagnosis of SLE.

Reference Values:
Negative

Clinical References: 1. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for systemic lupus erythematosus. Arthritis Rheumatol. 2019;71(9):1400-1412. doi:10.1002/art.40930 2. Petri M, Orbai AM, Alarcon GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):

2677-2686. doi:10.1002/art.34473 3. Enocsson H, Sjowall C, Wirestam L, et al. Four anti-dsDNA antibody assays in relation to systemic lupus erythematosus disease specificity and activity. J Rheumatol. 2015;42(5):817-825. doi:10.3899/jrheum.140677 4. Sarbu MI, Salman-Monte TC, Munoz PR, Lisbona MP, Bernabe MA, Carbonell J. Differences between clinical and laboratory findings in patients with recent diagnosis of SLE according to the positivity of anti-dsDNA by the Crithidia luciliae method. Lupus. 2015;24(11):1198-1203. doi:10.1177/0961203315573852 5. Rekvig OP. Autoimmunity and SLE: factual and semantic evidence-based critical analyses of definitions, etiology, and pathogenesis. Front Immunol. 2020;11:569234. doi:10.3389/fimmu.2020.569234 6. Damoiseaux J, Andrade LEC, Carballo OG, et al. Clinical relevance of HEp-2 indirect immunofluorescent patterns: the International Consensus on ANA patterns (ICAP) perspective. Ann Rheum Dis. 2019;78(7):879-889. doi:10.1136/annrheumdis-2018-214436 7. Bragazzi NL, Watad A, Damiani G, Adawi M, Amital H, Shoenfeld Y. Role of anti-DNA auto-antibodies as biomarkers of response to treatment in systemic lupus erythematosus patients: hypes and hopes. Insights and implications from a comprehensive review of the literature. Expert Rev Mol Diagn. 2019;19(11):969-978. doi:10.1080/14737159.2019.1665511 8. Fox BJ, Hockley J, Rigsby P, Dolman C, Meroni PL, Ronnelid J. A WHO Reference Reagent for lupus (anti-dsDNA) antibodies: international collaborative study to evaluate a candidate preparation. Ann Rheum Dis. 2019;78(12):1677-1680. doi:10.1136/annrheumdis-2019-215845 9. Choi MY, Clarke AE, St Pierre Y, et al. Antinuclear antibody-negative systemic lupus erythematosus in an international inception cohort. Arthritis Care Res (Hoboken). 2019;71(7):893-902. doi:10.1002/acr.23712

DNJB9
71739

DNAJB9 Immunostain, Technical Component Only

Clinical Information: DNAJB9 (Dnaj [hsp40] homolog, subfamily b, member 9) is a heat shock protein that plays a role in protein folding. Proteomic analysis indicates that the DNAJB9 protein is specifically identified in glomeruli of patients with fibrillary glomerulonephritis (FGN). By immunohistochemistry there is an intense smudgy staining of extracellular glomerular deposits for DNAJB9 in patients with FGN.

Useful For: Diagnosis of fibrillary glomerulonephritis

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Nasr SH, Vrana JA, Dasari S, et al. DNAJB9 is a specific immunohistochemical marker for fibrillary glomerulonephritis. Kidney Int Rep. 2018;3(1):56-64 2. Dasari S, Alexander MP, Vrana JA, et al. DnaJ heat shock protein family B member 9 is a novel biomarker for fibrillary GN. J Am Soc Nephrol. 2018;29(1):51-56 3. Liang S, Chen D, Liang D, et al. Clinicopathological characteristics and outcome of patients with fibrillary glomerulonephritis: DNAJB9 is a valuable histologic marker. J Nephrol. 2020;34(3):883-892. doi:10.1007/s40620-020-00783-4 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FDKYE
57528

Dock Yellow (Rumex crispus) IgE

Interpretation: Class IgE (kU/L) Comment 0 <10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 17.50-49.99 Very High Positive 5 50.00-99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

DOGD
60108

Dog Dander, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to dog dander Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

DOGPF
616091

Dog Dander, IgE, with Reflex to Dog Dander Components, IgE, Serum

Clinical Information:

Useful For: Evaluating patients with suspected dog dander allergy

Interpretation: When detectable total dog dander IgE antibody is present (> or =0.10 IgE kUa/L), additional specific component IgE antibody testing will be performed. If at least one potential specific allergenic dog dander component IgE is detectable (> or =0.10 IgE kUa/L), an interpretative report will be provided. When the sample is negative for total dog dander IgE antibody (<0.10 IgE kUa/L), additional testing for specific dog component IgE antibodies will not be performed. Negative IgE results for total dog dander antibody may indicate a lack of sensitization to potential dog allergenic components.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Mattsson L, Lundgren T, Everberg H, et al: Prostatic kallikrein: a new major dog allergen. J Allergy Clin Immunol. 2009 Feb;123(2):362-368 2. Davila I, Dominguez-Ortega J, Navarro-Pulido A, et al: Consensus document on dog and cat allergy. Allergy. 2018 Jun;73(6):1206-1222. doi: 10.1111/all.13391 3. Nilsson OB, Binnmyr J, Zoltowska A, Saarne T, van Hage M, Gronlund H: Characterization of the dog lipocalin allergen Can f 6: the role in cross-reactivity with cat and horse. Allergy. 2012;67(6):751-757 4. Konieczny A, Morgenstern JP, Bizinkauskas CB, et al: The major dog allergens, Can f 1 and Can f 2, are salivary lipocalin proteins: cloning and immunological characterization of the recombinant forms. Immunology. 1997;92(4):577-586 5. Schou C, Svendsen UG, Lowenstein H: Purification and characterization of the major dog allergen, Can f I. Clin Exp Allergy. 1991;21(3):321-328 6. Bjerg A, Winberg A, Berthold M, Mattsson L, Borres MP, Ronmark E: A population-based study of animal component sensitization, asthma, and rhinitis in schoolchildren. Pediatr Allergy Immunol. 2015 Sept;26(6):557-563 7. Konradsen JR, Fujisawa T, van Hage M, et al: Allergy to furry animals: New insights, diagnostic approaches, and challenges. J Allergy Clin Immunol. 2015;135(3):616-625 8. Spitzauer S, Pandjaitan B, Soregi G, et al. IgE cross-reactivities against albumins in patients allergic to animals. J Allergy Clin Immunol. 1995;96(6 Pt 1):951-959 9. Chruszcz M, Mikolajczak K, Mank N, Majorek KA, Porebski PJ, Minor W: Serum albumins-unusual allergens. Biochim Biophys Acta. 2013;1830(12):5375-5381 10. Nwaru BI, Suzuki S, Ekerljung L, et al: Furry animal allergen component sensitization and clinical outcomes in adult asthma and rhinitis. J Allergy Clin Immunol Pract. 2019;7(4):1230-1238.e4 11. Schoos AM, Kattan JD, Gimenez G, Sampson HA: Sensitization phenotypes based on protein groups and associations to allergic diseases in children. J Allergy Clin Immunol. 2016

Apr;137(4):1277-1280 12. Rytkonen-Nissinen M, Saarelainen S, Randell J, Hayrinen J, Kalkkinen N, Virtanen T. IgE reactivity of the dog lipocalin allergen Can f 4 and the development of a sandwich ELISA for its quantification. Allergy Asthma Immunol Res. 2015 Jul;7(4):384-392 13. Schoos AM, Bonnelykke K, Chawes BL, Stokholm J, Bisgaard H, Kristensen B: Precision allergy: Separate allergies to male and female dogs. J Allergy Clin Immunol Pract. 2017 Nov-Dec;5(6):1754-1756 14. Basagana M, Bartolome B, Pastor-Vargas C, Mattsson L, Lidholm J, Labrador-Horrillo M: Involvement of Can f 5 in a case of human seminal plasma allergy. Int Arch Allergy Immunol. 2012;159(2):143-146 15. Chan SK, Leung DYM: Dog and cat allergies: Current state of diagnostic approaches and challenges. Allergy Asthma Immunol Res. 2018 Mar;10(2):97-105. doi: 10.4168/aair.2018.10.2.97 16. Salo PM, Arbes SJ Jr, Jaramillo R, et al: Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol. 2014 Aug;134(2):350-359. doi: 10.1016/j.jaci.2013.12.1071

FDFEN
75547

Dog Fennel (Anthemis cotula) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 17.50-49.99 Very High Positive 5 50.00-99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

DOG1
70422

DOG-1 Immunostain, Technical Component Only

Clinical Information: DOG-1 (discovered on gastrointestinal stromal tumors: GIST) is a calcium-regulated chloride channel protein that is expressed strongly on the cell surface of GIST and rarely in other soft tissue tumors, such as uterine type retroperitoneal leiomyomas, peritoneal leiomyomatosis, and synovial sarcomas. DOG-1 may aid in the differential diagnosis of GIST, including KIT-negative and PDGFRA-altered GIST cases.

Useful For: Identification of gastrointestinal stromal tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Khurram, SA, Speight, PM. Characterisation of DOG-1 expression in salivary gland tumours and comparison with myoepithelial markers. Head and Neck Pathol. 2019;13(2):140-148 2. Chetty R, Serra S. Molecular and morphological correlation in gastrointestinal stromal tumours (GISTs): an update and primer. Journal of Clin Pathol. 2016;69:754-760 3. Hemminger J, Iwenofu, OH. Discovered on gastrointestinal stromal tumours 1 (DOG1) expression in non-gastrointestinal stromal tumour (GIST) neoplasms. Histopathol. 2012;61(2):170-177 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FDLS
58007

Donath Landsteiner

Reference Values:
Negative

ADNA1
620809

Double-Stranded DNA (dsDNA) Antibodies, IgG, Serum

Clinical Information: Systemic lupus erythematosus (SLE) is a chronic autoimmune condition in which an inflammatory immune response leads to damage of a variety of organ systems, including the skin, joints, kidney, vasculature, lungs, and brain. In 2019, the European League Against Rheumatism/American College of Rheumatology published classification criteria for SLE,(1) which includes antibodies to double-stranded DNA (dsDNA) as an SLE-specific autoantibody within the immunology domain. Anti-dsDNA antibodies are also included in the Systemic Lupus International Collaborating Clinics classification criteria (SLICC) for SLE.(2) Detection of IgG antibodies to dsDNA is the most clinically useful isotype.(3-5) The diagnostic performance of dsDNA IgG antibodies in SLE is variable and dependent on several factors, including the immunological method used for their detection, the structure of the DNA antigen, the patient's disease state (early or active vs inactive), and specific clinical manifestations and patient demographics.(3-7) Weak-positive dsDNA IgG antibodies having low affinity and low avidity display variable clinical correlations with SLE.(3) Testing for IgG antibodies to dsDNA is indicated in patients with clinical features compatible with SLE who are positive for anti-cellular antibody (antinuclear antibody: ANA), particularly the homogeneous pattern identified using HEp-2 substrate by indirect immunofluorescence assay (IFA).(1,2,8) A minority of SLE patients may test negative using HEp-2 by IFA for nuclear antibodies.(8,9) For patients with features of neuropsychiatric disease, testing for antibodies associated with HEp-2 IFA cytoplasmic patterns such as ribosomal P IgG autoantibodies may be useful. In addition, some patients may benefit from testing for additional markers, including Smith, ribonucleoprotein, SSA-52, and SSA-60 antibodies.(8,9) The reactivity of antibodies to dsDNA may fluctuate with SLE disease activity. Increasing reactivity may be associated with flares while a decline or seronegativity may indicate response to treatment or disease remission. For more information see First-Line Screening for Autoimmune Liver Disease Algorithm.

Useful For: Evaluating patients with clinical features or at-risk for systemic lupus erythematosus (SLE) Monitoring disease activity, as an adjunct test, in patients with SLE previously positive for double-stranded DNA IgG antibodies

Interpretation: A positive result for double-stranded DNA (dsDNA) IgG antibodies in the appropriate clinical context is suggestive of systemic lupus erythematosus (SLE). The performance characteristics of dsDNA IgG antibodies in SLE is dependent on the immunological method used for their detection, the patient's disease state including clinical manifestations, and demographics. Weak-positive dsDNA IgG antibody results have a low-positive predictive value for SLE. Negative results do not rule out a diagnosis of SLE.

Reference Values:
<100 IU/mL (negative)
> or =100 IU/mL (positive)
Negative is considered normal.
Reference values apply to all ages.

Clinical References: 1. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol. 2019;71(9):1400-1412. doi:10.1002/art.40930 2. Petri M, Orbai AM, Alarcon GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677-2686. doi:10.1002/art.34473 3. Infantino M, Manfredi M, Merone M, et al. Analytical variability in the determination of anti-double-stranded DNA antibodies: the strong need of a better definition of the old and new tests. Immunol Res.

2018;66(3):340-347. doi:10.1007/s12026-018-8992-9 4. Fox BJ, Hockley J, Rigsby P, Dolman C, Meroni PL, Ronnelid J, et al. A WHO Reference Reagent for lupus (anti-dsDNA) antibodies: international collaborative study to evaluate a candidate preparation. Ann Rheum Dis. 2019;78(12):1677-1680. doi:10.1136/annrheumdis-2019-21584 5. Ambrose N, Morgan TA, Galloway J, et al. Differences in disease phenotype and severity in SLE across age groups. Lupus. 2016;25(14):1542-1550. doi:10.1177/0961203316644333 6. Rekvig OP. Autoimmunity and SLE: Factual and semantic evidence-based critical analyses of definitions, etiology, and pathogenesis. Front Immunol. 2020;11:569234. doi:10.3389/fimmu.2020.569234 7. Bragazzi NL, Watad A, Damiani G, Adawi M, Amital H, Shoenfeld Y. Role of anti-DNA auto-antibodies as biomarkers of response to treatment in systemic lupus erythematosus patients: hypes and hopes. Insights and implications from a comprehensive review of the literature. Expert Rev Mol Diagn. 2019;19(11):969-978. doi:10.1080/14737159.2019.1665511 8. Damoiseaux J, Andrade LEC, Carballo OG, et al. Clinical relevance of HEp-2 indirect immunofluorescent patterns: the International Consensus on ANA patterns (ICAP) perspective. Ann Rheum Dis. 2019;78(7):879-889. doi:10.1136/annrheumdis-2018-214436 9. Choi MY, Clarke AE, St Pierre Y, et al. Antinuclear antibody-negative systemic lupus erythematosus in an international inception cohort. Arthritis Care Res (Hoboken). 2019;71(7):893-902. doi:10.1002/acr.23712

DXPIN
63507

Doxepin and Nordoxepin, Serum

Clinical Information: Doxepin is recommended for the treatment of psychoneurotic patients with depression or anxiety, or with depression or anxiety associated with alcoholism or organic disease. Nordoxepin (N-desmethyldoxepin) is the major metabolite and is usually present at concentrations equal to doxepin. Optimal efficacy occurs at combined serum concentrations between 50 and 150 ng/mL. Like other tricyclic antidepressants, the major toxicity of doxepin is expressed as cardiac dysrhythmias, which occur at concentrations more than 500 ng/mL. Other side effects include nausea, hypotension, and dry mouth.

Useful For: Monitoring doxepin therapy Evaluating potential doxepin toxicity Evaluating patient compliance

Interpretation: Most individuals display optimal response to doxepin when combined serum levels of doxepin and nordoxepin are between 50 and 150 ng/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Risk of toxicity is increased with combined levels are above 500 ng/mL. Therapeutic ranges are based on specimens collected at trough (ie, immediately before the next dose).

Reference Values:
Therapeutic concentration (doxepin + nordoxepin): 50-150 ng/mL
Note: Therapeutic ranges are for specimens collected at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

Clinical References: 1. Wille SM, Cooreman SG, Neels HM, Lambert WE. Relevant issues in the monitoring and the toxicology of antidepressants. Crit Rev Clin Lab Sci. 2008;45(1):25-89 2. Thanacoody HK, Thomas SHL. Antidepressant poisoning. Clin Med (Lond). 2003;3(2):114-118 3. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51:9-62 4. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

CDA7X
62716

Drug Abuse Survey with Confirmation, Panel 9, Chain of

Custody, Random, Urine

Clinical Information: This assay was designed to test for and confirm the following drugs, by either gas chromatography-mass spectrometry (GC-MS), gas chromatography flame ionization detection (GC-FID), or liquid chromatography tandem mass spectrometry (LC-MS/MS): -Amphetamines -Barbiturates -Benzodiazepines -Cocaine -Ethanol -Opiates -Methadone -Phencyclidine -Tetrahydrocannabinol This test uses the simple screening technique which involves immunoassay testing for drugs by class. All positive immunoassay screening results will be confirmed by the definitive assay available and is described in each individual reflex test (eg, AMPHU / Amphetamines Confirmation, Random, Urine). All positive screening results are confirmed by either GC-MS, GC-FID, or LC-MS/MS and quantitated before a positive result is reported. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Useful For: Detecting drug abuse involving alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, and tetrahydrocannabinol This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis. This test is not intended for use in employment-related testing.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. For more information, see individual tests (eg, AMPHX / Amphetamines Confirmation, Chain of Custody, Random, Urine). For information about drug testing, including estimated detection times, see Drug Class Testing.

Reference Values:

Negative
Screening cutoff concentrations
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 100 ng/mL
Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
Ethanol: 10 mg/dL
Methadone metabolite: 300 ng/mL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL
This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

Clinical References: 1. Physicians Desk Reference (PDR). 60th edition. Medical Economics Company; 2006 2. Bruntman LL. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Book Company; 2006 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023: chap 43

CDAU7
81410

Drug Abuse Survey with Confirmation, Panel 9, Random, Urine

Clinical Information: This assay was designed to screen by immunoassay and confirm the following

drugs, by either gas chromatography mass spectrometry (GC-MS), gas chromatography-flame ionization detection (GC-FID), or liquid chromatography tandem mass spectrometry (LC-MS/MS): -Amphetamines -Barbiturates -Benzodiazepines -Cocaine -Ethanol -Opiates -Methadone -Phencyclidine -Tetrahydrocannabinol This test uses the simple screening technique which involves immunoassay testing for drugs by class. All positive immunoassay screening results will be confirmed by the definitive assay available and is described in each individual reflex test (eg, AMPHU / Amphetamines Confirmation, Random, Urine). All positive screening results are confirmed by either GC-MS, GC-FID, or LC-MS/MS and quantitated before a positive result is reported.

Useful For: Detecting drug abuse involving, amphetamines, barbiturates, benzodiazepines, cocaine, ethanol, methadone, opiates, phencyclidine, and tetrahydrocannabinol This test is intended to be used in a setting where the test results can be used definitively to make a diagnosis. This test is not intended for use in employment-related testing.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. For more information, see individual tests (eg, AMPHU / Amphetamines Confirmation, Random, Urine). For information about drug testing, including estimated detection times, see Drug Class Testing.

PNRCH
65061

Drug Immunoassay Panel, Urine

Clinical Information: This test uses the simple screening technique that involves immunoassay testing for drugs by class. All positive immunoassay screening results are confirmed by either gas chromatography mass spectrometry (GC-MS) or liquid chromatography tandem mass spectrometry (LC-MS/MS) and quantitated before a positive result is reported. This assay was designed to test for and confirm by GC-MS the following: -Barbiturates -Cocaine This assay was designed to test for and confirm by LC-MS/MS the following: -Carboxy-tetrahydrocannabinol This test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

Useful For: Detecting drug use involving barbiturates, cocaine, and carboxy-tetrahydrocannabinol This test is not intended for use in employment-related testing.

Interpretation: A positive result derived by this testing indicates that the patient has used one of the drugs detected by these techniques in the recent past. For information about drug testing, including estimated detection times and Result Interpretations, see Controlled Substance Monitoring on MayoClinicLabs.com.

Reference Values:
Only orderable as part of profile. For more information see:
-CSMPU / Controlled Substance Monitoring Panel, Random, Urine
-ADMPU / Addiction Medicine Profile with Reflex, 22 Drug Classes, High Resolution Mass Spectrometry and Immunoassay Screen, Random, Urine
-CSMEU / Controlled Substance Monitoring Enhanced Profile with Reflex, 21 Drug Classes, High Resolution Mass Spectrometry and Immunoassay Screen, Random, Urine

Negative
Screening cutoff concentrations:
Barbiturates: 200 ng/mL
Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

Clinical References: 1. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020:2343 2. Brunton LL, Hilal-Dandan R, Knollmann BC, eds. In: Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. McGraw-Hill; 2018 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 4. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline-Using clinical laboratory tests to monitor drug therapy in pain management patients. J Appl Lab Med. 2018;2(4):489-526

PDSUX 62741 Drug Screen, Prescription/Over the Counter, Chain of Custody, Random, Urine

Clinical Information: This test looks for a broad spectrum of prescription and over-the-counter drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient or to determine if a specific set of symptoms might be due to the presence of drugs. This test is not appropriate for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, and amphetamine type stimulants. Drugs of toxic significance that are not detected by this test are digoxin, lithium, salicylate, and many drugs of abuse or illicit drugs, some benzodiazepines, and some opiates. For these drugs, see Mayo Clinic Laboratories' drug abuse surveys, drug screens, or individual tests. Chain of custody is a record of the disposition of a specimen to document the personnel who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. For detection limits for drugs detected in this test see Prescription and Over-the-Counter Drug Screening List and Limits of Detection.

Useful For: Qualitative detection and identification of prescription or over-the-counter drugs frequently found in drug overdose or used with a suicidal intent Providing, when possible, the identification of all drugs in the specimen This test is not intended for use in employment-related testing. This test is not intended for therapeutic compliance testing. The assay's limits of detection have been established for drugs at overdose levels, which are generally much higher than therapeutic concentrations. This test is not useful for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, and amphetamine type stimulants. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The drugs that are detected by this test are listed in Prescription and Over-the-Counter Drug Screening List and Limits of Detection. A detailed discussion of each drug detected is beyond the scope of this text. Each report will indicate the drugs identified. If a clinical interpretation is required, contact Mayo Clinic Laboratories at 800-533-1710 and ask to speak to a toxicology consultant.

Reference Values:
Drugs detected are presumptive. Additional testing may be required to confirm the presence of any drugs detected.

Clinical References: 1. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 2. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020

PDSU
88760

Drug Screen, Prescription/Over the Counter, Random, Urine

Clinical Information: This test looks for a broad spectrum of prescription and over-the-counter medications. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to counteract the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient or to determine if a specific set of symptoms might be due to the presence of drugs. This test is not appropriate for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, and amphetamine-type stimulants. Drugs of toxic significance that are not detected by this test are digoxin, lithium, salicylate, and many drugs of abuse or illicit drugs, some benzodiazepines, and some opioids. For these drugs, see Mayo Clinic Laboratories' drug abuse surveys, drug screens, or individual tests. For detection limits for drugs detected in this test see Prescription and Over-the-Counter Drug Screening List and Limits of Detection.

Useful For: Qualitative detection and identification of prescription or over-the-counter drugs frequently found in drug overdose or used with a suicidal intent Providing, when possible, the identification of all drugs in the specimen This test is not intended for use in employment-related testing. This test is not intended for therapeutic compliance testing. The assay's limits of detection have been established for drugs at overdose levels, which are generally much higher than therapeutic concentrations. This test is not useful for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, and amphetamine type stimulants.

Interpretation: The drugs that are detected by this test are listed in Prescription and Over-the-Counter Drug Screening List and Limits of Detection. A detailed discussion of each drug detected is beyond the scope of this text. Each report will indicate the drugs identified. If a clinical interpretation is required, contact Mayo Clinic Laboratories at 800-533-1710 and ask to speak to a toxicology consultant.

Reference Values:
Drugs detected are presumptive. Additional testing may be required to confirm the presence of any drugs detected.

Clinical References: 1. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 2. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020

DSS
8421

Drug Screen, Prescription/Over the Counter, Serum

Clinical Information: This test looks for a broad spectrum of prescription and over-the-counter drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, or to determine if a specific set of symptoms might be due to the presence of drugs. This test is not appropriate for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, and amphetamine type stimulants. Drugs of toxic significance that are not detected by this test are digoxin, lithium, and many drugs of abuse or illicit drugs, some benzodiazepines, and some opioids. For detection limits for drugs detected in this test see Prescription and Over-the-Counter Drug Screening List and Limits of Detection.

Useful For: Detection and identification of prescription or over the counter drugs frequently found in drug overdose or used with a suicidal intent Qualitatively identifying drugs present in the specimen; quantification of identified drugs, when available, may be performed upon client request This test is not

intended for therapeutic drug monitoring or compliance testing. This test is not intended for use in employment-related testing. This test is not useful for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, amphetamine type stimulants.

Interpretation: The drugs that are detected by this test are listed in Prescription and Over-the-Counter Drug Screening List and Limits of Detection. The pharmacology of each drug determines how the test should be interpreted. A detailed discussion of each drug is beyond the scope of this text. If a clinical interpretation is required, contact Mayo Clinic Laboratories at 800-533-1710 and ask to speak to a toxicology consultant. Each report will indicate the drugs detected.

Reference Values:

Drugs detected are presumptive. Additional testing may be required to confirm the presence of any drugs detected.

Clinical References: 1. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 2. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020

FDA1S
75525

Drugs of Abuse (10 panel) and Alcohol Screen, Serum

Reference Values:

Reporting limit determined each analysis. Test	Result	Units
Ethanol	None Detected	mg/dL
Opiates	None Detected	ng/mL
Cocaine/Metabolites	None Detected	ng/mL
Benzodiazepines	None Detected	ng/mL
Cannabinoids	None Detected	ng/mL
Amphetamines	None Detected	ng/mL
Barbiturates	None Detected	mcg/mL
Methadone/Metabolite	None Detected	ng/mL
Phencyclidine	None Detected	ng/mL
Methamphetamine/MDMA	None Detected	ng/mL
Oxycodone/Oxymorphone	None Detected	ng/mL

DSM4X
62721

Drugs of Abuse Screen 4, Chain of Custody, Meconium

Clinical Information: Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress.(1) In the neonate, the mortality rate, as well as morbidity (eg, asphyxia, prematurity, low birthweight, hyaline membrane distress, infections, aspiration pneumonia, cerebral infarction, abnormal heart rate and breathing problems, and drug withdrawal) are increased.(1) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(2) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation and slowly moves into the colon by the 16th week of gestation.(3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure up to 5 months before birth, a longer historical measure than is possible by urinalysis.(2) Chain of custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Identifying amphetamines (and methamphetamines) and opiates, as well as metabolites of cocaine and marijuana in meconium specimen Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

Interpretation: A positive result indicates that the baby was exposed to the drugs indicated. The limit of quantitation varies for each of these drug groups. -Amphetamines: >100 ng/g -Methamphetamines: >100 ng/g -Cocaine and metabolite: >100 ng/g -Opiates: >100 ng/g -Tetrahydrocannabinol carboxylic acid: >20 ng/g

Reference Values:
Negative

Positive results are reported with a quantitative liquid chromatography tandem mass spectrometry result.

Cutoff concentrations by competitive chemiluminescent immunoassay:
Amphetamines: 100 ng/g
Methamphetamine: 100 ng/g
Benzoylecgonine (cocaine metabolite): 100 ng/g
Opiates: 100 ng/g
Tetrahydrocannabinol carboxylic acid (marijuana metabolite): 20 ng/g

Clinical References: 1. Ostrea EM Jr. Understanding drug testing in the neonate and the role of meconium analysis. J Perinat Neonatal Nurs. 2001;14(4):61-82; quiz 105-106 2. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989;115(3):474-477 3. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-56; quiz 73-74 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:454-454: chap 43 5. Langman LJ, Rushton AM, Thomas D, et al. Drug testing in support of the diagnosis of neonatal abstinence syndrome: The current situation. Clin Biochem. 2023;111:1-10. doi:10.1016/j.clinbiochem.2022.11.002 6. Marin SJ, Merrell M, McMillin GA. Drugs of abuse detection in meconium: a comparison between ELISA and biochip

microarray. J Anal Toxicol. 2011;35(1):40-45. doi:10.1093/anatox/35.1.40 7. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020

DSM5X
62722

Drugs of Abuse Screen 5, Chain of Custody, Meconium

Clinical Information: Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress.(1) In the neonate, the mortality rate, as well as morbidity (eg, asphyxia, prematurity, low birthweight, hyaline membrane disease, infections, aspirations pneumonia, cerebral infarction, abnormal heart rate and breathing patterns, drug withdrawal) are increased.(1) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(2) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation and slowly moves into the colon by the 16th week of gestation.(3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(2) Chain of custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Identifying amphetamines (and methamphetamines), opiates, and phencyclidine, as well as metabolites of cocaine and marijuana in meconium specimens Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

Interpretation: A positive result indicates that the baby was exposed to the drugs indicated. The limit of quantitation varies for each of these drug groups. -Amphetamines: >100 ng/g -Methamphetamines: >100 ng/g -Cocaine and metabolite: >100 ng/g -Opiates: >100 ng/g -Tetrahydrocannabinol carboxylic acid: >20 ng/g -Phencyclidine (PCP): >20 ng/g

Reference Values:
Negative

Positive results are reported with a quantitative liquid chromatography tandem mass spectrometry result.

Cutoff concentrations by competitive chemiluminescent immunoassay:
Amphetamines: 100 ng/g
Methamphetamine: 100 ng/g
Benzoylecgonine (cocaine metabolite): 100 ng/g
Opiates: 100 ng/g
Tetrahydrocannabinol carboxylic acid (marijuana metabolite): 20 ng/g
Phencyclidine: 20 ng/g

Clinical References: 1. Ostrea EM Jr. Understanding drug testing in the neonate and the role of meconium analysis. J Perinat Neonatal Nurs. 2001;14(4):61-106 2. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989;115(3):474-477 3. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG.

Meconium passage in utero: mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-74 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 5. Langman LJ, Rushton AM, Thomas D, et al. Drug testing in support of the diagnosis of neonatal abstinence syndrome: The current situation. Clin Biochem. 2023;111:1-10. doi:10.1016/j.clinbiochem.2022.11.002 6. Marin SJ, Merrell M, McMillin GA. Drugs of abuse detection in meconium: a comparison between ELISA and biochip microarray. J Anal Toxicol. 2011;35(1):40-45. doi:10.1093/anatox/35.1.40 7. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020

DASM4
60553

Drugs of Abuse Screen, Meconium 4

Clinical Information: Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress.(1) In the neonate, the mortality rate, as well as morbidity (eg, asphyxia, prematurity, low birthweight, hyaline membrane distress, infections, aspiration pneumonia, cerebral infarction, abnormal heart rate and breathing problems, and drug withdrawal) are increased.(1) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(2) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation and slowly moves into the colon by the 16th week of gestation.(3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(2)

Useful For: Identifying amphetamines (and methamphetamines), opiates, as well as metabolites of cocaine and marijuana in meconium specimens

Interpretation: A positive result indicates that the baby was exposed to the drugs indicated. The limit of quantitation varies for each of these drug groups. -Amphetamines: >100 ng/g -Methamphetamines: >100 ng/g -Cocaine and metabolite: >100 ng/g -Opiates: >100 ng/g -Tetrahydrocannabinol carboxylic acid: >20 ng/g

Reference Values:
Negative

Positives are reported with a quantitative liquid chromatography tandem mass spectrometry result.

Cutoff concentrations by competitive chemiluminescent immunoassay:
Amphetamines: 100 ng/g
Methamphetamine: 100 ng/g
Benzoylecgonine (cocaine metabolite): 100 ng/g
Opiates: 100 ng/g
Tetrahydrocannabinol carboxylic acid (marijuana metabolite): 20 ng/g

Clinical References: 1. Ostrea EM Jr: Understanding drug testing in the neonate and the role of meconium analysis. J Perinat Neonatal Nurs. 2001;14(4):61-106 2. Ostrea EM Jr, Brady MJ, Parks PM, et al. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989;115(3):474-477 3. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero: mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-74 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I,

Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:454-454: chap 43 5. Langman LJ, Rushton AM, Thomas D, et al. Drug testing in support of the diagnosis of neonatal abstinence syndrome: The current situation. Clin Biochem. 2023;111:1-10. doi:10.1016/j.clinbiochem.2022.11.002 6. Marin SJ, Merrell M, McMillin GA. Drugs of abuse detection in meconium: a comparison between ELISA and biochip microarray. J Anal Toxicol. 2011;35(1):40-5. doi:10.1093/anatox/35.1.40 7. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020

DASM5
60250

Drugs of Abuse Screen, Meconium 5

Clinical Information: Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress.(1) In the neonate, the mortality rate, as well as morbidity (eg, asphyxia, prematurity, low birthweight, hyaline membrane disease, infections, aspirations pneumonia, cerebral infarction, abnormal heart rate and breathing patterns, drug withdrawal) are increased.(1) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(2) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation and slowly moves into the colon by the 16th week of gestation.(3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(2)

Useful For: Identifying amphetamines (and methamphetamines), opiates, phencyclidine, as well as metabolites of cocaine and marijuana in meconium specimens

Interpretation: A positive result indicates that the baby was exposed to the drugs indicated. The limit of quantitation varies for each of these drug groups. -Amphetamines: >100 ng/g -Methamphetamines: >100 ng/g -Cocaine and metabolite: >100 ng/g -Opiates: >100 ng/g -Tetrahydrocannabinol carboxylic acid: >20 ng/g -Phencyclidine (PCP): >20 ng/g

Reference Values:
Negative

Positive results are reported with a quantitative liquid chromatography tandem mass spectrometry result.

Cutoff concentrations by competitive chemiluminescent immunoassay:
Amphetamines: 100 ng/g
Methamphetamine: 100 ng/g
Benzoylecgonine (cocaine metabolite): 100 ng/g
Opiates: 100 ng/g
Tetrahydrocannabinol carboxylic acid (marijuana metabolite): 20 ng/g
Phencyclidine: 20 ng/g

Clinical References: 1. Ostrea EM Jr. Understanding drug testing in the neonate and the role of meconium analysis. J Perinat Neonatal Nurs. 2001;14(4):61-106 2. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989;115(3):474-477 3. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero: mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-74 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier;

2023:chap 43 5. Langman LJ, Rushton AM, Thomas D, et al. Drug testing in support of the diagnosis of neonatal abstinence syndrome: The current situation. Clin Biochem. 2023;111:1-10. doi:10.1016/j.clinbiochem.2022.11.002 6. Marin SJ, Merrell M, McMillin GA. Drugs of abuse detection in meconium: a comparison between ELISA and biochip microarray. J Anal Toxicol. 2011;35(1):40-45. doi:10.1093/anatox/35.1.40 7. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020

FD10S
75352

Drugs of Abuse Screen, Serum

Reference Values:

Reporting limit determined each analysis. Test	Result	Units
Opiates	None Detected	ng/mL
Cocaine/Metabolites	None Detected	ng/mL
Benzodiazepines	None Detected	ng/mL
Cannabinoids	None Detected	ng/mL
Amphetamines	None Detected	ng/mL
Barbiturates	None Detected	mcg/mL
Fentanyl/Acetyl Fentanyl	None Detected	ng/mL
Methadone/Metabolite	None Detected	ng/mL
Phencyclidine	None Detected	ng/mL
Methamphetamine/MDMA	None Detected	ng/mL
Oxycodone/Oxymorphone	None Detected	ng/mL

DBMD
58125

Duchenne/Becker Muscular Dystrophy, DMD Gene, Large Deletion/Duplication Analysis, Varies

Clinical Information: Dystrophinopathies are X-linked disorders due to disease-causing variants in the DMD gene. DMD encodes for dystrophin, an integral muscle protein that plays a critical role in muscle membrane stability. A loss or reduction of dystrophin protein results in muscle degeneration over time. Duchenne muscular dystrophy (DMD) is a more severe form of dystrophinopathy characterized by proximal muscle weakness beginning before age 5 years. Affected individuals typically have pseudohypertrophy of the calf muscles and exhibit toe-walking, waddling gait, and the Gower sign (climbing up the legs when rising from a seated position on the floor). Initial symptoms are followed by dramatic progression of weakness leading to loss of ambulation by age 11 or 12 years. Additional associated clinical symptoms include developmental delay, pulmonary disease, cardiomyopathy, scoliosis and joint contractures. Death is often caused by cardiac failure in the second to third decade. The allelic Becker muscular dystrophy (BMD) has a similar presentation, although age

of onset is later with a slower clinical course and milder symptoms. Cardiac involvement can be the only feature, and patients are often ambulatory into their thirties or later. Management guidelines are available for DMD, and several US Food and Drug Administration-approved variant specific therapies are available and emerging, including exon skipping therapies and gene therapy. As an X-linked condition, dystrophinopathies typically affect 46,XY individuals or individuals assigned male at birth (AMAB); however, heterozygous 46,XX individuals with a disease-causing DMD variant may present with neuromuscular or cardiac symptoms, typically milder than those seen in 46,XY individuals. Approximately two-thirds of AMABs with a disease-causing DMD variant inherited the variant from a heterozygous 46,XX parent, while one-third of individuals with DMD have the condition as result of a de novo variant. In such cases, the recurrence risk is reduced, but not eliminated, as DMD is associated with germline mosaicism at an estimated frequency of 15%. Disease-causing DMD variants consist primarily of large deletions and duplications. Approximately 70% of patients have intragenic deletions and approximately 20% have intragenic duplications. Less frequently, DMD and BMD result from other types of variants such as missense, nonsense, splice site and small deletions and duplications, which are not detected by this assay.

Useful For: Confirmation of a clinical diagnosis of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) Distinguishing DMD from BMD in some cases, based on the type of deletion detected (allows for better prediction of prognosis) Determination of carrier status in family member at risk for DMD or BMD Prenatal diagnosis of DMD or BMD in at-risk pregnancies

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
The interpretive report will be provided.

Clinical References: 1. Darras BT, Urion DK, Ghosh PS. Dystrophinopathies. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated January 20, 2022. Accessed December 27, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1119/ 2. Pickart AM, Martin AS, Gross BN, et al. Genetic counseling for the dystrophinopathies-Practice resource of the National Society of Genetic Counselors. J Genet Couns. Published online April 29, 2024. doi:10.1002/jgc4.1892 3. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management [published correction appears in Lancet Neurol. 2018 Jun;17(6):495. doi: 10.1016/S1474-4422(18)30125-X]. Lancet Neurol. 2018;17(3):251-267. doi:10.1016/S1474-4422(18)30024-3 4. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurol. 2018;17(4):347-361. doi:10.1016/S1474-4422(18)30025-5

DUCK
82708

Duck Feathers, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant

allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to duck feathers Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FDME
57926

Duck Meat IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

DULOX
89305

Duloxetine, Serum

Clinical Information: Duloxetine is an antidepressant of the serotonin-norepinephrine reuptake inhibitor class. It is effective in treating symptoms of depression, including physical pain associated

with depression; other uses include therapy of neuropathic pain, fibromyalgia, and urinary stress incontinence. Duloxetine also inhibits serotonin uptake in human platelets and may be associated with potentiation of bleeding. Duloxetine undergoes extensive hepatic biotransformation to numerous inactive metabolites. The drug is metabolized by cytochrome P450 (CYP) 1A2 and CYP2D6, with moderate potential for drug interactions (duloxetine is both a substrate and a moderate inhibitor of CYP2D6). The mean elimination half-life is 12.5 hours with steady-state concentrations occurring in about 3 days. Specimens for therapeutic monitoring should be collected immediately before the next scheduled dose (ie, trough). Duloxetine is not recommended for patients with hepatic impairment, substantial alcohol use, or chronic liver disease. Use in patients with kidney disease significantly increases exposure to duloxetine due to decreased elimination. Patients with mild-to-moderate kidney dysfunction should be monitored closely; use of duloxetine is not recommended for patients with kidney failure.

Useful For: Monitoring duloxetine serum concentration during therapy Evaluating potential duloxetine toxicity Evaluating patient compliance

Interpretation: Therapeutic ranges are not well-established, but literature suggests that patients receiving duloxetine monotherapy for depression responded well when trough concentrations were 30 to 120 ng/mL. Higher levels may be tolerated by individual patients. The therapeutic relevance of this concentration range to other uses of duloxetine therapy is currently unknown.

Reference Values:
30-120 ng/mL

Clinical References: 1. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62 2. Westanmo AD, Gayken J, Haight R. Duloxetine: a balanced and selective norepinephrine- and serotonin-reuptake inhibitor. Am J Health-Syst Pharm. 2005;62(23):2481-2490 3. Waldschmitt C, Vogel F, Pfuhlmann B, Hiemke C. Duloxetine serum concentrations and clinical effects. Data from a therapeutic drug monitoring (TDM) survey. Pharmacopsychiatry. 2009;42(5):189-193 4. Feighner JP, Cohn JB. Double-blind comparative trials of fluoxetine and doxepin in geriatric patients with major depressive disorder. J Clin Psychiatry. 1985;46(3 Pt 2):20-25 5. Kelly MW, Perry PJ, Holstad SG, Garvey MJ. Serum fluoxetine and norfluoxetine concentrations and antidepressant response. Ther Drug Monit. 1989;11:165-170 6. Benfield P, Heel RC, Lewis SP. Fluoxetine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. Drugs. 1986;32(6):481-508 7. Wille SM, Cooreman SG, Neels, et al. Relevant issues in the monitoring and toxicology of antidepressants. Crit Rev Clin Lab Sci. 2008;45(1):25-89

DYS2 92121 Dysautonomia, Autoimmune/Paraneoplastic Evaluation, Serum

Clinical Information: Autoimmune dysautonomia encompasses disorders of peripheral autonomic synapses, ganglionic neurons, autonomic nerve fibers, and central autonomic pathways mediated by neural-specific IgG or effector T cells. These disorders may be idiopathic or paraneoplastic, subacute or insidious in onset, and may present as a limited disorder or generalized pandysautonomia. Pandysautonomia is usually subacute in onset and severity and includes impaired pupillary light reflex, anhidrosis, orthostatic hypotension, cardiac arrhythmias, gastrointestinal dysmotility, sicca manifestations, and bladder dysfunction. Limited dysautonomia is confined to one or just a few domains, is often mild, and may include sicca manifestations, postural orthostatism and cardiac arrhythmias, bladder dysfunction, or gastrointestinal dysmotility. Diagnosis of limited dysautonomia requires documentation of objective abnormalities by autonomic reflex testing, thermoregulatory sweat test, or gastrointestinal motility studies. The most frequently encountered autoantibody marker of autoimmune dysautonomia is the neuronal ganglionic alpha-3-acetylcholine receptor (AChR) autoantibody. To date, this autoantibody to is the only proven effector of autoimmune dysautonomia. A direct relationship has

been demonstrated between antibody titer and severity of dysautonomia in both alpha-3-AChR-immunized animals and patients with autoimmune dysautonomia. Patients with high alpha-3-AChR autoantibody values (>1.0 nmol/L) generally have profound pandysautonomia. Dysautonomic patients with lower alpha-3-AChR autoantibody values (0.03-0.99 nmol/L) have limited dysautonomia. Importantly, cancer is detected in 30% of patients with alpha-3-AChR autoantibody. Cancers recognized include small-cell lung carcinomas, thymoma, lymphoma, and adenocarcinomas of breast, lung, prostate, and gastrointestinal tract. Cancer risk factors include a previous or family history of cancer, history of smoking, or social or environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favors neurologic improvement and lessens morbidity. Autoantibodies to other onconeural proteins shared by neurons, glia, or muscle (eg, antineuronal nuclear antibody-type 1 [ANNA-1], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG]) serve as additional markers of paraneoplastic or idiopathic dysautonomia. A specific neoplasm is often predictable by the individual patient's autoantibody profile.

Useful For: Investigating idiopathic dysautonomic symptoms Directing a focused search for cancer in patients with idiopathic dysautonomia Investigating autonomic symptoms that appear in the course or wake of cancer therapy and are not explainable by recurrent cancer or metastasis (detection of autoantibodies in this profile helps differentiate autoimmune dysautonomia from the effects of chemotherapy)

Interpretation: Antibodies directed at onconeural proteins shared by neurons, muscle, and glia are valuable serological markers of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects and are usually accompanied by subacute neurological signs and symptoms. It is not uncommon for more than one autoantibody to be detected in patients with autoimmune dysautonomia. These include: -Plasma membrane cation channel antibodies (neuronal ganglionic [alpha-3]). These autoantibodies are potential effectors of autonomic dysfunction. -Antineuronal nuclear antibody-type 1 (ANNA-1) -Neuronal and muscle cytoplasmic antibodies (collapsin response-mediator protein-5 neuronal [CRMP-5 IgG]) A rising autoantibody titer in previously seropositive patients suggests cancer recurrence.

Reference Values:

Test ID	Reporting name	Methodology*	Reference value
ADEI	Dysautonomia, Interpretation, S	Medical interpretation	Interpretive report
GANG	AChR Ganglionic Neuronal Ab, S	RIA	< or =0.02 nmol/L
ANN1S	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
APBIS	AP3B2 IFA, S	IFA	Negative
CS2CS	CASPR2-IgG CBA, S	CBA	Negative
CRMS	CRMP-5-IgG, S	IFA	Negative
DPPCS	DPPX Ab CBA, S	CBA	Negative
LG1CS	LGI1-IgG CBA, S	CBA	Negative
PCAB2	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
Reflex Information: Test ID	Reporting name	Methodology*	Reference value
AN1BS	ANNA-1 Immunoblot, S	IB	Negative

AN1TS	ANNA-1 Titer, S	IFA	
AN2BS	ANNA-2 Immunoblot, S	IB	Negative
APBCS	AP3B2 CBA, S	CBA	Negative
APBTS	AP3B2 IFA Titer, S	IFA	
CRMTS	CRMP-5-IgG Titer, S	IFA	
CRMWS	CRMP-5-IgG Western Blot, S	WB	Negative
DPPTS	DPPX Ab IFA Titer, S	IFA	
PC2TS	PCA-2 Titer, S	IFA	

Clinical References: 1. Cutsforth-Gregory JK, McKeon A, Coon EA, et al. Ganglionic antibody level as a predictor of severity of autonomic failure. Mayo Clin Proc. 2018;93(10):1440-1447. doi:10.1016/j.mayocp.2018.05.033 2. Tobin WO, Lennon VA, Komorowski L, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. Neurology. 2014;83(20):1797-1803.doi:10.1212/WNL.0000000000000991

ECADB
603211

E-Cadherin Immunostain, Bone Marrow, Technical Component Only

Clinical Information: Membrane protein expressed on normal breast epithelial cells. Expression can be lost on lobular neoplasms of the breast, in contrast to ductal neoplasms of the breast.

Useful For: Differentiation between lobular and ductal neoplasms of the breast

Interpretation: This test does not include pathologist interpretation: only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Engstrom MJ, Opdahl S, Vatten LJ, Haugen OA, Bofin AM. Invasive lobular breast cancer: The prognostic impact of histopathological grade, E-cadherin and molecular subtypes. Histopathol. 2015;66(3):409-419 2. Dabbs DJ, Schnitt SJ, Geyer FC, et al. Lobular neoplasia of the breast revisited with emphasis on the role of e-cadherin immunohistochemistry. Am J Surg Pathol. 2013;37(7);e1-e11 3. Liu J, Feng C, Deng M, et al. E-cadherin expression phenotypes associated with molecular subtypes in invasive non-lobular breast cancer: evidence from a retrospective study and meta-analysis. World J Surg Onc. 2017;15(1):139 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

ECAD
70423

E-Cadherin Immunostain, Technical Component Only

Clinical Information: Membrane protein expressed on normal breast epithelial cells. Expression can

be lost on lobular neoplasms of the breast, in contrast to ductal neoplasms of the breast.

Useful For: Differentiation between lobular and ductal neoplasms of the breast

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Engstrom MJ, Opdahl S, Vatten LJ, et al. Invasive Lobular Breast Cancer: The Prognostic Impact of Histopathological Grade, E-cadherin and Molecular Subtypes. Histopathol. 2015;66(3):409-419 2. Dabbs DJ, Schnitt SJ, Geyer FC et al. Lobular neoplasia of the breast revisited with emphasis on the role of e-cadherin immunohistochemistry. Am J Surg Pathol. 2013;37:e1-e11 3. Liu J, Feng C, Deng M, et al. E-cadherin expression phenotypes associated with molecular subtypes in invasive non-lobular breast cancer: evidence from a retrospective study and meta-analysis. World J Surg Onc. 2017;15:139 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

EOIBD
620120

Early Onset Monogenic Inflammatory Bowel Disease (IBD) Gene Panel, Varies

Clinical Information: Inflammatory bowel disease (IBD) is a term encompassing numerous disorders featuring chronic intestinal inflammation. These conditions are typically classified as either Crohn disease or ulcerative colitis based on clinical features, colonoscopy findings, histologic changes, and the anatomical distribution of disease. However, some cases are not readily classified or may have overlapping features and are classified as IBD-unspecified (IBD-U). The incidence of IBD has rapidly increased in children and adults over the past few decades. Common symptoms include diarrhea, abdominal pain, fatigue, and failure to thrive or unintentional weight loss. Inflammatory bowel disease is caused by a combination of dysregulated immune response, microbial dysbiosis, and environmental triggers and occurs in individuals with genetic susceptibility. Most IBD is thought to be either polygenic or multifactorial. However, in rare cases, IBD or IBD-like intestinal inflammation can be attributed to disease-causing variants in a single gene (ie, monogenic inheritance) that result in a highly penetrant condition that presents early in life. Many monogenic forms of IBD are disorders of immune deficiency or dysregulation. Genes associated with IBD continue to be identified with advances in sequencing technology. However, 70% to 80% of patients have IBD without a known genetic etiology. While the peak age of onset of IBD is between the ages of 20 and 40 years, the incidence of IBD in pediatric patients is increasing. When IBD presents in children younger than 6 years, it is described as very early onset IBD (VEO-IBD). IBD that presents in children younger than 2 years is described as infantile-onset IBD. VEO-IBD differs from IBD in older patients in that it is more likely to be IBD-U and have a monogenic cause, particularly among those with infantile-onset IBD. Conditions associated with VEO-IBD can be grouped into the following broad, sometimes overlapping categories: disorders of general immune dysregulation (eg, IL-10 signaling defects, IPEX syndrome, STAT3 gain of function); T- and B-cell defects (eg, LRBA deficiency, CTLA4 deficiency, Wiskott Aldrich syndrome, severe combined immunodeficiency [SCID]/Omenn syndrome); phagocytic defects (eg, chronic granulomatous disease); hyper- or auto-inflammatory disorders (eg, familial Mediterranean fever, familial hemophagocytic lymphohistiocytosis); epithelial barrier dysfunction (eg, TTC7A deficiency, nuclear factor kappa B essential modulator [NEMO] deficiency); and syndromic conditions (eg, trichohepatoenteric syndrome, CHAPLE [CD55 deficiency with hyper-activation of complement, angiopathic thrombosis, and severe protein-losing enteropathy] syndrome). Previous reports indicate patients with a monogenic form of IBD may not respond as well to conventional treatment modalities. Identification of the genetic cause of disease in these individuals is important as it may change their treatment plan. Depending on the genetic

cause, targeted therapies or allogeneic hematopoietic stem cell transplantation may be beneficial. Therefore, early diagnosis and identification of the specific underlying genetic alteration is important in order to inform treatment, such as medical therapy, surgery, and stem cell transplant, and to reduce the high morbidity and mortality associated with these conditions. Individuals with polygenic or monogenic IBD may have other family members affected with IBD. A family history of IBD is more common among those with VEO-IBD. If a monogenic cause is identified in an individual, family members may be tested for the genetic variant to assess their risk of developing IBD or to guide therapy for those who are affected.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an inherited inflammatory bowel disorder Establishing a diagnosis of a monogenic early onset inflammatory bowel disease, allowing for appropriate management and surveillance for disease features based on the gene or variant involved Identifying variants within genes known to be associated with monogenic early onset inflammatory bowel disease, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Uhlig HH, Schwerd T, Koletzko S, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology. 2014;147(5):990-1007 2. Uhlig HH, Schwerd T. From genes to mechanisms. The expanding spectrum of monogenic disorders associated with inflammatory bowel disease. Inflamm Bowel Dis. 2016;22(1):202-212 3. Kelsen JR, Baldassano RN, Artis D, Sonnenberg GF. Maintaining intestinal health: the genetics and immunology of very early-onset inflammatory bowel disease. Cell Mol Gastroenterol Hepatol. 20151;1(5):462-476 4. Ouahed J, Spencer E, Kotlarz D, et al. Very early onset inflammatory bowel disease: A clinical approach with a focus on the role genetics and underlying immune deficiencies. Inflamm Bowel Dis. 2020;26(6):820-842 5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5)405-24

EEPC
83917

Eastern Equine Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid

Clinical Information: Eastern equine encephalitis (EEE) is within the alphavirus group. It is a low-prevalence cause of human disease in the Eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when humans may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. Central nervous system involvement is demonstrated in only a minority of infected individuals and is more abrupt and more severe than with other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70% EEE. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod, relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age.

Useful For: Aiding in the diagnosis of Eastern equine encephalitis using spinal fluid specimens

Interpretation: Detection of organism-specific antibodies in the spinal fluid (CSF) may suggest central nervous system (CNS) infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

Reference Values:

IgG: <1:1
IgM: <1:1
Reference values apply to all ages.

Clinical References: Piantadosi A, Kanjilal S. Diagnostic approach for arboviral infections in the United States. J Clin Microbiol. 2020;58(12):e01926-19. doi:10.1128/JCM.01926-19

EEEP
83155

Eastern Equine Encephalitis Antibody, IgG and IgM, Serum

Clinical Information: Eastern equine encephalitis (EEE) is within the alphavirus group. It is a low prevalence cause of human disease in the Eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when humans may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. Central nervous system involvement is demonstrated in only a minority of infected individuals; it is more abrupt and more severe with EEE than other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70% for EEE.

Useful For: Aiding in the diagnosis of Eastern equine encephalitis using serum specimens

Interpretation: In patients infected with this virus, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Single serum specimen IgG greater than or equal to 1:10 indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicate recent infection. In the United States it is unusual for any patient to show positive reactions to more than 1 of the arboviral antigens, although Western equine encephalitis and Eastern equine encephalitis antigens will show a noticeable cross-reactivity. Infections can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age and sex, as well as the occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age.

Reference Values:

IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

Clinical References: 1. Gonzalez-Scarano F, Nathanson N. Bunyaviruses. In: Fields BN, Knipe DM, eds. Fields Virology. Vol 1. 2nd ed. Raven Press; 1990:1195-1228 2. Donat JF, Rhodes KH, Groover RV, Smith TF. Etiology and outcome in 42 children with acute nonbacterial meningoencephalitis. Mayo Clin Proc. 1980;55(3):156-160 3. Tsai TF. Arboviruses. In: Murray PR, Baron EJ, Pfaller MA, et al, eds. Manual of Clinical Microbiology. 7th ed. American Society for Microbiology; 1999:1107-1124 4. Calisher CH. Medically important arboviruses of the United States and Canada. Clin Microbiol Rev. 1994;7(1):89-116 5. Markoff L. Alphaviruses (Chikungunya, Eastern

equine encephalitis). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:1997-2006

ESYC
82721

Eastern Sycamore, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Eastern Sycamore Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ECHNG
616731

Echinococcus Antibody, IgG, Serum

Clinical Information: Echinococcosis, also referred to as hydatidosis or hydatid disease, is 1 of the 17 neglected tropical diseases recognized by the World Health Organization and affects over 1 million people worldwide. Echinococcus species are tapeworms or cestodes, and 2 main species infect humans: Echinococcus granulosus and Echinococcus multilocularis. With respect to geographic distribution, E granulosus can be found worldwide but, more frequently, is found in rural grazing areas where dogs may feed on infected sheep or cattle carcasses. E multilocularis is largely localized to the northern hemisphere. The definitive hosts for E granulosus are dogs or other canids, while the definitive host for E multilocularis are foxes and, to a much lesser extent, canids. Echinococcus tapeworms reside in the small intestine of definitive hosts and release eggs that are passed in the feces and ingested by an intermediate host, typically sheep or cattle in the case of E granulosus or small rodents for E multilocularis. The eggs hatch in the small bowel, releasing an oncosphere that penetrates the intestinal wall and migrates through the circulatory system to various organs where it develops into a cyst that gradually enlarges, producing protoscolices and daughter cysts, which fill the interior. The definitive host becomes infected following ingestion of these infectious cysts. Humans become accidentally infected following ingestion of Echinococcus eggs. In humans, E granulosus (cystic echinococcal disease) cysts typically develop in the lungs and liver. The infection may remain silent or latent for years (5-20 years) prior to cyst enlargement and symptom manifestation. Symptomatic manifestations include chest pain, hemoptysis, and cough for pulmonary involvement and abdominal pain and biliary duct obstruction for liver infection. E multilocularis (alveolar echinococcal disease) infections manifest more rapidly than those of E granulosus and similarly to a rapidly growing, destructive tumor, resulting in abdominal pain and biliary obstruction. Rupture of cysts can produce fever, urticaria, and anaphylactic shock. Diagnosis of echinococcal infections relies on characteristic findings by ultrasound or other imaging techniques and serologic findings. Fine-needle aspirates of cystic fluid may be performed; however, they carry the risk of cyst puncture and fluid leakage, potentially leading to severe allergic reactions. Importantly, infected individuals do not shed eggs in stool.

Useful For: Detection of antibodies to Echinococcus granulosus

Interpretation: Negative: The absence of antibodies to Echinococcus species suggests that the individual has not been exposed to this cestode. A single negative result should not be used to rule out infection (see Cautions). Positive: Results suggest infection with Echinococcus. False-positive results may occur in settings of infection with other helminths or in patients with chronic immune disorders. Results should be considered alongside other clinical findings (eg, characteristic findings on imaging) and exposure history.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Agudelo Higuita NI, Brunetti E, McCloskey C. Cystic Echinococcosis. J Clin Microbiol. 2016;54(3):518-523 2. Sarkari B, Rezaei Z. Immunodiagnosis of human hydatid disease: Where do we stand? World J Methodol. 2015;5(4):185-195

ECMP
618696

Eculizumab Monitoring Panel, Serum

Clinical Information: Eculizumab (Soliris, Alexion Pharmaceuticals), a humanized monoclonal IgG2/4 kappa antibody therapeutic directed against complement component C5, has been heralded as a breakthrough treatment for paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). More recently, eculizumab has been approved to treat aquaporin-4 (AQP4) IgG positive neuromyelitis optica spectrum disorder and generalized myasthenia gravis. By association with

C5, eculizumab inhibits the terminal complement pathway through simultaneous blockade of the generation of the potent prothrombotic and proinflammatory molecule, C5a, and the formation of membrane attack complex initiator, C5b. Eculizumab is administered as an intravenous infusion and the dosing regimen prescribed for an average adult diagnosed with PNH is 600 mg weekly for the first 4 weeks, followed by 900 mg for the fifth dose 1 week later, then 900 mg every 2 weeks thereafter. Eculizumab has been evaluated in aHUS patients through 2 prospective, open-label, single-arm studies (C08-002 and C08-003) as well as a single-arm retrospective study. In aHUS, it is prescribed for an average adult at 900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter. Eculizumab was generally well tolerated, and no significant adverse effects were attributed to drug treatment; some adverse reactions included upper respiratory tract infections and diarrhea in prospective and retrospective studies, hypertension, headache, and leucopenia (C08-002/C08-003), and fever (C09-001R). Additional case reports suggest that eculizumab may prevent post-transplantation recurrence of aHUS, even in those patients harboring CFH/CFHR1 hybrid gene variants who are at very high risk of recurrence. Further research is needed to determine the duration of eculizumab therapy in the context of the genetic background of aHUS cases and risk of disease relapse. Therapeutic drug monitoring of eculizumab is helpful when providers are considering personalized treatment decisions such as therapy discontinuation or extending dose intervals when patients are in remission states. In PNH, a minimum therapeutic concentration is expected to be above 35 mcg/mL and in aHUS, the therapeutic concentrations are expected to be above 50 to 100 mcg/mL of eculizumab. Complement blockage studies can aid in determining that a therapeutic concentration of the drug has blocked the complement function and subsequent production of sC5b-9. Here we offer a panel of eculizumab concentration plus alternative pathway function to monitor eculizumab therapy efficacy.

Useful For: Monitoring of complement blockage by eculizumab Assessing the response to eculizumab therapy Assessing the need for dose escalation Evaluating the potential for dose de-escalation or discontinuation of therapy in remission states Monitoring patients who need to be above a certain eculizumab concentration to improve the odds of a clinical response for therapy optimization This test is not useful as the sole basis for a diagnosis or treatment decisions.

Interpretation: Minimum trough therapeutic concentrations (immediately before next infusion) of eculizumab are expected to be above 35 mcg/mL for paroxysmal nocturnal hemoglobinuria and above 50 mcg/mL for atypical hemolytic uremic syndrome. For the complement blockage monitoring of eculizumab: -When eculizumab is present in serum at concentrations around 100 mcg/mL, the results are below the limit of quantitation of the assay (<10% of normal).

Reference Values:

ECULIZUMAB QUANTITATION:
Lower limit of quantitation =5.0 mcg/mL
>35 mcg/mL: Therapeutic concentration for paroxysmal nocturnal hemoglobinuria (PNH)
>50 mg/mL: Therapeutic concentration for atypical hemolytic uremic syndrome (aHUS)

ECULIZUMAB COMPLEMENT BLOCKAGE:
> or =46% normal

Clinical References: 1. Frazer-Abel A, Sepiashvili L, Mbughuni MM, Willrich MA. Overview of laboratory testing and clinical presentations of complement deficiencies and dysregulation. Adv Clin Chem. 2016;77:1-75. doi:10.1016/bs.acc.2016.06.001 2. Go RS, Winters JL, Leung N, et al. Thrombotic microangiopathy care pathway: A consensus statement for the Mayo Clinic Complement Alternative Pathway-Thrombotic Microangiopathy (CAP-TMA) Disease-Oriented Group. Mayo Clin Proc. 2016;91(9):1189-1211. doi:10.1016/j.mayocp.2016.05.015 3. Willrich MAV, Andreguetto BD, Sridharan M, et al: The impact of eculizumab on routine complement assays. J Immunol Methods. 2018;460:63-71. doi:10.1016/j.jim.2018.06.010 4. Ardissino G, Tel F, Sgarbanti M, et al. Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome: an update. Pediatr Nephrol. 2018;33(3):457-461 5. Volokhina EB, van de Kar NC, Bergseth G, et al. Sensitive, reliable and

easy-performed laboratory monitoring of eculizumab therapy in atypical hemolytic uremic syndrome. Clin Immunol. 2015;160(2):237-243 6. Sridharan M, Willrich MA, Go RS. Personalized Dosing of Eculizumab Using C5 Functional Activity and Eculizumab Level in Complement-mediated Thrombotic Microangiopathy: A Safe and Cost-saving Approach. XXVIII Congress of the International Society on Thrombosis and Haemostasis. Virtual ISTH 2020; July 12-14, 2020. 7. Cataland S, Ariceta G, Chen P, et al. Discordance between free C5 and CH50 complement assays in measuring complement C5 inhibition in patients with aHUS treated with ravulizumab. Blood. 2019;134(Supplement_1):1099 8. Willrich MA, Murray DL, Barnidge DR, Ladwig PM, Snyder MR. Quantitation of infliximab using clonotypic peptides and selective reaction monitoring by LC-MS/MS. Int Immunopharmacol. 2015;28(1):513-520. doi:10.1016/j.intimp.2015.07.007 9. Ladwig PM, Barnidge DR, Willrich MA. Quantification of the IgG2/4 kappa monoclonal therapeutic eculizumab from serum using isotype specific affinity purification and microflow LC-ESI-Q-TOF Mass Spectrometry. J Am Soc Mass Spectrom. 2017;28(5):811-817. doi:10.1007/s13361-016-1566-y 10. Ladwig PM, Barnidge DR, Willrich MA. Mass spectrometry approaches for identification and quantitation of therapeutic monoclonal antibodies in the clinical laboratory. Clin Vaccine Immunol. 2017;24(5):e00545-16. doi:10.1128/CVI.00545-16 11. Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019;133(6):540-549. doi:10.1182/blood-2018-09-876805 12. Stern RM, Connell NT. Ravulizumab: a novel C5 inhibitor for the treatment of paroxysmal nocturnal hemoglobinuria. Ther Adv Hematol. 2019;10:2040620719874728. doi:10.1177/2040620719874728 13. Alexion Pharmaceuticals. BLA 761108-S1 Multi-disciplinary review and evaluation: Ultomiris (ravulizumab-cwvz). FDA; April 2, 2019. Available at www.fda.gov/media/135113/download 14. Willrich MAV, Ladwig PM, Martinez MA, et al. Monitoring Ravulizumab effect on complement assays. J Immunol Methods. 2021;490:112944. doi:10.1016/j.jim.2020.112944 15. Wong EK, Goodship TH, Kavanagh D. Complement therapy in atypical haemolytic uraemic syndrome (aHUS). Mol Immunol. 2013;56(3):199-212 16. Rother RP, Rollins SA, Mojcik CF, Brodsky RA, Bell L. Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. Nat Biotechnol. 2007;25(11):1256-1264 17. Zuber J, Le Quintrec M, Krid S, et al. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation. Am J Transplant. 2012;12(12):3337-3354 18. Andreguetto B, Murray D, Snyder M, et al: The impact of eculizumab in complement assays. Mol Immunol. 2015;67:119-120 19. Willrich MAV, Braun KMP, Moyer AM, Jeffrey DH, Frazer-Abel A. Complement testing in the clinical laboratory. Crit Rev Clin Lab Sci. 2021;58(7):447-478. doi:10.1080/10408363.2021.1907297 20. Pittock SJ, Berthele A, Fujihara K, et al: Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. N Engl J Med. 2019;381(7):614-625. doi:10.1056/NEJMoa1900866 21. Dhillon S. Eculizumab: A review in generalized myasthenia gravis. Drugs. 2018;78(3):367-376. doi:10.1007/s40265-018-0875-9 22. Howard JF Jr, Utsugisawa, K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol. 2017;16(12):976-986. doi:10.1016/S1474-4422(17)30369-1

ECULI
65676

Eculizumab, Serum

Clinical Information: Eculizumab (Soliris, Alexion Pharmaceuticals) is a humanized monoclonal IgG2/4 kappa antibody therapeutic directed against complement component 5 (C5). By association with C5, eculizumab inhibits the terminal complement pathway through simultaneous blockade of the generation of the potent prothrombotic and proinflammatory molecule, C5a, and the formation of membrane attack complex initiator, C5b. Eculizumab is administered as an IV infusion. The dosing regimen prescribed for an average adult diagnosed with paroxysmal nocturnal hemoglobinuria (PNH) is 600 mg weekly for the first 4 weeks, followed by 900 mg for the fifth dose 1 week later, and 900 mg every 2 weeks thereafter. Eculizumab has been evaluated in patients with atypical hemolytic uremic syndrome (aHUS) through 2 prospective, open-label, single-arm studies (C08-002 and C08-003) as well as a single-arm retrospective study. In aHUS, it is prescribed for an average adult at 900 mg weekly for

the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter. Eculizumab was generally well tolerated, and no significant adverse effects were attributed to drug treatment; some adverse reactions included upper respiratory tract infections and diarrhea in prospective and retrospective studies, hypertension, headache, and leucopenia (C08-002/C08-003), and fever (C09-001R). Additional case reports suggest that eculizumab may prevent post transplantation recurrence of aHUS, even in those patients harboring CFH/CFHR1 hybrid gene variants, who are at very high risk of recurrence. Further research is needed to determine the duration of eculizumab therapy in the context of the genetic background of aHUS cases and risk of disease relapse. Therapeutic drug monitoring of eculizumab is helpful when providers are considering personalized treatment decisions, such as therapy discontinuation or extending dose intervals when patients are in remission states. In PNH, a minimum therapeutic concentration is expected to be above 35 mcg/mL. In aHUS, the therapeutic concentrations are expected to be above 50 to 100 mcg/mL of eculizumab. Complement blockage studies can aid in determining if a therapeutic concentration of the drug has blocked the complement function and subsequent production of sC5b-9. A panel that includes both eculizumab concentration and eculizumab complement blockage testing is available; see ECMP / Eculizumab Monitoring Panel, Serum.

Useful For: Assessing the response to eculizumab therapy Assessing the need for dose escalation Evaluating the potential for dose de-escalation or discontinuation of therapy in remission states Monitoring patients who need to be above a certain eculizumab concentration in order to improve the odds of a clinical response for therapy optimization

Interpretation: Minimum trough therapeutic concentrations (immediately before next infusion) of eculizumab are expected to be above 35 mcg/mL for paroxysmal nocturnal hemoglobinuria and above 50 mcg/mL for atypical hemolytic uremic syndrome.

Reference Values:
Lower limit of quantitation =5.0 mcg/mL
>35 mcg/mL: Therapeutic concentration for paroxysmal nocturnal hemoglobinuria (PNH)
>50 mcg/mL: Therapeutic concentration for atypical hemolytic uremic syndrome (aHUS)

Clinical References: 1. Ladwig PM, Barnidge DR, Willrich MA. Quantification of the IgG2/4 kappa monoclonal therapeutic eculizumab from serum using isotype specific affinity purification and microflow LC-ESI-Q-TOF mass spectrometry. J Am Soc Mass Spectrom. 2017;28(5):811-817 2. Willrich MA, Murray DL, Barnidge DR, et al. Quantitation of infliximab using clonotypic peptides and selective reaction monitoring by LC-MS/MS. Int Immunopharmacol. 2015;28(1):513-520 3. Ladwig PM, Barnidge DR, Willrich MA. Mass spectrometry approaches for identification and quantitation of therapeutic monoclonal antibodies in the clinical laboratory. Clin Vaccine Immunol. 2017;24(5):e00545-16

EGFRS
614665

EGFR Gene, Targeted Mutation Analysis, 51 Mutation Panel, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Epidermal growth factor receptor (EGFR) protein is activated by the binding of specific ligands, resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately leading to cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression for many solid tumors. Targeted therapies directed to tumors harboring activating mutations within the EGFR tyrosine kinase domain (exons 18-21) have demonstrated some success in treating a subset of patients with non-small cell lung cancer. As a result, the mutation status of EGFR can be a

useful marker by which patients are selected for EGFR-targeted therapy.

Useful For: Identifying non-small cell lung cancers that may respond to epidermal growth factor receptor-targeted therapies

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer. 2007;7(3):169-181. doi:10.1038/nrc2088 2. Gao G, Ren S, Li A, et al. Epidermal growth factor receptor-tyrosine kinase inhibitor therapy is effective as first- line treatment of advanced non-small-cell lung cancer with mutated EGFR: a meta-analysis from six phase III randomized controlled trials. Int J Cancer. 2012;131(5):E822-829. doi:10.1002/ijc.27396 3. Mok TS. Personalized medicine in lung cancer: what we need to know. Nat Rev Clin Oncol. 2011;8(11):661-668. doi:10.1038/nrclinonc.2011.126 4. Lee CS, Sharma S, Miao E, Mensah C, Sullivan K, Seetharamu N. A comprehensive review of contemporary literature for epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer and their toxicity. Lung Cancer (Auckl). 2020;11:73-103. doi:10.2147/LCTT.S258444

EGFRW 614666 EGFR Targeted Mutation Analysis with ALK Reflex, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Epidermal growth factor receptor (EGFR) protein is activated by the binding of specific ligands, resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade, ultimately leading to cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression for many solid tumors. Targeted therapies directed to tumors harboring activating mutations within the EGFR tyrosine kinase domain (exons 18-21) have demonstrated some success in treating a subset of patients with non-small cell lung cancer (NSCLC). As a result, the mutation status of EGFR can be a useful marker by which patients are selected for EGFR-targeted therapy. Rearrangements of the anaplastic lymphoma kinase (ALK) locus are found in a subset of lung carcinomas (generally EGFR wildtype tumors) and their identification by fluorescence in situ hybridization (FISH) may guide important therapeutic decisions for the management of these tumors. The fusion of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the ALK gene results from an inversion of chromosome band 2p23. The ALK-EML4 rearrangement has been identified in 3% to 5% of NSCLC with the majority occurring in adenocarcinoma and younger male patients who were light or nonsmokers. Recent studies have demonstrated that lung cancers harboring ALK rearrangements are resistant to EGFR tyrosine kinase inhibitors but may be highly sensitive to ALK inhibitors, like crizotinib (Xalkori). The drug crizotinib works by blocking certain kinases, including those produced by the abnormal ALK gene. Clinical studies have demonstrated that crizotinib treatment of patients with tumors exhibiting ALK rearrangements can halt tumor progression or result in tumor regression. The ALK/EML4 FISH assay is an FDA-approved companion diagnostic test for crizotinib, which was recently approved by the FDA to treat certain patients with late-stage (locally advanced or metastatic), non-small cell lung cancers that harbor ALK gene rearrangements. It is useful for the identification of patients with lung cancer who will benefit from crizotinib therapy.

Useful For: Identifying non-small cell lung cancers that may benefit from treatment with epidermal growth factor receptor -targeted therapies or anaplastic lymphoma kinase inhibitors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Sharma SV, Bell DW, Settleman J, Haber DA: Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer. 2007 Mar;7(3):169-181. doi: 10.1038/nrc2088 2. Gao G, Ren S, Li A, et al: Epidermal growth factor receptor-tyrosine kinase inhibitor therapy is effective as first- line treatment of advanced non-small-cell lung cancer with mutated EGFR: a meta-analysis from six phase III randomized controlled trials. Int J Cancer. 2012 Sep 1;131(5):E822-829. doi: 10.1002/ijc.27396 3. Mok TS: Personalized medicine in lung cancer: what we need to know. Nat Rev Clin Oncol. 2011 Aug 23;8(11):661-668. doi: 10.1038/nrclinonc.2011.126 4. Cheng L, Alexander RE, Maclennan GT, et al: Molecular pathology of lung cancer: key to personalized medicine. Mod Path 2012 Mar;25(3):346-369. doi: 10.1038/modpathol.2011.215

EGGPF
610705

Egg Comprehensive Profile, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. Allergy to egg represents one of the most common causes of food allergy, especially in children. The evaluation for egg-related IgE antibodies can identify up to 95% of individuals at risk for clinical allergic reactions. The most clinically prevalent allergens in egg are found in the egg white, but egg yolk also contains clinically significant specific IgE-binding allergens. The allergenic egg proteins found in egg white include ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3) and lysozyme (Gal d 4). Ovomucoid has been demonstrated to be the most clinically significant egg allergen, in part due to its heat and digestion resistance. In the yolk, the protein alpha-livetin (Gal d 5) is the major allergen and is involved in bird-egg syndrome. Foods that may contain egg include salad dressings, breads, breaded foods, muffins, cakes, marshmallows, prepared soups and beverages, frostings, ice cream and sherbets, pie fillings, sausages, prepared meats, mayonnaise, coatings and breading for fried foods, and some sauces. Sensitization to allergic reaction to inhaled egg-white allergens has been reported in egg-processing workers and bakers. Certain vaccines grown on chick embryos may cause severe allergic reactions in patients when injected. Further development of vaccines, most of which are no longer grown on egg protein, seems to have decreased or even eliminated the risk. There is cross-reactivity between chicken egg white and turkey, duck, goose, and gull egg whites. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease.

Useful For: Identifying egg allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy This test is not useful for patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or for patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Whole egg includes proteins and potential allergens from both egg white and egg yolk. Egg white is generally more allergenic than egg yolk. Clinical reactions to egg are predominantly IgE-mediated immediate reactions characterized by atopic dermatitis, urticarial (hives), angioedema, vomiting,

diarrhea, rhinoconjunctivitis, and asthma. Children with atopic dermatitis may have an immediate exacerbation of symptoms or a delayed reaction causing a worsening of their dermatitis 1 to 2 days after exposure to egg. Eosinophilic esophagitis as a result of allergy to egg has been described. Egg white is often responsible for the early development of urticaria and eczema during infancy. In egg yolk, alpha-livetin (Gal d 5) is the major allergen and allergenicity to Gal d 5 is involved in bird-egg syndrome characterized egg intolerance in adults is due to sensitization by inhalation of bird dander. In these cases, there is secondary sensitization or cross-reactivity with serum albumin in egg yolk (Gal d 5) resulting in potential respiratory symptoms, including asthma or rhinitis with bird exposure and additional allergic symptoms to egg. Table. Major Egg Allergens Egg white allergen Common name Heat-and digestion stability Allergenic activity Gal d 1 Ovomucoid Stable +++ (major allergen) Gal d 2 Ovalbumin Unstable ++ Gal d 3 Ovotransferrin/conalbumin Unstable + Gal d 4 Lysozyme Unstable ++ Egg yolk allergen Gal d 5 Alpha-livetin, serum albumin Partially stable ++ Gal d 6 YGP42, a lipoprotein Stable + Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/Equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Caubet JC, Wang J: Current understanding of egg allergy. Pediatr Clin North Am. 2011;58(2):427-xi. doi: 10.1016/j.pcl.2011.02.014 3. Shin M, Han Y, Ahn K: The influence of the time and temperature of heat treatment on the allergenicity of egg white proteins. Allergy Asthma Immunol Res. 2013 Mar;5(2):96-101. doi: 10.4168/aair.2013.5.2.96 4.Allergen Encyclopedia. ThermoFisher Scientific; 2023. Accessed February 22, 2023. Available at www.thermofisher.com/diagnostic-education/hcp/us/en/resource-center/allergen-encyclopedia.html

EGWTP
610706

Egg White Component Profile, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. Allergy to egg represents one of the most common causes of food allergy, especially in children. The evaluation for egg-related IgE antibodies can identify up to 95% of individuals at risk for clinical allergic reactions. The most clinically prevalent allergens in egg are found in the egg white, but

egg yolk also contains clinically significant specific IgE-binding allergens. The allergenic egg proteins found in egg white include ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3), and lysozyme (Gal d 4). Ovomucoid has been demonstrated to be the most clinically significant egg allergen, in part due to its heat and digestion resistance. In the yolk, the protein alpha-livetin (Gal d 5) is the major allergen and is involved in bird-egg syndrome. Foods that may contain egg include salad dressings, breads, breaded foods, muffins, cakes, marshmallows, prepared soups and beverages, frostings, ice cream and sherbets, pie fillings, sausages, prepared meats, mayonnaise, coatings and breading for fried foods, and some sauces. Sensitization to allergic reaction to inhaled egg-white allergens has been reported in egg-processing workers and bakers. Certain vaccines grown on chick embryos may cause severe allergic reactions in patients when injected. Further development of vaccines, most of which are no longer grown on egg protein, seems to have decreased or even eliminated the risk. There is cross-reactivity between chicken egg white and turkey, duck, goose, and gull egg whites. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease.

Useful For: Identifying egg white allergens: -Responsible for allergic disease and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy This test is not useful for patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or for patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Whole egg includes proteins and potential allergens from both egg white and egg yolk. Egg white is generally more allergenic than egg yolk. Clinical reactions to egg are predominantly IgE-mediated immediate reactions characterized by atopic dermatitis, urticarial (hives), angioedema, vomiting, diarrhea, rhinoconjunctivitis, and asthma. Children with atopic dermatitis may have an immediate exacerbation of symptoms or a delayed reaction causing a worsening of their dermatitis 1 to 2 days after exposure to egg. Eosinophilic esophagitis as a result of allergy to egg has been described. Egg white is often responsible for the early development of urticaria and eczema during infancy. In egg yolk, alpha-livetin (Gal d 5) is the major allergen and allergenicity to Gal d 5 is involved in bird-egg syndrome characterized egg intolerance in adults is due to sensitization by inhalation of bird dander. In these cases, there is secondary sensitization or cross-reactivity with serum albumin in egg yolk (Gal d 5) resulting in potential respiratory symptoms including asthma or rhinitis with bird exposure and additional allergic symptoms to egg. Table. Major Egg Allergens Egg white allergen Common name Heat-and digestion stability Allergenic activity Gal d 1 Ovomucoid Stable +++ (major allergen) Gal d 2 Ovalbumin Unstable ++ Gal d 3 Ovotransferrin/conalbumin Unstable + Gal d 4 Lysozyme Unstable ++ Egg yolk allergen Gal d 5 Alpha-livetin, serum albumin Partially stable ++ Gal d 6 YGP42, a lipoprotein Stable + Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Caubet JC, Wang J: Current understanding of egg allergy. Pediatr Clin North Am. 2011;58(2):427-xi. doi:10.1016/j.pcl.2011.02.014 3. Shin M, Han Y, Ahn K: The influence of the time and temperature of heat treatment on the allergenicity of egg white proteins. Allergy Asthma Immunol Res. 2013 Mar;5(2):96-101. doi: 10.4168/aair.2013.5.2.96 4.Allergen Encyclopedia. ThermoFisher Scientific; 2023. Accessed February 22, 2023.Available at www.thermofisher.com/diagnostic-education/hcp/us/en/resource-center/allergen-encyclopedia.html

FEGWH
57584

Egg White IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

FEWG4
57529

Egg White IgG4

Interpretation: The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests.

EGG
82872

Egg White, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to egg white Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the

specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FEWHG
57530

Egg Whole IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

FEGYK
57582

Egg Yolk IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the

food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

YOLK
82753

Egg Yolk, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to egg yolk Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

EGGP
82477

Eggplant, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to eggplant Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

EDSGG
617253

Ehlers-Danlos Syndrome Gene Panel, Varies

Clinical Information: The Ehlers-Danlos syndromes (EDS) are a clinically and genetically diverse group of heritable connective tissue disorders characterized by joint hypermobility, skin hyperextensibility, and tissue fragility. EDS has an overall estimated prevalence between 1:5000 and 1:25,000. The classification system proposed by the International EDS Consortium identifies 13 subtypes of EDS.(1) A helpful chart delineating the various forms of EDS and their corresponding genes is provided by the Ehlers-Danlos Society.(2) This panel includes genes associated with autosomal dominant and autosomal recessive forms of EDS, including classical, classical-like EDS, vascular, dermatosparaxis, spondylodysplastic, musculocontractural, cardiac-valvular EDS, myopathic, and kyphoscoliotic forms. Of note, hypermobile EDS is inherited in an autosomal dominant inheritance pattern, however, the molecular basis of this condition is unknown, and a diagnosis is based on clinical criteria. Other conditions with phenotypic overlap with EDS covered by this panel include X-linked occipital horn syndrome (ATP7A gene), X-linked periventricular nodular heterotopia (FLNA gene), and brittle cornea syndrome (PRDM5 and ZNF469 genes).

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of Ehlers-Danlos syndrome and related conditions Establishing a diagnosis for Ehlers-Danlos syndrome, X-linked occipital horn syndrome, X-linked periventricular nodular heterotopia, and brittle cornea syndrome

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):8-26. doi:10.1002/ajmg.c.31552 2. The Ehlers-Danlos Society. EDS types. The Ehlers-Danlos Society; 2017. Accessed March 20, 2024. Available at: www.ehlers-danlos.com/eds-types/ 3. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30

EHRCP
81480

Ehrlichia Antibody Panel, Serum

Clinical Information: Anaplasma phagocytophilum is an intracellular rickettsia-like bacterium that preferentially infects granulocytes and forms inclusion bodies, referred to as morulae. A phagocytophilum is transmitted by Ixodes species ticks, which also transmit Borrelia burgdorferi and Babesia species. Infection with A phagocytophilum is also referred to as human granulocytic anaplasmosis (HGA) or human granulocytic ehrlichiosis, and symptoms in otherwise healthy individuals are often mild and nonspecific, including fever, myalgia, arthralgia, and nausea. Clues to the diagnosis of anaplasmosis in a patient with an acute febrile illness after tick exposure include laboratory findings of leukopenia or thrombocytopenia and elevated liver enzymes. HGA is most prevalent in the upper Midwest and in other areas of the United States that are endemic for Lyme disease. Ehrlichia chaffeensis is an intracellular rickettsia-like bacterium that preferentially infects monocytes and is sequestered in parasitophorous vacuoles referred to as morulae. Infections with E chaffeensis are also referred to as human monocytotropic ehrlichiosis (HME). E chaffeensis is transmitted by Amblyomma species ticks, which are found throughout the Southeastern and South-Central United States. Many

cases of HME are subclinical or mild, however, the infection can be severe and life-threatening, particularly in immunosuppressed individuals. Reported mortality rates range from 2% to 3%. Fever, fatigue, malaise, headache, and other "flu-like" symptoms occur most commonly. Leukopenia, thrombocytopenia, and elevated hepatic transaminases are frequent laboratory findings.

Useful For: An adjunct in the diagnosis of infection with Anaplasma phagocytophilum or Ehrlichia chaffeensis Seroepidemiological surveys of the prevalence of the infection in certain populations

Interpretation: A positive immunofluorescence assay result (titer > or =1:64) suggests current or previous infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology result although antibody levels decline significantly during the year following infection.

Reference Values:
ANAPLASMA PHAGOCYTOPHILUM
<1:64
Reference values apply to all ages.

EHRLICHIA CHAFFEENSIS
<1:64
Reference values apply to all ages.

Clinical References: Centers for Disease Control and Prevention (CDC), Division of Vector-Borne Diseases: Tickborne Diseases of the United States: A Reference Manual for Healthcare Providers. 6th ed. US Department of Health and Human Services; 2022. Accessed September 5, 2024. Available at www.cdc.gov/ticks/tickbornediseases/TickborneDiseases-P.pdf

EHRC
81478

Ehrlichia chaffeensis (HME) Antibody, IgG, Serum

Clinical Information: Ehrlichia chaffeensis is an intracellular rickettsia-like bacterium that preferentially infects monocytes and is sequestered in parasitophorous vacuoles referred to as morulae. Infections with E chaffeensis are also referred to as human monocytotropic ehrlichiosis (HME). E chaffeensis is transmitted by Amblyomma species ticks, which are found throughout the Southeastern and South-central United States. Many cases of HME are subclinical or mild, however, the infection can be severe and life-threatening, particularly in immunosuppressed individuals. Reported mortality rates range from 2% to 3%. Fever, fatigue, malaise, headache, and other "flu-like" symptoms occur most commonly. Leukopenia, thrombocytopenia, and elevated hepatic transaminases are frequent laboratory findings.

Useful For: An adjunct in the diagnosis of ehrlichiosis Seroepidemiological surveys of the prevalence of the infection in certain populations

Interpretation: A positive immunofluorescence assay result (titer > or =1:64) suggests current or previous infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology result although antibody levels decline significantly during the year following infection.

Reference Values:
<1:64
Reference values apply to all ages.

Clinical References: Centers for Disease Control and Prevention (CDC): Tickborne Diseases of the

United States: A Reference Manual for Healthcare Providers. 6th ed. US Department of Health and Human Services; 2022. Accessed September 5, 2024. Available at www.cdc.gov/ticks/tickbornediseases/TickborneDiseases-P.pdf

EPCRB
618301

Ehrlichia/Anaplasma, Molecular Detection, PCR, Blood

Clinical Information: Ehrlichiosis and anaplasmosis are emerging zoonotic tick-borne infections caused by Ehrlichia and Anaplasma species, respectively. These obligate intracellular, gram-negative rickettsial organisms infect leukocytes and cause a potentially serious febrile illness in humans. Human granulocytic anaplasmosis (HGA), formerly known as human granulocytic ehrlichiosis, is caused by Anaplasma phagocytophilum, which is transmitted through the bite of an infected Ixodes species tick. The epidemiology of this infection in the US is similar to that of Lyme disease (caused by Borrelia burgdorferi and Borrelia mayonii) and babesiosis (caused primarily by Babesia microti), which all have the same tick vector. HGA is most prevalent in the upper Midwest and the Northeastern US. Human monocytic ehrlichiosis (HME) is caused by Ehrlichia chaffeensis, which is transmitted by the Lone Star tick, Amblyomma americanum. Most cases of HME have been reported from the Southeastern and South-Central regions of the United States. Ehrlichia ewingii, the known cause of canine granulocytic ehrlichiosis, can occasionally cause an HME-like illness in humans. Clinical features and laboratory abnormalities are similar to those of E chaffeensis infection, and antibodies to E ewingii cross-react with current serologic assays for detection of antibodies to E chaffeensis. Most recently, Mayo Clinic Laboratories detected a new species of Ehrlichia in patients with exposure to ticks in Wisconsin and Minnesota. This new pathogen, called Ehrlichia muris eauclairensis, causes a similar disease to ehrlichiosis due to E chaffeensis and E ewingii and may cause more severe disease in immunocompromised hosts. Most cases of anaplasmosis and ehrlichiosis are subclinical or mild, but infection can be severe and life-threatening in some individuals. Fever, fatigue, malaise, headache, and other "flu-like" symptoms, including myalgias, arthralgias, and nausea, occur most commonly. Central nervous system involvement can result in seizures and coma. Diagnosis may be challenging since the patient's clinical course is often mild and nonspecific. This symptom complex is easily confused with other illnesses such as influenza or other tick-borne zoonoses. Clues to the diagnosis of anaplasmosis/ehrlichiosis in an acutely febrile patient after tick exposure include laboratory findings of leukopenia, thrombocytopenia, and elevated serum aminotransferase levels. Intra-granulocytic morulae may be observed on peripheral blood smear in approximately 70% of cases of anaplasmosis, but intra-leukocytic morulare are rarely seen in human ehrlichiosis. Definitive diagnosis is usually accomplished through polymerase chain reaction (PCR) and serologic methods, with the preferred method varying based on the time of presentation in relation to the onset of clinical symptoms. PCR is the most sensitive and specific method of detection in the first week of illness, whereas serology is the preferred method after this period. The Mayo Clinic PCR assay is capable of detecting and differentiating A phagocytophilum, E chaffeensis, E ewingii, and E muris eauclairensis. It is important to note that concurrent infection with A phagocytophilum, Borrelia burgdorferi, and Babesia microti is not uncommon, as these organisms share the same Ixodes tick vector. Additional testing for these pathogens, including Lyme disease serology, may be indicated.

Useful For: Evaluating patients suspected of acute anaplasmosis or ehrlichiosis This test should not be used for screening asymptomatic individuals.

Interpretation: Positive results indicate presence of specific DNA from Ehrlichia chaffeensis, Ehrlichia ewingii, Ehrlichia muris eauclairensis organism, or Anaplasma phagocytophilum and support the diagnosis of ehrlichiosis or anaplasmosis. Negative results indicate absence of detectable DNA from any of these 4 pathogens in specimens but do not exclude the presence of these organisms or active or recent disease. Since DNA of E ewingii is indistinguishable from that of Ehrlichia canis by this rapid polymerase chain reaction assay, a positive result for E ewingii/canis indicates the presence of DNA from either of these 2 organisms.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Theel ES, Pritt BS. Ehrlichia, Anaplasma, and Related Intracellular Bacteria. In: Carroll KC, Pfaller MA, eds. Manual of Clinical Microbiology 13th ed. ASM Press; 2023 2. Pritt BS, Sloan LM, Johnson DK, et al. Emergence of a new pathogenic Ehrlichia species, Wisconsin and Minnesota, 2009. N Engl J Med. 2011;365(5):422-429 3. Johnson DKH, Schiffman EK, Davis JP, et al. Human infection with Ehrlichia muris-like pathogen, United States, 2007-2013. Emerg Infect Dis. 2015;21(10):1794-1799 4. Dixon EM, Branda JA, Clark SH, et al. Ehrlichiosis and Anaplasmosis subcommittee report to the Tick-Borne Disease working group. Ticks and Tick Borne Dis. 2021;12(6):101823

EHBAP 608396 Ehrlichia/Babesia Antibody Panel, Immunofluorescence, Serum

Clinical Information: Anaplasma phagocytophilum: Anaplasma phagocytophilum is an intracellular rickettsia-like bacterium that preferentially infects granulocytes and forms inclusion bodies referred to as morulae. A phagocytophilum is transmitted by Ixodes species ticks, which also transmit Borrelia burgdorferi and Babesia species. Infection with A phagocytophilum is also referred to as human granulocytic anaplasmosis (HGA) or human granulocytic ehrlichiosis. Symptoms in otherwise healthy individuals are often mild and nonspecific, including fever, myalgia, arthralgia, and nausea. Clues to the diagnosis of anaplasmosis in a patient with an acute febrile illness after tick exposure include laboratory findings of leukopenia or thrombocytopenia and elevated liver enzymes. HGA is most prevalent in the upper Midwest and in other areas of the US that are endemic for Lyme disease. Ehrlichia chaffeensis: Ehrlichia chaffeensis is an intracellular rickettsia-like bacterium that preferentially infects monocytes and is sequestered in parasitophorous vacuoles referred to as morulae. Infections with E chaffeensis are also referred to as human monocytotropic ehrlichiosis (HME). E chaffeensis is transmitted by Amblyomma species ticks, which are found throughout the Southeastern and South-Central US. Many cases of HME are subclinical or mild; however, the infection can be severe and life-threatening, particularly in immunosuppressed individuals. Reported mortality rates range from 2% to 3%. Fever, fatigue, malaise, headache, and other "flu-like" symptoms occur most commonly. Leukopenia, thrombocytopenia, and elevated hepatic transaminases are frequent laboratory findings. Babesia microti: Babesiosis is a zoonotic infection caused by the protozoan parasite Babesia microti. The infection is acquired by contact with Ixodes ticks carrying the parasite. The deer mouse is the animal reservoir, and overall, the epidemiology of this infection is much like that of Lyme disease. Babesiosis is most prevalent in the Northeast, upper Midwest, and Pacific Coast of the US. Infectious forms (sporozoites) are injected during tick bites, and the organism enters the vascular system where it infects red blood cells (RBC). During this intraerythrocytic stage, it becomes disseminated throughout the reticuloendothelial system. Asexual reproduction occurs in RBC, and daughter cells (merozoites) are formed, which are liberated on rupture (hemolysis) of the RBC. Most cases of babesiosis are subclinical or mild, but the infection can be severe and life-threatening, especially in older or asplenic patients. Fever, fatigue, malaise, headache, and other flu-like symptoms occur most commonly. In the most severe cases, hemolysis, acute respiratory distress syndrome, and shock may develop. Patients may have hepatomegaly and splenomegaly. A serologic test can be used as an adjunct in the diagnosis and follow-up of babesiosis, when infection is chronic or persistent, or in seroepidemiologic surveys of the prevalence of the infection in certain populations. Babesiosis is usually diagnosed by observing the organisms in infected RBC on Giemsa-stained thin blood films of smeared peripheral blood. Serology may also be useful if the parasitemia is too low to detect or if the infection has cleared naturally or following treatment.

Useful For: As an adjunct in the diagnosis of infection with Anaplasma phagocytophilum, Ehrlichia chaffeensis, or Babesia microti Seroepidemiological surveys of the prevalence of the infection in certain populations

Interpretation: Anaplasma phagocytophilum: A positive result of an immunofluorescence assay (IFA) test (titer > or =1:64) suggests current or previous infection with human granulocytic ehrlichiosis (anaplasmosis). In general, the higher the titer, the more likely it is that the patient has an active infection. Seroconversion may also be demonstrated by a significant increase in IFA titers. During the acute phase of the infection, serologic tests are often nonreactive, polymerase chain reaction (PCR) testing is available to aid in the diagnosis of these cases (see EPCRB / Ehrlichia/Anaplasma, Molecular Detection, PCR, Blood). Ehrlichia chaffeensis: A positive IFA result (titer > or =1:64) suggests current or previous infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology result although antibody levels decline significantly during the year following infection. Babesia microti: A positive result of an indirect fluorescent antibody test (titer > or =1:64) suggests current or previous infection with Babesia microti. In general, the higher the titer, the more likely it is that the patient has an active infection. Patients with documented infections have usually had titers ranging from 1:320 to 1:2560.

Reference Values:

ANAPLASMA PHAGOCYTOPHILUM
<1:64
Reference values apply to all ages.

EHRLICHIA CHAFFEENSIS
<1:64
Reference values apply to all ages.

BABESIA MICROTI
<1:64
Reference values apply to all ages.

Clinical References: Centers for Disease Control and Prevention (CDC). Tickborne Diseases of the United States: A Reference Manual for Healthcare Providers. 6th ed. US Department of Health and Human Services; 2022. Accessed December 9, 2024. Available at www.cdc.gov/ticks/tickbornediseases/TickborneDiseases-P.pdf

FPCEL
75901

Elastase, Pancreatic, Serum

Clinical Information: Serum Elastase, also called Pancreatopeptidase, is a protease present in pancreatic secretion with the unique ability to rapidly hydrolyze elastin. Elastin is a fibrillar protein found in connective tissue. Elastin forms the elastic fibers found mostly in lungs and skin. Elastase is able to hydrolyze denatured hemoglobin, casein, fibrin, albumin, and denatured but not native collagen. Elastase has been implicated in the pathogenesis of pulmonary emphysema, atherosclerosis and in the vascular injury of acute pancreatic necrosis. Elastase activity is inhibited by protease inhibitors including a1-Anti-Trypsin, a1-anti-Chymotrypsin, anti-Thrombin III, a2-Macroglobulin and b1-anti-Collagenase. Patients with thyroid dysfunction have decreased Elastase activity. Serum pancreatic levels quantify EL 1 for the diagnosis or exclusion of an acute pancreatitis or an inflammatory episode of chronic pancreatitis or gallstone induced pancreatitis.

Reference Values:

Normal pancreatic exocrine function: Less than 3.5 ng/mL

No pediatric reference ranges are available for this test.

ELDR
82392

Elder, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to elder Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

EFPO
35091

Electrolyte and Osmolality Panel, Feces

Clinical Information: The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors: -Normal daily dietary intake of electrolytes -Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure -Electrolyte transport into fecal water due to exogenous substances and rare toxins (eg, cholera toxin) Fecal osmolality is normally in equilibrium with vascular osmolality, and sodium is the major effector of this equilibrium. Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or drugs inducing secretions, such as phenolphthalein or bisacodyl. Osmotic diarrhea is caused by ingestion of poorly absorbed ions or sugars.(1) There are multiple potential causes of osmotic diarrhea. Measurement of phosphate and/or magnesium in liquid stool can assist in identifying intentional or inadvertent use of magnesium and/or phosphate containing laxatives as the cause.(2-4) The other causes of osmotic diarrhea include ingestion of osmotic agents such as sorbitol or polyethylene glycol laxatives, or carbohydrate malabsorption due most commonly to lactose intolerance. Carbohydrate malabsorption can be differentiated from other osmotic causes by a low stool pH (<6).(5,6) Non-osmotic causes of diarrhea include bile acid malabsorption, inflammatory bowel disease, endocrine tumors, and neoplasia.(1) Secretory diarrhea is classified as non-osmotic and is caused by disruption of epithelial electrolyte transport when secretory agents such as anthraquinones, phenolphthalein, bisacodyl, or cholera toxin are present. The fecal fluid usually has elevated electrolytes (primarily sodium and chloride) and a low osmotic gap (<50 mOsm/kg). Infection is a common secretory process; however, it does not typically cause chronic diarrhea (defined as symptoms >4 weeks). Differentiating osmotic from non-osmotic causes of diarrhea is the goal of liquid stool testing.(1,7) The primary way this is accomplished is through the measurement of sodium and chloride and calculation of the osmotic gap, which uses an assumed normal osmolality of 290 mOsm/kg rather than direct measurement of the osmolality. Measurement of osmolality can be useful in the evaluation of chronic diarrhea to help identify whether a specimen has been diluted with hypotonic fluid to simulate diarrhea.(1,8) Chronic diarrhea with elevations in fecal chloride concentrations are caused by congenital chloridorrhea. This is a rare condition associated with a genetic defect in a protein responsible for transport of chloride ions across the mucosal membranes in the lower intestinal tract in exchange for bicarbonate ions. It plays an essential part in intestinal chloride absorption, therefore mutations in this gene have been associated with congenital chloride diarrhea.(9) Acquired chloridorrhea is a rare condition which has been described as causing profuse, chloride-rich diarrhea and a surprising contraction metabolic alkalosis rather than metabolic acidosis often associated with typical diarrhea. Contributors to acquired chloridorrhea include chronic intestinal inflammation and reduction of chloride/bicarbonate transporter expression in genetically susceptible persons post-bowel resection and ostomy placement. Acquired chloridorrhea is rare but may be an under-recognized condition in post-bowel resection patients.(10)

Useful For: Workup of cases of chronic diarrhea Diagnosis of factitious diarrhea (where patient adds water to stool to simulate diarrhea)

Interpretation: Osmotic Gap: Osmotic gap is calculated as 290 mOsm/kg-(2[Na]+2[K]). Typically, stool osmolality is similar that seen in serum since the gastrointestinal (GI) tract does not secrete water.(1) An osmotic gap above 50 mOsm/kg is suggestive of an osmotic component contributing to the symptoms of diarrhea.(1,5,7) Magnesium-induced diarrhea should be considered if the osmotic gap is above 75 mOsm/kg and is likely if the magnesium concentration is above110 mg/dL.(1) An osmotic gap of50 mOsm/kg or less is suggestive of secretory causes of diarrhea.(1,5,7) A highly negative osmotic gap or a fecal sodium concentration greater than plasma or serum suggests the possibility of either sodium phosphate or sodium sulfate ingestion by the patient.(4) Phosphorus: Phosphorus elevation above 102 mg/dL is suggestive of phosphate-induced diarrhea.(4) Osmolality: Osmolality below 220 mOsm/kg indicates dilution with a hypotonic fluid.(1) Sodium and Potassium: High sodium and potassium in the absence of an osmotic gap indicate active electrolyte transport in the GI tract that might be induced by agents such as cholera toxin or hypersecretion of vasoactive intestinal peptide.(1) Sodium: Sodium is typically found at lower concentrations (mean 30 +/- 5 mmol/L) in patients with osmotic diarrhea caused by magnesium-containing laxatives, while typically at higher concentrations

(mean 104 +/- 5 mmol/L) in patients known to be taking secretory laxatives.(8) Chloride: Chloride may be low (<20 mmol/L) in sodium sulfate-induced diarrhea.(5) Markedly elevated fecal chloride concentration in infants (>60 mmol/L) and adults (>100 mmol/L) is associated with congenital and secondary chloridorrhea.(6)

Reference Values:
An interpretive report will be provided

Clinical References: 1. Steffer KJ, Santa Ana CA, Cole JA, Fordtran JS: The practical value of comprehensive stool analysis in detecting the cause of idiopathic chronic diarrhea. Gastroenterol Clin North Am. 2012 Sep;41(3):539-560 2. Ho J, Moyer TP, Phillips SF: Chronic diarrhea: the role of magnesium. Mayo Clin Proc. 1995 Nov;70(11):1091-1092 3. Fine KD, Santa Ana CA, Fordtran JS: Diagnosis of magnesium-induced diarrhea. N Engl J Med. 1991 Apr 11;324(15):1012-1017 4. Fine KD, Ogunji F, Florio R, Porter J, Ana CS: Investigation and diagnosis of diarrhea caused by sodium phosphate. Dig Dis Sci. 1998 Dec;43(12):2708-2714 5. Eherer AJ, Fordtran JS: Fecal osmotic gap and pH in experimental diarrhea of various causes. Gastroenterology. 1992 Aug;103(2):545-551 6. Caspary WF: Diarrhea associated with carbohydrate malabsorption. Clin Gastroenterol. 1986 Jul;15(3):631-655 7. Sweetser S: Evaluating the patient with diarrhea: a case-based approach. Mayo Clin Proc. 2012 Jun;87(6):596-602 8. Phillips S, Donaldson L, Geisler K, Pera A, Kochar R: Stool composition in factitial diarrhea: a 6-year experience with stool analysis. Ann Intern Med. 1995 Jul 15;123(2):97-100 9. Makela S, Kere J, Holmberg C, Hoglund P: SLC26A3 mutations in congenital chloride diarrhea. Hum Mutat. 2002 Dec;20(6):425-438. doi: 10.1002/humu.10139 10. Ali OM, Shealy C, Saklayen M: Acute pre-renal failure: acquired chloride diarrhea after bowel resection. Clin Kidney J. 2012 Aug;5(4):356-358. doi: 10.1093/ckj/sfs082

ELPSR
113632

Electrolyte Panel, Serum

Clinical Information: The electrolyte panel is ordered to identify electrolyte, fluid, or pH imbalance. Electrolyte concentrations are evaluated to assist in investigating conditions that cause electrolyte imbalances such as dehydration, kidney disease, lung diseases, or heart conditions. Repeat testing of the electrolyte or its components may be used to monitor the patient's response to treatment of any condition that may be causing the electrolyte, fluid or pH imbalance. Electrolyte and acid-base imbalances can often be indicative of many acute and chronic illnesses. For this reason, the electrolyte panel is often used in the hospital and emergency settings to evaluate patients.

Useful For: Identifying a suspected imbalance in electrolytes or acid/base imbalance

Interpretation: With an imbalance of a single electrolyte, such as sodium or potassium, repeat testing may be ordered of that particular electrolyte, can be used to monitor the imbalance until remedied. With an acid-base imbalance, blood gases may be ordered, which will measure the oxygen, carbon dioxide, and pH levels in the arterial blood. These tests assist in evaluating the acuteness of the imbalance and monitoring the response to treatment.

Reference Values:
SODIUM
<1 year: not established
> or =1 year: 135-145 mmol/L

POTASSIUM
<1 year: not established
> or =1 year: 3.6-5.2 mmol/L

CHLORIDE
<1 year: not established
1-17 years: 102-112 mmol/L
> or =18 years: 98-107 mmol/L

BICARBONATE
Males
<1 year: not established
1-2 years: 17-25 mmol/L
3 years: 18-26 mmol/L
4-5 years: 19-27 mmol/L
6-7 years: 20-28 mmol/L
8-17 years: 21-29 mmol/L
> or =18 years: 22-29 mmol/L
Females
<1 year: not established
1-3 years: 18-25 mmol/L
4-5 years: 19-26 mmol/L
6-7 years: 20-27 mmol/L
8-9 years: 21-28 mmol/L
> or =10 years: 22-29 mmol/L

ANION GAP
<7 years: not established
> or =7 years: 7-15

Clinical References: 1. Oh MS: Evaluation of renal function, water, electrolytes, and acid-base balance. In Henry's Clinical Diagnosis and Management by Laboratory Methods. 22nd edition. Edited by RA McPherson, MR Pincus. Philadelphia, PA: Elsevier Saunders; 2011:chap 14 2. AACC: Lab Tests Online: Access 03/22/2017. Available at https://labtestsonline.org/understanding/analytes/electrolyes

EM
70316

Electron Microscopy, Varies

Clinical Information: Transmission electron microscopy is an important diagnostic tool used in the comprehensive assessment of human disease and is most often used in conjunction with other methods such as light microscopy and immunohistopathological techniques. This fundamental technology can provide both confirmatory and diagnostic value to the pathologist and clinician.

Useful For: Providing information to aid in the diagnosis of medical disorders such as storage diseases, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), and primary ciliary dyskinesia

Interpretation: The images and case histories are correlated and interpreted by a pathologist who is an expert in the field of the suspected diagnoses. Results will be provided by telephone. If requested, representative images showing diagnostic features will be sent.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Jennette JC, D'Agati VD, eds. Heptinstall's Pathology of the Kidney. 7th ed. Wolters Kluwer; 2023 2. Shoemark A, Boon M, Brochhausen C, et al. International consensus guideline for reporting transmission electron microscopy results in the diagnosis of primary ciliary

dyskinesia (BEAT PCD TEM Criteria). Eur Respir J. 2020;55(4):1900725. doi:10.1183/13993003.00725-2019 3. Schroder JA. Diagnostic transmission electron microscopy. Imaging and Microscopy. 2012. Accessed October 14, 2022. Available at www.imaging-git.com/science/electron-and-ion-microscopy/diagnostic-transmission-electron-microscopy

PEL
800301

Electrophoresis, Protein, Serum

Clinical Information: Serum proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin, which represents almost two-thirds of the total serum protein -Alpha-1, composed primarily of alpha-1-antitrypsin (A1AT), an alpha-1-acid glycoprotein -Alpha-2, composed primarily of alpha-2-macroglobulin and haptoglobin -Beta, composed primarily of transferrin and C3 -Gamma, composed primarily of immunoglobulins The concentration of these fractions and the electrophoretic pattern may be characteristic of diseases such as monoclonal gammopathies, A1AT deficiency disease, nephrotic syndrome, and inflammatory processes associated with infection, liver disease, and autoimmune diseases.

Useful For: Monitoring patients with monoclonal gammopathies Diagnosis of monoclonal gammopathies

Interpretation: Monoclonal Gammopathies: -A characteristic monoclonal band (M spike) is often found on protein electrophoresis (PEL) in the gamma-globulin region and more rarely in the beta or alpha-2 regions. The finding of a M-spike, restricted migration, or hypogammaglobulinemic PEL pattern is suggestive of a possible monoclonal protein and should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine, which includes immunofixation (IF), to identify the immunoglobulin heavy chain and/or light chain. -A monoclonal IgG or IgA greater than 3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgG or IgA less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. -A monoclonal IgM greater than 3 g/dL is consistent with macroglobulinemia. -The initial identification of a serum M-spike greater than 1.5 g/dL on PEL should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, should be followed by SVISC / Viscosity, Serum. -After the initial identification of an M-spike, quantitation of the M-spike on follow-up PEL can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM), quantitative immunoglobulin levels may be a more useful tool to follow the monoclonal protein level than PEL. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. -Patients suspected of having a monoclonal gammopathy may have normal serum PEL patterns. Approximately 11% of patients with MM have a completely normal serum PEL, with the monoclonal protein only identified by IF. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on PEL but identified by IF. Accordingly, a normal serum PEL does not rule out the disease and should not be used to screen for the disorder. The MPSS / Monoclonal Protein Study, Serum, which includes immunofixation, and FLCS / Immunoglobulin Free Light Chains, Serum should be done to screen if the clinical suspicion is high. Other Abnormal PEL Findings: -A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. -A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. -A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephrotic syndrome, and when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent. -An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).

Reference Values:
PROTEIN, TOTAL
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are younger than 12 months of age.

PROTEIN ELECTROPHORESIS
Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL
An interpretive comment is provided with the report.
Reference values have not been established for patients that are younger than 16 years of age.

Clinical References: 1. Sykes E, Posey Y: Immunochemical characterization of immunoglobulins in serum, urine, and cerebrospinal fluid. In: Detrick B, Schmitz JL, Hamilton RG, eds. Manual of Molecular and Clinical Laboratory Immunology. 8th ed. ASM Press; 2016:89-100 2. Katzmann JA, Keren DF: Strategy for detecting and following monoclonal gammopathies. In: Detrick B, Schmitz JL, Hamilton RG, eds. Manual of Molecular and Clinical Laboratory Immunology. 8th ed. ASM Press; 2016:112-124 3. Kyle RA, Katzmann JA, Lust JA, Dispenzieri A: Clinical indications and applications of electrophoresis and immunofixation. In: Rose NR, Hamilton RG, Detrick B, eds. Manual of Clinical Laboratory Immunology. 6th ed. ASM Press; 2002:66-70

ELM
82672

Elm, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to elm Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

EMR
113366

EM, Renal Biopsy (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

EMICZ
610074

Emicizumab, Modified One Stage Assay Factor VIII, Plasma

Clinical Information: Emicizumab (Hemlibra) is a bispecific antibody directed toward factor IXa and factor X, bridging in close enough proximity to mimic and replace factor VIII. Emicizumab has been approved by the US Food and Drug Administration for prevention of bleeding in hemophilia A patients, both with and without inhibitors to factor VIII. In clinical trials, clinical outcomes were achieved without the measurement of plasma emicizumab levels to inform and make management decisions. However, in selected clinical situations, measurement of drug level would be useful. (eg, for patients experiencing break through bleeding episodes, if levels are not detectable or below the published [observed] ranges, this may imply noncompliance or development of an antidrug antibody.)

Useful For: Monitoring compliance or potential development of an antidrug antibody This assay is not indicated for monitoring factor VIII infusions or for making a diagnosis of hemophilia.

Interpretation: Therapeutic ranges for plasma emicizumab concentrations have not been established. Trough plasma concentrations observed during clinical trials ranged between 35 and 55 micrograms/mL.

Reference Values:
<1 mcg/mL

Clinical References: 1. Knight T, Callaghan MU. The role of emicizumab, a bispecific factor IXa- and factor X-directed antibody, for the prevention of bleeding episodes in patients with hemophilia A. Ther Adv Hematol. 2018;9(10):319-334. doi:10.1177/2040620718799997 2. Jenkins PV, Bowyer A, Burgess C, et al. Laboratory coagulation tests and emicizumab treatment A United Kingdom Haemophilia

Centre Doctors' Organisation guideline. Haemophilia. 2020;26(1):151-155. doi:10.1111/hae.13903 3. Jonsson F, Schmitt C, Petry C, Mercier F, Frey N, Retout S. Exposure-response modeling of emicizumab for the prophylaxis of bleeding in hemophilia A patients with and without inhibitors against factor VIII. Poster PB0325 presented at: The XXVII Congress of the International Society on Thrombosis and Haemostasis. July 6-10, 2019; Melbourne, Australia 4. Pipie SW, Shima M, Lehle M, et al. Efficacy, safety and pharmacokinetics emicizumab prophylaxis given every 4 weeks in people with haemophilia (HAVEN 4): a multicenter, open-label, non-randomized phase 3 study. Lancet Haematol. 2019;6(6):e295-e305. doi:10.1016/S2352-3026(19)30054-7

FENC 90087 Encainide (Enkaid), ODE and MODE

Reference Values:

Encainide:
Reference Range: 15 - 100 ng/mL

O-Demethylencainide (ODE):
Reference Range: 100 - 300 ng/mL

3-Methoxy-ODE (MODE):
Reference Range: 60 - 300 ng/mL

10% of patients do not form therapeutic concentrations of the active metabolites, ODE and MODE. In these patients the recommended range for the encainide concentration is 300 - 1200 ng/mL.

ENS2 92116 Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum

Clinical Information: Autoimmune encephalopathies extend beyond the classically recognized clinical and radiological spectrum of "limbic encephalitis." They encompass a diversity of neurological presentations with subacute or insidious onset, including confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, eye movement problems, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation. A diagnosis of autoimmune encephalopathy should be suspected based on the clinical course, coexisting autoimmune disorder (eg, thyroiditis, diabetes), serological evidence of autoimmunity, spinal fluid evidence of intrathecal inflammation, neuroimaging or electroencephalographic abnormalities, and favorable response to trial of immunotherapy. Detection of one or more neural autoantibodies aids the diagnosis of autoimmune encephalopathy and may guide a search for cancer. Pertinent autoantibody specificities include: -Neurotransmitter receptors and ion channels, such as neuronal voltage-gated potassium channels (and interacting synaptic and axonal proteins, leucine-rich glioma inactivated 1 [LGI1] protein and contactin associated protein 2 [CASPR2]), ionotropic glutamate receptors (N-methyl-D-aspartate receptor [NMDA] and 2-amino-3-[5-methyl-3-oxo-1,2- oxazol-4-yl] propanoic acid [AMPA]), metabotropic gamma-aminobutyric acid (GABA)-B receptors -Enzymes, signaling molecules, and RNA-regulatory proteins in the cytoplasm and nucleus of neurons (glutamic acid decarboxylase 65 [GAD65], collapsin response-mediator protein-5 neuronal [CRMP-5], antineuronal nuclear antibody-type 1 [ANNA-1], and ANNA-2) Importantly, autoimmune encephalopathies are reversible. Misdiagnosis as a progressive (currently irreversible) neurodegenerative condition is not uncommon and has devastating consequences for the patient. Clinicians must consider the possibility of an autoimmune etiology in the differential diagnoses of encephalopathy. For example, a potentially reversible disorder justifies a trial of immunotherapy for the detection of neural autoantibodies in patients presenting with symptoms of personality change, executive dysfunction, and psychiatric manifestations. A triad of clues helps to

identify patients with an autoimmune encephalopathy: 1. Clinical presentation (subacute symptoms, onset rapidly progressive course, and fluctuating symptoms) and radiological findings consistent with inflammation 2. Detection of neural autoantibodies in serum or cerebrospinal fluid (CSF) 3. Favorable response to a trial of immunotherapy Detection of neural autoantibodies in serum or CSF informs healthcare professionals of a likely autoimmune etiology, may heighten suspicion for a paraneoplastic basis, and guide the search for cancer. Neurological accompaniments of neural autoantibodies are generally not syndromic but diverse and multifocal. For example, the LGI1 antibody was initially considered to be specific for autoimmune limbic encephalitis, but, over time, other presentations have been reported, including a rapidly progressive course of cognitive decline mimicking neurodegenerative dementia. Comprehensive antibody testing is more informative than selective testing for 1 or 2 neural antibodies. Some antibodies strongly predict an underlying cancer. For example, small-cell lung carcinoma (ANNA-1, CRMP-5-IgG), ovarian teratoma (NMDA-R), and thymoma (CRMP-5 IgG). An individual patient's autoantibody profile may be informative for a specific cancer type. For example, in a patient presenting with encephalitis who has CRMP 5 IgG, and subsequent testing reveals muscle acetylcholine receptor (AChR) binding antibody, the findings should raise a high suspicion for thymoma. Testing of CSF for autoantibodies is particularly helpful when serum testing is negative, although in some circumstances testing both serum and CSF simultaneously is pertinent. Testing of CSF is recommended for some antibodies (eg, NMDA-R antibody and glial fibrillary acidic protein [GFAP]-IgG) because CSF testing is both more sensitive and specific. In contrast, serum testing for LGI1 antibody is more sensitive than CSF testing.

Useful For: Evaluating, using serum specimens, new onset encephalopathy (noninfectious or metabolic) comprising confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation The following accompaniments should increase of suspicion for autoimmune encephalopathy: -Headache -Autoimmune stigmata (personal or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) -History of cancer -Smoking history (20 or more pack-years) or other cancer risk factors -Inflammatory cerebral spinal fluid (or isolated protein elevation) -Neuroimaging signs suggesting inflammation Evaluating limbic encephalitis (noninfectious) Directing a focused search for cancer Investigating encephalopathy appearing during or after cancer therapy and not explainable by metastasis or drug effect

Interpretation: Neuronal, glial, and muscle autoantibodies are valuable serological markers of autoimmune encephalopathy and of a patient's immune response to cancer. These autoantibodies are usually accompanied by subacute neurological symptoms and signs are not found in healthy subjects. It is not uncommon for more than 1 of the following autoantibody specificities to be detected in patients with an autoimmune encephalopathy: -Plasma membrane autoantibodies: N-methyl-D-aspartate (NMDA) receptor; 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid (AMPA) receptor; gamma-amino butyric acid (GABA-B) receptor; neuronal acetylcholine receptor. These are all potential effectors of neurological dysfunction. -Neuronal nuclear autoantibodies: Type 1 (ANNA-1), type 2 (ANNA-2), or type 3 (ANNA-3) -Neuronal or muscle cytoplasmic antibodies: Amphiphysin, Purkinje cell antibodies (PCA-1 and PCA-2), collapsin response-mediator protein-5 (CRMP-5), glutamic acid decarboxylase (GAD65), or striational

Reference Values:

Test ID	Reporting name	Methodology*	Reference value
AEESI	Encephalopathy, Interpretation, S	Medical interpretation	Interpretive report
AMPCS	AMPA-R Ab CBA, S	CBA	Negative
AMPHS	Amphiphysin Ab, S	IFA	Negative

AGN1S	Anti-Glial Nuclear Ab, Type 1	IFA	Negative
ANN1S	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2S	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3S	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
CS2CS	CASPR2-IgG CBA, S	CBA	Negative
CRMS	CRMP-5-IgG, S	IFA	Negative
DPPCS	DPPX Ab CBA, S	CBA	Negative
GABCS	GABA-B-R Ab CBA, S	CBA	Negative
GD65S	GAD65 Ab Assay, S	RIA	< or =0.02 nmol/L Reference values apply to all ages.
GFAIS	GFAP IFA, S	IFA	Negative
GL1IS	mGluR1 Ab IFA, S	IFA	Negative
IG5CS	IgLON5 CBA, S	CBA	Negative
LG1CS	LGI1-IgG CBA, S	CBA	Negative
NCDIS	Neurochondrin IFA, S	IFA	Negative
NIFIS	NIF IFA, S	IFA	Negative
NMDCS	NMDA-R Ab CBA, S	CBA	Negative
PCABP	Purkinje Cell Cytoplasmic Ab Type 1	IFA	Negative
PCAB2	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
PCATR	Purkinje Cell Cytoplasmic Ab Type Tr	IFA	Negative
PDEIS	PDE10A Ab IFA, S	IFA	Negative
SP7IS	Septin-7 IFA, S	IFA	Negative
T46IS	TRIM46 IFA, S	IFA	Negative
Reflex Information: Test ID	Reporting name	Methodology*	Reference value
AGNBS	AGNA-1 Immunoblot, S	IB	Negative
AGNTS	AGNA-1 Titer, S	IFA	
AINCS	Alpha Internexin CBA, S	CBA	Negative
AMPIS	AMPA-R Ab IF Titer Assay, S	IFA	
APHTS	Amphiphysin Ab Titer, S	IFA	
AMIBS	Amphiphysin Immunoblot, S	IB	Negative

AN1BS	ANNA-1 Immunoblot, S	IB	Negative
AN1TS	ANNA-1 Titer, S	IFA	
AN2BS	ANNA-2 Immunoblot, S	IB	Negative
AN2TS	ANNA-2 Titer, S	IFA	
AN3TS	ANNA-3 Titer, S	IFA	
CRMTS	CRMP-5-IgG Titer, S	IFA	
CRMWS	CRMP-5-IgG Western Blot, S	WB	Negative
DPPTS	DPPX Ab IFA Titer, S	IFA	
GABIS	GABA-B-R Ab IF Titer Assay, S	IFA	
GFACS	GFAP CBA, S	CBA	Negative
GFATS	GFAP IFA Titer, S	IFA	
IG5TS	IgLON5 IFA Titer, S	IFA	
GL1CS	mGluR1 Ab CBA, S	CBA	Negative
GL1TS	mGluR1 Ab IFA Titer, S	IFA	
NCDCS	Neurochondrin CBA, S	CBA	Negative
NCDTS	Neurochondrin IFA Titer, S	IFA	
NFHCS	NIF Heavy Chain CBA, S	CBA	Negative
NIFTS	NIF IFA Titer, S	IFA	
NFLCS	NIF Light Chain CBA, S	CBA	Negative
NMDIS	NMDA-R Ab IF Titer Assay, S	IFA	
PC1BS	PCA-1 Immunoblot, S	IB	Negative
PC1TS	PCA-1 Titer, S	IFA	
PC2TS	PCA-2 Titer, S	IFA	
PCTBS	PCA-Tr Immunoblot, S	IB	Negative
PCTTS	PCA-Tr Titer, S	IFA	
PDETS	PDE10A Ab IFA Titer, S	IFA	
SP7CS	Septin-7 CBA, S	CBA	Negative
SP7TS	Septin-7 IFA Titer, S	IFA	
T46CS	TRIM46 CBA, S	CBA	Negative
T46TS	TRIM46 IFA Titer, S	IFA	

Clinical References: 1. Orozco E, Valencia-Sanchez C, Britton J, et al. Autoimmune encephalitis criteria in clinical practice. Neurol Clin Pract. 2023;13(3):e200151. doi:10.1212/CPJ.0000000000200151 2. Flanagan EP, Geschwind MD,

Lopez-Chiriboga AS, et al. Autoimmune encephalitis misdiagnosis in adults. JAMA Neurol. 2023;80(1):30-39. doi:10.1001/jamaneurol.2022.4251 3. Budhram A, Dubey D, Sechi E, et al. Neural Antibody Testing in Patients with Suspected Autoimmune Encephalitis. Clin Chem. 2020;66(12):1496-1509. doi:10.1093/clinchem/hvaa254 4. Abboud H, Probasco JC, Irani S, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. J Neurol Neurosurg Psychiatry. 2021;92(7):757-768. doi:10.1136/jnnp-2020-325300 5. Dubey D, Pittock SJ, Kelly CR, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. Ann Neurol. 2018;83(1):166-177. doi:10.1002/ana.25131

ENC2
92117

Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

Clinical Information: Autoimmune encephalopathies extend beyond the classically recognized clinical and radiological spectrum of "limbic encephalitis." They encompass a diversity of neurological presentations with subacute or insidious onset, including confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, eye movement problems, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation. A diagnosis of autoimmune encephalopathy should be suspected based on the clinical course, coexisting autoimmune disorder (eg, thyroiditis, diabetes), serological evidence of autoimmunity, spinal fluid evidence of intrathecal inflammation, neuroimaging or electroencephalographic abnormalities, and favorable response to trial of immunotherapy. Detection of one or more neural autoantibodies aids the diagnosis of autoimmune encephalopathy and may guide a search for cancer. Pertinent autoantibody specificities include: -Neurotransmitter receptors and ion channels, such as neuronal voltage-gated potassium channels (and interacting synaptic and axonal proteins, leucine-rich glioma inactivated 1 [LGI1] protein and contactin associated protein 2 [CASPR2]), ionotropic glutamate receptors (N-methyl-D-aspartate receptor [NMDA] and 2-amino-3-[5-methyl-3-oxo-1,2- oxazol-4-yl] propanoic acid [AMPA]), metabotropic gamma-aminobutyric acid (GABA)-B receptors -Enzymes, signaling molecules, and RNA-regulatory proteins in the cytoplasm and nucleus of neurons (glutamic acid decarboxylase 65 [GAD65], collapsin response-mediator protein-5 neuronal [CRMP-5], antineuronal nuclear antibody-type 1 [ANNA-1], and ANNA-2) Importantly, autoimmune encephalopathies are reversible. Misdiagnosis as a progressive (currently irreversible) neurodegenerative condition is not uncommon and has devastating consequences for the patient. Clinicians must consider the possibility of an autoimmune etiology in the differential diagnoses of encephalopathy. For example, a potentially reversible disorder justifies a trial of immunotherapy for the detection of neural autoantibodies in patients presenting with symptoms of personality change, executive dysfunction, and psychiatric manifestations. A triad of clues helps to identify patients with an autoimmune encephalopathy: 1. Clinical presentation (subacute symptoms, onset rapidly progressive course, and fluctuating symptoms) and radiological findings consistent with inflammation 2. Detection of neural autoantibodies in serum or cerebrospinal fluid (CSF) 3. Favorable response to a trial of immunotherapy Detection of neural autoantibodies in serum or CSF informs the physician of a likely autoimmune etiology, may heighten suspicion for a paraneoplastic basis, and guide the search for cancer. Neurological accompaniments of neural autoantibodies are generally not syndromic but diverse and multifocal. For example, LGI1 antibody was initially considered to be specific for autoimmune limbic encephalitis, but, over time, other presentations have been reported, including rapidly progressive course of cognitive decline mimicking neurodegenerative dementia. Comprehensive antibody testing is more informative than selective testing for 1 or 2 neural antibodies. Some antibodies strongly predict an underlying cancer. For example, small-cell lung carcinoma (ANNA-1, CRMP-5-IgG), ovarian teratoma (NMDA-R), and thymoma (CRMP-5 IgG). An individual patient's profile autoantibody may be informative for a specific cancer type. For example, in a patient presenting with encephalitis who has CRMP 5 IgG, and subsequent testing reveals muscle acetylcholine receptor (AChR) binding antibody, the findings should raise a high suspicion for thymoma. Testing of CSF for autoantibodies is particularly helpful when serum testing is negative, though in some circumstances testing both serum and CSF simultaneously is pertinent. Testing of CSF is recommended

for some antibodies (eg, NMDA-R antibody and glial fibrillary acidic protein [GFAP]-IgG) because CSF testing is more sensitive and specific. In contrast, serum testing for LGI1 antibody is more sensitive than CSF testing.

Useful For: Evaluating new onset encephalopathy (noninfectious or metabolic) comprising confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation using spinal fluid specimens The following accompaniments should increase of suspicion for autoimmune encephalopathy: -Headache -Autoimmune stigmata (personal or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) -History of cancer -Smoking history (20 or more pack-years) or other cancer risk factors -Inflammatory cerebrospinal fluid (or isolated protein elevation) -Neuroimaging signs suggesting inflammation Evaluating limbic encephalitis (noninfectious) Directing a focused search for cancer Investigating encephalopathy appearing during or after cancer therapy and not explainable by metastasis or drug effect

Interpretation: Neuronal, glial, and muscle autoantibodies are valuable serological markers of autoimmune encephalopathy and of a patient's immune response to cancer. These autoantibodies are usually accompanied by subacute neurological symptoms and signs are not found in healthy subjects. It is not uncommon for more than 1 of the following autoantibody specificities to be detected in patients with an autoimmune encephalopathy: -Plasma membrane autoantibodies: These are all potential effectors of neurological dysfunction: N-methyl-D-aspartate (NMDA) receptor; 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA) receptor; gamma-amino butyric acid (GABA-B) receptor; neuronal acetylcholine receptor. -Neuronal nuclear autoantibodies: Type 1 (ANNA-1), type 2 (ANNA-2), or type 3 (ANNA-3) -Neuronal or muscle cytoplasmic antibodies: Amphiphysin, Purkinje cell antibodies (PCA-1 and PCA-2), collapsin response-mediator protein-5 (CRMP-5), or glutamic acid decarboxylase (GAD65).

Reference Values:

Test ID	Reporting name	Methodology*	Reference value
AEECI	Encephalopathy, Interpretation, CSF	Medical interpretation	Interpretive report
AMPCC	AMPA-R Ab CBA, CSF	CBA	Negative
AMPHC	Amphiphysin Ab, CSF	IFA	Negative
AGN1C	Anti-Glial Nuclear Ab, Type 1	IFA	Negative
ANN1C	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2C	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3C	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
CS2CC	CASPR2-IgG CBA, CSF	CBA	Negative
CRMC	CRMP-5-IgG, CSF	IFA	Negative
DPPCC	DPPX Ab CBA, CSF	CBA	Negative
GABCC	GABA-B-R Ab CBA, CSF	CBA	Negative
GD65C	GAD65 Ab Assay, CSF	RIA	< or =0.02 nmol/L Reference values apply to

all ages.

GFAIC	GFAP IFA, CSF	IFA	Negative
GL1IC	mGluR1 Ab IFA, CSF	IFA	Negative
IG5CC	IgLON5 CBA, CSF	CBA	Negative
LG1CC	LGI1-IgG CBA, CSF	CBA	Negative
NCDIC	Neurochondrin IFA, CSF	IFA	Negative
NIFIC	NIF IFA, CSF	IFA	Negative
NMDCC	NMDA-R Ab CBA, CSF	CBA	Negative
PCTRC	Purkinje Cell Cytoplasmc Ab Type Tr	IFA	Negative
PCA1C	Purkinje Cell Cytoplasmic Ab Type 1	IFA	Negative
PCA2C	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
PDEIC	PDE10A Ab IFA, CSF	IFA	Negative
SP7IC	Septin-7 IFA, CSF	IFA	Negative
T46IC	TRIM46 IFA, CSF	IFA	Negative
Reflex Information: Test ID	Reporting name	Methodology*	Reference value
AGNBC	AGNA-1 Immunoblot, CSF	IB	Negative
AGNTC	AGNA-1 Titer, CSF	IFA	
AINCC	Alpha Internexin CBA, CSF	CBA	Negative
AMPIC	AMPA-R Ab IF Titer Assay, CSF	IFA	
AMIBC	Amphiphysin Immunoblot, CSF	IB	Negative
AN1BC	ANNA-1 Immunoblot, CSF	IB	Negative
AN1TC	ANNA-1 Titer, CSF	IFA	
AN2BC	ANNA-2 Immunoblot, CSF	IB	Negative
AN2TC	ANNA-2 Titer, CSF	IFA	
AN3TC	ANNA-3 Titer, CSF	IFA	
APHTC	Amphiphysin Ab Titer, CSF	IFA	
CRMTC	CRMP-5-IgG Titer, CSF	IFA	
CRMWC	CRMP-5-IgG Western Blot, CSF	WB	Negative
DPPTC	DPPX Ab IFA Titer, CSF	IFA	

GABIC	GABA-B-R Ab IF Titer Assay, CSF	IFA	
GFACC	GFAP CBA, CSF	CBA	Negative
GFATC	GFAP IFA Titer, CSF	IFA	
IG5TC	IgLON5 IFA Titer, CSF	IFA	
GL1CC	mGluR1 Ab CBA, CSF	CBA	Negative
GL1TC	mGluR1 Ab IFA Titer, CSF	IFA	
NCDCC	Neurochondrin CBA, CSF	CBA	Negative
NCDTC	Neurochondrin IFA Titer, CSF	IFA	
NFLCC	NIF Light Chain CBA, CSF	CBA	Negative
NFHCC	NIF Heavy Chain CBA, CSF	CBA	Negative
NIFTC	NIF IFA Titer, CSF	IFA	
NMDIC	NMDA-R Ab IF Titer Assay, CSF	IFA	
PC1BC	PCA-1 Immunoblot, CSF	IB	Negative
PC1TC	PCA-1 Titer, CSF	IFA	
PC2TC	PCA-2 Titer, CSF	IFA	
PCTBC	PCA-Tr Immunoblot, CSF	IB	Negative
PCTTC	PCA-Tr Titer, CSF	IFA	
PDETC	PDE10A Ab IFA Titer, CSF	IFA	
SP7CC	Septin-7 CBA, CSF	CBA	Negative
SP7IC	Septin-7 IFA Titer, CSF	IFA	
T46CC	TRIM46 CBA, CSF	CBA	Negative
T46TC	TRIM46 IFA Titer, CSF	IFA	

Clinical References: 1. Orozco E, Valencia-Sanchez C, Britton J, et al. Autoimmune encephalitis criteria in clinical practice. Neurol Clin Pract. 2023;13(3):e200151. doi:10.1212/CPJ.0000000000200151 2. Flanagan EP, Geschwind MD, Lopez-Chiriboga AS, et al. Autoimmune encephalitis misdiagnosis in adults. JAMA Neurol. 2023;80(1):30-39. doi:10.1001/jamaneurol.2022.4251 3. Budhram A, Dubey D, Sechi E, et al. Neural Antibody Testing in Patients with Suspected Autoimmune Encephalitis. Clin Chem. 2020;66(12):1496-1509. doi:10.1093/clinchem/hvaa254 4. Abboud H, Probasco JC, Irani S, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. J Neurol Neurosurg Psychiatry. 2021;92(7):757-768. doi:10.1136/jnnp-2020-325300 5. Dubey D, Pittock SJ, Kelly CR, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. Ann Neurol. 2018;83(1):166-177. doi:10.1002/ana.25131

MPS1R
622360

Endogenous Mucopolysaccharidosis Type I (IDUA [Alpha-L-Iduronidase]) Biomarker Reflex, Blood Spot

Clinical Information: Mucopolysaccharidosis type I (MPS I) is an autosomal recessive disorder caused by reduced or absent activity of the enzyme alpha-L-iduronidase due to variants in the IDUA gene. Deficiency of alpha-L-iduronidase can result in a wide range of phenotypes categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because these syndromes cannot be distinguished biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, intellectual disabilities or learning difficulties, and cardiac valvular disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Individuals with MPS I typically demonstrate elevated levels of the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate (see MPSQU / Mucopolysaccharides Quantitative, Random, Urine; MPSBS / Mucopolysaccharides, Blood Spot), as well as elevated levels of GAG fragments known as endogenous disaccharide biomarkers that are specific to the deficiency of alpha-L-iduronidase. Reduced or absent activity of alpha L-iduronidase (see IDUAW / Alpha-L-Iduronidase, Leukocytes) can confirm a diagnosis of MPS I but may also be deficient in unaffected individuals who are carriers or with pseudodeficiency. Molecular sequence analysis of the IDUA gene allows for detection of disease-causing variants in affected individuals and subsequent carrier detection in relatives (see MPS1Z / Hurler Syndrome, Full Gene Analysis, Varies).

Useful For: Second-tier testing of newborns with an abnormal primary screening result for mucopolysaccharidosis type I (MPS I, decreased alpha-L-iduronidase activity) where quantitation of the glycosaminoglycans dermatan and heparan sulfate is desired in the presence of elevated endogenous MPS I biomarkers Follow-up testing for evaluation of an abnormal newborn screening result for MPS I This test is not useful a monitoring test for individuals with MPS I. This test is not appropriate for carrier detection.

Interpretation: The measurements of mucopolysaccharidosis type I (MPS I) specific endogenous biomarker is compared to the reference value. This report is in text form only, indicating if the MPS I specific endogenous biomarker value is or is not suggestive of a biochemical diagnosis of MPS I. In any specimen where the MPS I specific endogenous biomarker value is elevated, quantitative analysis of heparan, dermatan, and keratan sulfate will be performed. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay and quantitative glycosaminoglycan measurement) or molecular genetic analyses are required, many of which are offered within Mayo Clinic Laboratories. Recommendations for additional biochemical testing and confirmatory studies (biomarker, enzyme assay, molecular analysis) are provided in the interpretative report.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Newborn Screening ACT Sheet [alpha-L-iduronidase deficiency with or without glycosaminoglycan (GAG) accumulation] Mucopolysaccharidosis Type I (MPS I). American College of Medical Genetics and Genomics; 2022. Updated November 2023. Accessed October 23, 2024. Available at www.acmg.net/PDFLibrary/MPS-II.pdf 2. Saville JT, Herbst ZM, Gelb MH, Fuller M. Endogenous, non-reducing end glycosaminoglycan biomarkers for the mucopolysaccharidoses: Accurate diagnosis and elimination of false positive newborn screening results. Mol Gen Metab. 2023;140(3):107685 3. Herbst ZM, Hong X, Urdaneta L, et al. Endogenous, non-reducing end glycosaminoglycan biomarkers are superior to internal disaccharide

glycosaminoglycan biomarkers for newborn screening of mucopolysaccharidoses and GM1 gangliosidosis. Mol Genet Metab. 2023;140(1-2):107632 4. Peck DS, Lacey JM, White AL, et al. Incorporation of second-tier biomarker testing improves the specificity of newborn screening for mucopolysaccharidosis type I. Int J Neonatal Screen. 2020;6(1):10. doi:10.3390/ijns6010010

MPS1B
622354

Endogenous Mucopolysaccharidosis Type I (IDUA [Alpha-L-Iduronidase]) Biomarker, Blood Spot

Clinical Information: Mucopolysaccharidosis type I (MPS I) is an autosomal recessive disorder caused by reduced or absent activity of the enzyme alpha-L-iduronidase due to variants in the IDUA gene. Deficiency of alpha-L-iduronidase can result in a wide range of phenotypes categorized into 3 syndromes: Hurler syndrome, Scheie syndrome, and Hurler-Scheie syndrome. Because these syndromes cannot be distinguished biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, intellectual disabilities or learning difficulties, and cardiac valvular disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Individuals with MPS I typically demonstrate elevated levels of the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate (see MPSQU / Mucopolysaccharides Quantitative, Random, Urine; MPSBS / Mucopolysaccharides, Blood Spot), as well as elevated levels of GAG fragments known as endogenous disaccharide biomarkers that are specific to the deficiency of alpha-L-iduronidase. Reduced or absent activity of alpha L-iduronidase (see IDUAW / Alpha-L-Iduronidase, Leukocytes) can confirm a diagnosis of MPS I but may also be deficient in unaffected individuals who are carriers or with pseudodeficiency. Molecular sequence analysis of the IDUA gene allows for detection of disease-causing variants in affected individuals and subsequent carrier detection in relatives (see MPS1Z / Hurler Syndrome, Full Gene Analysis, Varies).

Useful For: Second-tier testing of newborns with an abnormal primary screening result for mucopolysaccharidosis type I (MPS I) (decreased alpha-L-iduronidase activity) Follow-up testing for evaluation of an abnormal newborn screening result for MPS I This test is not useful a monitoring test for individuals with MPS I. This test is not appropriate for carrier detection.

Interpretation: The measurements of mucopolysaccharidosis type I (MPS I) specific endogenous biomarkers are compared to the reference value. The report is in text form only, indicating if the MPS I specific endogenous biomarker value is or is not suggestive of a biochemical diagnosis of MPS I. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay and quantitative glycosaminoglycan measurement) or molecular genetic analyses are required, many of which are offered within Mayo Clinic Laboratories. Recommendations for additional biochemical testing and confirmatory studies (biomarker, enzyme assay, molecular analysis) are provided in the interpretative report.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Newborn Screening ACT Sheet [alpha-L-iduronidase deficiency with or without glycosaminoglycan (GAG) accumulation] Mucopolysaccharidosis Type I (MPS I). American College of Medical Genetics and Genomics; 2022. Updated November 2023. Accessed October 23, 2024. Available at www.acmg.net/PDFLibrary/MPS-II.pdf 2. Saville JT, Herbst ZM, Gelb MH, Fuller M. Endogenous, non-reducing end glycosaminoglycan biomarkers for the mucopolysaccharidoses: Accurate diagnosis and elimination of false positive newborn screening results. Mol Gen Metab. 2023;140(3):107685 3. Herbst ZM, Hong X, Urdaneta L, et al.

Endogenous, non-reducing end glycosaminoglycan biomarkers are superior to internal disaccharide glycosaminoglycan biomarkers for newborn screening of mucopolysaccharidoses and GM1 gangliosidosis. Mol Genet Metab. 2023;140(1-2):107632 4. Herbst ZM, Urdaneta L, Klein T, Fuller M, Gelb MH. Evaluation of multiple methods for quantification of glycosaminoglycan biomarkers in newborn dried blood spots from patients with severe and attenuated mucopolysaccharidosis-I. Int J Neonatal Screen. 2020;6(3):69

MPS2R
622363

Endogenous Mucopolysaccharidosis Type II (I2S [Iduronate-2-Sulfatase]) Biomarker Reflex, Blood Spot

Clinical Information: Mucopolysaccharidosis II (MPS II; Hunter syndrome) is an X-linked lysosomal disorder caused by the deficiency of iduronate-2-sulfatase enzyme due to variants in the IDS gene. Clinical features and severity of symptoms are widely variable ranging from severe infantile onset disease to an attenuated form, which generally has a later onset with a milder clinical presentation. Symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. As an X-linked disorder, MPS II occurs primarily in male patients with an estimated incidence of 1 in 120,000 male births, although symptomatic carrier females have been reported. Treatment availability, including hematopoietic stem cell transplantation and enzyme replacement therapy, makes early diagnosis desirable, as early initiation of treatment has been shown to improve clinical outcomes. Newborn screening for MPS II has been implemented in some states. Individuals with MPS II typically demonstrate elevated levels of the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate (see MPSQU / Mucopolysaccharides Quantitative, Random, Urine; or MPSBS / Mucopolysaccharides, Blood Spot), as well as elevated levels of GAG fragments known as endogenous disaccharide biomarkers that are specific to the deficiency of iduronate-2-sulfatase. Reduced or absent activity of iduronate-2-sulfatase (see I2SWB / Iduronate-2-Sulfatase, Leukocytes) can confirm a diagnosis of MPS II but may also be deficient in unaffected individuals with pseudodeficiency as well as in individuals with multiple sulfatase deficiency. Enzymatic testing is not reliable to detect carriers. Molecular genetic testing of the IDS gene allows for detection of the disease-causing variant in affected patients and subsequent carrier detection in female relatives (see MPS2Z / Hunter Syndrome, Full Gene Analysis, Varies).

Useful For: Second-tier testing of newborns with an abnormal primary screening result for mucopolysaccharidosis type II (MPS II, decreased iduronate-2-sulfatase) where quantitation of the glycosaminoglycans dermatan and heparan sulfate is desired in the presence of elevated endogenous MPS II biomarkers Follow-up testing for evaluation of an abnormal newborn screening result for MPS II. This test is not useful a monitoring test for individuals with MPS II. This test is not appropriate for carrier detection.

Interpretation: The qualitative measurement of mucopolysaccharidosis type II (MPS II) specific endogenous biomarker is compared to the reference value. This report is in text form only, indicating if the MPS II specific endogenous biomarker value is or is not suggestive of a biochemical diagnosis of MPS II. In any specimen where the MPS II specific endogenous biomarker value is elevated, quantitative analysis of heparan, dermatan, and keratan sulfate will be performed. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay or quantitative glycosaminoglycan measurement) or molecular genetic analyses are required, many of which are offered within Mayo Clinic Laboratories. Recommendations for additional biochemical testing and confirmatory studies (biomarker, enzyme assay, molecular analysis) are provided in the interpretative report.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Newborn Screening ACT Sheet [Iduronate 2-Sulfatase Deficiency] Mucopolysaccharidosis Type II. American College of Medical Genetics and Genomics; 2022 .Accessed October 23, 2024. Available at www.acmg.net/PDFLibrary/MPS-II.pdf 2. Saville JT, Herbst ZM, Gelb MH, Fuller M. Endogenous, non-reducing end glycosaminoglycan biomarkers for the mucopolysaccharidoses: Accurate diagnosis and elimination of false positive newborn screening results. Mol Gen Metab. 2023;140(3):107685 3. Herbst ZM, Hong X, Urdaneta L, et al. Endogenous, non-reducing end glycosaminoglycan biomarkers are superior to internal disaccharide glycosaminoglycan biomarkers for newborn screening of mucopolysaccharidoses and GM1 gangliosidosis. Mol Genet Metab. 2023;140(1-2):107632 4. Peck DS, Lacey JM, White AL, et al. Incorporation of second-tier biomarker testing improves the specificity of newborn screening for mucopolysaccharidosis type I. Int J Neonatal Screen. 2020;6(1):10. doi:10.3390/ijns6010010

MPS2B
622357

Endogenous Mucopolysaccharidosis Type II (I2S [Iduronate-2-Sulfatase]) Biomarker, Blood Spot

Clinical Information: Mucopolysaccharidosis type II (MPS II; Hunter syndrome) is an X-linked lysosomal disorder caused by the deficiency of iduronate-2-sulfatase enzyme due to variants in the IDS gene. Clinical features and severity of symptoms are widely variable ranging from severe infantile onset disease to an attenuated form, which generally has a later onset with a milder clinical presentation. Symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. As an X-linked disorder, MPS II occurs primarily in male patients with an estimated incidence of 1 in 120,000 male births, although symptomatic carrier females have been reported. Treatment availability, including hematopoietic stem cell transplantation and enzyme replacement therapy, makes early diagnosis desirable, as early initiation of treatment has been shown to improve clinical outcomes. Newborn screening for MPS II has been implemented in some states. Individuals with MPS II typically demonstrate elevated levels of the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate (see MPSQU / Mucopolysaccharides Quantitative, Random, Urine; or MPSBS / Mucopolysaccharides, Blood Spot), as well as elevated levels of GAG fragments known as endogenous disaccharide biomarkers that are specific to the deficiency of iduronate-2-sulfatase. Reduced or absent activity of iduronate-2-sulfatase (see I2SWB / Iduronate-2-Sulfatase, Leukocytes) can confirm a diagnosis of MPS II but may also be deficient in unaffected individuals with pseudodeficiency as well as in individuals with multiple sulfatase deficiency. Enzymatic testing is not reliable to detect carriers. Molecular genetic testing of the IDS gene allows for detection of the disease-causing variant in affected patients and subsequent carrier detection in female relatives (see MPS2Z / Hunter Syndrome, Full Gene Analysis, Varies).

Useful For: Second-tier testing of newborns with an abnormal primary screening result for mucopolysaccharidosis type II (MPS II, decreased iduronate-2-sulfatase) Follow-up testing for evaluation of an abnormal newborn screening result for MPS II This test is not useful a monitoring test for individuals with MPS II. This test is not appropriate for carrier detection.

Interpretation: The qualitative measurement of mucopolysaccharidosis type II (MPS II) specific endogenous biomarkers is compared to the reference value. This report is in text form only, indicating if the MPS II specific endogenous biomarker value is or is not suggestive of a biochemical diagnosis of MPS II. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay and quantitative glycosaminoglycan measurement) or molecular genetic analyses are required, many of which are offered within Mayo Clinic Laboratories. Recommendations for additional biochemical testing and confirmatory studies (biomarker, enzyme assay, molecular analysis) are provided in the interpretative report.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Newborn Screening ACT Sheet [Iduronate 2-Sulfatase Deficiency] Mucopolysaccharidosis Type II. American College of Medical Genetics and Genomics; 2022. Accessed October 23, 2024. Available at www.acmg.net/PDFLibrary/MPS-II.pdf 2. Saville JT, Herbst ZM, Gelb MH, Fuller M. Endogenous, non-reducing end glycosaminoglycan biomarkers for the mucopolysaccharidoses: Accurate diagnosis and elimination of false positive newborn screening results. Mol Gen Metab. 2023;140(3):107685. 3. Herbst ZM, Hong X, Urdaneta L, et al. Endogenous, non-reducing end glycosaminoglycan biomarkers are superior to internal disaccharide glycosaminoglycan biomarkers for newborn screening of mucopolysaccharidoses and GM1 gangliosidosis. Mol Genet Metab. 2023;140(1-2):107632 4. Herbst ZM, Urdaneta L, Klein T, Fuller M, Gelb MH. Evaluation of multiple methods for quantification of glycosaminoglycan biomarkers in newborn dried blood spots from patients with severe and attenuated mucopolysaccharidosis-I. Int J Neonatal Screen. 2020;6(3):69

ESTUF 35851 Endometrial Stromal Tumors (EST), 7p15 (JAZF1), 6p21.32 (PHF1), 17p13.3 (YWHAE) Rearrangement, FISH, Tissue

Clinical Information: Endometrial stromal tumors (EST) arise from the uterus and include the benign endometrial stromal nodule (ESN) and infiltrative endometrial stromal sarcoma (ESS). Rearrangement of JAZF1 occurs in approximately 75% of ESN and approximately 60% of ESS. PHF1 is specific to ESS and can rearrange with both known and unknown partners in addition to JAZF1. YWHAE rearrangements occur in high-grade ESS; JAZF1 and YWHAE rearrangements are mutually exclusive.

Useful For: Supporting the diagnosis of endometrial stromal tumors when used in conjunction with an anatomic pathology consultation

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for any given probe. A positive result supports a diagnosis of an endometrial stromal tumor of various subtypes. A negative result does not exclude the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours. Female Genital Tumours. 5th ed. IARC; 2020:286-288. WHO Classification of Tumours. Vol 4 2. Nomura Y, Tamura D, Horie M, et al. Detection of MEAF6-PHF1 translocation in an endometrial stromal nodule. Genes Chromosomes Cancer. 2020;59(12):702-708 3. Conklin CM, Longacre TA. Endometrial stromal tumors: the new WHO classification. Adv Anat Pathol. 2014;21(6):383-393 4. Antonescu CR, Kao YC, Xu B, et al. Undifferentiated round cell sarcoma with BCOR internal tandem duplications (ITD) or YWHAE fusions: a clinicopathologic and molecular study. Mod Pathol. 2020;33(9):1669-1677 5. O'Meara E, Stack D, Lee CH, et al. Characterization of the chromosomal translocation t (10; 17)(q22; p13) in clear cell sarcoma of kidney. J Pathol. 2012;227(1):72-80 6. Chiang S, Ali R, Melnyk N, et al. Frequency of known gene rearrangements in endometrial stromal tumors. Am J Surg Pathol. 2011;35(9):1364-1372 7. Lee CH, Marino-Enriquez A, Ou W, et al. The clinicopathologic features of YWHAE-FAM22 endometrial stromal sarcomas: A histologically high-grade and clinically aggressive tumor. Am J Surg Pathol. 2012;36(5):641-653 8. Panagopoulos I, Mertens F, Griffin CA, et al. An endometrial stromal sarcoma cell line with the JAZF1/PHF1 chimera. Cancer Genet Cytogenet. 2008;185(2):74-77 9. Lee CH, Ou WB, Marino-Enriquez A, et al. 14-3-3 fusion oncogenes in high-grade endometrial stromal sarcoma. Proc Natl Acad Sci U S A. 2012;109(3):929-934 10. Micci F, Panagopoulos I, Bjerkehagen B, et al. Consistent rearrangement of chromosomal band 6p21 with generation of fusion genes JAZF1/PHF1 and EPC1/PHF1 in endometrial stromal sarcoma. Cancer Res. 2006;66(1):107-112 11. Gebre-Medhin S, Nord KH, Moller E, et al. Recurrent rearrangement of the PHF1 gene in ossifying

fibromyxoid tumors. Am J Pathol. 2012;181(3):1069-1077

EMA
9360

Endomysial Antibodies, IgA, Serum

Clinical Information: Circulating IgA endomysial antibodies are present in 70% to 80% of patients with dermatitis herpetiformis or celiac disease, and in nearly all such patients who have high grade gluten-sensitive enteropathy and are not adhering to a gluten-free diet. Because of the high specificity of endomysial antibodies for celiac disease, this test may obviate the need for multiple small bowel biopsies to verify the diagnosis. This may be particularly advantageous in the pediatric population, including the evaluation of children with failure to thrive.

Useful For: Analysis of IgA-endomysial antibodies for the diagnosis of dermatitis herpetiformis and celiac disease Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

Interpretation:

Reference Values:
Negative in normal individuals; also negative in dermatitis herpetiformis or celiac disease patients adhering to gluten-free diet.

Clinical References: 1. Peters MS, McEvoy MT. IgA antiendomysial antibodies in dermatitis herpetiformis. J Am Acad Dermatol. 1989;21(6):1225-1231 2. Chorzelski TP, Buetner EH, Sulej J, et al. IgA anti-endomysium antibody. A new immunological marker of dermatitis herpetiformis and coeliac disease. Br J Dermatol. 1984;111(4):395-402 3. Kapuscinska A, Zalewski T, Chorzelski TP, et al. Disease specificity and dynamics of changes in IgA class anti-endomysial antibodies in celiac disease. J Pediatr Gastroenterol Nutr. 1987;6(4):529-534. doi:10.1097/00005176-198707000-00006 4. Elwenspoek MMC, Jackson J, Dawson S, et al. Accuracy of potential diagnostic indicators for coeliac disease: a systematic review protocol. BMJ Open. 2020;10(10):e038994. doi:10.1136/bmjopen-2020-038994

EMAT
65091

Endomysial Antibodies, IgA, Titer, Serum

Clinical Information: Circulating IgA endomysial antibodies are present in 70% to 80% of patients with dermatitis herpetiformis or celiac disease, and in nearly all such patients who have high grade gluten-sensitive enteropathy and are not adhering to a gluten-free diet. Because of the high specificity of endomysial antibodies for celiac disease, the test may obviate the need for multiple small bowel biopsies to verify the diagnosis. This may be particularly advantageous in the pediatric population, including the evaluation of children with failure to thrive.

Useful For: Confirmation of a positive IgA-endomysial antibodies result

Interpretation: The finding of IgA-endomysial antibodies (EMA) is highly specific for dermatitis herpetiformis or celiac disease. The titer of IgA-EMA generally correlates with the severity of gluten-sensitive enteropathy. If patients strictly adhere to a gluten-free diet, the titer of IgA-EMA should begin to decrease within 6 to 12 months of onset of dietary therapy. Occasionally, the staining results cannot be reliably interpreted as positive or negative because of strong smooth muscle staining, weak EMA staining, or other factors. In these cases, the results will be reported as "indeterminate," and additional testing is recommended; see TTGA / Tissue Transglutaminase Antibody, IgA, Serum and IGA / Immunoglobulin A (IgA), Serum.

Reference Values:
Only orderable as a reflex. For more information see EMA / Endomysial Antibodies, IgA, Serum.

Negative

Clinical References: 1. Peters MS, McEvoy MT. IgA antiendomysial antibodies in dermatitis herpetiformis. J Am Acad Dermatol. 1989;21(6):1225-1231. doi:10.1016/s0190-9622(89)70335-2 2. Chorzelski TP, Buetner EH, Sulej J, et al. IgA anti-endomysium antibody: a new immunological marker of dermatitis herpetiformis and coeliac disease. Br J Dermatol. 1984;111(4):395-402. doi:10.1111/j.1365-2133.1984.tb06601.x 3. Kapuscinska A, Zalewski T, Chorzelski TP, et al. Disease specificity and dynamics of changes in IgA class anti-endomysial antibodies in celiac disease. J Pediatr Gastroenterol Nutr. 1987;6(4):529-534. doi:10.1097/00005176-198707000-00006 4. Elwenspoek MMC, Jackson J, Dawson S, et al. Accuracy of potential diagnostic indicators for coeliac disease: a systematic review protocol. BMJ Open. 2020;10(10):e038994. doi:10.1136/bmjopen-2020-038994

EMAIG
608880

Endomysial Antibodies, IgG, Serum

Clinical Information: Circulating IgG endomysial antibodies are present in 70% to 80% of patients with dermatitis herpetiformis or celiac disease, and in nearly all such patients who have high grade gluten-sensitive enteropathy and are not adhering to a gluten-free diet. Because of the high specificity of endomysial antibodies for celiac disease, the test may obviate the need for multiple small bowel biopsies to verify the diagnosis. This may be particularly advantageous in the pediatric population, including the evaluation of children with failure to thrive.

Useful For: Analysis of IgG-endomysial antibodies for the diagnosis of dermatitis herpetiformis and celiac disease Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

Interpretation: The finding of IgG-endomysial antibodies (EMA) is highly specific for dermatitis herpetiformis or celiac disease. The titer of IgG-EMA generally correlates with the severity of gluten-sensitive enteropathy. If patients strictly adhere to a gluten-free diet, the titer of IgG-EMA should begin to decrease within 6 to 12 months of onset of dietary therapy. Occasionally, the staining results cannot be reliably interpreted as positive or negative because of strong smooth muscle staining, weak EMA staining or other factors; in this case, the results will be recorded as "indeterminate." In this setting, further testing with measurement of TTGA / Tissue Transglutaminase Antibody, IgA, Serum and IGG / Immunoglobulin G (IgG), Serum levels are recommended.

Reference Values:
Negative in normal individuals; also negative in patients with either dermatitis herpetiformis or celiac disease while adhering to gluten-free diet.

Clinical References: 1. Dahlbom I, Olsson M, Forooz NK, Sjoholm AG, Truedsson L, Hannson T. Immunoglobulin G (IgG) anti-tissue transglutaminase antibodies used as markers for IgA-deficient celiac disease patients. Clin Diagn Lab Immunol. 2005;12(2): 254-258. doi:10.1128/CDLI.12.2.254-258.2005 2. Korponay-Szabo IR, Dahlbom I, Laurila K, et al. Elevation of IgG antibodies against tissue transglutaminase as a diagnostic tool for coeliac disease in selective IgA deficiency. Gut. 2003;52(11):1567-1571. doi:10.1136/gut.52.11.1567 3. Kumar V, Jarzabek-Chorzelska M, Sulej J, Karnewska K, Farrell T, Jablonska S. Celiac disease and immunoglobulin A deficiency: How effective are the serological methods of diagnosis? Clin Diagn Lab Immunol. 2002;9(6):1295-1300. doi:10.1128/CDLI.9.6.1295-1300.2002 4. Elwenspoek MMC, Jackson J, Dawson S, et al. Accuracy of potential diagnostic indicators for coeliac disease: a systematic review protocol. BMJ Open. 2020;10(10):e038994. doi:10.1136/bmjopen-2020-038994

FENDI
75913

Endothelin I

Clinical Information: Endothelin I is a 21 amino acid peptide produced primarily by vascular endothelial cells. It is also produced by renal mesangial and epithelial cells. Endothelin I has potent effects on peripheral vascular resistance, renal blood flow and glomerular filtration rate. Endothelin I appears to be a mediator of hypertension and acute renal failure of hemolytic uremic syndrome. Levels of Endothelin I are increased in patients with hemolytic uremic syndrome with hypertension anuria and oligonuria. Endothelin I has potent vasoconstriction properties. Endothelin I stimulates the oppositive vasodilator called Endothelium Derived Releasing Factor. Levels are also increased in trauma patients.

Reference Values:
Adult Reference Range(s)
4.0-9.0 pg/mL

EGPL
82704

English Plantain, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to English plantain Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive

4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

EHOLG
616732

Entamoeba histolytica Antibody, Serum

Clinical Information: Amebiasis is an infection caused by the protozoan parasite, Entamoeba histolytica. The infection is acquired by ingestion of cysts in fecally contaminated food or water; excystation and infection occur in the large intestine. After excystation, trophozoites attach to the intestinal wall and excrete extracellular enzymes that enable invasion of the mucosa and spread to other organs, especially the liver and lung where abscesses may develop. Amebiasis (or amebic dysentery) can cause bloody diarrhea accompanied by fever and prostration. White and red blood cells are found in the stool. Liver abscess can develop several weeks to months later producing hepatomegaly and fever. Serology may be particularly useful in supporting the diagnosis of invasive disease with E histolytica, which is most commonly associated with amebic liver abscess. Serology should not be used to identify or diagnose amebic dysentery due to poor sensitivity in acute, noninvasive disease.

Useful For: As an adjunct in the diagnosis of extraintestinal, invasive amebiasis

Interpretation: Negative: No antibodies to Entamoeba histolytica detected. This assay is intended for assessment of invasive amebiasis. Repeat testing in 2 to 3 weeks if clinically indicated. Equivocal: Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive: Results are suggestive of current or past infection with Entamoeba histolytica. Direct detection of E histolytica in stool or other specimen sources is recommended to diagnose acute amebiasis.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Bruckner DA. Amebiasis. Clin Microbiol Rev. 1992;5(4):356-369. doi: 10.1128/CMR.5.4.356 2. Petri WA, Haque R, Moonah SN: Entamoeba species, including amebic colitis and liver abscess. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3273-3286

FEHAG
75350

Entamoeba histolytica Antigen, EIA

Clinical Information:

Reference Values:
Entamoeba histolytica Antigen: Not Detected

The Entamoeba histolytica Antigen EIA test detects only the antigen of the pathogenic E. histolytica; the non-pathogenic E. dispar is not detected.

STL
8098

Enteric Pathogens Culture, Feces

Clinical Information: Diarrhea may be caused by a number of agents (eg, bacteria, viruses, parasites, and chemicals) and these agents may result in similar symptoms. A thorough patient history covering symptoms, severity, duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the physician categorize the disease and ensure that any special requests are communicated to the laboratory.

Useful For: Determining whether a bacterial enteric pathogen is the cause of diarrhea May be helpful in identifying the source of the infectious agent (eg, dairy products, poultry, water, or meat) This test is generally not useful for patients hospitalized more than 3 days because the yield from specimens from these patients is very low, as is the likelihood of identifying a pathogen that has not been detected previously.

Interpretation: The growth of an enteric pathogen identifies the cause of diarrhea.

Reference Values:
No growth of pathogens

Clinical References: 1. York MK, Rodrigues-Wong P, Church L: Fecal culture for aerobic pathogens of gastroenteritis. In: Clinical Microbiology Procedures Handbook. 3rd ed. ASM Press; 2010:Section 3.8.1 2. Jerris RC, Fields PI, Nicholson MA: Fecal culture for Campylobacter and related organisms. In: Clinical Microbiology Procedures Handbook. 3rd ed. ASM Press; 2010:Section 3.8.2 3. DuPont HL. Persistent diarrhea: A clinical review. JAMA. 2016;315(24):2712-2723. doi:10.1001/jama.2016.7833

ENTP
89893

Enterovirus, Molecular Detection, PCR, Plasma

Clinical Information: Enteroviruses are positive-sense RNA viruses in the Picornaviridae family. These viruses were initially classified by serotype as polioviruses (3 types), echoviruses (31 types, including types 22 and 23, which are now classified as parechoviruses), coxsackievirus A (23 types), and coxsackievirus B (6 types). However, genomic studies have demonstrated that there is significant overlap in the biological characteristics of different serotypes and, more recently, isolated enteroviruses are now named with consecutive numbers (eg, EV68, EV69). The normal site of enterovirus replication is the gastrointestinal tract where the infection is typically subclinical. However, in a proportion of cases, the virus spreads to other organs, causing systemic manifestations, including mild respiratory disease (eg, common cold); conjunctivitis; hand, foot, and mouth disease; aseptic meningitis; myocarditis; and acute flaccid paralysis. Collectively, enteroviruses are the most common cause of upper respiratory tract disease in children. In addition, the enteroviruses are the most common cause of central nervous system (CNS) disease; they account for almost all viruses recovered in culture from spinal fluid. Differentiation of enteroviruses from other viruses and bacteria that cause CNS disease is important for the appropriate medical management of these patients. Traditional cell culture methods require 6 days, on average, for enterovirus detection. In comparison, real-time polymerase chain reaction (PCR) allows same-day detection. Detection of enterovirus nucleic acid by PCR is also the most sensitive diagnostic method for the diagnosis of CNS infection caused by these viruses.

Useful For: Aiding in diagnosing enterovirus infections using plasma specimens This test should not be used to screen asymptomatic patients.

Interpretation: A positive result indicates the presence of enterovirus RNA in the specimen.

Reference Values:
Negative

Clinical References: 1. Harvala H, Broberg E, Benschop K, et al: Recommendations for enterovirus diagnostics and characterisation within and beyond Europe. J Clin Virol. 2018 Apr;101:11-17 2. Khetsuriani N, Lamonte-Fowlkes A, Oberst S, et al: Enterovirus surveillance-United States, 1970-2005. MMWR Surveill Summ, 2006 Sep 15;55(8):1-20 3. Foray S, Pailloud F, Thouvenot D, Floret D, Aymard M, Lina B: Evaluation of combining upper respiratory tract swab samples with cerebrospinal fluid examination for the diagnosis of enteroviral meningitis in children. J Med Virol. 1999 Feb;57(2):193-197 4. Furione M, Zavattoni M, Gatti M, Percivalle E, Fioroni N, Gerna G: Rapid detection of enteroviral RNA in cerebrospinal fluid (CSF) from patients with aseptic meningitis by reverse transcription-nested polymerase chain reaction. New Microbiol. 1998 Oct;21(4):343-351

LENT
80066

Enterovirus, Molecular Detection, PCR, Varies

Clinical Information: Enteroviruses are positive-sense RNA viruses in the Picornaviridae family. These viruses were initially classified by serotype as polioviruses (3 types), echoviruses (31 types, including types 22 and 23, which are now classified as parechoviruses), coxsackievirus A (23 types), and coxsackievirus B (6 types). However, genomic studies have demonstrated that there is significant overlap in the biological characteristics of different serotypes and more recently isolated enteroviruses are now named with consecutive numbers (eg, EV68, EV69). The normal site of enterovirus replication is the gastrointestinal tract where the infection is typically subclinical. However, in a proportion of cases, the virus spreads to other organs, causing systemic manifestations, including mild respiratory disease (eg, the common cold); conjunctivitis; hand, foot, and mouth disease; aseptic meningitis; myocarditis; and acute flaccid paralysis. Collectively, enteroviruses are the most common cause of upper respiratory tract disease in children. In addition, the enteroviruses are the most common cause of central nervous system (CNS) disease; they account for almost all viruses recovered in culture from spinal fluid. Differentiation of enteroviruses from other viruses and bacteria that cause CNS disease is important for the appropriate medical management of these patients. Traditional cell culture methods require 6 days, on average, for enterovirus detection. In comparison, real-time polymerase chain reaction (PCR) allows same-day detection. Detection of enterovirus nucleic acid by PCR is also the most sensitive diagnostic method for the diagnosis of CNS infection caused by these viruses.

Useful For: Aiding in diagnosing enterovirus infections This test should not be used to screen asymptomatic patients.

Interpretation: A positive result indicates the presence of enterovirus RNA in the specimen.

Reference Values:
Negative

Clinical References:

EDN
618211

Eosinophil Derived Neurotoxin, Serum

Clinical Information: Eosinophils are a type of white blood cell (WBC) that derives from myeloid progenitor cells.(1) They are a critical part of the immune response to helminth and other infections and play a significant role in allergic diseases. Eosinophils are characterized by their cytoplasmic granules, which appear dark red when stained with eosin. These cytoplasmic granules contain a number of cytotoxic proteins, including major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin (EDN). Upon activation, eosinophils degranulate, with subsequent release of these proteins

into the extracellular space. These proteins exhibit a variety of activities, with EDN being a ribonuclease having antiviral activity. Eosinophils generally comprise less than 5% of the total WBC count. Eosinophilia, or elevated numbers of eosinophils in the peripheral blood, can be defined as mild (up to 1500/mcL), moderate (1500-5000/mcL), or severe (>5000/mcL).(2) Hypereosinophilia (HE) identifies a situation in which peripheral eosinophils >1500/mcL are detected at least 2 occasions at least 4 weeks apart. Causes of HE can be classified as secondary (reactive), primary (neoplastic) or idiopathic. Some secondary (reactive) causes of HE include allergy, parasite infection, and autoimmunity. Additionally, secondary (reactive) HE can occur in the context of a malignancy (paraneoplastic), such as solid-organ cancer, T-cell lymphoma/leukemia, and Hodgkin lymphoma. In contrast, primary (neoplastic) HE occurs in situations of clonal myeloid/lymphoid stem cells; in this case, the eosinophils originate from the malignant clone. Lastly, idiopathic HE is reserved for cases where no underlying cause can be identified. In some cases, peripheral HE leads to infiltration of tissues by the eosinophils. Hypereosinophilic syndrome (HES) identifies patients in whom organ damage occurs and is caused by degranulation of eosinophils within the target organ. The most commonly involved organ systems in HES are the skin, lungs, and gastrointestinal tract.(2) Evaluation of patients with peripheral HE begins with screening for second causes (infection, allergy, etc) and assessing for organ damage though imaging, functional testing, and tissue pathology.(3) Although peripheral blood eosinophil counts are used to identify patients with HE, they may not always accurately reflect elevated numbers of eosinophils found in tissues. In addition, absolute counts also do not indicate the level of eosinophil activation and degranulation. EDN concentrations have been shown to correlate with peripheral blood eosinophil counts and may provide additional information related to activation status.(4,5)

Useful For: Evaluating patients suspected to have a condition associated with eosinophilia or hypereosinophilia Evaluating patients with elevated peripheral blood eosinophil counts Managing patients with elevated eosinophil-derived neurotoxin in the context of eosinophil-associated diseases

Interpretation: Eosinophil-derived neurotoxin (EDN) concentrations greater than or equal to 100 mcg/L, in the presence of elevated numbers of peripheral blood or tissue-resident eosinophils, may be suggestive of inflammation or increased disease activity in patients with eosinophil-associated diseases. In the context of normal eosinophil counts, EDN concentrations greater than 70 mcg/L may indicate cellular activation and degranulation. In the context of elevated eosinophil counts, EDN concentrations less than or equal to 70 mcg/L may indicate limited or absent cellular activation.

Reference Values:

<70 mcg/L: Normal
70-99 mcg/L: Borderline
> or =100 mcg/L: Elevated
Reference values apply to all ages.

Clinical References: 1. Wechsler ME, Munitz A, Ackerman SJ, et al. Eosinophils in health and disease: A state-of-the-art review. Mayo Clin Proc. 2021;96(10):2694-2707 2. Mattis DM, Wang SA, Lu CM. Contemporary classification and diagnostic evaluation of hypereosinophilia. Am J Clin Pathol. 2020;154(3):305-318 3. Shomali W, Gotlib J. World Health Organization and International Consensus Classification of eosinophilic disorders: 2024 update on diagnosis, risk stratification and management. Am J Hematol. 2024;99(5):946-968 4. Rutten B, Young S, Rhedin M, et al. Eosinophil-derived neurotoxin: A biologically and analytically attractive asthma biomarker. PLoS ONE. 2021;16(2):e0246627 5. Rydell N, Nagao M, Ekoff H, et al. Development of an automated ImmunoCAP research assay for eosinophil derived neurotoxin and its use in asthma diagnosis in children. Pract Lab Med. 2019;17:300138

EOSU1 Eosinophils, Random, Urine

610552

Clinical Information: Eosinophils are white blood cells that normally do not appear in urine. The presence of eosinophils in the urine is seen in acute interstitial nephritis, which is caused by an allergic reaction, typically to drugs.

Useful For: Investigation of possible acute interstitial nephritis

Interpretation: Results of greater than 5% eosinophils are indicative of acute interstitial nephritis; results between 1% and 5% eosinophils are indeterminant.

Reference Values:
0%

Clinical References: 1. Hansel FK. In: Clinical Allergy. CV Mosby Company; 1953 2. Brunzel NA. Microscopic examination of urine sediment. In: Fundamentals of Urine and Body Fluid Analysis. 4th ed. Saunders; 2017:141 3. Muriithi AK, Leung N, Valeri AM, et al. Biopsy-proven acute interstitial nephritis, 1993-2011: a case series. Am J Kidney Dis. 2014;64(4):558-566. doi:10.1053/j.ajkd.2014.04.027

FEPHD
90109

Ephedrine, Serum

Reference Values:
Reference Range: 35 - 80 ng/mL

EPUR
82854

Epicoccum purpurascens, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Epicoccum purpurascens Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SPBX
70599

Epidermal Nerve Fiber Density Consultation, Varies

Clinical Information: Small fiber peripheral neuropathy is a common neurological complaint and a frequent source of morbidity in many patient populations. Direct investigation of small fiber involvement has been limited as most classical techniques (eg, electromyography, nerve conduction studies, and nerve biopsy) focus on large diameter nerve fibers and may be normal in patients with small fiber neuropathies. The advent of epidermal skin biopsies and PGP 9.5 (protein gene product 9.5) immunohistochemistry allows the direct visualization and morphologic assessment of small sensory fibers innervating the skin.(1) Assessment of intraepidermal nerve fiber density has been used to reliably demonstrate pathologic abnormalities in small fiber neuropathy of various etiologies including diabetes, HIV, systemic lupus erythematosus, and neurosarcoidosis. Further, the technique has been validated, shown to have acceptable sensitivity and specificity, and is minimally invasive. The publication of normative data for commonly tested sites such as the distal and proximal legs and arms permits direct comparison of patients to age- and sex-matched controls facilitating localization and diagnosis.(2-4) Based on class 1 evidence and American Medical Association CPT code review process acceptance, intraepidermal nerve fiber density (IENFD) measurements are now an accepted investigational method in the workup of polyneuropathy, including the characterization and diagnosis of varieties of length-dependent small fiber polyneuropathies. IEFND measurements have been incorporated in recent practice guidelines published by the American Academy of Neurology and the European Federation of Neurological Science.(5,6)

Useful For: Investigating polyneuropathies

Interpretation: The number of intraepidermally originating nerve fibers that cross the basement membrane between the dermis and epidermis are counted in several sections.(2,5) The total linear length of the epidermis is measured using standard morphometric techniques and a density of epidermal nerve fibers (number of fibers/mm) is reported. This value is compared to previously published normative data.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Lauria G, Lombardi R, Camozzi F, Devigili G. Skin biopsy for the diagnosis of peripheral neuropathy. Histopathology. 2009;54(3):273-285 2. McArthur JC, Stocks EA, Hauer P, Cornblath DR, Griffin JW. Epidermal nerve fiber density: normative reference range and diagnostic efficiency. Arch Neurol. 1998;55(12):1513-1520 3. Goransson LG, Mellgren SI, Lindal S, Omdal R. The effect of age and gender on epidermal nerve fiber density. Neurology. 2004;62(5):774-777 4. Umapathi T, Tan WL, Tan NCK, Chan YH. Determinants of epidermal nerve fiber density in normal individuals. Muscle Nerve. 2006;33(6):742-746 5. Lauria G, Cornblath DR, Johansson O, et al. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. Eur J Neurol. 2005;12(10):747-758 6. England JD, Gronseth GS, Franklin G, et al. Practice parameter: evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology. 2009;72(2):177-184 7. Engelstad JK, Taylor SW, Witt LV, et al. Epidermal nerve fibers: confidence intervals and continuous measures with nerve conduction. Neurology. 2012;79(22):2187-2193 8. England JD, Gronseth GS, Franklin G, et al. Evaluation of distal symmetric polyneuropathy: the role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Muscle Nerve. 2009;39(1):106-115 9. Landowski LM, Dyck PJB, Engelstad J, Taylor BV. Axonopathy in peripheral neuropathies: Mechanisms and therapeutic approaches for regeneration. J Chem Neuroanat. 2016;76(Pt A):19-27. doi:10.1016/j.jchemneu.2016.04.006

FEPI
57960

Epidermophyton floccosum IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

EPS2
92118

Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum

Clinical Information: Antiepileptic drugs (AED) are the mainstay of treatment for epilepsy, but seizures continue in one-third of patients despite appropriate AED therapeutic trials. The etiology of epilepsy often remains unclear. Seizures are a common symptom in autoimmune neurological disorders, including limbic encephalitis and multifocal paraneoplastic disorders. Seizures may be the exclusive manifestation of an autoimmune encephalopathy without evidence of limbic encephalitis. Autoimmune epilepsy is increasingly recognized in the spectrum of neurological disorders characterized by detection of neural autoantibodies in serum or spinal fluid (CSF) and responsiveness to immunotherapy. The advent of more sensitive and specific serological detection methods is increasingly revealing previously underappreciated autoimmune epilepsies. Neural autoantibodies specific for intracellular and plasma membrane antigens aid the diagnosis of autoimmune epilepsy, but no single antibody is specific for this diagnosis. Autoantibody specificities most informative for autoimmune epilepsies include leucine-rich glioma inactivated protein-1 (LGI1), glutamic acid decarboxylase-65 (GAD65), N-methyl-D-aspartate receptor (NMDA-R), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA-R), and gamma-aminobutyric acid type B receptor (GABA-B-R) antibodies. Autoantibodies recognizing onconeural proteins shared by neurons, glia, or muscle (eg, antineuronal nuclear antibody, type 1 [ANNA 1]; collapsin response-mediator protein-5 neuronal [CRMP-5-IgG]; N-type calcium channel antibody), also serve as markers of paraneoplastic or idiopathic autoimmune epilepsies. A specific neoplasm is often predictable by the individual patient's autoantibody profile. Suspicion for autoimmune epilepsy on clinical grounds justifies comprehensive evaluation of CSF and serum for neural autoantibodies. Selective testing for individual autoantibodies is not advised because each is

individually rare, and a timely diagnosis is critical. Collectively, the antibodies tested for in the autoimmune epilepsy evaluations represent a broad spectrum of treatable disorders, some of which are associated with occult cancer. Testing of CSF for autoantibodies is particularly helpful when serum testing is negative, although, in some circumstances, testing both serum and CSF simultaneously is pertinent. Testing of CSF is recommended for some antibodies (eg, NMDA-R antibody and glial fibrillary acidic protein [GFAP]-IgG) because CSF testing is both more sensitive and specific. In contrast, serum testing for LGI1 antibody is more sensitive than CSF testing. Failure to detect a neural antibody does not exclude the diagnosis of autoimmune epilepsy when other clinical clues exist. A trial of immunotherapy is justifiable in those cases.

Useful For: Investigating new onset cryptogenic epilepsy with incomplete seizure control and duration of less than 2 years, using serum specimens Investigating new onset cryptogenic epilepsy plus 1 or more of the following accompaniments: -Psychiatric accompaniments (psychosis, hallucinations) -Movement disorder (myoclonus, tremor, dyskinesias) -Headache -Cognitive impairment/encephalopathy -Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, premature graying of hair, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, idiopathic adrenocortical insufficiency), or multiple sclerosis -History of cancer -Smoking history (20 or more pack-years) or other cancer risk factors -Investigating seizures occurring within the context of a subacute multifocal neurological disorder without obvious cause, especially in a patient with a past or family history of cancer -A rising autoantibody titer in a previously seropositive patient suggests cancer recurrence

Interpretation: Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune dementia. -Plasma membrane antibodies (N-methyl-D-aspartate [NMDA] receptor; 2-amino-3-[5-methyl-3-oxo-1,2-oxazol-4-yl] propanoic acid [AMPA] receptor; gamma-amino butyric acid [GABA-B] receptor). These autoantibodies are all potential effectors of dysfunction. -Antineuronal nuclear antibody, type 1 (ANNA-1) or type 3 (ANNA-3). -Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2 [PCA-2], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG], or glutamic acid decarboxylase [GAD65] antibody).

Reference Values:

Test ID	Reporting Name	Methodology*	Reference Value
AEPSI	Epilepsy, Interpretation, S	Medical interpretation	Interpretive report
AMPCS	AMPA-R Ab CBA, S	CBA	Negative
AMPHS	Amphiphysin Ab, S	IFA	Negative
AGN1S	Anti-Glial Nuclear Ab, Type 1	IFA	Negative
ANN1S	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2S	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3S	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
CS2CS	CASPR2-IgG CBA, S	CBA	Negative
CRMS	CRMP-5-IgG, S	IFA	Negative

DPPCS	DPPX Ab CBA, S	CBA	Negative
GABCS	GABA-B-R Ab CBA, S	CBA	Negative
GD65S	GAD65 Ab Assay, S	RIA	< or =0.02 nmol/L Reference values apply to all ages
GFAIS	GFAP IFA, S	IFA	Negative
LG1CS	LGI1-IgG CBA, S	CBA	Negative
GL1IS	mGluR1 Ab IFA, S	IFA	Negative
NCDIS	Neurochondrin IFA, S	IFA	Negative
NMDCS	NMDA-R Ab CBA, S	CBA	Negative
PCAB2	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
PCATR	Purkinje Cell Cytoplasmic Ab Type Tr	IFA	Negative
PDEIS	PDE10A Ab IFA, S	IFA	Negative
T46IS	TRIM46 Ab IFA, S	IFA	Negative
Reflex Information: Test ID	Reporting Name	Methodology*	Reference Value
AGNBS	AGNA-1 Immunoblot, S	IB	Negative
AGNTS	AGNA-1 Titer, S	IFA	
AMPIS	AMPA-R Ab IF Titer Assay, S	IFA	
AMIBS	Amphiphysin Immunoblot, S	IB	Negative
AN1BS	ANNA-1 Immunoblot, S	IB	Negative
AN1TS	ANNA-1 Titer, S	IFA	
AN2BS	ANNA-2 Immunoblot, S	IB	Negative
AN2TS	ANNA-2 Titer, S	IFA	
AN3TS	ANNA-3 Titer, S	IFA	
APHTS	Amphiphysin Ab Titer, S	IFA	
CRMTS	CRMP-5-IgG Titer, S	IFA	
CRMWS	CRMP-5-IgG Western Blot, S	WB	Negative
DPPTS	DPPX Ab IFA Titer, S	IFA	
GABIS	GABA-B-R Ab IF Titer Assay, S	IFA	
GFACS	GFAP CBA, S	CBA	Negative
GFATS	GFAP IFA Titer, S	IFA	
GL1CS	mGluR1 Ab CBA, S	CBA	Negative
GL1TS	mGluR1 Ab IFA Titer, S	IFA	

NCDCS	Neurochondrin CBA, S	CBA	Negative
NCDTS	Neurochondrin IFA Titer, S	IFA	
NMDIS	NMDA-R Ab IF Titer Assay, S	IFA	
PC2TS	PCA-2 Titer, S	IFA	
PCTBS	PCA-Tr Immunoblot, S	IB	Negative
PCTTS	PCA-Tr Titer, S	IFA	
PDETS	PDE10A Ab IFA Titer, S	IFA	
T46CS	TRIM46 Ab CBA, S	CBA	Negative
T46TS	TRIM46 Ab IFA Titer, S	IFA	

Clinical References: 1. Smith KM, Britton JW, Thakolwiboon S, et al. Seizure characteristics and outcomes in patients with neurological conditions related to high-risk paraneoplastic antibodies. Epilepsia. 2023;64(9):2385-2398. doi:10.1111/epi.17695 2. Garrido Sanabria ER, Zahid A, Britton J, et al. CASPR2-IgG-associated autoimmune seizures. Epilepsia. 2022;63(3):709-722. doi:10.1111/epi.17164 3. Smith KM, Zalewski NL, Budhram A, et al. Musicogenic epilepsy: Expanding the spectrum of glutamic acid decarboxylase 65 neurological autoimmunity. Epilepsia. 2021;62(5):e76-e81. doi:10.1111/epi.16888 4. Steriade C, Britton J, Dale RC, et al. Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: Conceptual definitions. Epilepsia. 2020;61(7):1341-1351. doi:10.1111/epi.16571 5. Dubey D, Singh J, Britton JW, et al. Predictive models in the diagnosis and treatment of autoimmune epilepsy. Epilepsia. 2017;58(7):1181-1189. doi:10.1111/epi.13797

EPC2
92119

Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

Clinical Information:

Useful For: Investigating new onset cryptogenic epilepsy with incomplete seizure control and duration of fewer than 2 years using spinal fluid specimens Investigating new onset cryptogenic epilepsy plus 1 or more of the following accompaniments: -Psychiatric accompaniments (psychosis, hallucinations) -Movement disorder (myoclonus, tremor, dyskinesias) -Headache -Cognitive impairment/encephalopathy -Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, premature graying of hair, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, idiopathic adrenocortical insufficiency) or "multiple sclerosis" -History of cancer -Smoking history (20 or more pack-years) or other cancer risk factors -Investigating seizures occurring within the context of a subacute multifocal neurological disorder without an obvious cause, especially in a patient with a past or family history of cancer

Interpretation: Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and a patient's immune response to cancer. These autoantibodies are not found in healthy subjects and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune epilepsy: -Plasma membrane antibodies (N-methyl-D-aspartate [NMDA] receptor; 2-amino-3-[5-methyl-3-oxo-1,2-oxazol-4-yl] propanoic acid [AMPA] receptor; gamma-aminobutyric acid [GABA-B] receptor). These autoantibodies are all potential effectors of dysfunction -Antineuronal nuclear antibody, type 1 (ANNA-1) or ANNA-3 -Neuronal or muscle cytoplasmic antibodies

(amphiphysin, Purkinje cell antibody-type 2 [PCA-2], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG], or glutamic acid decarboxylase [GAD65] antibody) A rising autoantibody titer in a previously seropositive patient suggests cancer recurrence.

Reference Values:

Test ID	Reporting Name	Methodology*	Reference Value
AEPCI	Epilepsy, Interpretation, CSF	Medical interpretation	Interpretive report
AMPCC	AMPA-R Ab CBA, CSF	CBA	Negative
AMPHC	Amphiphysin Ab, CSF	IFA	Negative
AGN1C	Anti-Glial Nuclear Ab, Type 1	IFA	Negative
ANN1C	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2C	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3C	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
CS2CC	CASPR2-IgG CBA, CSF	CBA	Negative
CRMC	CRMP-5-IgG, CSF	IFA	Negative
DPPCC	DPPX Ab CBA, CSF	CBA	Negative
GABCC	GABA-B-R Ab CBA, CSF	CBA	Negative
GD65C	GAD65 Ab Assay, CSF	RIA	< or =0.02 nmol/L Reference values apply to all ages.
GFAIC	GFAP IFA, CSF	IFA	Negative
LG1CC	LGI1-IgG CBA, CSF	CBA	Negative
GL1IC	mGluR1 Ab IFA, CSF	IFA	Negative
NCDIC	Neurochondrin IFA, CSF	IFA	Negative
NMDCC	NMDA-R Ab CBA, CSF	CBA	Negative
PCTRC	Purkinje Cell Cytoplasmic Ab Type Tr	IFA	Negative
PCA2C	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
PDEIC	PDE10A Ab IFA, CSF	IFA	Negative
T46IC	TRIM46 Ab IFA, CSF	IFA	Negative
Reflex Information: Test ID	Reporting Name	Methodology*	Reference Value
AGNBC	AGNA-1 Immunoblot, CSF	IB	Negative
AGNTC	AGNA-1 Titer, CSF	IFA	

AMPIC	AMPA-R Ab IF Titer Assay, CSF	IFA	
AMIBC	Amphiphysin Immunoblot, CSF	IB	Negative
AN1BC	ANNA-1 Immunoblot, CSF	IB	Negative
AN1TC	ANNA-1 Titer, CSF	IFA	
AN2BC	ANNA-2 Immunoblot, CSF	IB	Negative
AN2TC	ANNA-2 Titer, CSF	IFA	
AN3TC	ANNA-3 Titer, CSF	IFA	
APHTC	Amphiphysin Ab Titer, CSF	IFA	
CRMTC	CRMP-5-IgG Titer, CSF	IFA	
CRMWC	CRMP-5-IgG Western Blot, CSF	WB	Negative
DPPTC	DPPX Ab IFA Titer, CSF	IFA	
GABIC	GABA-B-R Ab IF Titer Assay, CSF	IFA	
GFACC	GFAP CBA, CSF	CBA	Negative
GFATC	GFAP IFA Titer, CSF	IFA	
GL1CC	mGluR1 Ab CBA, CSF	CBA	Negative
GL1TC	mGluR1 Ab IFA Titer, CSF	IFA	
NCDCC	Neurochondrin CBA, CSF	CBA	Negative
NCDTC	Neurochondrin IFA Titer, CSF	IFA	
NMDIC	NMDA-R Ab IF Titer Assay, CSF	IFA	
PC2TC	PCA-2 Titer, CSF	IFA	
PCTBC	PCA-Tr Immunoblot, CSF	IB	Negative
PCTTC	PCA-Tr Titer, CSF	IFA	
PDETC	PDE10A Ab IFA Titer, CSF	IFA	
T46CC	TRIM46 Ab CBA, CSF	CBA	Negative
T46TC	TRIM46 Ab IFA Titer, CSF	IFA	

Clinical References: 1. Smith KM, Britton JW, Thakolwiboon S, et al. Seizure characteristics and outcomes in

patients with neurological conditions related to high-risk paraneoplastic antibodies. Epilepsia. 2023;64(9):2385-2398. doi:10.1111/epi.17695 2. Garrido Sanabria ER, Zahid A, Britton J, et al. CASPR2-IgG-associated autoimmune seizures. Epilepsia. 2022;63(3):709-722. doi:10.1111/epi.17164 3. Smith KM, Zalewski NL, Budhram A, et al. Musicogenic epilepsy: Expanding the spectrum of glutamic acid decarboxylase 65 neurological autoimmunity. Epilepsia. 2021;62(5):e76-e81. doi:10.1111/epi.16888 4. Steriade C, Britton J, Dale RC, et al. Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: Conceptual definitions. Epilepsia. 2020;61(7):1341-1351. doi:10.1111/epi.16571 5. Dubey D, Singh J, Britton JW, et al. Predictive models in the diagnosis and treatment of autoimmune epilepsy. Epilepsia. 2017;58(7):1181-1189. doi:10.1111/epi.13797

EPIP1
81709

Epithelia Panel # 1, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cat, cow, dog, or horse Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive

6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

EPIP2
81881

Epithelia Panel # 2, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to guinea pig, hamster, mouse, rabbit, or rat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

EMAI
70424

Epithelial Membrane Antigen (EMA) Immunostain, Technical Component Only

Clinical Information: Epithelial membrane antigen (EMA), also known as mucin 1, is expressed by epithelial cells of all types, mesothelial cells, perineural cells, and a subset of plasma cells. EMA is expressed by meningiomas, synovial sarcoma, epithelioid sarcoma, a subset of peripheral nerve sheath tumors, the lymphocyte-predominant cells of lymphocyte-predominant Hodgkin lymphoma, and anaplastic large cell lymphoma. Diagnostically, EMA is useful in recognizing epithelial derivation of poorly differentiated malignant tumors and, in conjunction with a panel of mucin markers (MUC2, MUC5AC, and MUC6), may be used in subtyping intraductal papillary mucinous neoplasms.

Useful For: Recognizing epithelial derivation of poorly differentiated malignant tumors Subtyping intraductal papillary mucinous neoplasms when used in conjunction with mucin (MUC) 2, MUC5AC and MUC6

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Kwak HA, Liu X, Allende DS, Pai RK, Hart J, Xiao SY. Interobserver variability in intraductal papillary mucinous neoplasm subtypes and application of their mucin immunoprofiles. Mod Pathol. 2016;29(9):977-984. doi:10.1038/modpathol.2016.93 2. Ramezani M, Mohamadzaheri E, Khazaei S, et al. Comparison of EMA,CEA, CD10 and Bcl-2 Biomarkers by Immunohistochemistry in Squamous Cell Carcinoma and Basal Cell Carcinoma of the Skin. Asian Pac J Cancer Prev. 2016;17(3):1379-1383. doi:10.7314/apjcp.2016.17.3.1379 3. Song W, Flucke U, Suurmeijer AJH. Myoepithelial Tumors of Bone. Surg Pathol Clin. 2017;10(3):657-674. doi:10.1016/j.path.2017.04.010 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

EBNA2
71487

Epstein Barr Nuclear Antigen 2 (EBNA2) Immunostain, Technical Component Only

Clinical Information: Epstein Barr virus (EBV) nuclear antigen 2 (EBNA2) is an EBV-encoded nuclear protein of 82 kD. EBNA2 is necessary for transformation of EBV-infected B lymphocytes and has been shown to modulate the activity of several viral and cellular promoters. This immunostain may be useful in the diagnosis of reactive and neoplastic lymphoproliferative and plasma cell proliferative disorders.

Useful For: Identification of Epstein Barr virus infection in normal, inflammatory, and neoplastic tissues

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic

evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Wood CD, Carvell T, Gunnell A, et al. Enhancer control of microRNA miR-155 expression in Epstein-Barr virus-infected B cells. J Virol. 2019;93(3):e01893-18. doi:10.1128/JVI.01893-18 2. Anastasiadou E, Stroopinsky D, Alimperti S, et al. Epstein-Barr virus-encoded EBNA2 alters immune checkpoint PD-L1 expression by downregulating miR-34a in B-cell lymphomas. Leukemia. 2019;33(1):132-147 3. Hudnall SD, Ge Y, Wei L, et al. Distribution and phenotype of Epstein-Barr virus-infected cells in human pharyngeal tonsils. Mod Pathol. 2005;18(4):519-527 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

EBLPD
619788

Epstein Barr Virus (EBV) Susceptibility and Lymphoproliferative Disorders Gene Panel, Varies

Clinical Information: Epstein-Barr virus (EBV) is a ubiquitous virus, and over 90% of adults have been infected by, and now carry, the virus. While infection is often asymptomatic in children, it may cause infectious mononucleosis in older children and adults. Additionally, EBV has been associated with multiple cancer types. The majority of healthy individuals control EBV in a latent state through the action of natural killer (NK) cells and T cells. Individuals with inborn errors of immunity may experience severe and fatal consequences of EBV infection, including severe infectious mononucleosis, lymphoproliferation, hemophagocytic lymphohistiocytosis (HLH), and lymphoma. The inborn errors of immunity that contribute to susceptibility to EBV infection can follow several mechanisms. In one group, genetic variants may result in EBV-induced HLH and a lack of NK and CD8+ T-cell cytotoxicity due to issues with the cytotoxic granules. Another group is characterized by impaired activation and expansion of T cells that specifically target EBV and may be due to genetic variants in genes involved in T-cell receptor signaling, DNA metabolism and synthesis, or the costimulatory receptors of the tumor necrosis factor-receptor superfamily. In general, disease-causing variants in SH2D1A, CD27, CD70, and TNFRSF9 may result in a more selective predisposition to EBV infection, while other defects may result in broader viral susceptibility.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of Epstein-Barr virus (EBV) susceptibility or a heritable predisposition to lymphoproliferative disease Establishing a diagnosis of a hereditary form of EBV susceptibility or a related disorder, allowing for appropriate management and surveillance for disease features based on the gene or variant involved Identifying variants within genes known to be associated with heritable EBV susceptibility and/or lymphoproliferative disease, allowing for predictive testing of at-risk family members This test is not useful for diagnosing acute/recent EBV infection.

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-424. 2. Tangye SG. Genetic susceptibility to EBV infection: insights from inborn errors

of immunity. Hum Genet. 2020;139(6-7):885-901 3. Fournier B and Latour S. Immunity to EBV as revealed by immunedeficiencies. Curr Opin Immunol. 2021;72:107-115 4. Ravell JC, Chauvin SD, He T, Lenardo M. An update on XMEN disease. J Clin Immunol. 2020;40(5):671-681 5. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507. doi:10.1007/s10875-022-01289-3

LMP1I
70502

Epstein Barr Virus Latency Membrane Protein 1 Immunostain, Technical Component Only

Clinical Information: The latent membrane protein 1 (LMP-1) oncogene of Epstein-Barr virus (EBV) is believed to contribute to the development of many EBV-associated tumors. This antibody may be useful in the diagnosis of reactive and neoplastic lymphoproliferative and plasma cell proliferative disorders.

Useful For: Identification of Epstein Barr virus infection in normal, inflammatory, and neoplastic tissues

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Qi ZL, Han XQ, Hu J, Wang GH, Gao JW, Wang X, Liang DY. Comparison of three methods for the detection of Epstein-Barr virus in Hodgkin's lymphoma in paraffin-embedded tissues. Mol Med Rep. 2013;7(1):89-92 2. Zhao Y, Wang Y, Zeng S, Hu X. LMP1 expression is positively associated with metastasis of nasopharyngeal carcinoma: evidence from a meta-analysis. J Clin Pathol. 2012;65(1):41-45. doi:10.1136/jclinpath-2011-200198 3. Ayee R, Ofori MEO, Wright E, Quaye O. Epstein Barr virus associated lymphomas and epithelia cancers in humans. J Cancer. 2020;11(7):1737-1750. doi:10.7150/jca.37282 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

SEBV
800033

Epstein-Barr Virus (EBV) Antibody Profile, Serum

Clinical Information: Epstein-Barr virus (EBV), a member of the herpesvirus group, is the etiologic agent of infectious mononucleosis. EBV infections are difficult to diagnose in the laboratory since the virus does not grow in standard cell cultures. The majority of infections can be recognized, however, by testing the patient's serum for heterophile antibodies (rapid latex slide agglutination test, eg, MONOS / Infectious Mononucleosis, Rapid Test, Serum), which usually appear within the first 3 weeks of illness but then decline rapidly within a few weeks. The heterophile antibody, however, fails to develop in about 10% of adults, more frequently in children, and almost uniformly in infants with primary EBV infections. Most of these heterophile antibody-negative cases of infectious mononucleosis-like infections are due to cytomegalovirus, but in a series of 43 cases, EBV was the cause in 7. In cases where EBV is suspected but the heterophile antibody is not detected, an evaluation of the EBV-specific antibody profile (eg, EBV viral capsid antigen [VCA] IgM, EBV VCA IgG, and EBV nuclear antigen [EBNA]) may be useful. Infection with EBV usually occurs early in life. For several weeks to months after acute onset of the infection, it is spread by upper respiratory secretions that contain the virus. Among the clinical disorders due to EBV infection, infectious mononucleosis is the most common. Other disorders due to EBV infection have been recognized for several years, including African-type

Burkitt lymphoma and nasopharyngeal carcinoma. EBV infection may also cause lymphoproliferative syndromes, especially in patients who have undergone kidney or bone marrow transplantation and in those who have AIDS.

Useful For: Diagnosing infectious mononucleosis when a mononucleosis screening procedure is negative and infectious mononucleosis or a complication of Epstein-Barr virus infection is suspected This assay is not intended for viral isolation or identification.

Interpretation: The test has 3 components: viral capsid antigen (VCA) IgG, VCA IgM, and Epstein-Barr nuclear antigen (EBNA). Presence of VCA IgM antibodies indicates recent primary infection with Epstein-Barr virus (EBV). The presence of VCA IgG antibodies indicates infection sometime in the past. Antibodies to EBNA develop 6 to 8 weeks after primary infection and are detectable for life. Over 90% of the normal adult population has IgG class antibodies to VCA and EBNA. Few patients who have been infected with EBV will fail to develop antibodies to the EBNA (approximately 5%-10%). Table. Possible Results VCA IgG VCA IgM EBNA IgG Interpretation - - - No previous exposure + + - Recent infection + - + Past infection + - - See note* + + + Past infection *Results indicate infection with EBV at some time (VCA IgG positive). However, the time of the infection cannot be predicted (ie, recent or past) since antibodies to EBNA usually develop after primary infection (recent) or, alternatively, approximately 5% to 10% of patients with EBV never develop antibodies to EBNA (past).

Reference Values:

Epstein-Barr Virus (EBV) VIRAL CAPSID ANTIGEN (VCA) IgM ANTIBODY:
Negative

Epstein-Barr Virus (EBV) VIRAL CAPSID ANTIGEN (VCA) IgG ANTIBODY:
Negative

EPSTEIN-BARR NUCLEAR ANTIGEN (EBNA) ANTIBODIES:
Negative

Clinical References: 1. Knipe DM, Howley PM, Griffin DE, et al, eds. Fields' Virology. 5th ed. Lippincott Williams and Wilkins; 2007 2. Linde A, Falk KI. Epstein-Barr virus. In: Manual of Clinical Microbiology. Barron EJ, Jorgensen JH, Landry ML, eds. 9th ed. ASM Press; 2007:1564-1573 3. Johannsen EC, Kaye KM. Epstein-Barr virus (infectious mononucleosis, Epstein-Barr virus-associated malignant diseases, and other diseases). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:1872-1890

EBV
70469

Epstein-Barr Virus (EBV) In Situ Hybridization, Technical Component Only

Clinical Information: Epstein-Barr virus plays a pathogenic role in a variety of disease states, including infectious mononucleosis, nasopharyngeal carcinoma, Burkitt lymphoma, B-cell lymphomas in patients with congenital or acquired immunodeficiency, and some cases of classical Hodgkin lymphoma.

Useful For: Detection of Epstein-Barr virus (EBV)-encoded RNA in the diagnosis of EBV-associated conditions

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical

history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Yu F, Lu Y, Petersson F, Wang DY, Loh KS. Presence of lytic Epstein-Barr virus infection in nasopharyngeal carcinoma. Head Neck. 2018;40(7):1515-1523. doi:10.1002/hed.25131 2. Randhawa PS, Jaffe R, Demetris AJ, et al. The systemic distribution of Epstein-Barr virus genomes in fatal post-transplantation lymphoproliferative disorders. An in situ hybridization study. Am J Pathol. 1991;138(4):1027-1033 3. Chang KL, Chen YY, Shibata D, Weiss LM. Description of an in situ hybridization methodology for detection of Epstein-Barr Virus RNA in paraffin-embedded tissues, with a survey of normal and neoplastic tissues. Diagn Mol Pathol. 1992;1(4):246-255 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

EBVE
800748

Epstein-Barr Virus (EBV), IgG Antibody to Early Antigen, Serum

Clinical Information: Epstein-Barr virus (EBV), a member of the herpesvirus group, is the etiologic agent of infectious mononucleosis. EBV infections are difficult to diagnose in the laboratory since the virus does not grow in standard cell cultures. The majority of infections can be identified, by testing the patient's serum for heterophile antibodies (rapid latex slide agglutination test, eg, MONOS / Infectious Mononucleosis, Rapid Test, Serum). Heterophile antibodies usually appear within the first 3 weeks of illness but decline rapidly within a few weeks. However, this heterophile antibody fails to develop in about 10% of adults, more frequently in children, and almost uniformly in infants with primary EBV infections. Most of these heterophile antibody negative cases of infectious mononucleosis-like infections are due to cytomegalovirus, but in one series of 43 cases, EBV was the cause in 7. In cases where EBV is suspected but the heterophile antibody is not detected, an evaluation of EBV-specific antibodies (eg, IgM and IgG antibodies to EBV viral capsid antigen [VCA]) and antibodies to EBV nuclear antigen (EBNA) may be useful. The EBV enzyme immunoassays that detect antibodies to the EBV VCA and early antigen (EA) are more sensitive than heterophile antibody tests. Infection with EBV usually occurs early in life. For several weeks to months after acute onset of the infection, it is spread by upper respiratory secretions that contain the virus. Among the clinical disorders due to EBV infection, infectious mononucleosis is the most common. Other disorders due to EBV infection include African-type Burkitt lymphoma and nasopharyngeal carcinoma (NPC). EBV infection may also cause lymphoproliferative syndromes, especially in patients with AIDS and in patients who have undergone kidney or bone marrow transplantation. Using immunofluorescent staining techniques, 2 patterns of EA are seen: diffuse staining of both cytoplasm and nucleus (early antigen-diffuse: EA-D) and cytoplasmic or early antigen restricted (EA-R). Antibodies responsible for the diffuse staining pattern are seen in infectious mononucleosis and NPC and are measured in this assay.

Useful For: A third-order test in the diagnosis of infectious mononucleosis, especially in situations when initial testing results (heterophile antibody test) are negative and follow-up testing (viral capsid antigen: VCA IgG, VCA IgM, and Epstein-Barr nuclear antigen) yields inconclusive results Aiding in the diagnosis of type 2 or type 3 nasopharyngeal carcinoma (NPC) This test is not useful for screening patients for NPC.

Interpretation: Generally, this antibody can only be detected during active Epstein-Barr virus (EBV) infection, such as in patients with infectious mononucleosis. Clinical studies have indicated that patients who have chronic active or reactivated EBV infection commonly have elevated levels of IgG-class antibodies to the early antigen (EA) of EBV. IgG antibody specific for the diffuse early antigen of EBV is often found in patients with nasopharyngeal carcinoma (NPC). Of patients with type 2 or 3 NPC (World Health Organization classification), 94% and 83% respectively, have positive-antibody responses to EA. Only 35% of patients with type 1 NPC have a positive response. The specificity of the test is such that 82% to 91% of healthy blood donor controls and patients who do not have NPC have

negative responses (9%-18% false-positive results). Although this level of specificity is useful for diagnostic purposes, the false-positive rate indicates that the test is not useful for NPC screening.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Fields BN, Knipe DM: Epstein-Barr virus. In: Fields BN, Knipe DM, Howley PM, eds. Fields Virology. 4th ed. Lippincott Williams and Wilkins; 2001 2. Lennette ET: Epstein-Barr virus. In: Murray PR, Baron EJ, Pfaller MA, et al, eds. Manual of Clinical Microbiology. 6th ed. ASM Press; 1995:905-910 3. Fugl A, Andersen CL: Epstein-Barr virus and its association with disease - a review of relevance to general practice. BMC Fam Pract. 2019 May 14;20(1):62. doi: 10.1186/s12875-019-0954-3

LEBV
800244

Epstein-Barr Virus (EBV), Molecular Detection, PCR, Varies

Clinical Information: Epstein-Barr virus (EBV) is the causative agent of infectious mononucleosis, Burkitt lymphoma, and in Southern China, nasopharyngeal carcinoma. EBV-associated central nervous system (CNS) disease is most frequently associated with primary CNS lymphoma in patients with AIDS. In addition, CNS infection associated with the detection of EBV DNA can be seen in immunocompetent patients.

Useful For: Rapid qualitative detection of Epstein-Barr virus (EBV) DNA in specimens Diagnosis of disease due to EBV This test should not be used to screen asymptomatic patients.

Interpretation: Detection of Epstein-Barr virus (EBV) DNA in cerebrospinal fluid (CSF) supports the clinical diagnosis of central nervous system (CNS) disease due to the virus. EBV DNA is not detected in CSF from patients without CNS disease caused by this virus.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Allen UD, Preiksaitis JK. AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652. doi:10.1111/ctr.13652 2. Nowalk A, Green M. Epstein-Barr Virus. Microbiol Spectr. 2016;4(3). doi:10.1128/microbiolspec.DMIH2-0011-2015 3. AbuSalah MAH, Gan SH, Al-Hatamleh MAI, Irekeola AA, Shueb RH, Yean Yean C. Recent Advances in Diagnostic Approaches for Epstein-Barr Virus. Pathogens. 2020;9(3):226. doi:10.3390/pathogens9030226

EBVPV
618306

Epstein-Barr Virus (EBV), Molecular Detection, PCR, Varies

Clinical Information: Epstein-Barr virus (EBV) is the causative agent of infectious mononucleosis, Burkitt lymphoma, and in Southern China, nasopharyngeal carcinoma. EBV-associated central nervous system (CNS) disease is most frequently associated with primary CNS lymphoma in patients with AIDS. In addition, CNS infection associated with the detection of EBV DNA can be seen in immunocompetent patients.

Useful For: Rapid qualitative detection of Epstein-Barr virus (EBV) DNA in specimens Diagnosis of disease due to EBV This test should not be used to screen asymptomatic patients.

Interpretation: Detection of Epstein-Barr virus (EBV) DNA in cerebrospinal fluid (CSF) supports the

clinical diagnosis of central nervous system (CNS) disease due to the virus. EBV DNA is not detected in CSF from patients without CNS disease caused by this virus.

Reference Values:

Negative
Reference values apply to all ages.

Clinical References: 1. Tachikawa N, Goto M, Hoshino Y, et al. Detection of toxoplasma gondii, epstein-barr virus, and JC virus DNAs in the cerebrospinal fluid in acquired immunodeficiency syndrome patients with focal central nervous system complications. Intern Med. 1999;38(7):556-562. doi:10.2169/internalmedicine.38.556 2. Antinori A, Cingolani A, De Luca A, et al. Epstein-Barr virus in monitoring the response to therapy of acquired immunodeficiency syndrome-related primary central nervous system lymphoma. Ann Neurol. 1999;45(2):259-261 3. Cingolani A, De Luca A, Larocca LM, et al. Minimally invasive diagnosis of acquired immunodeficiency syndrome-related primary central nervous system lymphoma. J Natl Cancer Inst. 1998 ;90(5):364-369. doi:10.1093/jnci/90.5.364 4. Niller HH, Wolf H, Minarovits J: Regulation and dysregulation of epstein-barr virus latency: implications for the development of autoimmune disease. Autoimmunity. 2008:41(4):298-328. doi:10.1080/08916930802024772 5. Studahl M, Hagberg L, Rekvdar E, Bergstrom T. Herpesvirus DNA detection in cerebrospinal fluid: difference in clinical presentation between alph-, beta-, and gamma-herpes viruses. Scand J Infect Dis. 2000;32(3):237-248. doi:10.1080/00365540050165857 6. Lau AH, Soltys K, Sindhi RK, Bond G, Mazariegos GV, Green M. Chronic high epstein-barr viral load carriage in pediatric small bowel transplant recipients. Pediatr Transplant. 2010;14(4):549-553. doi:10.1111/j.1399-3046.2009.01283.x 7. Fugl A, Andersen CL Epstein-barr virus and its association with disease - a review of relevance to general practice. BMC Fam Pract. 2019;20(1):62. doi:10.1186/s12875-019-0954-3

EBVAB
621373

Epstein-Barr Virus Antibody Profile, Serum

Clinical Information: Epstein-Barr virus (EBV), a member of the herpesvirus group, is the etiologic agent of infectious mononucleosis. Infection with EBV usually occurs early in life. For several weeks to months after acute onset of the infection, EBV is spread by upper respiratory secretions that contain the virus. Among the EBV-associated clinical manifestations, infectious mononucleosis is the most common. EBV infection can be severe in immunosuppressed patients who may develop lymphoproliferative syndromes, especially in patients with advanced HIV and in patients who have undergone kidney or bone marrow transplantation. Other, rare manifestations include African-type Burkitt lymphoma and nasopharyngeal carcinoma. EBV does not grow in standard cell cultures and molecular testing is the primary means of diagnosis and monitoring response to therapy in immunosuppressed patients. Serologic testing for EBV remains important for diagnosis of infectious mononucleosis in otherwise healthy individuals and for pre-transplant or pre-immunosuppression screening purposes. The majority of infections in healthy individuals can be identified by testing patient sera for heterophile antibodies using a rapid latex slide agglutination test (MONOS / Infectious Mononucleosis, Rapid Test, Serum). Heterophile antibodies usually appear within the first 3 weeks of illness but decline rapidly within thereafter. However, heterophile antibodies fail to develop in about 10% of adults and in more than 75% of infants and young children under the age of 4. In cases where EBV is suspected but the heterophile antibody is not detected or if confirmation is needed, or if patients are undergoing pre-immunosuppression screening, evaluation of EBV-specific antibodies, including assessment for IgM and IgG against the EBV viral capsid antigen and IgG against the EBV nuclear antigen is useful.

Useful For: Diagnosis of Epstein-Barr virus (EBV) infectious mononucleosis or other EBV related infections Identification of prior EBV infection as part of pre-immunosuppression screening This assay is not intended for viral isolation or identification.

Interpretation: The profile has 3 components: viral capsid antigen (VCA) IgG, VCA IgM, and Epstein-Barr nuclear antigen (EBNA). Presence of VCA IgM antibodies suggests an acute or recent primary infection with Epstein-Barr virus (EBV). Presence of VCA IgG antibodies indicates infection sometime in the recent or remote past. Antibodies to EBNA develop 6 to 8 weeks after primary infection and are detectable for life. Refer to table below for interpretation of EBV antibody results. VCA IgM result VCA IgG result EBNA IgG result Interpretation Negative Positive Negative Results suggest recent EBV infection. The detection of only anti-VCA IgG should be interpreted with caution in immunocompromised patients, as this population may demonstrate diminishing or undetectable levels of anti-EBNA IgG antibodies. Positive Positive Negative Results suggest recent EBV infection. Positive Negative Negative Positive Equivocal Equivocal Results suggest recent EBV infection. Recommend follow-up testing in 10-14 days if clinically indicated. Positive Equivocal Negative Positive Positive Equivocal Positive Negative Equivocal Positive Positive Positive Results may suggest recent EBV recovery or reactivation. Positive Equivocal Positive Positive Negative Positive Negative Negative Negative Results suggest no prior exposure to EBV. However, a second serum specimen should be tested in 10-14 days if clinically indicated. Negative Positive Positive Results suggest past EBV infection. Negative Negative Positive Negative Equivocal Positive Negative Positive Equivocal Detection of anti-VCA IgG only should be interpreted with caution in immunocompromised patients, as this population may demonstrate diminishing or undetectable levels of anti-EBNA IgG antibodies. Recommend follow-up testing in 10-14 days if clinically indicated. Equivocal Negative Positive Results suggest past EBV infection. Recommend follow-up testing in 10-14 days if clinically indicated. Equivocal Equivocal Positive Results with unclear clinical significance Negative Negative Equivocal Recommend follow-up testing in 10-14 days if clinically indicated. Negative Equivocal Negative Negative Equivocal Equivocal Equivocal Negative Negative Equivocal Negative Equivocal Equivocal Equivocal Negative Equivocal Equivocal Equivocal Equivocal Positive Negative Equivocal Positive Equivocal Equivocal Positive Positive

Reference Values:

Epstein-Barr Virus VIRAL CAPSID ANTIGEN (VCA) IgM ANTIBODY:
Negative

Epstein-Barr Virus VIRAL CAPSID ANTIGEN (VCA) IgG ANTIBODY:
Negative

EPSTEIN-BARR VIRUS NUCLEAR ANTIGEN (EBNA) IgG ANTIBODY:
Negative

Clinical References: 1. Knipe DM, Howley PM, Griffin DE, et al, eds. Fields' Virology. 5th ed. Lippincott Williams and Wilkins; 2007 2. Linde A, Falk KI. Epstein-Barr virus. Manual of Clinical Microbiology. . In: Barron EJ, Jorgensen JH, Landry ML, eds. 9th ed. ASM Press; 2007:1564-1573 3. Johannsen EC, Kaye KM. Epstein-Barr virus (infectious mononucleosis, Epstein-Barr virus-associated malignant diseases, and other diseases). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:1872-1890

EBVQN
615297

Epstein-Barr Virus DNA Detection and Quantification, Plasma

Clinical Information: Primary infection with Epstein-Barr virus (EBV), a DNA virus in the Herpesviridae family, may cause infectious mononucleosis resulting in a benign lymphoproliferative condition characterized by fever, fatigue, sore throat, and lymphadenopathy. Infection occurs early in life, and by 10 years of age, 70% to 90% of children have been infected with this virus. Usually, infection in children is asymptomatic or mild and may be associated with minor illnesses, such as upper respiratory tract infection, pharyngitis, tonsillitis, bronchitis, and otitis media. The target cell for EBV infection is the B lymphocyte. Immunocompromised individuals lacking antibody to EBV are at risk for acute EBV infection that may cause lymphoproliferative disorders in organ transplant recipients (post-transplant lymphoproliferative disorders: PTLD) and AIDS-related lymphoma. The incidence of PTLD ranges from

1% for kidney transplant recipients to as high as 9% for heart/lung transplants and 12% for pancreas transplant patients. EBV DNA can be detected in the blood of patients with this viral infection. Increasing serial levels of EBV DNA in plasma have been shown to correlate highly with subsequent (in 3-4 months) development of PTLD in susceptible patients. Organ transplant recipients (at risk for primary EBV infection) who are seronegative for EBV (most often children) and receive antilymphocyte globulin for induction immunosuppression and OKT-3 treatment for early organ rejection are at the highest risk for developing PTLD when compared to immunologically normal individuals with prior EBV infection.

Useful For: Diagnosis of Epstein-Barr virus (EBV)-associated infectious mononucleosis in individuals with equivocal or discordant EBV serologic marker test results Diagnosis of post-transplant lymphoproliferative disorders (PTLD), especially in EBV-seronegative organ transplant recipients receiving antilymphocyte globulin for induction immunosuppression and OKT-3 treatment for early organ rejection Monitoring progression of EBV-associated PTLD in organ transplant recipients This test should not be used to screen asymptomatic patients.

Interpretation: The quantification range of this assay is 35 to 100,000,000 IU/mL (1.54 log to 8.00 log IU/mL), with a limit of detection (95% detection rate) at 19 IU/mL. Increasing levels of Epstein-Barr virus (EBV) DNA in serial plasma specimens of a given organ transplant recipient may indicate possible development of post-transplant lymphoproliferative disorder (PTLD). An "Undetected" result indicates that EBV DNA is not detected in the plasma specimen (see Cautions). If clinically indicated, repeat testing in 1 to 2 months is recommended. A result of "<35 IU/mL" indicates that the EBV DNA level present in the plasma specimen is below 35 IU/mL (1.54 log IU/mL), and the assay cannot accurately quantify the EBV DNA present below this level. A quantitative value (reported in IU/mL and log IU/mL) indicates the EBV DNA level (ie, viral load) present in the plasma specimen. A result of ">100,000,000 IU/mL" indicates that the EBV DNA level present in the plasma specimen is above 100,000,000 IU/mL (8.00 log IU/mL), and this assay cannot accurately quantify the EBV DNA present above this level. An "Inconclusive" result indicates that the presence or absence of EBV DNA in the plasma specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to polymerase chain reaction inhibition or presence of interfering substance. Submission of a new specimen for testing is recommended if clinically indicated.

Reference Values:
Undetected

Clinical References: 1. San-Juan R, Comoli P, Caillard S, et al. Epstein-Barr virus-related post-transplant lymphoproliferative disorder in solid organ transplant recipients. Clin Microbiol Infect. 2014;20 Suppl 7 :109-118. doi:10.1111/1469-0691.12534 2. Jiang SY, Yang JW, Shao JB, Liao XL, Lu ZH, Jiang H: Real-time polymerase chain reaction for diagnosing infectious mononucleosis in pediatric patients: A systematic review and meta-analysis. J Med Virol. 2016;88(5):871-876. doi:10.1002/jmv.24402 3. Allen UD, Preiksaitis JK, AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13652. doi:10.1111/ctr.13652 4. Kimura H, Kwong YL. EBV Viral Loads in diagnosis, monitoring, and response assessment. Front Oncol. 2019 12;9:62. doi:10.3389/fonc.2019.00062

EAEBV
621374

Epstein-Barr Virus Early Antigen, IgG, Serum

Clinical Information: Epstein-Barr virus (EBV), a member of the herpesvirus group, is the etiologic agent of infectious mononucleosis. Infection with EBV usually occurs early in life. For several weeks to months after acute onset of the infection, EBV is spread by upper respiratory secretions that

contain the virus. Among the EBV-associated clinical manifestations, infectious mononucleosis (IM) is the most common. EBV infection can be severe in immunosuppressed patients who may develop lymphoproliferative syndromes, especially in patients with advanced HIV and in patients who have undergone kidney or bone marrow transplantation. Other rare manifestations include African-type Burkitt lymphoma and nasopharyngeal carcinoma (NPC). EBV does not grow in standard cell cultures and molecular testing is the primary means of diagnosis and monitoring response to therapy in immunosuppressed patients. Serologic testing for EBV remains important for diagnosis of infectious mononucleosis in otherwise healthy individuals and for pre-transplant or pre-immunosuppression screening purposes. The majority of infections in healthy individuals can be identified by testing patient sera for heterophile antibodies using a rapid latex slide agglutination test (MONOS / Infectious Mononucleosis, Rapid Test, Serum). Heterophile antibodies usually appear within the first 3 weeks of illness but decline rapidly within thereafter. However, heterophile antibodies fail to develop in about 10% of adults and in more than 75% of infants and young children under the age of 4. In cases where EBV is suspected but the heterophile antibody is not detected or if confirmation is needed, or if patients are undergoing pre-immunosuppression screening, evaluation of EBV-specific antibodies, including assessment for IgM and IgG against the EBV viral capsid antigen (VCA) and IgG against the EBV nuclear antigen (EBNA) is useful. The EBV early antigen (EA) has two forms, including the diffuse (ie, present in cytoplasm and nucleus of infected cells [EA-D]) and restricted (ie, present only in the cytoplasm of infected cells [EA-R]) forms. Generally, IgG antibodies to the EA, specifically the EA-D form, are only detected during active EBV infection, such as in patients with IM. Additionally, IgG antibodies to EA-D are also found in patients with NPC. Of patients with type 2 or 3 NPC (World Health Organization classification), 94% and 83% respectively, have positive antibody responses to EA. Only 35% of patients with type 1 NPC have a positive response. The specificity of the test is such that 82% to 91% of healthy blood donor controls and patients who do not have NPC have negative responses (9%-18% false-positive results). Although this level of specificity is useful for diagnostic purposes, the false-positive rate indicates that the test is not useful for NPC screening.

Useful For: Diagnosis of Epstein Barr virus (EBV) infectious mononucleosis in cases when heterophile antibody test results are negative and EBV-specific serologic testing is inconclusive Aiding in the diagnosis of type 2 or type 3 nasopharyngeal carcinoma (NPC) This test is not useful for screening patients for NPC.

Interpretation: Positive - IgG antibodies specific to EBV early antigen detected. Equivocal - Recommend follow-up testing in 10-14 days if clinically indicated Negative - No IgG to EBV early antigen detected. Do not make a diagnosis based on ZEUS ELISA EBV-EA IgG Test System alone. Interpret test results for anti-EBV-early antigen (EA) in conjunction with the clinical evaluation and the results of other diagnostic procedures. Consider test results for VCA and EBNA when evaluating patient specimens for EBV serological status.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Fields BN, Knipe DM. Epstein-Barr virus. In: Fields BN, Knipe DM, Howley PM, eds. Fields Virology. 4th ed. Lippincott Williams and Wilkins; 2001 2. Lennette ET. Epstein-Barr virus. In: Murray PR, Baron EJ, Pfaller MA, et al, eds. Manual of Clinical Microbiology. 6th ed. ASM Press; 1995:905-910 3. Fugl A, Andersen CL. Epstein-Barr virus and its association with disease - a review of relevance to general practice. BMC Fam Pract. 2019;20(1):62. doi:10.1186/s12875-019-0954-3

ERG
70426

ERG Immunostain, Technical Component Only

Clinical Information: ETS-related gene (ERG) is a member of the erythroblast transformation

specific (ETS) family of transcription factors. Expression of ERG is observed in prostate cancers where the TMPRSS2-ERG gene rearrangement has occurred.

Useful For: Identification of erythroblast transformation specific (ETS)-related gene (ERG) protein expression

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. He H, Magi-Galluzzi C, Li J, et al. The diagnostic utility of novel immunohistochemical marker ERG in the workup of prostate biopsies with "atypical glands suspicious for cancer". Am J Surg Pathol. 2011;35(4):608-614 2. Park K, Tomlins SA, Mudaliar KM, et al. Antibody-based detection of ERG rearrangement-positive prostate cancer. Neoplasia. 2010;12(7):590-598 3. Karnes RJ, Cheville JC, Ida CM, et al. The ability of biomarkers to predict systemic progression in men with high-risk prostate cancer treated surgically is dependent on ERG status. Cancer Res. 2010;70(22):8994-9002 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

REVE2
618830

Erythrocytosis Evaluation, Blood

Clinical Information: Erythrocytosis (polycythemia) is identified by a sustained increase in hemoglobin or hematocrit. An isolated increase in red blood cell count (in the absence of chronic phlebotomy or coincident iron deficiency) may occur in thalassemia or other causes and does not indicate erythrocytosis. Erythrocytosis may occur as a primary disorder, due to an intrinsic defect of bone marrow stem cells, or secondary in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders, including chronic lung disease, chronic increase in carbon monoxide, cyanotic heart disease, high-altitude living, kidney cysts and tumors, hepatoma, and other EPO-secreting tumors. Rare plasma cell dyscrasia-associated syndromes such as POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) and TEMPI (telangiectasias, elevated EPO and erythrocytosis, monoclonal gammopathy, perinephric fluid collections, and intrapulmonary shunting) can be associated with increased hemoglobin levels. When these causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be present. It is important to differentiate polycythemia vera (PV) from heritable causes of erythrocytosis, the latter of which can be passed to progeny but does not carry the risks of clonal evolution or marrow fibrosis associated with PV. The most common cause of hereditary erythrocytosis is the presence of a high-oxygen-affinity (HOA) hemoglobin variant. A subset of hemoglobins with increased oxygen (O2) affinity results in clinically evident erythrocytosis caused by decreased O2 unloading at the tissue level. Many are asymptomatic; however, some patients have recurrent headaches, dizziness, fatigue, and restless legs. A subset of patients experience thrombotic episodes. Affected individuals can be plethoric, and many are misclassified as polycythemia vera, particularly prior to more recent genetic testing availability. The O2-dissociation curve is left-shifted (p50 values are decreased) in HOA variants. Changes to the amino acid sequence of the hemoglobin molecule may distort the protein structure, affecting O2 transport or unloading and the binding of 2,3-bisphosphoglyceric acid (2,3-BPG). 2,3-BPG stabilizes the deoxygenated state of hemoglobin. Therefore, a decrease in the 2,3-BPG concentration results in greater O2 affinity of the normal hemoglobin molecule. Rare cases of erythrocytosis have been associated with a reduction in 2,3-BPG formation. This is due to variants in the converting enzyme, bisphosphoglycerate mutase (BPGM). Truncating variants in the erythropoietin receptor gene, EPOR, have been shown to be a cause of the

autosomal dominant primary familial and congenital polycythemia (OMIM 133100). In addition, O2-sensing pathway variants, EPAS1(HIF2A) (OMIM 611783); EGLN1(PHD2) (OMIM 609820), and VHL (OMIM 263400) cause hereditary erythrocytosis and a subset are associated with pheochromocytoma and paragangliomas. All have shown an autosomal dominant pattern of inheritance, except VHL-associated erythrocytosis, which is an autosomal recessive disorder. Homozygous VHL R200W alterations have been shown to be causative of Chuvash polycythemia, an endemic heritable erythrocytic disorder first described in Russia but subsequently found in other ethnic groups. The prevalence of causative variants in EPOR and the O2-sensing pathway genes is unknown; however, in our experience, they are less prevalent than genetic variants that cause HOA hemoglobin variants and are much less prevalent than polycythemia vera. Because there are many causes of erythrocytosis, an algorithmic and reflexive testing strategy is useful for evaluating these disorders. Initial JAK2 V617F alteration testing and serum EPO levels are useful. Importantly, a significant subset of HOA hemoglobin variants can be electrophoretically silent on multiple routine screening platforms; however, most, and possibly all, HOA hemoglobin variants can be identified with addition of the intact mass spectrometry method. Our extensive experience with these disorders allows an economical, comprehensive evaluation with high sensitivity.

Useful For: Definitive, comprehensive, and economic evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased hemoglobin or hematocrit

Interpretation: The evaluation includes testing for a hemoglobinopathy. Reflex testing for EPOR, EGLN1 (PHD2), EPAS1 (HIF2a), VHL, and BPGM will be performed as needed. A hematopathology expert in these disorders will evaluate the case, have the appropriate tests performed, and issue an interpretive report.

Reference Values:
Definitive results and an interpretive report will be provided.

Clinical References: 1. Patnaik MM, Tefferi A. The complete evaluation of erythrocytosis: congenital and acquired. Leukemia. 2009;23(5):834-844 2. McMullin MF. The classification and diagnosis of erythrocytosis. Int J Lab Hematol. 2008;30(6):447-459 3. Percy MJ, Lee FS. Familial erythrocytosis: molecular links to red blood cell control. Haematologica. 2008;93(7):963-967 4. Huang LJ, Shen YM, Bulut GB. Advances in understanding the pathogenesis of primary familial and congenital polycythaemia. Br J Haematol. 2010;148(6):844-852 5. Maran J, Prchal J. Polycythemia and oxygen sensing. Pathol Biol. 2004;52(5):280-284 6. Lee F. Genetic causes of erythrocytosis and the oxygen-sensing pathway. Blood Rev. 2008;22(6):321-332 7. Merchant SH, Oliveira JL, Hoyer JD, Viswanatha DS. Erythrocytosis. In: His ED, ed. Hematopathology. 2nd ed. Elsevier Saunders; 2012:722-723 8. Zhuang Z, Yang C, Lorenzo F, et al. Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. N Engl J Med. 2012;367(10):922-930 9. Oliveira JL, Coon LM, Frederick LA, et al. Genotype-phenotype correlation of hereditary erythrocytosis mutations, a single center experience. Am J Hematol. 2018. doi:10.1002/ajh.25150 10. Gangat N, Oliveira JL, Hoyer JD, Patnaik MM, Pardanani A, Tefferi A. High-oxygen-affinity hemoglobinopathy-associated erythrocytosis: Clinical outcomes and impact of therapy in 41 cases. Am J Hematol. 2021;96(12):1647-1654. doi:10.1002/ajh.26375 11. Gangat N, Oliveira JL, Porter TR, et al. Erythrocytosis associated with EPAS1(HIF2A), EGLN1(PHD2), VHL, EPOR or BPGM mutations: the Mayo Clinic experience. Haematologica. 2022;107(5):1201-1204. doi:10.3324/haematol.2021.280516

REVEI
608426

Erythrocytosis Interpretation

Clinical Information: Erythrocytosis (polycythemia) is identified by a sustained increase in hemoglobin or hematocrit. An isolated increase in red blood cell count (in the absence of chronic phlebotomy or coincident iron deficiency) may occur in thalassemia or other causes and does not indicate

erythrocytosis. Erythrocytosis may occur as a primary disorder, due to an intrinsic defect of bone marrow stem cells, or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders, including chronic lung disease, chronic increase in carbon monoxide, cyanotic heart disease, high-altitude living, kidney cysts and tumors, hepatoma, and other EPO-secreting tumors. Rare plasma cell dyscrasia-associated syndromes such as POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) and TEMPI (telangiectasias, elevated EPO and erythrocytosis, monoclonal gammopathy, perinephric fluid collections, and intrapulmonary shunting) can be associated with increased hemoglobin levels. When these causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be present. It is important to differentiate polycythemia vera (PV) from heritable causes of erythrocytosis, the latter of which can be passed to progeny but does not carry the risks of clonal evolution or marrow fibrosis associated with PV. The most common cause of hereditary erythrocytosis is the presence of a high-oxygen-affinity (HOA) hemoglobin variant. A subset of hemoglobins with increased oxygen (O2) affinity result in clinically evident erythrocytosis caused by decreased O2 unloading at the tissue level. Many are asymptomatic; however, some patients have recurrent headaches, dizziness, fatigue, and restless legs. A subset of patients experience thrombotic episodes. Affected individuals can be plethoric, and many are misclassified as polycythemia vera, particularly prior to more recent genetic testing availability. The O2-dissociation curve is left-shifted (p50 values are decreased) in HOA variants. Changes to the amino acid sequence of the hemoglobin molecule may distort the protein structure, affecting O2 transport or unloading and the binding of 2,3-bisphosphoglyceric acid (2,3-BPG). 2,3-BPG stabilizes the deoxygenated state of hemoglobin. Therefore, a decrease in the 2,3-BPG concentration results in greater O2 affinity of the normal hemoglobin molecule. Rare cases of erythrocytosis have been associated with a reduction in 2,3-BPG formation. This is due to variants in the converting enzyme, bisphosphoglycerate mutase (BPGM). Truncating variants in the erythropoietin receptor gene, EPOR, have been shown to be a cause of the autosomal dominant primary familial and congenital polycythemia (OMIM 133100). In addition, O2-sensing pathway variants, EPAS1(HIF2A) (OMIM 611783); EGLN1(PHD2) (OMIM 609820), and VHL (OMIM 263400) cause hereditary erythrocytosis, and a subset are associated with pheochromocytoma and paragangliomas. All have shown an autosomal dominant pattern of inheritance, except VHL-associated erythrocytosis, which is an autosomal recessive disorder. Homozygous VHL R200W alterations have been shown to be causative of Chuvash polycythemia, an endemic heritable erythrocytic disorder first described in Russia but subsequently found in other ethnic groups. The prevalence of causative variants in EPOR and the O2-sensing pathway genes is unknown; however, in our experience, they are less prevalent than genetic variants that cause HOA hemoglobin variants and are much less prevalent than polycythemia vera. Because there are many causes of erythrocytosis, an algorithmic and reflexive testing strategy is useful for evaluating these disorders. Initial JAK2 V617F alteration testing and serum EPO levels are useful. Importantly, a significant subset of HOA hemoglobin variants can be electrophoretically silent on multiple routine screening platforms; however, most, and possibly all, HOA hemoglobin variants can be identified with addition of the intact mass spectrometry method. Our extensive experience with these disorders allows an economical, comprehensive evaluation with high sensitivity.

Useful For: Interpretation of Erythrocytosis Evaluation profile test Definitive, comprehensive, and economical evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased hemoglobin or hematocrit

Interpretation: The evaluation includes testing for a hemoglobinopathy. Reflex testing for EPOR, EGLN1 (PHD2), EPAS1 (HIF2a), VHL, and BPGM will be performed as needed.

Reference Values:
Only orderable as part of a profile. For more information see REVE2 / Erythrocytosis Evaluation, Blood.

Definitive results and an interpretative report will be provided.

Clinical References: 1. Patnaik MM, Tefferi A. The complete evaluation of erythrocytosis: congenital and acquired. Leukemia. 2009;23(5):834-844 2. McMullin MF. The classification and diagnosis of erythrocytosis. Int J Lab Hematol. 2008;30(6):447-459 3. Percy MJ, Lee FS. Familial erythrocytosis: molecular links to red blood cell control. Haematologica. 2008;93(7):963-967 4. Huang LJ, Shen YM, Bulut GB. Advances in understanding the pathogenesis of primary familial and congenital polycythaemia. Br J Haematol. 2010;148(6):844-852 5. Maran J, Prchal J. Polycythemia and oxygen sensing. Pathol Biol. 2004;52(5):280-284 6. Lee F. Genetic causes of erythrocytosis and the oxygen-sensing pathway. Blood Rev. 2008;22(6):321-332 7. Merchant SH, Oliveira JL, Hoyer JD, Viswanatha DS. Erythrocytosis. In: His ED, ed. Hematopathology. 2nd ed. Elsevier Saunders; 2012: 722-723 8. Zhuang Z, Yang C, Lorenzo F, et al. Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. N Engl J Med. 2012;367(10):922-930 9. Oliveira JL, Coon LM, Frederick LA, et al. Genotype-phenotype correlation of hereditary erythrocytosis mutations, a single center experience. Am J Hematol. 2018. doi:10.1002/ajh.25150 10. Gangat N, Oliveira JL, Hoyer JD, Patnaik MM, Pardanani A, Tefferi A. High-oxygen-affinity hemoglobinopathy-associated erythrocytosis: Clinical outcomes and impact of therapy in 41 cases. Am J Hematol. 2021;96(12):1647-1654. doi:10.1002/ajh.26375 11. Gangat N, Oliveira JL, Porter TR, et al. Erythrocytosis associated with EPAS1(HIF2A), EGLN1(PHD2), VHL, EPOR or BPGM mutations: the Mayo Clinic experience. Haematologica. 2022;107(5):1201-1204. doi:10.3324/haematol.2021.280516

REVE0
608094

Erythrocytosis Summary Interpretation

Clinical Information: The etiology of congenital (inherited) erythrocytosis can be due to one of several abnormalities. This includes high oxygen affinity hemoglobin variants, genetic variants in the erythropoietin receptor gene, genetic variants in the genes involved in the oxygen-sensing pathway (PHD2/EGLN1, HIF2A/EPAS1, VHL) or BPGM variants causing 2,3-BPG (2,3-bisphosphoglycerate) deficiency. To determine the underlying abnormality frequently requires molecular testing. A summary interpretation that incorporates all testing performed is beneficial to the ordering clinician.

Useful For: Incorporating and summarizing subsequent results into an overall interpretation for the REVE2 / Erythrocytosis Evaluation, Blood

Interpretation: An interpretive report will be provided that summarizes all testing as well as any pertinent clinical information.

Reference Values:
Only orderable as a reflex. For more information see REVE2 / Erythrocytosis Evaluation, Blood.

An interpretive report will be provided.

Clinical References: 1. Patnaik MM, Tefferi A. The complete evaluation of erythrocytosis: congenital and acquired. Leukemia. 2009;23(5):834-844 2. Percy MJ, Lee FS. Familial erythrocytosis: molecular links to red blood cell control. Haematologica. 2008;93(7):963-967 3. Maran J, Prchal J. Polycythemia and oxygen sensing. Pathol Biol (Paris). 2004;52(5):280-284 4. Merchant SH, Oliveira JL, Hoyer JD, Viswanatha DS. Erythrocytosis. In: His ED, ed. Hematopathology. 2nd ed. Elsevier Saunders; 2012:722-723 5. Harteveld CL, Higgs DR. Alpha-thalassemia. Orphanet J Rare Dis. 2010;5:13 6. Thein SL. The molecular basis of beta-thalassemia. Cold Spring Harb Persepct Med. 2013 1;3(5):a011700 7. Crowley MA, Mollan TL, Abdulmalik OY, et al. A hemoglobin variant associated with neonatal cyanosis and anemia. N Engl J Med. 2011;364(19):1837-1843 8. Kipp BR, Roellinger SE, Lundquist PA, Highsmith WE, Dawson DB. Development and clinical implementation of a combination deletion PCR and multiplex ligation-dependent probe amplification assay for detecting deletions involving the human alpha-globin gene cluster. J Mol Diagn. 2011;13(5):549-557. doi:10.1016/j.jmoldx.2011.04.001 9. Hein MS, Oliveira JL, Swanson KC, et al. Large deletions involving the beta globin gene complex: genotype-

phenotype correlation of 119 cases. Blood. 2015;126:3374

EPOR 61679 Erythropoietin Receptor (EPOR) Gene, Exon 8 Sequencing, Whole Blood

Clinical Information: Erythrocytosis (ie, increased red blood cell [RBC] mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, kidney cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases are associated with pheochromocytoma or paraganglioma formation. Hereditary erythrocytosis is caused by variants in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new alterations to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (see Table). The true prevalence of hereditary erythrocytosis-causing alterations is unknown. The hemoglobin genes, HBA1/HBA2 and HBB are not assayed in this profile. Table. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum EPO JAK2 V617F Acquired Decreased JAK2 exon 12 Acquired Decreased EPOR Dominant Decreased PHD2/EGLN1 Dominant Normal level BPGM Recessive Normal level Beta Globin Dominant Normal level to increased Alpha Globin Dominant Normal level to increased HIF2A/EPAS1 Dominant Normal level to increased VHL Recessive Normal level to increased The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the PHD2 (EGLN1) gene. Genetic variants resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants in PHD2/EGLN1 and HIF2A/EPAS1 have also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating variants in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known alterations have been localized to exon 8 and are heterozygous truncating variants. EPOR variants are associated with decreased EPO levels (see Table).

Useful For: Assessing EPOR in the evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased red blood cell (RBC) mass, elevated RBC count, hemoglobin, or hematocrit

Interpretation: Assessing EPOR in the evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased red blood cell (RBC) mass, elevated RBC

count, hemoglobin, or hematocrit

Reference Values:
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations, Whole Blood.

An interpretive report will be provided.

Clinical References: 1. Patnaik MM, Tefferi A: The complete evaluation of erythrocytosis: congenital and acquired. Leukemia. 2009 May;23(5):834-844. doi: 10.1038/leu.2009.54 2. McMullin MF: The classification and diagnosis of erythrocytosis. Int J Lab Hematol. 2008;30:447-459 3. Percy MJ, Lee FS: Familial erythrocytosis: molecular links to red blood cell control. Haematologica. 2008 Jul;93(7):963-967. doi: 10.3324/haematol.13250 4. Huang LJ, Shen YM, Bulut GB: Advances in understanding the pathogenesis of primary familial and congenital polycythaemia. Br J Haematol. 2010 Mar;148(6):844-852 5. Maran J, Prchal J: Polycythemia and oxygen sensing. Pathologie Biologie. 2004 Jun;52(5):280-284 6. Lee F: Genetic causes of erythrocytosis and the oxygen-sensing pathway. Blood Rev. 2008 Nov;22(6):321-332 7. Merchant SH, Oliveira JL, Hoyer JD, Viswanatha DS: Erythrocytosis. In: His ED, ed. Hematopathology. 2nd ed. Elsevier Saunders; 2012:22-723 8. Zhuang Z, Yang C, Lorenzo F, et al: Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. N Engl J Med. 2012 Sep 6;367(10):922-930 9. Ladroue C, Carcenac R, Leporrier M, et al: PHD2 mutation and congenital erythrocytosis with paraganglioma. N Engl J Med. 2008 Dec 18;359(25):2685-2692 10. Lorenzo FR, Yang C, Ng Tang Fui M, et al: A novel EPAS1/HIF2A germline mutation in congenital polycythemia with paraganglioma. J Mol Med. 2013 Apr;91(4):507-512 11. Tarade D, Robinson CM, Lee JE, Ohh M: HIF-2alpha-pVHL complex reveals broad genotype-phenotype correlations in HIF-2aalpha-driven disease. Nat Commun. 2018 Aug 22;9(1):3359 12. Oliveira JL: Algorithmic evaluation of hereditary erythrocytosis: Pathways and caveats. Int J Lab Hematol. 2019 May;41 Suppl 1:89-94. doi: 10.1111/ijlh.13019

EPO
80173

Erythropoietin, Serum

Clinical Information: Erythropoietin (EPO), a large (193 amino acid residue) glycoprotein hormone secreted by the kidney, regulates red blood cell (RBC) production. Normally, EPO levels vary inversely with hematocrit. Hypoxia stimulates EPO release, which, in turn, stimulates bone marrow erythrocyte production. High blood levels of RBC, hemoglobin, hematocrit, or oxygen suppress the release of EPO. Primary polycythemia (polycythemia vera) is a neoplastic (clonal) blood disorder characterized by autonomous production of hematopoietic cells. Increased RBCs result in compensatory suppression of EPO levels. Findings consistent with polycythemia vera include hemoglobin greater than 18.5 g/dL, persistent leukocytosis, persistent thrombocytosis, unusual thrombosis, splenomegaly, and erythromelalgia (dysesthesia and erythema involving the distal extremities). Secondary polycythemias may either be due to an appropriate or an inappropriate increase in red cell mass. Appropriate secondary polycythemias (eg, high-altitude living and pulmonary disease) are characterized by hypoxia and a compensatory increase in red cell mass. EPO production is increased in an attempt to increase the delivery of oxygen by increasing the number of oxygen-carrying RBCs. Some tumors secrete EPO or EPO-like proteins; examples include tumors of the kidney, liver, lung, and brain. Such increases result in inappropriate secondary polycythemias. Abnormal EPO levels also may be seen in renal failure. The majority of EPO production is in the kidneys. Therefore, chronic kidney failure may result in decreased EPO production and, subsequently, anemia. In addition to the kidneys, the liver also produces a small amount of EPO. Thus, patients who are anephric have a residual amount of EPO produced by the liver. Patients in chronic kidney failure, as well as patients with anemia due to a variety of other causes including chemotherapy, HIV/AIDS, and some hematologic disorders, may be candidates for treatment with recombinant human EPO. Recombinant EPO compounds used to treat anemia include epoetin alpha and darbepoetin. Epoetin alpha is a 165 amino acid glycoprotein produced in mammalian cells and has an identical amino acid sequence to natural human EPO. It has 3 oligosaccharide chains and a molecular

mass of 30.4 kDa. Darbepoetin alpha is a 165 amino acid glycoprotein that is also produced in mammalian cells. It has 2 additional N-linked oligosaccharide chains and a molecular mass of 37 kDa. There are no specific assays for measuring recombinant EPO compounds. Drug levels can only be roughly estimated from the cross reactivity of the compounds in EPO assays. According to in-house studies, epoetin and darbepoetin show approximately 58% and 36% cross-reactivity, respectively, in the EPO assay.

Useful For: An aid in distinguishing between primary and secondary polycythemia Differentiating between appropriate secondary polycythemia (eg, high-altitude living, pulmonary disease, tobacco use) and inappropriate secondary polycythemia (eg, tumors) Identifying candidates for erythropoietin (EPO) replacement therapy (eg, those with chronic renal failure) Evaluating patients undergoing EPO replacement therapy who demonstrate an inadequate hematopoietic response

Interpretation: In the appropriate clinical setting (eg, confirmed elevation of hemoglobin >18.5 g/dL, persistent leukocytosis, persistent thrombocytosis, unusual thrombosis, splenomegaly, and erythromelalgia), polycythemia vera is unlikely when erythropoietin (EPO) levels are elevated but is likely when EPO levels are suppressed. EPO levels are also increased in patients with anemia of bone marrow failure, iron deficiency, or thalassemia. Patients, who have either a poor or no erythropoietic response to EPO therapy, but high-normal or high EPO levels, may have additional, unrecognized causes for their anemia. If no contributing factors can be identified after adequate further study, the possibility that the patient may have developed EPO-antibodies should be considered. This can be a serious clinical situation that can result in red cell aplasia and should prompt expeditious referral to hematologists or immunologists skilled in diagnosing and treating this disorder.

Reference Values:
2.6-18.5 mIU/mL

Clinical References: 1. Tefferi A: Diagnosing polycythemia vera: a paradigm shift. Mayo Clin Proc. 1999;74:159-162 2. Hoagland HC: Myelodysplastic (preleukemia) syndromes: the bone marrow factory failure problem. Mayo Clin Proc. 1995;70:673-677 3. Casadeval N: Pure red cell aplasia and anti-erythropoietin antibodies in patients treated with epoetin. Nephrol Dial Transplant. 2003;18 (Suppl. 8):viii37-viii41 4. Fisher JW: Erythropoietin: physiology and pharmacology update. Exp Biol Med. 2003;228:1-14 5. Strippoli GFM, Manno C, Schena FP, Craig JC: Haemoglobin and haematocrit targets for the anaemia of chronic kidney disease. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD003967 6. Tefferi A: Polycythemia vera and essential thrombocythemia: 2012 update on diagnosis, risk stratification, and management. Am J Hematol. 2012 Mar;87:285-293. doi: 10.1002/ajh.23135 7. Moore E, Bellomo R: Erythropoietin (EPO) in acute kidney injury. Ann Intensive Care. 2011 March;1(3). doi: 10.1186/2110-5820-1-3 8. Macdougall I: Anaemia and chronic renal failure. Medicine. 2011;39(7):425-428. doi: 10.1016/j.mpmed.2011.04.009

E157C
606219

Escherichia coli O157:H7 Culture, Feces

Clinical Information: Diarrhea may be caused by a number of agents, including bacteria, viruses, parasites, and chemicals; these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the healthcare professional determine the appropriate testing to be performed. Shiga toxin-producing Escherichia coli (STEC) are E coli strains capable of producing Shiga toxin, which can result in diarrhea that can be bloody. The incubation period between exposure and symptom onset is 1 to 9 days. Hemolytic-uremic syndrome (HUS) is a systemic complication of STEC infection and is characterized by kidney failure, microangiopathic hemolytic anemia, and nonimmune thrombocytopenia. HUS complicates approximately 15% of STEC infections in children younger than 10 years and 6% to 9% overall.

Treatment of STEC infection consists of supportive care. Antibiotic therapy is generally not beneficial in patients with STEC infection and has been associated with development of HUS in some studies. Thus, when STEC is clinically suspected, antibiotics should be withheld. Antiperistaltic agents also increase the risk of systemic complications and should be avoided.

Useful For: Determining whether Escherichia coli O157:H7 may be the cause of diarrhea Reflexive testing for Shiga toxin and/or E coli O157:H7 nucleic acid amplification test-positive feces This test is generally not useful for patients hospitalized more than 3 days because the yield from specimens from these patients is very low, as is the likelihood of identifying a pathogen that has not been detected previously.

Interpretation: The growth of Escherichia coli O157:H7 identifies a potential cause of diarrhea.

Reference Values:
No growth of Escherichia coli O157:H7

Clinical References: 1. DuPont HL. Persistent diarrhea: A clinical review. JAMA. 2016;315(24):2712-2723. doi:10.1001/jama.2016.7833 2. Page AV, Liles WC. Enterohemorrhagic Escherichia coli infections and the hemolytic-uremic syndrome. Med Clin North Am. 2013;97(4):681-695 3. Nelson JM, Griffin PM, Jones TF, et al. Antimicrobial and antimotility agent use in persons with shiga toxin-producing Escherichia coli O157 infection in FoodNet Sites. Clin Infect Dis. 2011;52(9):1130-1130

ESR1T
616500

ESR1 Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information: The ESR1 (estrogen receptor 1) gene encodes an estrogen receptor that regulates cell growth through activation of downstream signaling pathways upon binding of estrogen. Tumors demonstrating estrogen receptor expression by immunohistochemistry (ER-positive) are candidates for endocrine therapy, such as selective estrogen receptor modulators (SERM), selective estrogen receptor degraders/downregulators (SERD), and aromatase inhibitors. ESR1 mutations are rarely observed in untreated breast cancers; however, mutations in the ligand-binding domain of ESR1 can occur secondarily after exposure to aromatase inhibitors and other endocrine therapies in ER-positive metastatic breast tumors, frequently with multiple different mutations in ESR1 occurring together. Current data suggests that ESR1 mutations mediate resistance to endocrine therapy. Studies also suggest that ESR1 mutations are an independent indicator of poor prognosis. This test assesses for somatic mutations in ESR1, including the ligand-binding domain(exons 4-9 in reference transcript NM_001122740). Breast cancers with mutations in the ligand binding domain of ESR1 may be responsive to elacestrant (Orserdu), an endocrine therapy in the SERD class of drugs that is clinically approved for postmenopausal women or adult men with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

Useful For: Assisting in the clinical management of patients with metastatic breast cancer by identifying tumors with evolving resistance to endocrine therapy Stratifying prognosis of metastatic breast cancer

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation

sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. Arenedos M, Vicier C, Loi S, et al. Precision medicine for metastatic breast cancer-limitations and solutions. Nat Rev Clin Oncol. 2015;12(12):693-704. doi: 10.1038/nrclinonc.2015.123 4. Angus L, Beije N, Jager A, et al. ESR1 mutations: Moving towards guiding treatment decision-making in metastatic breast cancer patients. Cancer Treat Rev. 2017;52:33-40. doi: 10.1016/j.ctrv.2016.11.001 5. Gradishar WJ, Moran MS, Abraham J, et al. NCCN Guidelines Insights: Breast Cancer, version 4.2021. J Natl Compr Canc Netw. 2021;19(5):484-493. doi: 10.6004/jnccn.2021.0023 6. Toy W, Shen Y, Won H, et al. ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. Nat Genet. 2013;45(12):1439-1445. doi: 10.1038/ng.2822 7. Robinson DR, Wu YM, Vats P, et al. Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet. 2013;45(12):1446-1451. doi: 10.1038/ng.2823 8. Toy W, Weir H, Razavi P, et al. Activating ESR1 mutations differentially affect the efficacy of ER antagonists. Cancer Discov. 2017;7(3):277-287. doi: 10.1158/2159-8290.CD-15-1523 9. Bidard FC, Kaklamani VG, Neven P et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized phase III EMERALD trial. J Clin Oncol. 2022;40(28):3246-3256

FFES
91215

Estradiol Free, Serum (includes Estradiol and SHBG)

Reference Values:

Estradiol, Serum MS
Units: pg/mL

Age	Range
Newborn	

Levels are markedly elevated at birth and fall rapidly during the first week to prepubertal values of <15.

Males <6 m

Levels increase to 10 - 32 between 30 and 60 days, then decline to prepubertal levels of <15 by six months.

Females <1 y

Levels increase to 5.0 - 50 between 30 and 60 days, then decline to prepubertal levels of <15 during the first year.

Prepubertal	<15
Adult Males	8.0 - 35
Adult Females	
Follicular	30 - 100
Luteal	70 - 300
Postmenopausal	<15

Free Estradiol, Percent
Units: %

Age	Range
Adult Males	1.7 - 5.4
Adult Females	1.6 - 3.6

Free Estradiol, Serum

Units: pg/mL

Age	Range
Adult Males	0.2 - 1.5
Adult Females	0.6 - 7.1

Sex Hormone Binding Globulin
Units: nmol/L

Age	Range
Infants (1 - 23m)	60.0 - 252.0
Prepubertal	72.0 - 220.0
Pubertal	
Males	16.0 - 100.0
Females	36.0 - 125.0
Adult Males	
20 - 49 y	16.5 - 55.9
>49y	19.3 - 76.4
Adult Females	
20 – 49y	24.6 - 122.0
>49y	17.3 - 125.0

ESTS
8575

Estradiol, Rapid, Immunoassay, Serum

Clinical Information: Estrogens are responsible for the development and maintenance of female sex organs and female secondary sex characteristics. In conjunction with progesterone, they participate in regulation of the menstrual cycle, breast and uterine growth, and in the maintenance of pregnancy. Estrogens affect calcium homeostasis and have a beneficial effect on bone mass. They decrease bone resorption, and in prepubertal girls, estrogen accelerates linear bone growth. Long-term estrogen depletion is associated with loss of bone mineral content, an increase in stress fractures, and postmenopausal osteoporosis. The 3 most biologically active estrogens in order of potency are estrone, estradiol (E2), and estriol. Estrogens are produced primarily in the ovary (follicle, corpus luteum), but small quantities are also formed in the testes and in the adrenal cortex. During pregnancy, estrogens are mainly formed in the placenta. About 98% of estradiol is bound to transport proteins (sex hormone-binding globulin) and albumin. Estrogen secretion is biphasic during the menstrual cycle. The determination of E2 is utilized clinically in the elucidation of fertility disorders in the hypothalamus-pituitary-gonad axis, gynecomastia, estrogen-producing ovarian and testicular tumors, and in hyperplasia of the adrenal cortex. Additional clinical indications are the monitoring of fertility therapy and determining the time of ovulation within the framework of in vitro fertilization. The laboratory plays an important role in the process of ovulation induction. The principle involves administration of gonadotropins to stimulate follicular growth, followed by human chorionic gonadotropin (hCG) to stimulate ovulation follicular maturation. Clinical, laboratory, and ultrasound monitoring of the treatment cycle is necessary to identify the dose and length of therapy, determine when or whether to administer hCG, and obtain an adequate ovulatory response while avoiding hyperstimulation.

Useful For: Rapid assessment of ovarian status, including follicle development, for assisted reproduction protocols (eg, in vitro fertilization) Establishing time of ovulation and optimal time for conception

Interpretation: Optimal time for conception is within 48 to 72 hours following the midcycle estradiol peak. Serial specimens must be drawn over several days to evaluate baseline and peak estradiol levels. Low baseline levels and a lack of rise, as well as persistent high levels without midcycle rise, are indicative of anovulatory cycles. For determining the timing of initiation of ovarian stimulation in in vitro

fertilization (IVF) studies, low levels before stimulation are critical, as higher values often are associated with poor stimulation cycles. Before final human chorionic gonadotropin (hCG) stimulation at mid-IVF cycle, estradiol concentrations above 2000 to 3000 pg/mL are considered by some IVF specialists to be indicative of an increased likelihood of ovarian hyperstimulation and it may be advisable to consider withholding further hCG stimulation. Estradiol (E2) concentrations below 200 pg/mL following midcycle stimulation (hCG or follicle-stimulating hormone [FSH]) are associated with very low pregnancy success rates. Estradiol concentrations change during the menstrual cycle, as follows: -less than 50 pg/mL before midfollicular phase -250 to 500 pg/mL midcycle peak as the follicle matures -Abrupt decrease after ovulation -125 pg/mL peak during the luteal phase Estrogen replacement in reproductive-age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women and luteinizing hormone and FSH should be within the normal range.

Reference Values:

Males: 10-40 pg/mL
Females
Premenopausal: 15-350 pg/mL*
Postmenopausal: <10 pg/mL
*Estradiol concentrations vary widely throughout the menstrual cycle

Clinical References: 1. Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 2. Practice Committee of the American Society for Reproductive Medicine. Ovarian hyperstimulation syndrome. Fertil Steril. 2008;90(5 Suppl):S188-S193

EEST
81816

Estradiol, Serum

Clinical Information: Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important for many other, nongender-specific processes, including growth, nervous system maturation, bone metabolism/remodeling, and endothelial responsiveness. The 2 major biologically active estrogens in nonpregnant humans are estrone (E1) and estradiol (E2). A third bioactive estrogen, estriol (E3), is the main pregnancy estrogen, but plays no significant role in nonpregnant women or men. Estradiol is produced primarily in ovaries and testes by aromatization of testosterone. Small amounts are produced in the adrenal glands and some peripheral tissues, most notably fat. By contrast, most of the circulating E1 is derived from peripheral aromatization of androstenedione (mainly adrenal). E2 and E1 can be converted into each other, and both can be inactivated via hydroxylation and conjugation. E2 demonstrates 1.25 to 5 times the biological potency of E1. E2 circulates at 1.5 to 4 times the concentration of E1 in premenopausal, nonpregnant women. E2 levels in men and postmenopausal women are much lower than in nonpregnant women, while E1 levels differ less, resulting in a reversal of the premenopausal E2:E1 ratio. E2 levels in premenopausal women fluctuate during the menstrual cycle. They are lowest during the early follicular phase. E2 levels then rise gradually until 2 to 3 days before ovulation, at which stage they start to increase much more rapidly and peak just before the ovulation-inducing luteinizing hormone (LH)/follicle stimulating hormone (FSH) surge at 5 to 10 times the early follicular levels. This is followed by a modest decline during the ovulatory phase. E2 levels then increase again gradually until the midpoint of the luteal phase and, thereafter, decline to trough, early follicular levels. Measurement of serum E2 forms an integral part of the assessment of reproductive function in females, including assessment of infertility, oligo-amenorrhea, and menopausal status. In addition, it is widely used for monitoring ovulation induction, as well as during preparation for in vitro fertilization. For these applications E2 measurements with modestly sensitive assays suffice. However, extra sensitive E2 assays, simultaneous measurement of E1, or both are needed in a number of other clinical situations. These include inborn errors of sex steroid metabolism, disorders of puberty, estrogen deficiency in men, fracture risk assessment in menopausal women, and increasingly, therapeutic drug monitoring, either in

the context of low-dose female hormone replacement therapy or antiestrogen treatment. For more information see Steroid Pathways.

Useful For: All applications that require moderately sensitive measurement of estradiol: -Evaluation of hypogonadism and oligo-amenorrhea in females -Assessing ovarian status, including follicle development, for assisted reproduction protocols (eg, in vitro fertilization) -In conjunction with luteinizing hormone measurements, monitoring of estrogen replacement therapy in hypogonadal premenopausal women -Evaluation of feminization, including gynecomastia, in males -Diagnosis of estrogen-producing neoplasms in males and, to a lesser degree, females -As part of the diagnosis and workup of precocious and delayed puberty in females, and, to a lesser degree, males -As part of the diagnosis and workup of suspected disorders of sex steroid metabolism (eg, aromatase deficiency and 17 alpha-hydroxylase deficiency) -As an adjunct to clinical assessment, imaging studies and bone mineral density measurement in the fracture risk assessment of postmenopausal women, and, to a lesser degree, older men -Monitoring low-dose female hormone replacement therapy in postmenopausal women -Monitoring antiestrogen therapy (eg, aromatase inhibitor therapy)

Interpretation: Estradiol (E2) levels below the premenopausal reference range in young females indicate hypogonadism. If luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels are elevated, primary gonadal failure is diagnosed. The main causes are genetic (eg, Turner syndrome, familial premature ovarian failure), autoimmune (eg, autoimmune ovarian failure, possibly as part of autoimmune polyglandular endocrine failure syndrome type II), and toxic (eg, related to chemotherapy or radiation therapy for malignant disease). If LH/FSH levels are low or inappropriately "normal," a diagnosis of hypogonadotrophic hypogonadism is made. This can have functional causes, such as starvation, overexercise, severe physical or emotional stress, and heavy drug and/or alcohol use. It also can be caused by organic disease of the hypothalamus or pituitary. Further workup is usually necessary, typically including measurement of pituitary hormones (particularly prolactin), and possibly imaging. Irregular or absent menstrual periods with normal or high E2 levels (and often high estrone: E1 levels) are indicative of possible polycystic ovarian syndrome, androgen producing tumors, or estrogen producing tumors. Further workup is required and usually includes measurement of total and bioavailable testosterone, androstenedione, dehydroepiandrosterone (sulfate), sex hormone-binding globulin, and possibly imaging. Estradiol levels change during the menstrual cycle, as follows: -Post-menses, levels may be as low as 15 pg/mL -Levels then rise during the follicular phase to a preovulatory peak, typically in the 300+ pg/mL range -Levels fall in the luteal phase -Menses typically occur when E2 levels are in the 50 to 100 pg/mL range Estradiol analysis may be helpful in establishing time of ovulation and optimal time for conception. Optimal time for conception is within 48 to 72 hours following the midcycle E2 peak. Serial specimens must be collected over several days to evaluate baseline and peak total estrogen (E1 + E2) levels. Low baseline levels and a lack of rise, as well as persistent high levels without midcycle rise, are indicative of anovulatory cycles. For determining the timing of initiation of ovarian stimulation in vitro fertilization studies, low levels (around 30 pg/mL) before stimulation, are critical, as higher values often are associated with poor stimulation cycles. Estrogen replacement in reproductive-age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women, LH/FSH should be within the normal range, and E2 levels should ideally be higher than E1 levels. The current recommendations for postmenopausal female hormone replacement are to administer therapy in the smallest beneficial doses for as briefly as possible. Ideally, E2 and E1 levels should be held below, or near, the lower limit of the premenopausal female reference range. Postmenopausal women and older men in the lowest quartile of E2 levels are at increased risk of osteoporotic fractures. E2 levels are typically less than 5 pg/mL in these patients. Antiestrogen therapy with central or peripheral acting agents that are not pure receptor antagonists usually aims for complete suppression of E2 production, and in the case of aromatase inhibitors, complete E1 and E2 suppression. Gynecomastia or other signs of feminization in males may be due to an absolute or relative (in relation to androgens) surplus of estrogens. Gynecomastia is common during puberty in boys. Unless E1, E2, or testosterone levels exceed the adult male reference range, the condition is usually not due to hormonal disease (though it sometimes may still result in persistent breast tissue, which later needs to be surgically removed). For adults with gynecomastia, the workup should include testosterone and adrenal

androgen measurements, in addition to E2 and E1 measurements. Causes for increased E1 or E2 levels include: -High androgen levels caused by tumors or androgen therapy (medical or sport performance enhancing), with secondary elevations in E1 and E2 due to aromatization -Obesity with increased tissue production of E1 -Decreased E1 and E2 clearance in liver disease -Estrogen producing tumors -Estrogen ingestion Normal E1 and E2 levels in males may also be associated with feminization or gynecomastia if bioavailable testosterone levels are low due to primary/secondary testicular failure. This may occur, for example, when patients are receiving antiandrogen therapy or other drugs with antiandrogenic effects (eg, spironolactone, digitalis preparations). The gonadotrophin-releasing hormone stimulation test remains the central part of the workup for precocious puberty. However, baseline sex steroid and gonadotrophin measurements also are important. Prepubertal girls have E2 levels below 10 pg/mL (most <5 pg/mL). Levels in prepubertal boys are less than half the levels seen in girls. LH/FSH are very low or undetectable. E1 levels also are low but may rise slightly in obese children after onset of adrenarche. E2, which is produced in the gonads, should remain low in these children. In true precocious puberty, both E2 and LH/FSH levels are elevated above the prepubertal range. Elevation of E2 or E1 alone suggests pseudo-precocious puberty, possibly due to a sex steroid-producing tumor. In delayed puberty, estrogens and gonadotrophins are in the prepubertal range. A rise over time predicts the spontaneous onset of puberty. Persistently low estrogens and elevated gonadotrophins suggest primary ovarian failure, while low gonadotrophins suggest hypogonadotrophic hypogonadism. In this latter case, Kallmann syndrome (or related disorders) or hypothalamic/pituitary tumors should be excluded in well-nourished children. Inherited disorders of sex steroid metabolism are usually associated with production abnormalities of other steroids, most notably a lack of cortisol. Aromatase deficiency is not associated with cortisol abnormalities and usually results in some degree of masculinization in affected female patients, as well as primary failure of puberty. Male patients may show delayed puberty and delayed epiphyseal closure, as well as low bone-density. E2 and E1 levels are very low or undetectable. Various forms of testicular feminization are due to problems in androgen signaling pathways and are associated with female (or feminized) phenotypes in genetic males. E2 and E1 levels are above the male reference range, usually within the female reference range, and testosterone levels are very high. For more information see Steroid Pathways.

Reference Values:

CHILDREN* 1 to14 days: Estradiol levels in newborns are very elevated at birth but will fall to prepubertal levels within a few days. Males Tanner stages#	**Mean age**	**Reference range**
Stage I (>14 days and prepubertal)	7.1 years	Undetectable-13 pg/mL
Stage II	12.1 years	Undetectable-16 pg/mL
Stage III	13.6 years	Undetectable-26 pg/mL
Stage IV	15.1 years	Undetectable-38 pg/mL
Stage V	18 years	10-40 pg/mL
#Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/- 2) years. For boys, there is no proven relationship between puberty onset and body weight or ethnic	Mean age	Reference range

origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. Females

Tanner stages#		
Stage I (>14 days and prepubertal)	7.1 years	Undetectable-20 pg/mL
Stage II	10.5 years	Undetectable-24 pg/mL
Stage III	11.6 years	Undetectable-60 pg/mL
Stage IV	12.3 years	15-85 pg/mL
Stage V	14.5 years	15-350 pg/mL**

Clinical References: 1. Bidlingmaier F, Wagner-Barnack M, Butenandt O, Knorr D. Plasma estrogens in childhood and puberty under physiologic and pathologic conditions. Pediatr Res. 1973;7(11):901-907 2. Elmlinger MW, Kuhnel W, Ranke MB. Reference ranges for serum concentrations of lutropin (LH), follitropin (FSH), estradiol (E2), prolactin, progesterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), cortisol and ferritin in neonates, children and young adults. Clin Chem Lab Med. 2002;40 (11):1151-1160 3. Cummings SR, Browner WS, Bauer D, et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. N Engl J Med. 1998;339(11):733-738 4. Lughetti L, Predieri B, Ferrari M, et al. Diagnosis of central precocious puberty: endocrine assessment. J Pediatr Endocrinol Metab. 2000;13 Suppl 1:709-715 5. Ismail AA, Barth JH: Endocrinology of gynaecomastia. Ann Clin Biochem. 2001;38(Pt 6):596-607 6. Kligman I, Rosenwaks Z. Differentiating clinical profiles: predicting good responders, poor responders, and hyperresponders. Fertil Steril 2001;76(6):1185-1190 7. Traggiai C, Stanhope R. Delayed puberty. Best Pract Res Clin Endocrinol Metab. 2002;16(1):139-151 8. Anari MR, Bakhtiar R, Zhu B, Huskey S, et al. Derivatization of ethynylestradiol with dansyl chloride to enhance electrospray ionization: application in trace analysis of ethynylestradiol in Rhesus monkey plasma. Anal Chem. 2002;74(16):4136-4144 9. Mauras N, Ross JL, Gagliardi P, et al. Randomized trial of aromatase inhibitors, growth hormone, or combination in pubertal boys with idiopathic, short stature. J Clin Endocrinol Metab. 2016;101(12):4984-4993. doi:10.1210/jc.2016-2891 10. Ketha H, Girtman A, Singh RJ. Estradiol assays--The path ahead. Steroids. 2015;99(Pt A):39-44. doi:10.1016/j.steroids.2014.08.009 11. Ingle JN, Cairns J, Suman VJ, et al. Anastrozole has an association between degree of estrogen suppression and outcomes in early breast cancer and is a ligand for estrogen receptor a. Clin Cancer Res. 2020;26(12):2986-2996. doi:10.1158/1078-0432.CCR-19-3091 12. Richardson H, Ho V, Pasquet R, et al. Baseline estrogen levels in postmenopausal women participating in the MAP.3 breast cancer chemoprevention trial. Menopause. 2020;27(6):693-700. doi:10.1097/GME.0000000000001568

UE3
81711

Estriol, Unconjugated, Serum

Clinical Information: Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. There are 3 major biologically active estrogens in humans: estrone (E1), estradiol (E2), and estriol (E3). Like all members of the steroid hormone family, they diffuse into cells and bind to specific nuclear receptors, which in turn alter gene transcription in a tissue specific manner. E2 is the most potent natural human estrogen, closely followed by E1, while E3 possess only 20% of the E2 affinity for the estrogen receptor. In men and nonpregnant women, E1 and E2 are formed from the androgenic steroids, androstenedione and testosterone, respectively. E3 is derived largely through conversion of E2, and to a lesser degree from 16a-metabolites of E1. E2 and E1 can also be converted into each other, and both can be inactivated via hydroxylation and conjugation. During pregnancy E3 becomes the dominant estrogen. The fetal adrenal gland secretes dehydroepiandrosterone-sulfate, which is converted to E3 in the placenta and diffuses into the maternal circulation. The half-life of unconjugated E3 (uE3) in the maternal blood system is 20 to 30 minutes since the maternal liver quickly conjugates E3 to make it more water soluble for urinary excretion. E3 levels increase throughout the course of pregnancy, peaking at term.

Useful For: As an adjunct biomarker in the prenatal diagnosis of disorders of fetal steroid metabolism, including Smith-Lemli-Opitz syndrome (1,2) and X-linked ichthyosis (placental sulfatase deficiency disorders) Evaluating primary or secondary fetal adrenal insufficiency after excluding other rare single gene defects, including aromatase deficiency, 17 alpha-hydroxylase deficiency and/or various forms of congenital adrenal hyperplasia

Interpretation: A low uE3 level can indicate the possibility of aromatase deficiency, congenital adrenal hyperplasia, primary or secondary (including maternal corticosteroid therapy) fetal adrenal insufficiency and/or fetal demise. This test is reported in ng/mL only. If the multiple of the median (MoM) is desired, please consider ordering QUAD1 / Quad Screen (Second Trimester) Maternal, Serum.

Reference Values:
Males: <0.07 ng/mL
Females: <0.08 ng/mL

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Bradley LA, Palomaki GE, Knight GJ, et al. Levels of unconjugated estriol and other maternal serum markers in pregnancies with Smith Lemli Opitz (RSH) syndrome fetuses [letter]. Am J Med Genet. 1999;82:355-358 2. Reisch N, Idkowiak J, Hughes B. Prenatal diagnosis of congenital adrenal hyperplasia caused by P450 oxidoreductase deficiency. J Clin Endocrinol Metab. 2013;98(3):E528-E536. doi:10.1210/jc.2012-3449 3. Thaniyaporn S, Chanane W, Supatra S, et al. Association between isolated abnormal levels of maternal serum unconjugated estriol in the second trimester and adverse pregnancy outcomes. J Matern Fetal Neonatal Med. 2016;29:13, 2093-2097 4. Minsart AF, Van Onderbergen A, Jacques F, et al. Indication of prenatal diagnosis in pregnancies complicated by undetectable second-trimester maternal serum estriol levels. J Prenat Med. 2008;2(3):27-30 5. Yarbrough ML, Stout M, Gronowski AM. Pregnancy and its disorders. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1655-1696

ESTR
70427

Estrogen Receptor Immunostain, Technical Component Only

Clinical Information: Estrogen receptor alpha protein expression is limited to normal and neoplastic tissues related to the reproductive system (breast, cervix, endometrium, uterus, ovary, and prostate).

Useful For: Qualitative detection of estrogen receptor alpha protein in a diagnostic setting

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Peng Y, Butt YM, Chen B, Zhang X, Tang P. Update on immunohistochemical analysis in breast lesions. Arch Pathol Lab Med. 2017;141(8):1033-1051. doi:10.5858/arpa.2016-0482-RA 2. Gibert-Ramos A, Lopez C, Bosch R, et al. Immune response profile of primary tumour, sentinel and non-sentinel axillary lymph nodes related to metastasis in breast cancer: an immunohistochemical point of view. Histochem Cell Biol. 2019;152(3):177-193. doi:10.1007/s00418-019-01802-7 3. McCullough AE, Dell'orto P, Reinholz MM, et al. Central

pathology laboratory review of HER2 and ER in early breast cancer: an ALTTO trial (BIG 2-06/NCCTG N063D [Alliance]) ring study. Breast Cancer Res Treat. 2014;143(3):485-492. doi:10.1007/s10549-013-2827-0 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

ERPR
70589

Estrogen/Progesterone Receptor, Semi-Quantitative Immunohistochemistry, Manual

Clinical Information: The steroid hormone receptors, estrogen receptor (ER) and progesterone receptor (PR), are commonly used in the management of women with breast cancer. ER and PR status provide an indication of prognosis and of the potential benefit from hormonal therapy. Generally, ER/PR-positive tumors are more likely to respond to endocrine therapy and have a better prognosis, stage-for-stage, than receptor-negative tumors. While the test can be performed on any formalin-fixed, paraffin-embedded tissue, it is infrequently used for non-breast cancer specimens.

Useful For: Guiding decisions on hormonal therapy in patients with breast carcinomas This test is not useful for cases of lobular carcinoma in situ.

Interpretation: Immunoperoxidase-stained slides are examined microscopically by the consulting anatomic pathologist and interpreted as negative (<1% reactive cells), or positive. The percent of reactive cells is provided in the report.

Reference Values:
Negative: <1% reactive cells
Positive: > or =1% reactive cells

Clinical References: 1. Hammond ME, Hayes DF, Dowsett M, et al: American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med. 2010 Jun;134(6):907-22. doi: 10.1043/1543-2165-134.6.907. Erratum in: Arch Pathol Lab Med. 2010 Aug;134(8):1101 2. Allison KH, Hammond MEH, Dowsett M, et al: Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. J Clin Oncol. 2020 Apr 20;38(12):1346-1366. doi: 10.1200/JCO.19.02309

ESTF
84230

Estrogens, Estrone (E1) and Estradiol (E2), Fractionated, Serum

ESTRONE (E1) CHILDREN* 1 to14 days: Estrone levels in newborns are very elevated at birth but will fall to prepubertal levels within a few days. Males Tanner stages#	Mean age	Reference range
Stage I (>14 days and prepubertal)	7.1 years	Undetectable-16 pg/mL
Stage II	11.5 years	Undetectable-22 pg/mL
Stage III	13.6 years	10-25 pg/mL
Stage IV	15.1 years	10-46 pg/mL
Stage V	18 years	10-60 pg/mL
#Puberty onset (transition from Tanner	Mean age	Reference range

stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. Females Tanner stages#

Stage I (>14 days and prepubertal)	7.1 years	Undetectable-29 pg/mL
Stage II	10.5 years	10-33 pg/mL
Stage III	11.6 years	15-43 pg/mL
Stage IV	12.3 years	16-77 pg/mL
Stage V	14.5 years	17-200 pg/mL
#Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. *The reference ranges for children are based on the published literature,(1,2) cross-correlation of our assay with assays used to generate the literature data and on our data for young adults. ADULTS Males: 10-60 pg/mL Females Premenopausal: 17-200 pg/mL Postmenopausal: 7-40 pg/mL Conversion factor E1: pg/mL x 3.704=pmol/L (molecular weight=270) ESTRADIOL (E2) CHILDREN* 1 to14 days: Estradiol levels in newborns are very elevated at birth but will fall to prepubertal levels within a few days. Males Tanner stages#	Mean age	Reference range
Stage I (>14 days and prepubertal)	7.1 years	Undetectable-13 pg/mL
Stage II	12.1 years	Undetectable-16 pg/mL
Stage III	13.6 years	Undetectable-26 pg/mL
Stage IV	15.1 years	Undetectable-38 pg/mL
Stage V	18 years	10-40 pg/mL
#Puberty onset	Mean age	Reference range

(transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. Females Tanner stages#

Stage I (>14 days and prepubertal)	7.1 years	Undetectable-20 pg/mL
Stage II	10.5 years	Undetectable-24 pg/mL
Stage III	11.6 years	Undetectable-60 pg/mL
Stage IV	12.3 years	15-85 pg/mL
Stage V	14.5 years	15-350 pg/mL**

Clinical References: 1. Bidlingmaier F, Wagner-Barnack M, Butenandt O, Knorr D. Plasma estrogens in childhood and puberty under physiologic and pathologic conditions. Pediatr Res 1973;7(11):901-907 2. Elmlinger MW, Kuhnel W, Ranke MB. Reference ranges for serum concentrations of lutropin (LH), follitropin (FSH), estradiol (E2), prolactin, progesterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), cortisol and ferritin in neonates, children and young adults. Clin Chem Lab Med. 2002;40 (11):1151-1160 3. Cummings SR, Browner WS, Bauer D, Stone K, et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. N Engl J Med. 1998;339:733-738 4. Iughetti L, Predieri B, Ferrari M, Gallo C, et al. Diagnosis of central precocious puberty: endocrine assessment. J Pediatr Endocrinol Metab. 2000;13 Suppl 1:709-715 5. Ismail AA, Barth JH. Endocrinology of gynaecomastia. Ann Clin Biochem. 2001;38:596-607 6. Kligman I, Rosenwaks Z. Differentiating clinical profiles: predicting good responders, poor responders, and hyperresponders. Fertil Steril. 2001;76:1185 7. Traggiai C, Stanhope R. Delayed puberty. Best Pract Res Clin Endocrinol Metab. 2002;16:139-151 8. Anari MR, Bakhtiar R, Zhu B, Huskey, et al. Derivatization of ethynylestradiol with dansyl chloride to enhance electrospray ionization: application in trace analysis of ethynylestradiol in Rhesus monkey plasma. Anal Chem. 2002;74, 4136. 9. Mauras N, Ross JL, Gagliardi P, et al. Randomized Trial of Aromatase Inhibitors, Growth Hormone, or Combination in Pubertal Boys with Idiopathic Short Stature. Clin Endocrinol Metab. 2016;101(12):4984-4993. doi:10.1210/jc.2016-2891 10. Ketha H, Girtman A, Singh RJ. Estradiol assays-The path ahead. Steroids. 2015l;99(Pt A):39-44. doi:10.1016/j.steroids.2014.08.009 11. Ingle JN, Cairns J, Suman VJ, et al. Anastrozole has an Assocaition Between Degree of Estrogen Suppression and Outcomes in Early Breast Cancer and is a Ligamd for Estrogen Receptor a. Clin Cancer Res. 2020;26(12):2986-2996. doi:10.1158/1078-0432.CCR-19-3091 12. Richardson H, Ho V, Pasquet R, et al. Baseline estrogen levels in postmenopausal women participating in the MAP.3 breast cancer chemoprevention trial. Menopause. 2020;27(6):693-700. doi:10.1097/GME.0000000000001568

E1
81418

Estrone, Serum

Clinical Information: Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important for many other, nongender-specific processes, including growth, nervous system maturation, bone metabolism/remodeling, and endothelial responsiveness. The 2 major biologically active estrogens in nonpregnant humans are estrone (E1) and estradiol (E2). A third bioactive estrogen, estriol, is the main pregnancy estrogen, but plays no significant role in nonpregnant women or men. Estradiol is produced primarily in ovaries and testes by aromatization of testosterone. Small amounts are produced in the adrenal glands and some peripheral tissues, most notably fat. By contrast, most of the circulating E1 is derived from peripheral aromatization of androstenedione (mainly adrenal). E2 and E1 can be converted into each other, and both can be inactivated via hydroxylation and conjugation. E2 demonstrates 1.25-5 times the biological potency of E1. E2 circulates at 1.5 to 4 times the concentration of E1 in premenopausal, nonpregnant women. E2 levels in men and postmenopausal women are much lower than in nonpregnant women, while E1 levels differ less, resulting in a reversal of the premenopausal E2:E1 ratio. E2 levels in premenopausal women fluctuate during the menstrual cycle. They are lowest during the early follicular phase. E2 levels then rise

gradually until 2 to 3 days before ovulation, at which stage they start to increase much more rapidly and peak just before the ovulation-inducing luteinizing hormone/follicle stimulating hormone surge at 5 to 10 times the early follicular levels. This is followed by a modest decline during the ovulatory phase. E2 levels then increase again gradually until the midpoint of the luteal phase and thereafter decline to trough, early follicular levels. Measurement of serum E2 forms an integral part of the assessment of reproductive function in females, including assessment of infertility, oligo-amenorrhea and menopausal status. In addition, it is widely used for monitoring ovulation induction, as well as during preparation for in vitro fertilization. For these applications E2 measurements with modestly sensitive assays suffice. However, extra sensitive E2 assays or simultaneous measurement of E1, or both are needed in a number of other clinical situations. These include inborn errors of sex steroid metabolism, disorders of puberty, estrogen deficiency in men, fracture risk assessment in menopausal women, and increasingly, therapeutic drug monitoring, either in the context of low-dose female hormone replacement therapy or antiestrogen treatment. For more information see Steroid Pathways.

Useful For: As part of the diagnosis and workup of precocious and delayed puberty in females and, to a lesser degree, males As part of the diagnosis and workup of suspected disorders of sex steroid metabolism (eg, aromatase deficiency and 17 alpha-hydroxylase deficiency) As an adjunct to clinical assessment, imaging studies and bone mineral density measurement in the fracture risk assessment of postmenopausal women, and, to a lesser degree, older men Monitoring low-dose female hormone replacement therapy in postmenopausal women Monitoring antiestrogen therapy (eg, aromatase inhibitor therapy)

Interpretation: Irregular or absent menstrual periods with normal or high estradiol (E2) levels (and often high estrone: E1 levels) are indicative of possible polycystic ovarian syndrome, androgen producing tumors, or estrogen producing tumors. Further work-up is required and usually includes measurement of total and bioavailable testosterone, androstenedione, dehydroepiandrosterone (sulfate), sex hormone-binding globulin, and possibly imaging. Estrogen replacement in reproductive age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women, luteinizing hormone/follicle-stimulating hormone (LH/FSH) should be within the normal range, and E2 levels should ideally be higher than E1 levels. Postmenopausal women and older men in the lowest quartile of E2 levels are at increased risk of osteoporotic fractures. E2 levels are typically less than 5 pg/mL in these patients. The current recommendations for postmenopausal female hormone replacement are to administer therapy in the smallest beneficial doses for as briefly as possible. Ideally, E2 and E1 levels should be held below, or near, the lower limit of the premenopausal female reference range. Antiestrogen therapy with central or peripheral acting agents that are not pure receptor antagonists usually aims for complete suppression of E2 production, and in the case of aromatase inhibitors, complete E1 and E2 suppression. Gynecomastia or other signs of feminization in males may be due to an absolute or relative (in relation to androgens) surplus of estrogens. Gynecomastia is common during puberty in boys. Unless E1, E2, or testosterone levels exceed the adult male reference range, the condition is usually not due to hormonal disease (though it sometimes may still result in persistent breast tissue, which later needs to be surgically removed). For adults with gynecomastia, the work-up should include testosterone and adrenal androgen measurements, in addition to E2 and E1 measurements. Causes for increased E1 or E2 levels include: -High androgen levels caused by tumors or androgen therapy (medical or sport performance enhancing), with secondary elevations in E1 and E2 due to aromatization -Obesity with increased tissue production of E1 -Decreased E1 and E2 clearance in liver disease -Estrogen producing tumors -Estrogen ingestion Normal male E1 and E2 levels also may be associated with feminization or gynecomastia if bioavailable testosterone levels are low due to primary/secondary testicular failure. This may occur, for example, when patients are receiving antiandrogen therapy or other drugs with antiandrogenic effects (eg, spironolactone, digitalis preparations). The gonadotrophin-releasing hormone stimulation test remains the central part of the work-up for precocious puberty. However, baseline sex steroid and gonadotrophin measurements also are important. Prepubertal girls have E2 levels less than 10 pg/mL (most <5 pg/mL). Levels in prepubertal boys are less than half the levels seen in girls. LH/FSH are very low or undetectable. E1 levels also are low, but may rise slightly in obese children after onset of adrenarche.

E2, which is produced in the gonads, should remain low in these children. In true precocious puberty, both E2 and LH/FSH levels are elevated above the prepubertal range. Elevation of E2 or E1 alone suggests pseudo precocious puberty, possibly due to a sex steroid-producing tumor. In delayed puberty, estrogens and gonadotrophins are in the prepubertal range. A rise over time predicts the spontaneous onset of puberty. Persistently low estrogens and elevated gonadotrophins suggest primary ovarian failure, while low gonadotrophins suggest hypogonadotrophic hypogonadism. In this latter case, Kallman syndrome (or related disorders) or hypothalamic/pituitary tumors should be excluded in well-nourished children. Inherited disorders of sex steroid metabolism are usually associated with production abnormalities of other steroids, most notably a lack of cortisol. Aromatase deficiency is not associated with cortisol abnormalities and usually results in some degree of masculinization in affected females, as well as primary failure of puberty. Males may show delayed puberty and delayed epiphyseal closure, as well as low bone-density. E2 and E1 levels are very low or undetectable. Various forms of testicular feminization are due to problems in androgen signaling pathways and are associated with female (or feminized) phenotypes in genetic males. E2 and E1 levels are above the male reference range, usually within the female reference range, and testosterone levels are very high. For more information see Steroid Pathways.

CHILDREN* 1-14 days: Estrone levels in newborns are very elevated at birth but will fall to prepubertal levels within a few days. Males Tanner stages#	**Mean age**	**Reference range**
Stage I (>14 days and prepubertal)	7.1 years	Undetectable-16 pg/mL
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Stage IV	15.1 years	10-46 pg/mL
Stage V	18 years	10-60 pg/mL
#Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. Females Tanner stages#	Mean age	Reference range
Stage I (>14 days and prepubertal)	7.1 years	Undetectable-29 pg/mL
Stage II	10.5 years	10-33 pg/mL
Stage III	11.6 years	15-43 pg/mL
Stage IV	12.3 years	16-77 pg/mL
Stage V	14.5 years	17-200 pg/mL

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ALC
8264

Ethanol, Blood

Clinical Information: Ethanol is one of the most widely abused legal substances in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral functions as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment becomes progressively increased. In most jurisdictions in the United States, the level of prima facie evidence of being under the influence of alcohol for purposes of driving a motor vehicle is 80 mg/dL (0.08% in whole blood).

Useful For: Detection of ethanol (ethyl alcohol) in blood to document prior consumption or administration of ethanol Quantification of the concentration of ethanol in blood correlates directly with degree of intoxication This test is not intended for use in employment-related testing.

Interpretation: The presence of ethanol in blood at concentrations above 30 mg/dL (>0.03% or g/dL) is generally accepted as a strong indicator of the use of an alcohol-containing beverage. Blood ethanol levels above 50 mg/dL (>0.05%) are frequently associated with a state of increased euphoria. Blood ethanol level above 80 mg/dL (>0.08%) exceeds Minnesota's legal limit for driving a motor vehicle. These levels are frequently associated with loss of manual dexterity and with sedation. A blood alcohol level of 400 mg/dL (> or =0.4%) or higher may be lethal as normal respiration may be depressed below the level necessary to maintain life. The blood ethanol level is also useful in diagnosis of alcoholism. A patient who chronically consumes ethanol will develop a tolerance to the drug and requires higher levels than described above to achieve various states of intoxication. An individual who can function in a relatively normal manner with a blood ethanol level above 150 mg/dL (>0.15%) is highly likely to have developed a tolerance to the drug achieved by high levels of chronic intake.

Reference Values:

Not detected (Positive results are quantified.)
Limit of detection: 10 mg/dL (0.01 g/dL)
Legal limit of intoxication is 80 mg/dL (0.08 g/dL).
Toxic concentration is dependent upon individual usage history.
Potentially lethal concentration: > or =400 mg/dL (0.4 g/dL)

Clinical References: Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:454

ALCX 62709 Ethanol, Chain of Custody, Blood

Clinical Information: Ethanol is one of the most widely abused legal substances in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral functions as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment becomes progressively increased. In most jurisdictions in the United States, the level of prima facie evidence of being under the influence of alcohol for purposes of driving a motor vehicle is 80 mg/dL (0.08%) in whole blood. Chain of custody is a record of the disposition of a specimen to document the personnel who collected it, handled it, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detection of ethanol (ethyl alcohol) in blood to document prior consumption or administration of ethanol Quantification of the concentration of ethanol in blood correlates directly with degree of intoxication All testing is performed under strict chain of custody Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited. This test is not intended for use in employment-related testing.

Interpretation: The presence of ethanol in blood at concentrations greater than 30 mg/dL (>0.03% or g/dL) is generally accepted as a strong indicator of the use of an alcohol-containing beverage. Blood ethanol levels above 50 mg/dL (>0.05%) are frequently associated with a state of increased euphoria. Blood ethanol level above 80 mg/dL (>0.08%) exceeds Minnesota's legal limit for driving a motor vehicle. These levels are frequently associated with loss of manual dexterity and with sedation. A blood alcohol level of 400 mg/dL (> or =0.4%) or more may be lethal as normal respiration may be depressed below the level necessary to maintain life. The blood ethanol level is also useful in diagnosis of alcoholism. A patient who chronically consumes ethanol will develop a tolerance to the drug and requires higher levels than described above to achieve various states of intoxication. An individual who can function in a relatively normal manner with a blood ethanol level above 150 mg/dL (>0.15%) is highly likely to have developed a tolerance to the drug achieved by high levels of chronic intake.

Reference Values:
Not detected (Positive results are quantified.)
Limit of detection: 10 mg/dL (0.01 g/dL)
Legal limit of intoxication is 80 mg/dL (0.08 g/dL).
Toxic concentration is dependent upon individual usage history.
Potentially lethal concentration: > or =400 mg/dL (0.4 g/dL)

Clinical References: Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier;

2023:454

ETX 8769 Ethosuximide, Serum

Clinical Information: Ethosuximide (Zarontin) is used in the treatment of absence (petit mal) epilepsy in adults and children 3 years and older. Ethosuximide is almost completely absorbed from the gastrointestinal tract, reaching a peak plasma concentration in 1 to 4 hours following oral administration. Approximately 10% to 20% of the drug is excreted unchanged in the urine; the remainder is metabolized by hepatic microsomal enzymes. The volume of distribution of ethosuximide is approximately 0.7 L/kg, and its half-life is 17 to 56 hours (adult) and 30 hours (pediatric). Minimal ethosuximide circulating in the blood is bound to protein (approximately 22%). Ethosuximide produces a barbiturate-like toxicity, characterized by central nervous system and respiratory depression, nausea, and vomiting, when the blood level is greater than 120 mcg/mL.

Useful For: Monitoring ethosuximide therapy Determining compliance Assessing ethosuximide toxicity

Interpretation: Dosage is guided by blood levels; the therapeutic range for ethosuximide is 40 to 100 mcg/mL. Toxic concentration: above 120 mcg/mL.

Reference Values:
Therapeutic: 40-100 mcg/mL
Critical value: >150 mcg/mL

Clinical References: 1. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453.e9 2. Brunton LL, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 14th ed. McGraw-Hill Education, 2023 3. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62

ETGX 63418 Ethyl Glucuronide Confirmation, Chain of Custody, Random, Urine

Clinical Information: Ethyl glucuronide and ethyl sulfate are minor metabolites of ethanol that are detectable in body fluids following alcohol consumption and, less commonly, following extraneous exposure. Ethyl glucuronide (EtG) and ethyl sulfate (EtS) are direct biomarkers or metabolites of ethanol. EtG and EtS can be detected up to 5 days in urine using a cutoff of 500 ng/mL.(1) Chain of custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Monitoring abstinence in clinical and justice system settings using ethyl glucuronide and ethyl sulfate as direct biomarkers or metabolites of ethanol This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: A positive interpretation will be given if either the ethyl glucuronide result is greater than or equal to 250 ng/mL or the ethyl sulfate is greater than or equal to 100 ng/mL. A "high" positive (ie, >1000 ng/mL) may indicate: -Heavy drinking on the same day or previously (ie, previous day or 2) -Light drinking the same day A "low" positive (ie, 500-1000 ng/mL) may indicate: -Previous heavy drinking (ie, previous 1-3 days) -Recent light drinking (ie, past 24 hours) -Recent intense "extraneous" exposure (ie, within 24 hours or less) A "very low" positive (ie, 100-500 ng/mL) may indicate: -Previous heavy drinking (ie, 1-3 days) -Previous light drinking (ie, 12-36 hours) -Recent "extraneous" exposure

Reference Values:
Negative
Positive results are reported with a quantitative result.

Cutoff Concentrations:

Immunoassay screen: 500 ng/mL

Liquid chromatography tandem mass spectrometry:
Ethyl glucuronide: 250 ng/mL
Ethyl sulfate: 100 ng/mL

Clinical References: 1. Reisfield GM, Goldberger BA, Crews BO, et al. Ethyl glucuronide, ethyl sulfate, and ethanol in urine after sustained exposure to an ethanol-based hand sanitizer. J Anal Toxicol. 2011;35(2):85-91. doi:10.1093/anatox/35.2.85 2. Substance Abuse and Mental Health Services Administration (SAMSHA) Advisory: The role of biomarkers in the treatment of alcohol use disorders, 2012 Revision. HHS; 2012;11(2):1-7. doi:10.1037/e558582006-001 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

ETGC
63421

Ethyl Glucuronide Confirmation, Random, Urine

Clinical Information: Ethyl glucuronide (EtG) and ethyl sulfate (EtS) are minor metabolites of ethanol that are detectable in body fluids following alcohol consumption and, less commonly, following extraneous exposure. EtG and EtS can be detected up to 5 days in urine using a cutoff of 500 ng/mL.(1)

Useful For: Monitoring abstinence in clinical and justice system settings

Interpretation: A positive interpretation will be given if either the ethyl glucuronide (EtG) result is greater than or equal to 250 ng/mL or the ethyl sulfate (EtS) is greater than or equal to 100 ng/mL. A "high" positive (ie, >1000 ng/mL) may indicate: -Heavy drinking on the same day or previously (ie, previous day or 2). -Light drinking the same day A "low" positive (ie, 500-1000 ng/mL) may indicate: -Previous heavy drinking (ie, previous 1-3 days) -Recent light drinking (ie, past 24 hours) -Recent intense "extraneous" exposure (ie, within 24 hours or less) A "very low" positive (ie, 100-500 ng/mL) may indicate: -Previous heavy drinking (ie, 1-3 days) -Previous light drinking (ie, 12-36 hours) -Recent "extraneous" exposure(2)

Reference Values:
Negative

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Ethyl glucuronide: 250 ng/mL
Ethyl sulfate: 100 ng/mL

Clinical References: 1. Reisfield GM, Goldberger BA, Crews BO, et al. Ethyl glucuronide, ethyl sulfate, and ethanol in urine after sustained exposure to an ethanol-based hand sanitizer. J Anal Toxicol. 2011;35(2):85-91. doi:10.1093/anatox/35.2.85 2. Substance Abuse and Mental Health Services Administration (SAMSHA) Advisory: The role of biomarkers in the treatment of alcohol use disorders, 2012 Revision. HHS; 2012;11(2):1-7. doi:10.1037/e558582006-001 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

ETGR
63419

Ethyl Glucuronide Screen with Reflex, Random, Urine

Clinical Information: Ethyl glucuronide is a direct metabolite of ethanol that is formed by enzymatic conjugation of ethanol with glucuronic acid. Alcohol in urine is normally detected for only a few hours, whereas ethyl glucuronide can be detected in the urine for 1 to 3 days. This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have false-positives due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay can also have false negatives due to the antibody's ability to cross react with different drugs in the class being screened. When the screen result is positive, liquid chromatography tandem mass spectrometry will be performed to confirm the result.

Useful For: Screening and confirmation for drug abuse involving alcohol

Interpretation: If the screen result is negative, ethyl glucuronide concentrations were not detected. If the screen result is positive, then confirmation by liquid chromatography tandem mass spectrometry will be performed. A positive interpretation will be given if either the ethyl glucuronide (EtG) result is greater than or equal to 250 ng/mL and/or the ethyl sulfate (EtS) is greater than or equal to 100 ng/mL. A "high" positive (ie, >1000 ng/mL) may indicate: -Heavy drinking on the same day or previously (ie, previous day or 2). -Light drinking the same day A "low" positive (ie, 500-1000 ng/mL) may indicate: -Previous heavy drinking (ie, previous 1 3 days). -Recent light drinking (ie, past 24 hours). -Recent intense "extraneous" exposure (ie, within 24 hours or less). A "very low" positive (ie, 100-500 ng/mL) may indicate: -Previous heavy drinking (ie, 1-3 days) -Previous light drinking (ie, 12-36 hours). -Recent "extraneous" exposure.(2)

Reference Values:
Negative
Screening cutoff concentration: 500 ng/mL

Clinical References: 1. Schmitt G, Aderjan R, Keller T, Wu M. Ethyl glucuronide: an unusual ethanol metabolite in humans. Synthesis, analytical data, and determination in serum and urine. J Anal Toxicol .1995;19(2):91-94. doi:10.1093/jat/19.2.91 2. Dahl H, Stephanson N, Beck O, Helander A. Comparison of urinary excretion characteristics of ethanol and ethyl glucuronide. J Anal Toxicol. 2002;26:201-204. doi:10.1093/jat/26.4.201 3. Wurst FM, Skipper GE, Weinmann W. Ethyl glucuronide--the direct ethanol metabolite on the threshold from science to routine use. Addiction. 2003;98 (Suppl 2):51-61. doi:10.1046/j.1359-6357.2003.00588.x 4. Zimmer H, Schmitt G, Aderjan R. Preliminary immunochemical test for the determination of ethyl glucuronide in serum and urine: comparison of screening method results with gas chromatography-mass spectrometry. J Anal Toxicol. 2002;26(1):11-16. doi:10.1093/jat/26.1.11 5. Weinmann W, Schaefer P, Thierauf A, Schreiber A, Wurst FM. Confirmatory analysis of ethyl glucuronide in urine by liquid chromatography/electrospray ionization/tandem mass spectrometry according to forensic guidelines. J Am Soc Mass Spectrom. 2004;15(2):188-193. doi:10.1016/j.jasms.2003.10.010 6. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook

of Laboratory Medicine. 7th ed. Elsevier; 2023:454

ETGSR 616033 Ethyl Glucuronide Screen with Reflex, Random, Urine

Clinical Information: This test uses immunoassay reagents designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) urine specimen; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate to the antibody's ability to cross-react with different drugs in the class being screened. Ethyl glucuronide is a direct metabolite of ethanol formed by enzymatic conjugation of ethanol with glucuronic acid. Alcohol in urine is normally detected for only a few hours, whereas ethyl glucuronide can be detected in the urine for 1 to 3 days.

Useful For: Screening for drug abuse involving alcohol

Interpretation: This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography tandem mass spectrometry) must be used to obtain a confirmed analytical result. A positive result using the ethyl glucuronide screen indicates only the potential presence of ethyl glucuronide and does not necessarily correlate with the extent of physiological and psychological effects.

Reference Values:
Only orderable as part of profile. For more information see CSMEU / Controlled Substance Monitoring Enhanced Profile with Reflex, 21 Drug Classes, High Resolution Mass Spectrometry and Immunoassay Screen, Random, Urine.

Negative

Screening cutoff concentration:
Ethyl glucuronide: 500 ng/mL

Clinical References: 1. Schmitt G, Aderjan R, Keller T, Wu M. Ethyl glucuronide: an unusual ethanol metabolite in humans. Synthesis, analytical data, and determination in serum and urine. J Anal Toxicol. 1995;19(2):91-94 2. Dahl H, Stephanson N, Beck O, Helander A. Comparison of urinary excretion characteristics of ethanol and ethyl glucuronide. J Anal Toxicol. 2002;26(4):201-204. doi:10.1093/jat/26.4.201 3. Wurst FM, Skipper GE, Weinmann W. Ethyl glucuronide--the direct ethanol metabolite on the threshold from science to routine use. Addiction. 2003;98 (Suppl 2):51-61. doi:10.1046/j.1359-6357.2003.00588.x 4. Zimmer H, Schmitt G, Aderjan R. Preliminary immunochemical test for the determination of ethyl glucuronide in serum and urine: comparison of screening method results with gas chromatography-mass spectrometry. J Anal Toxicol. 2002;26(1):11-16. doi:10.1093/jat/26.1.11 5. Weinmann W, Schaefer P, Thierauf A, Schreiber A, Wurst FM. Confirmatory analysis of ethyl glucuronide in urine by liquid chromatography/electrospray ionization/tandem mass spectrometry according to forensic guidelines. J Am Soc Mass Spectrom. 2004;15(2):188-193. doi:10.1016/j.jasms.2003.10.010 6. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

ETGS 63420 Ethyl Glucuronide Screen, Random, Urine

Clinical Information: Ethyl glucuronide is a direct metabolite of ethanol that is formed by enzymatic conjugation of ethanol with glucuronic acid. Alcohol in urine is normally detected for only a few hours,

whereas ethyl glucuronide can be detected in the urine for 1 to 3 days. This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have false-positives due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay can also have false negatives due to the antibody's ability to cross-react with different drugs in the class being screened for.

Useful For: Screening for drug abuse involving alcohol

Interpretation: This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography tandem mass spectrometry) must be used to obtain a confirmed analytical result. A positive result using the ethyl glucuronide screen indicates only the potential presence of ethyl glucuronide and does not necessarily correlate with the extent of physiological and psychological effects.

Reference Values:
Negative
Screening cutoff concentration: 500 ng/mL

Clinical References: 1. Schmitt G, Aderjan R, Keller T, Wu M. Ethyl glucuronide: an unusual ethanol metabolite in humans. Synthesis, analytical data, and determination in serum and urine. J Anal Toxicol. 1995;19(2):91-94. doi:10.1093/jat/19.2.91 2. Dahl H, Stephanson N, Beck O, Helander A. Comparison of urinary excretion characteristics of ethanol and ethyl glucuronide. J Anal Toxicol. 2002;26:201-104. doi:10.1093/jat/26.4.201 3. Wurst FM, Skipper GE, Weinmann W. Ethyl glucuronide--the direct ethanol metabolite on the threshold from science to routine use. Addiction. 2003;98 Suppl 2:51-61. doi:10.1046/j.1359-6357.2003.00588.x 4. Zimmer H, Schmitt G, Aderjan R. Preliminary immunochemical test for the determination of ethyl glucuronide in serum and urine: comparison of screening method results with gas chromatography-mass spectrometry. J Anal Toxicol. 2002;26(1):11-16. doi: 10.1093/jat/26.1.11 5. Weinmann W, Schaefer P, Thierauf A, Schreiber A, Wurst FM. Confirmatory analysis of ethylglucuronide in urine by liquid chromatography/electrospray ionization/tandem mass spectrometry according to forensic guidelines. J Am Soc Mass Spectrom. 2004;15(2):188-193. doi:10.1016/j.jasms.2003.10.010 6. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:454

ETGL
8749

Ethylene Glycol, Serum

Clinical Information: Ethylene glycol is present in antifreeze products, deicing products, detergents, paints, and cosmetics. Ethylene glycol has initial central nervous system (CNS) effects resembling those of ethanol and may be ingested accidentally or for the purpose of inebriation or suicide. Ethylene glycol itself is relatively nontoxic, however, metabolism of ethylene glycol by alcohol dehydrogenase results in the formation of a number of acid metabolites, including oxalic acid and glycolic acid. These acid metabolites are responsible for much of the toxicity of ethylene glycol. Clinically, poisoning has historically been divided into three stages, although timing may vary, and stages may overlap. The first stage typically begins 30 minutes to 12 hours after ingestion due to the intoxicating effects of the ethylene glycol and may range from mild CNS depression to coma. The second stage begins 12 to 24 hours after ingestion and is characterized severe metabolic acidosis, due to the accumulation of acid metabolites. The third stage occurs 24 to 72 hours after ingestion and is characterized by renal failure due to calcium oxalate crystal deposition in the proximal tubules. Ethylene glycol toxicity can be treated with 4-methylpyrazole (4-MP; fomepizole) or ethanol by competitively inhibiting alcohol dehydrogenase and thereby preventing conversion of ethylene glycol to its toxic metabolites.

Useful For: Confirming and monitoring ethylene glycol toxicity

Interpretation: Toxic concentrations are those greater than or equal to 20 mg/dL

Reference Values:
Toxic concentration: > or =20 mg/dL

Clinical References: 1. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:454-454.e484 2. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Seal Beach, CA: Biomedical Publications; 2020 3. Cohen JP, Quan D. Alcohols. In: Tintinalli JE, Ma OJ, Yealy DM, et al, eds. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 9th ed. McGraw-Hill Education; 2020

EOXD
82767

Ethylene Oxide, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to ethylene oxide Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive

4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ETV6F
63433

ETV6 (12p13.2) Rearrangement, FISH, Tissue

Clinical Information: ETV6 rearrangement has been identified in a wide variety of neoplasms including mammary analogue secretory carcinoma, secretory carcinoma of the breast, and infantile fibrosarcoma.

Useful For: Detection of ETV6 rearrangements irrespective of the ETV6 fusion partner gene
Supporting the diagnosis of many neoplasms including, but not limited to, mammary analogue secretory carcinoma, secretory carcinoma of the breast, and infantile fibrosarcoma when used in conjunction with pathologic assessment

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the ETV6 fluorescence in situ hybridization (FISH) probe set. A positive result is consistent with the presence of ETV6 rearrangement and likely reflects ETV6 fusion with a partner gene. The significance of this FISH result is dependent on clinical and pathologic features. A negative result does not exclude the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board. Breast Tumours. 5th ed. IARC; 2019. WHO Classification of Tumours. Vol 2 2. WHO Classification of Tumours Editorial Board. Soft Tissue and Bone Tumours. 5th ed. IARC; 2020. WHO Classification of Tumours. Vol 3 3. Skalova A, Vanecek T, Martinek P, et al. Molecular profiling of mammary analog secretory carcinoma revealed a subset of tumors harboring a novel ETV6-RET translocation. Am J Surg Pathol. 2018;42(2):234-246 4. Skalova A. Mammary analogue secretory carcinoma of salivary gland origin: an update and expanded morphologic and immunohistochemical spectrum of recently described entity. Head Neck Pathol 2013;7:S30-S36 5. Makretsov N, He M, Hayes M, et al. A fluorescence in situ hybridization study of ETV6-NTRK3 fusion gene in secretory breast carcinoma. Genes Chromosomes Cancer. 2004;40(2):152-157 6. Sheng WQ, Hisaoka M, Okamoto S, et al. Congenital-infantile fibrosarcoma. A clinicopathologic study of 10 cases and molecular detection pf the ETV6-NTRK3 fusion transcripts using paraffin-embedded tissues. Am J Clin Pathol. 2001;115(3):348-355 7. Steelman C, Katzenstein H, Parham D, et al. Unusual presentation of congenital infantile fibrosarcoma in seven infants with molecular-genetic analysis. Fetal Pediatr Pathol. 2011;30(5):329-337 8. Skalova A, Vanecek T, Sima R, et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. Am J Surg Pathol. 2010;34(5):599-608

EUCL
82758

Eucalyptus, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to eucalyptus Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FEUCT
75738

Euglobulin Clot Lysis Time

Reference Values:
>60 min

EMAY
82846

Euroglyphus maynei, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Euroglyphus maynei Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

EHOR
82662

European Hornet, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to European hornet Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

EVROL
35146

Everolimus, Blood

Clinical Information: Everolimus is an immunosuppressive agent derived from sirolimus (rapamycin). Both drugs function via inhibition of mTOR (mechanistic target of rapamycin) signaling and share similar pharmacokinetic and toxicity profiles. Everolimus has a shorter half-life than sirolimus,

which allows for more rapid achievement of steady-state pharmacokinetics. Everolimus is extensively metabolized, primarily by cytochrome P450 (CYP) 3A4, thus its use with inducers or inhibitors of that enzyme may require dose adjustment. The most common adverse effects include hyperlipidemia, thrombocytopenia, and nephrotoxicity. Everolimus is useful as adjuvant therapy in renal cell carcinoma and other cancers. It recently gained US Food and Drug Administration approval for prophylaxis of graft rejection in solid organ transplant, an application that has been accepted for years in Europe. The utility of therapeutic drug monitoring has not been established for everolimus as an oncology chemotherapy agent; however, measuring blood drug concentrations is common practice for its use in transplant. Therapeutic targets vary depending on the transplant site and institution protocol. Guidelines for heart and kidney transplants suggest that trough (immediately prior to the next scheduled dose) blood concentrations between 3 and 8 ng/mL provide optimal outcomes.

Useful For: Managing everolimus immunosuppression in solid organ transplant

Interpretation: Therapeutic targets vary by transplant site and institution protocol. Heart and kidney transplant guidelines suggest a therapeutic range of 3 to 8 ng/mL. Measurement of drug concentrations in oncology chemotherapy is less common, thus no therapeutic range is established for this application.

Reference Values:
3-8 ng/mL

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.

Clinical References: 1. Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med. 2003;349(9):847-858 2. Kovarik JM, Beyer D, Schmouder RL. Everolimus drug interactions: application of a classification system for clinical decision making. Biopharm Drug Dispos. 2006;27(9):421-426 3. Rothenburger M, Zuckermann A, Bara C, et al. Recommendations for the use of everolimus (Certican) in heart transplantation: results from the second German-Austrian Certican Consensus Conference. J Heart Lung Transplant. 2007;26(4):305-311 4. Sanchez-Fructuoso AI. Everolimus: an update on the mechanism of action, pharmacokinetics and recent clinical trials. Expert Opin Drug Metab Toxicol. 2008;4(6):807-819 5. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:800-831 6.van Gelder T, Fischer L, Shihab F, Shipkova M. Optimizing everolimus exposure when combined with calcineurin inhibitors in solid organ transplantation. Transplant Rev (Orlando). 2017;31(3):151-157. doi:10.1016/j.trre.2017.02.007

EWSF
35268

Ewing Sarcoma, 22q12 (EWSR1) Rearrangement, FISH, Tissue

Clinical Information: The Ewing sarcoma breakpoint region 1 (EWSR1) gene encodes a protein with numerous complex activities within the cell including acting as a transcriptional regulator and mediating the activity of other proteins.(1) Oncogenic fusion of EWSR1 at 22q12 with FLI1 at 11q24 resulting from t(11;22) or with ERG at 21q22 resulting from t(21;22) was initially shown to be associated with and characteristic of Ewing sarcoma. Fusion of EWSR1 with various partner genes has since been identified in a wide variety of neoplasms.

Useful For: Detection of EWSR1 rearrangements irrespective of the EWSR1 fusion partner gene Supporting the diagnosis of many neoplasms including, but not limited to, Ewing sarcoma, extraskeletal myxoid chondrosarcoma, desmoplastic small round cell tumor, clear cell sarcoma, and myxoid

liposarcoma when used in conjunction with pathologic assessment

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the Ewing sarcoma breakpoint region 1 (EWSR1) fluorescence in situ hybridization (FISH) probe set A positive result is consistent with the presence of EWSR1 rearrangement and likely reflects EWSR1 fusion with a partner gene. The significance of this FISH result is dependent on clinical and pathologic features. A negative result does not exclude the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Rossow KL, Janknecht R. The Ewing's sarcoma gene product functions as a transcriptional activator. Cancer Res. 2001;61(6):2690-2695 2. Romeo S, Dei Tos AP. Soft tissue tumors associated with EWSR1 translocation. Virchows Arch. 2010;456(2):219-234. doi:10.1007/s00428-009-0854-3 3. Fisher C. The diversity of soft tissue tumours with EWSR1 gene rearrangements: a review. Histopathology. 2014;64(1):134-150. doi:10.1111/his.12269 4. WHO Classification of Tumours Editorial Board. Soft Tissue and Bone Tumours. 5th ed. IARC; 2020. WHO Classification of Tumours Series. Vol. 3

EXT2
614548

Exostosin 2 (EXT2) Immunostain, Technical Component Only

Clinical Information: Primary membranous nephropathy is an autoimmune disease of the kidney where antibodies target an antigen in the glomerular basement membrane resulting in kidney damage or failure. In up to 75% of primary membranous nephropathy cases phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain-containing 7A (THSD7A) are the target antigens. Exostosin 1 (EXT1) and exostosin 2 (EXT2), a recently identified set of novel proteins are associated with a subset of PLA2R and TSD7A double-negative MN. EXT1 and EXT2 may represent the target antigens or biomarker proteins of secondary (autoimmune) MN.

Useful For: Identification of exostosin 2 associated membranous nephropathy

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Bobart SA, Tehranian S, Sethi S, et al. A target antigen-based approach to the classification of membranous nephropathy. Mayo Clin Proc. 2021;96(3):577-591 2. Ravindran A, Moura MC, Fervenza FC, et al. In Patients with membranous lupus nephritis, exostosin-positivity and exostosin-negativity represent two different phenotypes. JASN. 2021;32(3):695-706 3. Sethi S, Madden BJ, Debiec H, et al. Exostosin1/exostosin 2-associated membranous nephropathy. JASN. 2019;30(6):1123-1136 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FEBGP
75552

Exotic Bird Panel IgG

Clinical Information: Although there have been many publications concerning the measurement of allergen-specific IgG, the clinical utility of such tests has not been established except in special situations.

Thus, the quantitative IgG test should only be ordered by specialists who recognize the limitations of the test. The normal reference ranges reported represent the expected results for individuals who have no unusual exposure and have not been immunized with the indicated allergen. The ranges reported have no disease-associated significance.

Reference Values:

Canary Feathers IgG
Finch Feathers IgG
Parrot Australian (Budgerigar) Droppings IgG
Pigeon Feathers IgG

PANGP
621965

Expanded Pancreatitis Gene Panel, Varies

Clinical Information: Hereditary pancreatitis (HP) is defined as 2 or more individuals in a family affected with pancreatitis involving at least 2 generations.(1) Variants in several genes, including PRSS1, CFTR, CTRC, and SPINK1 have demonstrated genetic susceptibility to chronic pancreatitis. Disease susceptibility may be monogenic, as is the case with PRSS1, digenic or multigenic, and multifactorial in which multiple genes and environmental factors play a role in disease expression. Additional genes - CASR, CEL, CPA1, CLDN2 and TRPV6, are also associated with an increased risk for pancreatitis, including early-onset chronic pancreatitis or progression from recurrent acute to chronic pancreatitis. PRSS1: The most common monogenic cause of HP is the presence of a variant in the cationic trypsinogen (PRSS1) gene. Variants in the PRSS1 gene are inherited in an autosomal dominant manner. It has been reported that as many as 80% of patients with symptomatic hereditary pancreatitis have a causative PRSS1 variant.(1) HP cannot be clinically distinguished from other forms of pancreatitis. However, PRSS1 variants are generally restricted to individuals with a family history of pancreatitis and are infrequently found in patients with alcohol-induced pancreatitis. Although several variants have been identified, the p.R122H, p.N29I, and p.A16V variants are the most common disease-causing variants in PRSS1 associated with HP.(2) Patients with HP are also at an increased risk for developing pancreatic cancer. Studies have estimated the lifetime risk of developing pancreatic cancer to be as high as 40%.(3) SPINK1: Biallelic variants in the SPINK1 gene have been associated with increased susceptibility to chronic pancreatitis especially in families without PRSS1 variants; however, it is unknown if biallelic variants alone are sufficient to cause chronic pancreatitis. Additionally, heterozygous SPINK1 variants appear to modify disease severity when observed in combination with variants in other genes.(1-2,4) Unlike PRSS1 variants, SPINK1 variants have been associated with alcohol-induced pancreatitis.(4) CFTR: Pancreatitis is a known manifestation of an atypical CFTR-related disorder, which results from biallelic disease-causing variants in the CFTR gene. However, CFTR variants can also co-occur with variants in CTRC, SPINK1, or CASR to confer pancreatitis disease susceptibility.(1-4) When observed in the context of a SPINK1 variant, for example, heterozygous variants in CFTR are associated with a 2- to 5-fold increased risk for pancreatitis as compared to the general population.(4) CTRC: Variants in CTRC have been observed in individuals with chronic pancreatitis in association with other risk factors such as variants in CFTR or SPINK1 or specific environmental risk factors. Thus, chronic pancreatitis may be attributable to the presence of CTRC variants in the context of other risk factors as opposed to CTRC variants alone.(1) CASR: Although disease-causing variants in CASR are typically associated with familial hypocalciuric hypercalcemia (FHH), some loss-of-function variants have been found to infer an increased risk for pancreatitis in individuals who also have variants in PRSS1, SPINK1, or CFTR. Gain-of-function

variants in CASR have also been reported to be risk alleles for alcohol-induced pancreatitis.(3) CEL: Variants in CEL have been found to be associated with maturity-onset diabetes of the young (MODY8), which includes pancreatic atrophy secondary to exocrine pancreatic insufficiency. The exocrine pancreatic insufficiency may lead to chronic pancreatitis, suggesting that variants in CEL are associated with an increased risk for pancreatitis and are implicated in less than 1% of individuals with chronic pancreatitis.(1,5) CPA1: Monoallelic variants in the CPA1 gene have been associated with an increased risk for early onset, nonalcoholic chronic pancreatitis. Specifically, risk allele variants have been more commonly observed in European populations and account for approximately 9.7% of cases of chronic pancreatitis in children younger than 10 years and approximately 1% of adult individuals. Some of these affected individuals have also been found to have a disease-causing variant in another hereditary pancreatitis gene such as PRSS1, SPINK1, CFTR and CTRC, although the majority of reported cases have not been found to have a second variant.(3,6,7) CLDN2: CLDN2 variants have been observed in individuals with chronic pancreatitis in association with other risk factors such as alcohol consumption. The gene is located on the X chromosome and therefore the risk for pancreatitis in association with other risk factors is increased in hemizygous male patients and homozygous female patients. Variants have been reported to be associated with a mild-to-moderate risk of pancreatitis progression from recurrent acute pancreatitis to chronic pancreatitis.(3,7,8) TRPV6: Variants in the TRPV6 gene have been found to increase the risk of early-onset chronic pancreatitis (individuals younger than 20 years). Previous studies have shown that loss-of-function variants are observed more frequently in a cohort of individuals with nonalcoholic chronic pancreatitis as compared to the unaffected control group. The majority of these individuals had either two disease-causing variants or were homozygous for a TRPV6 variant. They also had other underlying factors that increased their risk for chronic pancreatitis, suggesting that TRPV6 is a susceptibility gene.(3,9,10)

Useful For: Confirmation of suspected clinical diagnosis of familial or hereditary pancreatitis in patients with chronic pancreatitis Identification of gene variants contributing to pancreatitis in an individual or family Identification of gene variants to allow for predictive and diagnostic testing in family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(11) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Raphael KL, Willingham FF. Hereditary pancreatitis: current perspectives. Clin Exp Gastroenterol. 2016;9:197-207 2. Suzuki M, Minowa K, Nakano S, Isayama H, Shimizu T. Genetic abnormalities in pancreatitis: An update on diagnosis, clinical features, and treatment. Diagnostics (Basel). 2020;11(1):31 3. Shelton C, LaRusch J, Whitcomb DC. Pancreatitis overview. In: Adam MP, Feldman J, Mirzaa GM, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2014. Updated July 2, 2020. Accessed March 31, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK190101/ 4. Hasan A, Moscoso DI, Kastrinos F. The role of genetics in pancreatitis. Gastrointest Endosc Clin N Am. 2018;28(4):587-603 5. Johansson BB, Fjeld K, El Jellas K, et al. The role of the carboxyl ester lipase (CEL) gene in pancreatic disease. Pancreatology. 2018;18(1):12-19. doi:10.1016/j.pan.2017.12.001 6. Witt H, Beer S, Rosendahl J, et al. Variants in CPA1 are strongly associated with early onset chronic pancreatitis. Nat Genet. 2013;45(10):1216-1220. doi:10.1038/ng.2730 7. Khan E, Chakrabarty S, Shariff S, Bardhan M. Genetics and genomics of chronic pancreatitis with a focus on disease biology and molecular pathogenesis. Glob Med Genet. 2023;10(4):324-334. Published 2023 Nov 22. doi:10.1055/s-0043-1776981 8. Whitcomb DC, LaRusch J, Krasinskas AM, et al. Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. Nat Genet. 2012;44(12):1349-1354. doi:10.1038/ng.2466 9. Dermine S, Masson E, Girodon-Boulandet E, et al. Diagnostic yield of repeat genetic testing in idiopathic

chronic pancreatitis. Clin Res Hepatol Gastroenterol. 2024;48(6):102346. doi:10.1016/j.clinre.2024.102346 10. Masamune A, Kotani H, Sorgel FL, et al. Variants that affect function of calcium channel TRPV6 are associated with early-onset chronic pancreatitis. Gastroenterology. 2020;158(6):1626-1641.e8. doi:10.1053/j.gastro.2020.01.005 11. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-424

ESBLS
607828

Extended-Spectrum Beta-Lactamase-Producing Gram-Negative Bacteria Surveillance Culture, Feces

Clinical Information: In June 2019, the US Food and Drug Administration recommended stool testing of fecal microbiota transplant (FMT) donors to assess for the presence of certain infectious agents.(1) FMT donor feces should be screened for extended-spectrum beta-lactamase (ESBL)-producing organisms. ESBLs are enzymes that confer variable resistance to third- and fourth-generation cephalosporins as well as aztreonam. Because these resistance genes are encoded on plasmids, which are easily transmissible, ESBL-producing organisms raise important infection control issues. FMT donor feces may be screened on a regularly scheduled basis for ESBL-producers. Screening will be performed via culture of stool samples using vancomycin, amphotericin B, ceftazidime, and clindamycin (VACC) agar. Remel VACC agar is a primary selective medium for the isolation of ESBL-producing Enterobacterales. In addition to multiple substrates necessary for bacterial growth, this medium also contains multiple antimicrobials which inhibit normal intestinal microbiota. Possible ESBL-producers isolated on VACC agar will be confirmed by the Clinical and Laboratory Standards Institute ESBL disk diffusion test.(2)

Useful For: Screening for colonization of extended-spectrum beta-lactamase (ESBL)-producing organisms in stool Screening fecal microbiota transplant donor feces for ESBL-producing organisms. This test is not intended for medicolegal use.

Interpretation: Exclusion of feces from use in fecal microbiota transplantation is recommended if extended-spectrum beta-lactamase -producing bacteria are detected. Refer to US Food and Drug Administration guidance for details.(3)

Reference Values:
Negative for extended-spectrum beta-lactamase-producing organisms

Positive for extended-spectrum beta-lactamase-producing organisms

Clinical References: 1. Food and Drug Administration (FDA) Safety and Availability (Biologics) Communication. Information Pertaining to Additional Safety Protections Regarding Use of Fecal Microbiota for Transplantation - Screening and Testing of Stool Donors for Multi-drug Resistant Organisms. FDA; June 18, 2019. Accessed November 17, 2023. Available at www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation 2. Clinical and Laboratory Standards Institute [CLSI]. Performance Standards for Antimicrobial Susceptibility Testing. 31st ed. CLSI supplement M100. CLSI; 2021. 3. Food and Drug Administration (FDA) Safety and Availability (Biologics) Communication. Important Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms. FDA; June 13, 2019. Updated December 04, 2020. Accessed November 17, 2023. Available at www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse

F2ISO
607698

F2-Isoprostanes, Random, Urine

Clinical Information:

Useful For: Assessment of in vivo lipid peroxidation Considered to be an index of systemic oxidative stress over time

Interpretation: Elevated urinary F2-isoprostanes reflect widespread oxidative stress and systemic burden of lipid peroxidation end products. Quantitation of F2-isoprostanes in urine is highly dependent upon the methodology utilized; however, mass spectrometry methods (gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry) assays yield superior sensitivity and analytical specificity compared with immunoassays. F2-isoprostanes demonstrate superior clinical sensitivity compared to other oxidative stress biomarkers but lack clinical specificity for any particular disease. Pharmacological treatment with antioxidant supplementation, hypoglycemic agents in diabetes, smoking cessation, and weight reduction have all been shown to decrease production of F2-isoprostanes.

Reference Values:
> or =18 years: < or =1.0 ng/mg creatinine
Reference values have not been established for patients who are younger than 18 years of age

Clinical References: 1. Strobel NA, Fassett RG, Marsh SA, Coombes JS. Oxidative stress biomarkers as predictors of cardiovascular disease. Int J Cardiol. 2011;147(2):191-201 2. Davies SS, Roberts, LJ. F2-isoprostanes as an indicator and risk factor for coronary heart disease. Free Radic Biol Med. 2011;50(5):559-566 3. Kontush A, de Faria EC, Chantepie S, Chapman MJ. A normotriglyceridemic, low HDL-cholesterol phenotype is characterized by an elevated oxidative stress and HDL particles with attenuated antioxidative activity. Atherosclerosis. 2005;182(2):277-285 4. Vassale C, Botto N, Andreassi MG, et al. Evidence for enhanced 8-isoprostane plasma levels, as an index of oxidative stress in vivo, for patients with coronary artery disease. Coron Artery Dis. 2003 May;14(3):213-218 5. Milne GL, Sanchez SC, Musiek, ES, Morrow JD. Quantification of F2-isoprostanes as a biomarker of oxidative stress. Nature Prot. 2007;2(1):221-226 6. Zhang Z. Systematic review on the association between F2-isoprostanes and cardiovascular disease. Ann Clin Biochem. 2013;50(Pt 2):108-114 7. Wu J, Marchioli R, Silletta MG, et al. Oxidative stress biomarkers and the incidence of postoperative atrial fibrillation in the Omega-3 Fatty Acids for Prevention of Postoperative Atrial Fibrillation (OPERA) Trial. J Am Heart Assoc. 2015;4(5):e001886 8. Vazzana N, Ganci A, Cefalu AB, et al. Enhanced lipid peroxidation and platelet activation as potential contributors to increased cardiovascular risk in the low-HDL phenotype. J Am Heart Assoc. 2013;2(2):e000063

FABRZ
35415

Fabry Disease, Full Gene Analysis, Varies

Clinical Information: Fabry disease is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Reduced alpha-Gal A activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual alpha-Gal A activity. Males with less than 1% alpha-Gal A activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. By middle age, most patients develop renal insufficiency leading to end-stage kidney disease, as well as cardiac and cerebrovascular disease. Males with greater than 1% alpha-Gal A activity may present with a variant form of Fabry disease. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end-stage kidney disease. Individuals with the renal variant may or may not have other symptoms of classic Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy or

mitral insufficiency later in life. The cardiac variant is not associated with renal failure. Female carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severe. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals have normal levels of alpha-Gal A. Variants in the GLA gene result in deficiency of alpha-Gal A. Most of the disease causing variants identified to date are family specific. Full sequencing of the GLA gene identifies over 98% of the sequence variants in the coding region and splice junctions. In addition, this assay detects the intron 4 alteration common in the Taiwanese population.(1) The recommended first-tier test for males with suspected Fabry disease is biochemical testing that measures alpha-galactosidase enzyme activity in blood or serum: AGAW / Alpha-galactosidase, Leukocytes or AGAS / Alpha-galactosidase, Serum. Additionally, testing for the glycosphingolipid, globotriaosylsphingosine (LGb3) may aid in further clarifying disease status in both males and females with suspected Fabry disease (LGB3S / Globotriaosylsphingosine, Serum). Individuals with decreased or absent enzyme activity and elevated LGb3 are more likely to have an identifiable disease-causing variants in the GLA gene by molecular genetic testing. However, enzymatic testing alone is not reliable to detect female carriers. The following algorithms are available: -Fabry Disease: Newborn Screen-Positive Follow-up algorithm -Fabry Disease Diagnostic Testing Algorithm

Useful For: Confirmation of a diagnosis of classic or variant Fabry disease in affected males with reduced alpha- galactosidase A enzyme activity Carrier or diagnostic testing for asymptomatic or symptomatic females, respectively

Interpretation: All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics recommendations.(2) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Accessed September 25, 2024. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Hwu WL, Chien YH, Lee NC, et al. Newborn screening for Fabry disease in Taiwan reveals a high incidence of the later-onset GLA mutation c.936+919G>A). Hum Mutat. 2009:30(10):1397-1405 3. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 4. Germain DP. Fabry disease. Orphanet J Rare Dis. 2010;5:30 5 Wang RY, Lelis A, Mirocha J, Wilcox WR. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. Genet Med. 2007;9(1):34-35 6. Henderson N, Berry L, Laney DA. Fabry Disease practice resource: Focused revision. J Genet Couns. 2020;29(5):715-717

FA13R
75852

Factor 13 1:1 Mix

Reference Values:
Only orderable as a reflex test.
For more information, see FA13Q.

FA13Q
75851

Factor 13, Qualitative, with Reflex to Factor 13 1:1 Mix

Reference Values:
Factor XIII, Qualitative: No Lysis

FC13A
70428

Factor 13a Immunostain, Technical Component Only

Clinical Information: Factor XIIIa, a blood and intracellularly produced coagulation factor, has been found in a variety of cell types, including fibroblast-like mesenchymal cells, and has been shown to stimulate the proliferation of fibroblasts and neoplastic cells in vitro. Immunohistochemical staining for factor XIIIa labels normal dermal dendrocytes, the large stellate fibroblasts found in acquired digital fibrokeratomas, angiofibromas, and oral fibroma, and a proportion of cells in histiocytomas. Factor XIIIa immunostain also produces cytoplasmic staining of dermal dendrocytes in normal skin and of a proportion of cells in histiocytomas.

Useful For: Aiding in the identification of acquired digital fibrokeratomas, angiofibromas, and oral fibroma, and a proportion of cells in histiocytomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. West KL, Cardona DM, Su Z, Puri PK. Immunohistochemical markers in fibrohistiocytic lesions: factor XIIIa, CD34, S-100 and p75. Am J Dermatopathol. 2014;36(5):414-419. doi:10.1097/DAD.0b013e3182a70396 2. de Alvarenga Lira ML, Pagliari C, de Lima Silva AA, de Andrade HF Jr, Duarte MI. Dermal dendrocytes FXIIIa+ are essential antigen-presenting cells in indeterminate leprosy. Am J Dermatopathol. 2015;37(4):269-273. doi:10.1097/DAD.0000000000000238 3. Hirai KE, Aarao TL, Silva LM, et al. Langerhans cells (CD1a and CD207), dermal dendrocytes (FXIIIa) and plasmacytoid dendritic cells (CD123) in skin lesions of leprosy patients. Microb Pathog. 2016;91:18-25. doi:10.1016/j.micpath.2015.11.013 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FACR8
70430

Factor 8 Related Antigen Immunostain, Technical Component Only

Clinical Information: Factor 8-related antigen shows diffuse cytoplasmic staining of endothelial cells, megakaryocytes, and platelets. This immunostain may be used to support endothelial cell lineage in angiosarcoma.

Useful For: Marker of endothelial cell lineage

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Mak KM, Sehgal P, Harris CK. Factor VIII-related antigen detects phenotypic change of sinusoidal to vascular endothelium in hepatic fibrosis of elderly cadavers. Int Sch

Res Notices. 2014;2014:839560. doi:10.1155/2014/839560 2. Matino D, Gargaro M, Santagostino E, et al. IDO1 suppresses inhibitor development in hemophilia A treated with factor VIII. J Clin Invest. 2015;125(10):3766-3781. doi:10.1172/JCI81859 3. de Groot J. Tumor invasion after treatment of glioblastoma with bevacizumab: radiographic and pathologic correlation in humans and mice. Neuro-oncology. 2010;12.3:233-242 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

AFH
615249

Factor H Autoantibody, Serum

Clinical Information: Complement factor H (FH) is an important regulator of cell-bound activated C3b, and most importantly of activated C3b in the fluid phase. It is estimated that C3 activation takes place at a rate of 1% to 2%, thus constant activity of FH and other regulators is essential to retain control of complement's alternative pathway. Anti-factor H (AFH) is an autoantibody that interferes with the ability of FH to bind the C3 convertase, therefore allowing unrestricted amplification of C3b in the complement cascade. Anti-factor H is predominantly seen in children between the ages of 9 and 13 years but can also affect adults. AFH is found in atypical hemolytic uremic syndrome (aHUS) and in C3 glomerulopathies. AHUS is a form of thrombotic microangiopathy, a condition that can cause small blood vessels in the kidneys to become damaged and inflamed as a result of clots forming in the vessels. The clots clog the glomeruli of the kidneys and can cause problems with the kidney' s ability to filter and eliminate waste products. Compared to typical HUS, which is caused by Shiga toxin-producing bacterial infection, aHUS is a diagnosis of exclusion, associated with genetic variants in the complement alternative pathway or acquired autoantibodies that contribute to uncontrolled activation of the complement system. C3 glomerulopathies (C3G) are rare kidney diseases resulting from complement deposition in the kidney (mostly C3 fragments) and causing glomerular damage. C3G may have autoimmune or genetic causes and is attributed mostly to dysfunction of the complement alternative pathway. Anti-factor H are found in 6% to 10% of patients with aHUS, and the presence or absence of AFH can be a determinant of whether immunosuppressive therapy is warranted versus complement-blocking therapy.(1) Deletion of the CFHR1 gene, with or without other CFHR genes, can result in predisposition to generation of AFH; however, not all individuals with CFHR1 deletion develop AFH, and conversely, some individuals with the autoantibody do not have a CFHR1 deletion.(2) Most commonly, the deletion encompasses both the CFHR1 and CFHR3 genes. The allele frequency of the CFHR3/CFHR1 deletion varies among populations, from 0% in Japanese and South American populations to 54.7% in Nigeria; similarly, the frequency of homozygosity for the deletion ranges from 0% up to 33% in Nigeria.(3) Interestingly, while AFH are much more common in aHUS cohorts from India, accounting for approximately 50% of cases, the population frequency of homozygous CFHR1 deletion is 9.5%, which is not significantly higher than in other populations.(4,5) The mechanism that results in AFH formation in the presence of the deletion remains unknown. Most of the autoantibodies inhibit FH function by binding and blocking the C-terminus, impairing its ability to bind endothelial cell surfaces, sialic acids, and C3b; however, in some individuals, the AFH may recognize other regions, such as the N-terminal SCR1-4.

Useful For: Detection and quantification of antibodies to factor H Monitoring patients with known factor H autoantibodies Aiding in the differential diagnosis of thrombotic microangiopathy and C3 glomerulopathies

Interpretation: Absent (<15.8 U/mL): Antibodies to factor H are not detected. Present (> or =15.8 U/mL): Antibodies to factor H are detected. Clinical correlation recommended.

Reference Values:
<15.8 U/mL

Clinical References: 1. Ekdahl KN, Persson B, Mohlin C, Sandholm K, Skattum L, Nilsson B. Interpretation of serological complement biomarkers in disease. Front Immunol. 2018;9:2237. doi:10.3389/fimmu.2018.02237 2. Jozsi M, Licht C, Strobel S, et al. Factor H autoantibodies in atypical hemolytic uremic syndrome correlate with CFHR1/CFHR3 deficiency. Blood. 2008;111(3):1512-1514. doi:10.1182/blood-2007-09-109876 3. Holmes LV, Strain L, Staniforth SJ, et al. Determining the population frequency of the CFHR3/CFHR1 deletion at 1q32. PLoS One. 2013;8(4):e60352. doi:10.1371/journal.pone.0060352 4. Sinha A, Gulati A, Saini S, et al. Prompt plasma exchanges and immunosuppressive treatment improves the outcomes of anti-factor H autoantibody-associated hemolytic uremic syndrome in children. Kidney Int. 2014;85(5):1151-1160. doi:10.1038/ki.2013.373 5. Durey MA, Sinha A, Togarsimalemath SK, Bagga A. Anti-complement-factor H-associated glomerulopathies. Nat Rev Nephrol. 2016;12(9):563-578. doi:10.1038/nrneph.2016.99 6. Blanc C, Togarsimalemath SK, Chauvet S, et al. Anti-factor H autoantibodies in C3 glomerulopathies and in atypical hemolytic uremic syndrome: one target, two diseases. J Immunol. 2015;194(11):5129-5138. doi:10.4049/jimmunol.1402770 7. Zhang Y, Ghiringhelli Borsa N, Shao D, et al. Factor H autoantibodies and complement-mediated diseases. Front Immunol. 2020;11:607211. doi:10.3389/fimmu.2020.607211 8. Sanchez-Corral P, Pouw RB, Lopez-Trascasa M, Jozsi M. Self-damage caused by dysregulation of the complement alternative pathway: Relevance of the factor H protein family. Front Immunol. 2018;9:1607. doi:10.3389/fimmu.2018.01607 9. Dragon-Durey MA, Blanc C, Roumenina LT, et al. Anti-factor H autoantibodies assay. Methods Mol Biol. 2014;1100:249-56. doi:10.1007/978-1-62703-724-2_20

2INHE
607427

Factor II Inhibitor Evaluation, Plasma

Clinical Information: Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy or can either occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and in the older population. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

Useful For: Detection and quantitation of inhibitor to factor II This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

Interpretation: Normally, there is no inhibitor, ie, negative result. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

Reference Values:
FACTOR II ACTIVITY ASSAY
Adults: 75-145%
Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =25%) that may remain below adult levels for 180 days or more postnatal.*
*See Pediatric Hemostasis References in Coagulation Guidelines for Specimen Handling and Processing.

FACTOR II INHIBITOR SCREEN:
Negative

GENERAL FACTOR BETHESDA UNITS: < or =0.5 Bethesda Units

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK: Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86 3. Kottke-Marchant K, ed. Laboratory Hematology Practice. Wiley

Blackwell Publishing; 2012

2AINH
607445

Factor II Inhibitor Profile, Professional Interpretation

Clinical Information: Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy or can either occur spontaneously without known cause or in response to a variety of medical conditions, including the postpartum state, immunologic disorders, certain antibiotic therapies, and some malignancies, and in the older adult population. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

Useful For: Interpretation of testing for the detection and quantitation of inhibitor to factor II

Interpretation: When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, and elements of differential diagnosis.

Reference Values:
Only orderable as a reflex. For more information see 2INHE / Factor II Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds: Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK. Treatment of factor VIII inhibitors. Prog Hemost Thromb 1989;9:57-86 3. Kottke-Marchant K, ed. Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012

2INHT
607438

Factor II Inhibitor Profile, Technical Interpretation

Clinical Information: Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy or can either occur spontaneously without known cause or in response to a variety of medical conditions, including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and in the older population. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

Useful For: Technical interpretation of inhibitor to factor II testing This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

Interpretation: When testing is complete, if factor activity results fall within clinically normal ranges, an interpretive comment will be provided noting that inhibitor testing was not indicated and, therefore, not performed. If factor activity indicates the performance of inhibitor screen testing, an interpretive comment will be provided noting the presence or absence of a factor II inhibitor.

Reference Values:
Only orderable as part of a profile. For more information see 2INHE / Factor II Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK: Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86 3. Kottke-Marchant K, ed. Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012

F2_IS
7806

Factor II Inhibitor Screen, Plasma

Clinical Information: Patient plasma, normal pooled plasma (NPP), and a mixture of patient plasma and NPP are each tested for a specific factor, incubated at 37 degrees C for 1 hour, and then retested for the same factor. In addition, a new mixture of patient plasma and NPP is prepared using the incubated plasmas and tested after the 1 hour incubation. The percentage of the recovered factor for each individual plasma and mixture being tested is calculated and compared. The procedure demonstrates the effect of a specific coagulation factor inhibitor on that factor present in normal pooled plasma, over a specific period of time. An inhibitor directed against a coagulation factor may arise due to multiple exposures from transfusions in a patient deficient in that factor (as in the case of hemophiliacs), in response to certain disease states, or be drug-induced. Non-specific inhibitors may also be present in patients that will prolong screening tests (eg, prothrombin time and activated partial thromboplastin time). This test is used to qualitatively identify an inhibitor to a specific coagulation factor.

Useful For: Detecting the presence of a specific factor inhibitor directed against coagulation factor II

Interpretation: When testing is complete, if factor activity results fall within clinically normal ranges, an interpretive comment will be provided noting that inhibitor testing was not indicated and, therefore, not performed. If factor activity indicates the performance of inhibitor screen testing, an interpretive comment will be provided noting the presence or absence of a factor II inhibitor.

Reference Values:
Only orderable as part of a profile. For more information see:
2INHE / Factor II Inhibitor Evaluation, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
APROL / Prolonged Clot Time Profile, Plasma

Negative

Clinical References: 1. Bowie EJW, Thompson JH Jr, Didisheim P, Owen CA Jr. Mayo Clinic Laboratory Manual of Hemostasis. WB Saunders Company; 1971:111-115 2. Kottke-Marchant K. Laboratory Hematology Practice. Wiley Blackwell Publishing, 2012 3. Hoffman R, Benz EJ Jr, Silberstein, et al. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018

9INHE
607425

Factor IX Inhibitor Evaluation, Plasma

Clinical Information: Factor IX inhibitors arise in patients with severe hemophilia B after factor IX transfusion. Patients with factor IX inhibitors may also develop anaphylactic reactions in response to factor IX infusions. Acquired factor IX inhibitors, occurring in previously healthy people, are exceedingly rare.

Useful For: Detection and titering of coagulation inhibitor to the specific factor requested, primarily factor IX in patients with hemophilia B This test is not useful for the detection of a lupus-like circulating

anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

Interpretation: Normally, there is no inhibitor (ie, negative result). If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

Reference Values:
FACTOR IX ACTIVITY ASSAY
Adults: 65-140%
Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%) that may not reach adult levels for 180 days or more postnatal.*
*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing.

FACTOR IX INHIBITOR SCREEN:
Negative

GENERAL FACTOR BETHESDA UNITS:
< or =0.4 Bethesda Units

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Chitlur M, Warrier I, Rajpurkar M, et al. Inhibitors in factor IX deficiency a report of the ISTH-SSC international FIX inhibitor registry (1997-2006). Haemophilia. 2009;15(5):1027-1031. doi:10.1111/j.1365-2516.2009.02039.x

9INHT 607436 Factor IX Inhibitor Profile Technical Interpretation

Clinical Information: Factor IX inhibitors arise in patients with severe hemophilia B after factor IX transfusion. Patients with factor IX inhibitors may also develop anaphylactic reactions in response to factor IX infusions. Acquired factor IX inhibitors, occurring in previously healthy people, are exceedingly rare.

Useful For: Technical interpretation of inhibitor to factor IX testing for patients with hemophilia B

Interpretation: When testing is complete, if factor activity results fall within clinically normal ranges, an interpretive comment will be provided noting that inhibitor testing was not indicated and, therefore, not performed. If factor activity indicates the performance of inhibitor screen testing, an interpretive comment will be provided noting the presence or absence of a factor IX inhibitor.

Reference Values:
Only orderable as part of a profile. For more information see 9INHE / Factor IX Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Chitlur M, Warrier I, Rajpurkar M, et al. Inhibitors in factor IX deficiency a report of the ISTH-SSC international FIX inhibitor registry (1997-2006). Haemophilia. 2009;15(5):1027-1031

9AINH
607443

Factor IX Inhibitor Profile, Professional Interpretation

Clinical Information: Factor IX inhibitors arise in patients with severe hemophilia B after factor IX transfusion. Patients with factor IX inhibitors may also develop anaphylactic reactions in response to factor IX infusions. Acquired factor IX inhibitors occurring in previously healthy people are exceedingly rare.

Useful For: Interpretation for the detection and titering of coagulation inhibitor to the specific factor requested, primarily factor IX in patients with hemophilia B

Interpretation: When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, and elements of differential diagnosis.

Reference Values:
Only orderable as a reflex. For more information see 9INHE / Factor IX Inhibitor Evaluation, Plasma

An interpretive report will be provided.

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Chitlur M, Warrier I, Rajpurkar M, et al. Inhibitors in factor IX deficiency a report of the ISTH-SSC international FIX inhibitor registry (1997-2006). Haemophilia 2009;15(5):1027-1031

F9_IS
7802

Factor IX Inhibitor Screen, Plasma

Clinical Information: Patient plasma, normal pooled plasma (NPP), and a mixture of patient plasma and NPP are each tested for a specific factor, incubated at 37 degrees C for 1 hour, and then retested for the same factor. In addition, a new mixture of patient plasma and NPP is prepared using the incubated plasmas and tested after the 1 hour incubation. The percentage of the recovered factor for each individual plasma and mixture being tested is calculated and compared. The procedure demonstrates the effect of a specific coagulation factor inhibitor on that factor present in normal pooled plasma, over a specific period of time. An inhibitor directed against a coagulation factor may arise due to multiple exposures from transfusions in a patient deficient in that factor (as in the case of hemophiliacs), in response to certain disease states, or be drug-induced. Non-specific inhibitors may also be present in patients that will prolong screening tests (eg, prothrombin time and activated partial thromboplastin time). This test is used to qualitatively identify an inhibitor to a specific coagulation factor.

Useful For: Detecting the presence of a specific factor inhibitor directed against coagulation factor IX

Interpretation: When testing is complete, if factor activity results fall within clinically normal ranges, an interpretive comment will be provided noting that inhibitor testing was not indicated and, therefore, not performed. If factor activity indicates the performance of inhibitor screen testing, an interpretive comment will be provided noting the presence or absence of a factor IX inhibitor.

Reference Values:
Only orderable as a reflex. For more information see:
9INHE / Factor IX Inhibitor Evaluation, Plasma
ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma

APROL / Prolonged Clot Time Profile, Plasma

Negative

Clinical References: 1. Bowie EJW, Thompson JH Jr, Didisheim P, Owen CA Jr. Mayo Clinic Laboratory Manual of Hemostasis. WB Saunders Company; 1971:111-115 2. Chitlur M, Warrier I, Rajpurkar M, et al. Inhibitors in factor IX deficiency a report of the ISTH-SSC international FIX inhibitor registry (1997-2006). Haemophilia. 2009;15(5):1027-1031 3. Laboratory Hematology Practice. In: Kottke-Marchant K, ed. Wiley Blackwell Publishing; 2012 4. Favaloro EJ, Lippi G. Hemostasis and Thrombosis, Methods and Protocols. Humana Press; 2017

5BETH
607433

Factor V Bethesda Units, Plasma

Clinical Information: Significant bleeding can result from the presence of a coagulation factor inhibitor and could be life threatening. Whether the inhibitor is present due to hemophilia or is of an acquired nature, it greatly complicates the treatment process of a decreased factor level. The titer of the inhibitor may determine the mode of treatment. Bethesda units are a standardization to give a uniform definition of an inhibitor.

Useful For: Detecting and quantifying the presence and titer of a specific factor inhibitor directed against coagulation factor V

Interpretation: An interpretive report will be provided when testing is complete.

Reference Values:
Only orderable as a reflex. For more information see:
-ALUPP / Lupus Anticoagulant Profile, Plasma
-ALBLD / Bleeding Diathesis Profile, Limited, Plasma
-ACBL / Bleeding Diathesis Profile, Comprehensive, Plasma
-APROL / Prolonged Clot Time Profile, Plasma
-5INHE / Factor V Inhibitor Evaluation, Plasma

< or =0.5 Bethesda Units

Clinical References: 1. Biggs R, Bidwell E. A method for the study of antihemophiliac globulin inhibitors with reference to six cases. Br J Haematol. 1959;5:379-395 2. Hoyer LW: Factor VIII inhibitors. In: Hoyer LW, eds. Progress in Clinical and Biological Research. Vol 150. R Alan Liss Inc, 1984:87-98 3. Kasper CK, Aledort L, Aronson D, et al. Proceedings: A more uniform measurement of factor VIII inhibitors. Thromb Diath Haemorrh. 1975;34(2):61 4. Kasper C, Ewing N. Acquired inhibitors of plasma coagulation factors. J Med Tech 1986;38:431-439 5. Kottke-Marchant K, ed: Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012 6. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018

5INHE
607426

Factor V Inhibitor Evaluation, Plasma

Clinical Information: Factor V inhibitors can occur in patients with congenital factor V deficiency after transfusion of fresh frozen plasma, however, they more commonly occur spontaneously in previously healthy older patients who have no underlying diseases. Topical bovine thrombin or fibrin glue, which contain bovine thrombin and factor V, are commonly used in surgery for topical hemostasis and can result in development of anti-bovine thrombin/factor V inhibitors that cross-react with human thrombin and factor V. Other associations include antibiotics, transfusions, and malignancies.

Useful

For: Detection and quantitation of inhibitors against coagulation factor V This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

Interpretation: Normally, there is no inhibitor (ie, negative result). If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

Reference Values:

FACTOR V ACTIVITY ASSAY
>1 month: 70-165%
<1 month: Normal, full-term and premature newborn infants may have mildly decreased levels (> or =30% to 35%) that reach adult levels within 21 days postnatal.
*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing

FACTOR V INHIBITOR SCREEN:
Negative

GENERAL FACTOR BETHESDA UNITS: < or =0.5 Bethesda Units

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds: Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK: Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86 3. Kottke-Marchant K, ed. Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012

5AINH
607444

Factor V Inhibitor Profile, Professional Interpretation

Clinical Information: Significant bleeding can result from the presence of a coagulation factor inhibitor and could be life threatening. Whether the inhibitor is present due to hemophilia or is of an acquired nature, it greatly complicates the treatment process of a decreased factor level. The titer of the inhibitor may determine the mode of treatment. Bethesda units are a standardization to give a uniform definition of an inhibitor.

Useful For: Interpretation of testing for factor V inhibitors

Interpretation: When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, and elements of differential diagnosis.

Reference Values:

Only orderable as a reflex. For more information see 5INHE / Factor V Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

Clinical References: 1. Biggs R, Bidwell E. A method for the study of antihemophiliac globulin inhibitors with reference to six cases. Br J Haematol. 1959;5:379-395 2. Hoyer LW: Factor VIII inhibitors. In: Hoyer LW, ed. Progress in Clinical and Biological Research. Vol 150. R Alan Liss Inc; 1984:87-98 3. Kasper CK, Aledort L, Aronson D, et al. Proceedings: A more uniform measurement of factor VIII inhibitors. Thromb Diath Haemorrh. 1975;34(2):612. 4. Kasper C, Ewing N: Acquired inhibitors of plasma coagulation factors. J Med Tech 1986;38:431-439 5. Kottke-Marchant K, ed.

Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012 6. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds: Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018

5INHT
607437

Factor V Inhibitor Profile, Technical Interpretation

Clinical Information: Significant bleeding can result from the presence of a coagulation factor inhibitor and could be life threatening. Whether the inhibitor is present due to hemophilia or is of an acquired nature, it greatly complicates the treatment process of a decreased factor level. The titer of the inhibitor may determine the mode of treatment. Bethesda units are a standardization to give a uniform definition of an inhibitor.

Useful For: Technical interpretation of inhibitor to factor V testing

Interpretation: When testing is complete, if factor activity results fall within clinically normal ranges, an interpretive comment will be provided noting that inhibitor testing was not indicated and, therefore, not performed. If factor activity indicates the performance of inhibitor screen testing, an interpretive comment will be provided noting the presence or absence of a factor V inhibitor.

Reference Values:
Only orderable as part of a profile. For more information see 5INHE / Factor V Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds: Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK: Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86 3. Kottke-Marchant K, ed. Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012

F5_IS
7808

Factor V Inhibitor Screen, Plasma

Clinical Information: Patient plasma, normal pooled plasma (NPP), and a mixture of patient plasma and NPP are each tested for a specific factor, incubated at 37 degrees C for 1 hour, and then retested for the same factor. In addition, a new mixture of patient plasma and NPP is prepared using the incubated plasmas and tested after the 1 hour incubation. The percentage of the recovered factor for each individual plasma and mixture being tested is calculated and compared. The procedure demonstrates the effect of a specific coagulation factor inhibitor on that factor present in normal pooled plasma over a specific period of time. An inhibitor directed against a coagulation factor may arise due to multiple exposures from transfusions in a patient deficient in that factor (as in the case of hemophiliacs), in response to certain disease states, or be drug-induced. Nonspecific inhibitors may also be present in patients that will prolong screening tests (eg, prothrombin time and activated partial thromboplastin time). This test is used to qualitatively identify an inhibitor to a specific coagulation factor.

Useful For: Detecting the presence of a specific factor inhibitor directed against coagulation factor V

F5DNA
81419

Factor V Leiden (R506Q) Mutation, Blood

Clinical Information: Venous thromboembolism includes deep vein thrombosis and its complication, pulmonary embolism. Plasma from 12% to 20% of venous thromboembolism patients is

resistant to the anticoagulant effect of activated protein C (APC resistance). Essentially all patients with hereditary APC resistance have the factor V Leiden, F5 c.1601G>A, p.Arg534Gln (legacy R506Q) variant.

Useful For: Patients with clinically suspected thrombophilia and: 1. Activated protein C (APC)-resistance either proven or suspected by a low or borderline APC-resistance ratio or 2. A family history of factor V Leiden

Interpretation: The results will be reported as: -Negative for the F5 c.1601G>A, p.Arg534Gln variant -Heterozygous for the F5 c.1601G>A, p.Arg534Gln variant -Homozygous for the F5 c.1601G>A, p.Arg534Gln variant

Reference Values:
Negative

Clinical References: 1. Dahlback B, Carlsson M, Svensson PR: Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: prediction of a cofactor to activated protein C. Proc Natl Acac Sci USA. 1993;90:1004-1008 2. Bertina RM, Koeleman BP, Koster T, et al: Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994;369:64-67 3. Zoller B, Svensson PJ, He X, Dahlback B: Identification of the same factor V gene mutation in 47 out of 50 thrombosis-prone families with inherited resistance to activated protein C. J Clin Invest. 1994;94:2521-2524 4. Freed J, Bauer KA: Thrombophilia: clinical and laboratory assessment and management. In: Kitchens CS, Kessler CM, Konkle BA, Streiff MB, Garcia DA, eds. Consultative Hemostasis and Thrombosis. 4th ed. Elsevier; 2019:242-265

GNF7
619089

Factor VII Deficiency, F7 Gene, Next-Generation Sequencing, Varies

Clinical Information: Factor VII deficiency (FVIID) is a rare hereditary bleeding disorder associated with germline variants in the F7 gene. It is inherited in an autosomal recessive manner with variable expressivity; both male and female individuals may be affected. The estimated prevalence is 1 in 500,000 individuals.(1) FVIID is characterized by a deficiency or reduced activity of clotting factor VII. The symptoms and severity of FVIID are highly variable. Individuals with mild disease do not typically experience spontaneous bleeding but may have prolonged bleeding after trauma or surgery. For those with severe disease, symptoms include epistaxis, menorrhagia, easy bruising, gum bleeding, and post-surgical bleeding. Onset can occur within the first 6 months of life and include life-threatening intracranial and gastrointestinal hemorrhages. Joint and muscle bleeds are less common. FVIID does not protect against venous thromboembolism.(2-4) In many cases of FVIID, there is no consistent correlation between FVII plasma levels and disease severity.(1,4,5) However, good correlation has been demonstrated between FVII levels and genotype. Individuals with homozygous or compound heterozygous disease-causing variants in the F7 gene have been found to have significantly lower FVII levels than those individuals with heterozygous or no detectable F7 variants.(6) Causes of acquired (nongenetic) FVIID should be excluded prior to genetic testing, including vitamin K deficiency, use of vitamin K antagonists such as warfarin, liver disease, and sepsis.(7,8) The United Kingdom Haemophilia Centre Doctors' Organization provides guidelines regarding diagnosis and management for individuals with inherited bleeding disorders, including F7D.(9)

Useful For: Evaluating factor VII deficiency (FVIID) in patients with a personal or family history suggestive of FVIID Confirming an FVIID diagnosis with the identification of known or suspected disease-causing alterations in the F7 gene Determining the disease-causing alterations within the F7 gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of FVIID Identifying the causative alterations for genetic counseling purposes Prognosis and risk assessment based on the

genotype-phenotype correlations Carrier testing for close family members of an individual with a diagnosis of FVIID

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(10) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Palla R, Peyvandi F, Shapiro AD: Rare bleeding disorders: diagnosis and treatment. Blood. 2015 Mar;125(13):2052-2061 2. Lapecorella M, Mariani G, International Registry on Congenital Factor VII Deficiency: Factor VII deficiency: defining the clinical picture and optimizing therapeutic option. Haemophilia. 2008 Nov;14(6):1170-1175 3. Napolitano M, Siragusa S, Mariani G: Factor VII deficiency: Clinical phenotype, genotype and therapy. J Clin Med. 2017 Mar 28;6(4):38 4. Mariani G, Herrmann FH, Schulman S, International Factor VII Deficiency Study Group, et al: Thrombosis in inherited factor VII deficiency. J Thromb Haemost. 2003 Oct;1(10):2153-2158. 5. de Moerloose P, Schved J-F, Nugent D: Rare coagulation disorders: fibrinogen, factor VII and factor XIII. Haemophilia 2016. Jul;22 Suppl 5:61-65 6. Quintavalle G, Riccardi F, Rivolta GF, et al: F7 gene variants modulate protein levels in a large cohort of patients with factor VII deficiency. Results from a genotype-phenotype study. Thromb Haemost. 2017 Aug 1;117(8):1455-1464 7. da Silva VA, Silva SS, Martins FF: Acquired deficiency of coagulation factor VII. Rev Bras Hematol Hemoter. 2015 Jul-Aug;37(4):269-271 8. Mulliez SM, Devreese KM: Isolated acquired factor VII deficiency: a review of the literature. Acta Clin Belg. 2016 Apr;71(2):63-70 9. Mumford AD, Ackroyd S, Alikhan R, et al: Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2014 Nov;167(3):304-326 10. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

7INHE
607428

Factor VII Inhibitor Evaluation, Plasma

Clinical Information: Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy or can occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and in the older population. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

Useful For: Detection and quantitation of inhibitor to coagulation factor VII This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

Interpretation: Normally, there is no inhibitor (ie, negative result). If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

Reference Values:
FACTOR VII ACTIVITY ASSAY
Adults: 65-180%
Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%) that increase within the first postnatal week but may not reach adult levels for 180 days or more

postnatal.*
*See Pediatric Hemostasis References in Coagulation Guidelines for Specimen Handling and Processing.

FACTOR VII INHIBITOR SCREEN:
Negative

GENERAL FACTOR BETHESDA UNITS: < or =0.5 Bethesda Units

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK: Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86 3. Kottke-Marchant K, ed. Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012

7AINH
607446

Factor VII Inhibitor Profile, Professional Interpretation

Clinical Information: Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy or can occur spontaneously without known cause or in response to a variety of medical conditions, including the postpartum state, immunologic disorders, certain antibiotic therapies, and some malignancies, and in the older adult population. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

Useful For: Interpretation of testing for the detection and quantitation of inhibitor to factor VII

Interpretation: When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, and elements of differential diagnosis.

Reference Values:
Only orderable as a reflex. For more information see 7INHE / Factor VII Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK. Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86 3. Kottke-Marchant K, ed. Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012

7INHT
607439

Factor VII Inhibitor Profile, Technical Interpretation

Clinical Information: Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy or can occur spontaneously without known cause or in response to a variety of medical conditions, including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and in the older population. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

Useful For: Technical interpretation of inhibitor to coagulation factor VII testing

Interpretation: When testing is complete, if factor activity results fall within clinically normal ranges,

an interpretive comment will be provided noting that inhibitor testing was not indicated and, therefore, not performed. If factor activity indicates the performance of inhibitor screen testing, an interpretive comment will be provided noting the presence or absence of a factor VII inhibitor.

Reference Values:
Only orderable as part of a profile. For more information see 7INHE / Factor VII Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

Clinical References:

F7_IS
7810

Factor VII Inhibitor Screen, Plasma

Clinical Information: Patient plasma, normal pooled plasma (NPP), and a mixture of patient plasma and NPP are each tested for a specific factor, incubated at 37 degrees C for 1 hour, and then retested for the same factor. In addition, a new mixture of patient plasma and NPP is prepared using the incubated plasmas and tested after the 1 hour incubation. The percentage of the recovered factor for each individual plasma and mixture being tested is calculated and compared. The procedure demonstrates the effect of a specific coagulation factor inhibitor on that factor present in normal pooled plasma, over a specific period of time. An inhibitor directed against a coagulation factor may arise due to multiple exposures from transfusions in a patient deficient in that factor (as in the case of hemophiliacs), in response to certain disease states, or be drug-induced. Non-specific inhibitors may also be present in patients that will prolong screening tests (eg, prothrombin time and activated partial thromboplastin time). This test is used to qualitatively identify an inhibitor to a specific coagulation factor.

Useful For: Detecting the presence of a specific factor inhibitor directed against coagulation factor VII

Interpretation: When testing is complete, if factor activity results fall within clinically normal ranges, an interpretive comment will be provided noting that inhibitor testing was not indicated and, therefore, not performed. If factor activity indicates the performance of inhibitor screen testing, an interpretive comment will be provided noting the presence or absence of a factor VII inhibitor.

Reference Values:
Only orderable as part of a profile. For more information see:
7INHE / Factor VII Inhibitor Evaluation, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
APROL / Prolonged Clot Time Profile, Plasma

Negative

Clinical References:

8INHE
607424

Factor VIII Inhibitor Evaluation, Plasma

Clinical Information: Factor VIII (FVIII) inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may develop in 1 of 4 different patient populations: -Patients with congenital FVIII

deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate -Older nonhemophiliac adult patients (not previously factor VIII deficient) -Women in postpartum period -Patients with other autoimmune illnesses

Useful For: Detecting the presence and titer of a specific factor inhibitor directed against coagulation factor VIII This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

Interpretation: Normally, there is no inhibitor (ie, negative result). If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

Reference Values:
FACTOR VIII ACTIVITY ASSAY
Adults: 55-200%
Normal, full-term newborn infants or healthy premature infants typically have levels greater or equal to 40%.*
*See Pediatric Hemostasis References in Coagulation Guidelines for Specimen Handling and Processing.

FACTOR VIII INHIBITOR SCREEN:
Negative

GENERAL FACTOR BETHESDA UNITS: < or =0.5 Bethesda Units

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK. Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86 3. Peerschke EI, Castellone DD, Ledford-Kraemer M, et al. Laboratory assessment of FVIII inhibitor titer. Am J Clin Pathol. 2009;131(4):552-558. doi:10.1309/AJCPMKP94CODILWS 4. Pruthi RK, Nichols WL. Autoimmune factor VIII inhibitors. Curr Opin Hematol. 1999;6(5):314-322. doi:10.1097/00062752 5. Kottke-Marchant. K, ed. Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012

8AINH
607442

Factor VIII Inhibitor Profile, Professional Interpretation

Clinical Information: Factor VIII (FVIII) inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may develop in 1 of 4 different patient populations: -Patients with congenital FVIII deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate -Older nonhemophiliac adult patients (not previously factor VIII deficient) -Women in postpartum period -Patients with other autoimmune illnesses

Useful For: Interpretation for the detection of the presence and titer of a specific factor inhibitor directed against coagulation factor VIII

Interpretation: When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, and elements of differential diagnosis.

Reference Values:
Only orderable as a reflex. For more information see 8INHE / Factor VIII Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

Clinical References: 1. Kasper CK. Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86 2. Peerschke EI, Castellone DD, Ledford-Kraemer M, et al. Laboratory assessment of FVIII inhibitor titer. Am J Clin Pathol. 2009;131(4):552-558 3. Pruthi RK, Nichols WL. Autoimmune factor VIII inhibitors. Curr Opin Hematol. 1999;6(5):314-322 4. Kottke-Marchant K, ed. Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012 5. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018

8INHT
607435

Factor VIII Inhibitor Profile, Technical Interpretation

Clinical Information: Factor VIII (FVIII) inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may develop in 1 of 4 different patient populations: -Patients with congenital FVIII deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate -Older nonhemophiliac adult patients (not previously factor VIII deficient) -Women in postpartum period -Patients with other autoimmune illnesses

Useful For: Technical interpretation of inhibitor to factor VIII testing This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

Interpretation: When testing is complete, if factor activity results fall within clinically normal ranges, an interpretive comment will be provided noting that inhibitor testing was not indicated and, therefore, not performed. If factor activity indicates the performance of inhibitor screen testing, an interpretive comment will be provided noting the presence or absence of a factor VIII inhibitor.

Reference Values:
Only orderable as part of a profile. For more information see 8INHE / Factor VIII Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK. Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86 3. Peerschke EI, Castellone DD, Ledford-Kraemer M, et al. Laboratory assessment of FVIII inhibitor titer. Am J Clin Pathol. 2009;131(4):552-558 4. Pruthi RK, Nichols WL. Autoimmune factor VIII inhibitors. Curr Opin Hematol. 1999;6(5):314-322 5. Kottke-Marchant. K, ed. Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012

10INE
607429

Factor X Inhibitor Evaluation, Plasma

Clinical Information: Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy, or they can either occur spontaneously without known cause or in response to a variety of medical conditions, including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and in the older population. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

Useful For: Detection and quantitation of inhibitor to coagulation factor X This test is not useful for

the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

Interpretation: Normally, there is no inhibitor, ie, negative result. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

Reference Values:
FACTOR X ACTIVITY ASSAY
Adults: 70-150%
Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =15-20%) that may not reach adult levels for 180 days or more postnatal.*
*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing.

FACTOR X INHIBITOR SCREEN:
Negative

GENERAL FACTOR BETHESDA UNITS:
< or =0.5 Bethesda Units

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds: Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK. Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86

10AIH
607447

Factor X Inhibitor Profile, Professional Interpretation

Clinical Information: Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy, or they can either occur spontaneously without known cause or in response to a variety of medical conditions, including the postpartum state, immunologic disorders, certain antibiotic therapies, and some malignancies, and in the older adult population. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

Useful For: Interpretation of the detection and quantitation of inhibitor to coagulation factor X

Interpretation: When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, and elements of differential diagnosis.

Reference Values:
Only orderable as a reflex. For more information see 10INE / Factor X Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK. Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86

10INT
607440

Factor X Inhibitor Profile, Technical Interpretation

Clinical Information: Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy or they can either occur spontaneously without known cause or in response to a variety of medical conditions, including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and advanced age. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

Useful For: Technical interpretation of inhibitor to coagulation factor X testing

Interpretation: When testing is complete, if factor activity results fall within clinically normal ranges, an interpretive comment will be provided noting that inhibitor testing was not indicated and, therefore, not performed. If factor activity indicates the performance of inhibitor screen testing, an interpretive comment will be provided noting the presence or absence of a factor X inhibitor.

Reference Values:
Only orderable as part of a profile. For more information see 10INE / Factor X Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK. Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86

10_IS
7812

Factor X Inhibitor Screen, Plasma

Clinical Information: Patient plasma, normal pooled plasma (NPP), and a mixture of patient plasma and NPP are each tested for a specific factor, incubated at 37 degrees C for 1 hour, and then retested for the same factor. In addition, a new mixture of patient plasma and NPP is prepared using the incubated plasmas and tested after the 1 hour incubation. The percentage of the recovered factor for each individual plasma and mixture being tested is calculated and compared. The procedure demonstrates the effect of a specific coagulation factor inhibitor on that factor present in normal pooled plasma over a specific period of time. An inhibitor directed against a coagulation factor may arise due to multiple exposures from transfusions in a patient deficient in that factor (as in the case of hemophiliacs), in response to certain disease states, or be drug-induced. Non-specific inhibitors may also be present in patients that will prolong screening tests (eg, prothrombin time and activated partial thromboplastin time). This test is used to qualitatively identify an inhibitor to a specific coagulation factor.

Useful For: Detecting the presence of a specific factor inhibitor directed against coagulation factor X

11INE
607430

Factor XI Inhibitor Evaluation, Plasma

Clinical Information: Factor XI inhibitors typically arise in patients with congenital XI deficiency (hemophilia C) or after infusion of fresh frozen plasma or factor XI concentrates. Acquired factor XI inhibitors rarely occur spontaneously.

Useful For: Detection and quantitation of inhibitor to coagulation factor XI This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

Interpretation: Normally, there is no inhibitor, ie, negative. If the screening assays indicate the

presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

Reference Values:
FACTOR XI ACTIVITY ASSAY
Adults: 55-150%
Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =10%) that may not reach adult levels for 180 days or more postnatal.*
*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing.

FACTOR XI INHIBITOR SCREEN:
Negative

GENERAL FACTOR BETHESDA UNITS:
< or =0.5 Bethesda Units

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds: Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK. Treatment of factor VIII inhibitors. Prog Hemost Thromb 1989;9:57-86 3. Kottke-Marchant K, ed. Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012

11AIH
607448

Factor XI Inhibitor Profile, Professional Interpretation

Clinical Information: Factor XI inhibitors typically arise in patients with congenital XI deficiency (hemophilia C) or after infusion of fresh frozen plasma or factor XI concentrates. Acquired factor XI inhibitors rarely occur spontaneously.

Useful For: Interpretation of testing for the detection and quantitation of inhibitor to coagulation factor XI

Interpretation: When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, and elements of differential diagnosis.

Reference Values:
Only orderable as a reflex. For more information see 11INE / Factor XI Inhibitor Evaluation, Plasma.

An interpretive report will be provided.

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK: Treatment of factor VIII inhibitors. Prog Hemost Thromb. 1989;9:57-86 3. Kottke-Marchant K, ed: Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012

11INT
607441

Factor XI Inhibitor Profile, Technical Interpretation

Clinical Information: Factor XI inhibitors typically arise in patients with congenital XI deficiency (hemophilia C) or after infusion of fresh frozen plasma or factor XI concentrates. Acquired factor XI inhibitors rarely occur spontaneously.

Useful For: Technical interpretation of inhibitor to coagulation factor XI testing This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor, a nonspecific circulating anticoagulant, or other inhibitors that are not specific for coagulation factors.

Interpretation: When testing is complete, if factor activity results fall within clinically normal ranges, an interpretive comment will be provided noting that inhibitor testing was not indicated and, therefore, not performed. If factor activity indicates the performance of inhibitor screen testing, an interpretive comment will be provided noting the presence or absence of a factor XI inhibitor.

Reference Values:
Only orderable as part of a profile. For more information see 11INE / Factor XI Inhibitor Evaluation, Plasma

An interpretive report will be provided.

Clinical References: 1. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds: Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018 2. Kasper CK. Treatment of factor VIII inhibitors. Prog Hemost Thromb 1989;9:57-86 3. Kottke-Marchant K, ed. Laboratory Hematology Practice Wiley Blackwell Publishing; 2012

11_IS 7804 Factor XI Inhibitor Screen, Plasma

Clinical Information: Patient plasma, normal pooled plasma (NPP), and a mixture of patient plasma and NPP are each tested for a specific factor, incubated at 37 degrees C for 1 hour, and then retested for the same factor. In addition, a new mixture of patient plasma and NPP is prepared using the incubated plasmas and tested after the 1 hour incubation. The percentage of the recovered factor for each individual plasma and mixture being tested is calculated and compared. The procedure demonstrates the effect of a specific coagulation factor inhibitor on that factor present in normal pooled plasma, over a specific period of time. An inhibitor directed against a coagulation factor may arise due to multiple exposures from transfusions in a patient deficient in that factor (as in the case of hemophiliacs), in response to certain disease states, or be drug-induced. Non-specific inhibitors may also be present in patients that will prolong screening tests (eg, prothrombin time and activated partial thromboplastin time). This test is used to qualitatively identify an inhibitor to a specific coagulation factor.

Useful For: Detecting the presence of a specific factor inhibitor directed against coagulation factor XI

Interpretation: When testing is complete, if factor activity results fall within clinically normal ranges, an interpretive comment will be provided noting that inhibitor testing was not indicated and, therefore, not performed. If factor activity indicates the performance of inhibitor screen testing, an interpretive comment will be provided noting the presence or absence of a factor XI inhibitor.

Reference Values:
Only orderable as part of a profile. For more information see:
11INE / Factor XI Inhibitor Evaluation, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
APROL / Prolonged Clot Time Profile, Plasma

Negative

Clinical References: 1. Bowie EJW, Thompson JH Jr, Didisheim P, Owen CA Jr. Mayo Clinic

Laboratory Manual of Hemostasis. WB Saunders Company; 1971: 111-115 2. Laboratory Hematology Practice. In: Kottke-Marchant K, ed. Wiley Blackwell Publishing; 2012 3. Hematology: Basic Principles and Practice. 7th ed. In: Hoffman R, Benz EJ Jr, Silberstein LE, eds. Elsevier; 2018

FXIII
9068

Factor XIII (13), Screen, Plasma

Clinical Information: Factor XIII is found in plasma and platelets. Plasma factor XIII consists of 2 A-subunits and 2 B-subunits; platelet factor XIII consists of only 2 A-subunits. After factor XIII is activated by thrombin, it catalyzes the formation of peptide bonds between adjacent molecules of fibrin monomers, thus conferring mechanical and chemical stability to the fibrin clot. Fibrin that is not covalently cross-linked exhibits an increased susceptibility to fibrinolysis. Congenital factor XIII deficiency is an autosomal recessive bleeding disorder. Homozygous individuals (FXIII <1%) experience soft tissue hemorrhage, hemarthrosis, and hematomas. Typically, affected patients suffer from delayed bleeding occurring 24 to 48 hours after the initial hemostatic response to an injury. In newborns, bleeding from the umbilical stump may occur after separation of the umbilical cord, as well as intracranial bleeding. Poor wound healing and abnormal scar formation is also observed. Heterozygous carriers may be asymptomatic; however, females may experience recurrent spontaneous abortions. Acquired factor XIII deficiency is rare and typically occurs as a result of development of autoantibodies. These patients develop adult-onset bleeding.

Useful For: Screening for factor XIII deficiency

Interpretation: Normally, no clot dissolution is observed after 30 minutes in 1% monochloroacetic acid. Clot dissolution begins once factor XIII levels are reduced to 1% or 2%.

Reference Values:
Only orderable as part of a profile. For more information see ALBLD / Bleeding Diathesis Profile, Limited, Plasma.

Normal

Clinical References: 1. Anwar R, Miloszewski KJ. Factor XIII deficiency. Br J Haematol 1999;107(3):468-484 2. Kottke-Marchant K. Performance and interpretation of routine coagulation assays. In: Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012:420-434 3. Hoffman R, Benz EJ Jr, Siberstein LE, et al. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018

GNF13
619145

Factor XIII Deficiency, F13A1 and F13B Genes, Next-Generation Sequencing, Varies

Clinical Information: Factor XIII deficiency (FXIIID) is a rare hereditary bleeding disorder associated with germline variants in the F13A1 and F13B genes. It is inherited in an autosomal recessive manner with variable expressivity; both male and female patients may be affected. The estimated prevalence is 1 in 2 million individuals.(2-4) FXIIID caused by homozygous or compound heterozygous variants in F13A1 (FXIII-A deficiency) typically presents as a severe bleeding tendency. Onset of life-threatening symptoms often occurs early with umbilical cord and central nervous system bleeding. Additional symptoms include easy bruising, intramuscular and subcutaneous hematomas, oral mucosal bleeding, epistaxis, perioperative bleeding, and impaired wound healing. Among the rare bleeding disorders, FXIIID appears uniquely associated with pregnancy loss. Affected women have an increased risk of miscarriage, postpartum hemorrhage, menorrhagia, and intraperitoneal bleeding.(2- 7) Individuals with FXIIID caused by homozygous or compound heterozygous variants in F13B (FXIII-B deficiency)

tend to have a milder bleeding tendency, although a severe phenotype can occur.(1,2) Accurate correlation between genotype and phenotype in FXIIID has proven challenging due to the unpredictable nature and variability of disease symptoms, its rarity, and the limitation of some laboratory assays. Routine coagulation tests are often normal.(2,3,5) Several causes of acquired (nongenetic) FXIIID should be excluded prior to genetic testing, including leukemia, liver disease, Henoch-Schonlein purpura, inflammatory bowel diseases, disseminated intravascular coagulation, pulmonary embolism, stroke, sepsis, and exposure to valproate. FXIIID also may occur spontaneously in older adults.(1-3) The United Kingdom Haemophilia Centre Doctors' Organization provides guidelines regarding diagnosis and management for individuals with inherited bleeding disorders, including FXIIID.(8)

Useful For: Evaluating factor XIII deficiency (FXIIID) in patients with a personal or family history suggestive of FXIIID Confirming an FXIIID diagnosis with the identification of known or suspected disease-causing alterations in the F13A1 or F13B genes Determining the disease-causing alterations within the F13A1 or F13B genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of FXIIID Identifying the causative alterations for genetic counseling purposes Prognosis and risk assessment based on the genotype-phenotype correlations Carrier testing for close family members of an individual with a diagnosis of FXIIID

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(9) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Kohler HP, Ichinose A, Seitz R, et al: Diagnosis and classification of factor XIII deficiencies. J Thromb Haemost. 2011 Jul;9(7):1404-1406 2. Karimi M, Bereczky Z, Cohan N, Muszbek L: Factor XIII deficiency. Semin Thromb Hemost. 2009 Jun;35(4):426-438 3. Dorgalaleh A, Rashidpanah J: Blood coagulation factor XIII and factor XIII deficiency. Blood Rev. 2016 Nov;30(6):461-475 4. Palla R, Peyvandi F, Shapiro AD: Rare bleeding disorders: diagnosis and treatment. Blood. 2015 Mar;125(13):2052-2061 5. de Moerloose P, Schved JF, Nugent D: Rare coagulation disorders: fibrinogen, factor VII and factor XIII. Haemophilia. 2016 Jul;22 Suppl 5:61-65 6. Pelcovits A, Schiffman F, Niroula R: Factor XIII deficiency: a review of clinical presentation and management. Hematol Oncol Clin North Am. 2021 Dec;35(6):1171-1180 7. Sharief LAT, Kadir RA: Congenital factor XIII deficiency in women: a systematic review of literature. Haemophilia. 2013 Nov;19(6):e349-e357 8. Mumford AD, Ackroyd S, Alikhan R, et al: Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2014 Nov;167(3):304-326 9. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

FFX3F
75567

Factor XIII, Functional

Clinical Information: Factor XIII, Functional- Low Factor XIII levels, i.e., <15%, may cause a bleeding disorder and levels <2% have been associated with spontaneous introcranial hemorrhage.

Reference Values:
57 - 192 % activity

FRW
82684

False Ragweed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to false ragweed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FMTT
63032

Familial Variant, Targeted Testing, Varies

Clinical Information: This test is available for the analysis of up to 4 genetic variants (single nucleotide variant, small insertion/deletion, or exon level deletion/duplication). Targeted testing is used for diagnostic or predictive testing in family members of an affected individual with a previously detected variant, carrier screening, segregation analysis, confirmation of research results, or testing for germline status of a variant detected by somatic or tumor testing. This test is available for any of the genes on Mayo Clinic Laboratories' (MCL) test menu. In addition, genes not on the MCL test menu may be able to be tested. Call the laboratory at 800-533-1710 with specific inquiries.

Useful For: Diagnostic or predictive testing for specific conditions when a DNA variant of interest has been previously identified in a family member and follow-up testing for this specific variant in other family members is desired Carrier screening for individuals at risk for having a variant that was previously identified in a family member Segregation analysis for a familial DNA variant Confirmation of germline status for variants detected via somatic testing

Interpretation: Evaluation and categorization of variants are performed using American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

CMPRE 616069 Family Member Comparator Specimen for Exome Sequencing, Varies

Clinical Information: This test uses next-generation sequencing technology to assess for single nucleotide and copy number variants within the protein-coding regions (exons and splice junctions) of approximately 20,000 genes simultaneously. This information is used to assist in the interpretation of the patient's (proband's) whole exome sequencing results (WESDX / Whole Exome Sequencing for Hereditary Disorders, Varies). Ordering this test on biological family members of the affected proband can help determine the inheritance of genetic variants that are identified and if the variants segregate with a phenotype in the family. Submitting comparator samples from biological family members increases the chance of identifying a diagnosis in the proband. Whole exome sequencing has been shown to be most informative when samples from both biological parents are used as comparators.(1-3) Therefore, it is highly recommended that samples are also submitted from the patient's biological mother and biological father. If more than 2 biological family member comparator specimens are submitted, the additional comparator specimens may not be fully sequenced but rather used for confirmatory presence or absence of identified variants of interest after initial variant calling and review.

Useful For: Submitting a biological family member's specimen to be used as a comparator for affected patients (probands) undergoing whole exome sequencing

Interpretation: Interpretive information will only be provided on the proband's whole exome sequencing report (WESDX / Whole Exome Sequencing for Hereditary Disorders, Varies). Secondary Findings Patients are evaluated for medically actionable secondary findings and these findings are reported in accordance with the American College of Medical Genetics and Genomics recommendations.(4) The presence of a variant in family member comparator samples is stated on the proband's report. Variants that are present in family member comparator samples but absent from the proband sample are not evaluated. Variants in these genes will not be evaluated or reported if the

proband opts out of this evaluation.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Yang Y, Muzny DM, Xia F, et al: Molecular findings among patients referred for clinical whole-exome sequencing. JAMA. 2014 Nov 12;312(18):1870-1879 2. Lee H, Deignan JL, Dorrani N, et al: Clinical exome sequencing for genetic identification of rare Mendelian disorders. JAMA. 2014 Nov 12;312(18):1880-1887 3. Farwell KD, Shahmirzadi L, El-Khechen D, et al: Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. Genet Med. 2015 Jul;17(7):578-586 4. Miller DT, Lee K, Gordon AS, et al: Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021 Aug;23(8):1391-1398

CMPRG 614611 Family Member Comparator Specimen for Genome Sequencing, Varies

Clinical Information: Note: Where applicable, verbiage refers to sex assigned at birth. This test uses next-generation sequencing technology to assess the genome of patients with suspected underlying genetic disorders. This information is used to assist in the interpretation of the patient's (proband's) whole genome sequencing results (WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies). Ordering this test on biological family members of the affected proband can help determine the inheritance of genetic variants that are identified and if the variants segregate with a phenotype in the family. Submitting comparator samples from biological family members increases the chance of identifying a diagnosis in the proband. Whole genome sequencing is most informative when samples from both biological parents are used as comparators. Therefore, it is highly recommended that samples are also submitted from the patient's biological mother and biological father. If more than 2 biological family member comparator specimens are submitted, the additional comparator specimens may not be fully sequenced but rather used for confirmatory presence or absence of identified variants of interest after initial variant calling and review.

Useful For: Submitting a biological family member's specimen to be used as a comparator for affected patients (probands) undergoing whole genome sequencing

Interpretation: Interpretive information will only be provided on the proband's whole genome sequencing report (WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies). The presence of a variant in family member comparator samples is stated on the proband's report. Variants that are present in family member comparator samples but absent from the proband sample are not evaluated or reported. Secondary Findings: Patients are evaluated for medically actionable secondary findings and these findings are reported in accordance with the American College of Medical Genetics and Genomics recommendations.(1) The presence of a secondary finding in family member comparator samples is stated on the patient's (proband's) report unless family members opt-out of secondary findings. If the proband opts out, secondary findings will not be evaluated or reported in any family member comparators. Secondary findings that are present in family member comparators but absent from the patient (proband) are not evaluated or reported. The absence of a reportable secondary finding does not guarantee that there are no disease-causing or likely disease-causing variants in these genes, as review is limited to known or highly suspected pathogenic findings, and not all regions of these genes are adequately evaluated by this technology.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Miller DT, Lee K, Gordon AS, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(8):1391-1398

FASC
70431

Fascin Immunostain, Technical Component Only

Clinical Information: Fascin is an actin-bundling protein that is present in antigen-presenting cells and is upregulated in Epstein Barr virus-positive lymphocytes and Hodgkin cells. Antibodies to fascin result in distinct cytoplasmic staining of the Langerhans cells, follicular dendritic cells, and interdigitating reticulum cells in normal lymph nodes. Fascin is usually positive in classical Hodgkin lymphoma and negative in lymphocyte predominant Hodgkin lymphoma.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Sukswai N, Lyapichev K, Khoury JD, Medeiros LJ.: Diffuse large B-cell lymphoma variants: an update. Pathology. 2020;52(1):53-67 2. Aladily TN, Mansour A, Alsughayer A, et al. The utility of CD83, fascin and CD23 in the differential diagnosis of primary mediastinal large B-cell lymphoma versus classic Hodgkin lymphoma. Ann Diagn Pathol. 2019;40:72-76 3. Emara NM, Agina HA, Fahmy RR, et al. Study of the diagnostic utility of fascin and PU. 1 in Hodgkin's lymphoma, diffuse large B-cell lymphoma, and anaplastic large cell lymphoma. Egypt J Pathol. 2014;34(1):52-58 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FATF
607701

Fat, Feces

Clinical Information: Total fecal lipids include glycerides, phospholipids, glycolipids, soaps, sterols, cholesteryl esters, and sphingolipids. Excess fecal fat in feces, (steatorrhea) is indicative of malabsorption disorders, such as pancreatic insufficiency or Whipple disease. Therefore, measurement of the fecal fats can be useful in establishing a diagnosis of such pancreatic diseases as cystic fibrosis, chronic pancreatitis, neoplasia, or stone obstruction and such intestinal diseases as Whipple disease, regional enteritis, tuberculous enteritis, gluten-induced enteropathy (also called celiac disease or sprue), and the atrophy of malnutrition. Distinguishing free fatty acids from neutral fats, once thought to be helpful in the differential diagnosis of pancreatic disease, has fallen out of favor. Note that the composition of fats in the feces, normally predominately free fatty acids, can change significantly to predominately neutral fatty acids when the patient is on orlistat. This test does not distinguish between free and neutral fatty acids.

Useful For: Diagnosing fat malabsorption due to pancreatic or intestinal disorders Monitoring effectiveness of enzyme supplementation in certain malabsorption disorders This test is not useful for differentiating among pancreatic diseases.

Interpretation: Excretion of more than 7 grams fat/24 hours, when on a diet of 100 to 150 g of fat, is suggestive of a malabsorption defect. Abnormal results from a random specimen should be confirmed by submission of a timed collection. Test values for timed fecal fat collections will be reported in terms of g/24 hours; the duration of the collection may be 24, 48, 72, or 96 hours. Test values for random fecal

fat collections will be reported in terms of percent fat. Coefficient of Fat Absorption (CFA) can be calculated as follows: CFA = (grams of fat consumed - grams of fat excreted) x 100 / grams of fat consumed

Reference Values:

Timed Collection
> or =18 years: 2-7 g fat/24 h
Reference values have not been established for patients who are younger than 18 years.

Random Collection
All ages: 0-19% fat

Clinical References: 1. Hart PA, Conwell DL. Diagnosis of exocrine pancreatic insufficiency. Curr Treat Options Gastroenterol. 2015;13(3):347-353. doi:10.1007/s11938-015-0057-8 2. Sherwood RA, Walsham NE: Evaluation of fat absorption. In: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:764 3. Erchinger F, Engjom T, Jurmy P, Tjora E, Gilja OH, Dimcevski G. Fecal fat analyses in chronic pancreatitis importance of fat ingestion before stool collection. PLoS One. 2017;12(1):e0169993. Published 2017 Jan 17. doi:10.1371/journal.pone.0169993

HFAOP
608028

Fatty Acid Oxidation Gene Panel, Varies

Clinical Information: Mitochondrial fatty acid beta-oxidation plays an important role in energy production, particularly in skeletal and heart muscle, and in hepatic ketone body formation. Disorders of fatty acid oxidation (FAO) are characterized by hypoglycemia, hepatic dysfunction, encephalopathy, skeletal myopathy, and cardiomyopathy. Most FAO disorders have a similar presentation, and their biochemical diagnosis can, at times, be difficult. Commonly used metabolite screens such as urine organic acids, plasma acylcarnitines, and fatty acids are influenced by dietary factors and the clinical status of the patient. This often leads to incomplete diagnostic information or even false-negative results. Enzyme assays are limited to one enzyme per assay, which doesn't allow for comprehensive testing for all FAO disorders. A comprehensive gene panel is a helpful tool to establish a diagnosis for patients with suggestive clinical and biochemical features, given the broad clinical spectrum and genetic heterogeneity of FAO disorders. Acylcarnitine profile in plasma (ACRN / Acylcarnitines, Quantitative, Plasma) and urine organic acids (OAU / Organic Acids Screen, Random, Urine) are the recommended first-tier tests to assess individuals for a FAO disorder. Additional testing includes an assay in fibroblasts (FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture), which is useful following molecular testing to determine whether variants of uncertain significance are pathogenic. The purpose of the in vitro probe assay is to offer screening for several defects of FAO and organic acid metabolism under controlled laboratory conditions using fibroblast cultures.

Useful For: Follow up for abnormal biochemical results suggestive of a fatty acid oxidation disorder Establishing a molecular diagnosis for patients with a fatty acid oxidation disorder Identifying variants within genes known to be associated with a fatty acid oxidation disorder, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:

An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Vockley J, Bennett MJ, Gillingham MB. Mitochondrial fatty acid oxidation disorders. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Accessed March 8, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=247995158&bookid=2709&Resultclick=2

FAO
81927

Fatty Acid Oxidation Probe Assay, Fibroblast Culture

Clinical Information: Mitochondrial fatty acid beta-oxidation plays an important role in energy production during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue, taken up by the liver and muscles, and oxidized to acetyl-CoA (acetyl coenzyme A). In the liver, acetyl-CoA is the building block for the synthesis of ketone bodies, which enter the blood stream and provide an alternative substrate for production of energy in other tissues when the supply of glucose is insufficient to maintain a normal level of energy. Disorders of fatty acid oxidation (FAO) are characterized by hypoglycemia, hepatic dysfunction, encephalopathy, skeletal myopathy, and cardiomyopathy. Most FAO disorders have a similar presentation, and their biochemical diagnosis can, at times, be difficult. Commonly used metabolite screens, such as urine organic acids, plasma acylcarnitines, and fatty acids, are influenced by dietary factors and the clinical status of the patient. This can lead to incomplete diagnostic information or even false-negative results. The purpose of the in vitro probe assay is to offer screening for several defects of FAO and organic acid metabolism under controlled laboratory conditions using fibroblast cultures.

Useful For: In vitro confirmation of biochemical diagnoses of the following fatty acid oxidation disorders: -Short-chain acyl-CoA dehydrogenase deficiency -Medium-chain acyl-CoA dehydrogenase deficiency -Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency -Trifunctional protein deficiency -Very long-chain acyl-CoA dehydrogenase deficiency -Carnitine palmitoyl transferase deficiency type II -Carnitine-acylcarnitine translocase deficiency Confirmation of the following organic acid disorders: -2-Methylbutyryl-CoA dehydrogenase deficiency -Isobutyryl-CoA dehydrogenase deficiency This test is not useful for prenatal testing. This assay is not informative if the deficient enzyme is not physiologically expressed in skin fibroblasts.

Interpretation: Abnormal results will include a description of the abnormal profile in comparison to normal and abnormal controls. In addition, the concentration of the acylcarnitine species that abnormally accumulated in the cell medium are provided and compared to the continuously updated reference range based on analysis of normal controls. Interpretations of abnormal acylcarnitine profiles also include information about the results' significance, a correlation to available clinical information, possible differential diagnoses, recommendations for additional biochemical testing and confirmatory studies if indicated, name and phone number of contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring provider has additional questions.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Ensenauer R, Vockley J, Willard JM, et al. A common mutation is associated with a mild, potentially asymptomatic phenotype in patients with isovaleric acidemia diagnosed by newborn screening. Am J Hum Genet. 2004;75(6):1136-1142. doi:10.1086/426318 2. Rinaldo P, Matern D, Bennet MJ. Fatty acid oxidation disorders. Ann Rev Physiol. 2002;64:477-502 3. Shen JJ, Matern D, Millington DS, et al: Acylcarnitines in fibroblasts of patients with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency and other fatty acid oxidation disorders. J Inherit Metab

Dis. 2000;23:27-44. doi:10.1023/a:1005694712583 4. Matern D, Huey JC, Gregersen N, et al. In vitro diagnosis of short-chain acyl-CoA dehydrogenase (SCAD) deficiency. J Inherit Metab Dis. 2001;24(Suppl.1):66 5. Merritt JL, Norris M, Kanungo S. Fatty acid oxidation disorders. Ann. Transl. Med. 2018;6(24):473. doi:10.21037/atm.2018.10.57

PFAPC
60466

Fatty Acid Profile, Comprehensive (C8-C26), Plasma

Clinical Information: Fatty Acid Deficiency/Excess: Fats are important sources of energy for tissues and for the function and integrity of cellular membranes. Deficiencies are commonly caused by inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids, linoleic and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones. The Academy of Nutrition and Dietetics recommends that dietary fat for the healthy adult population should provide 20% to 35% of energy, with an increased consumption of n-3 polyunsaturated fatty acids and limited intake of saturated and trans fats.(1) Fatty Acid Oxidation Disorders: Mitochondrial beta-oxidation is the main source of energy to skeletal and heart muscle during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue and converted to ketone bodies through a series of steps providing an alternate source of energy. Deficient enzymes at any step in this pathway prevent the production of energy during periods of physiologic stress such as fasting or intercurrent illness. The major clinical manifestations associated with fatty acid oxidation (FAO) disorders include hypoketotic hypoglycemia, liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden unexpected death in early life. Signs and symptoms may vary greatly in severity, combination, and age of presentation. Life-threatening episodes of metabolic decompensation frequently occur after periods of inadequate calorie intake or intercurrent illness. When properly diagnosed, patients with FAO disorders respond favorably to fasting avoidance, diet therapy, and aggressive treatment of intercurrent illnesses, with significant reduction of morbidity and mortality. Disease-specific characteristic patterns of metabolites from FAO disorders are detectable in blood, bile, urine, and cultured fibroblasts of living and many deceased individuals. Quantitative determination of C8-C18 fatty acids is an important element of the workup and differential diagnosis of candidate patients. Fatty acid profiling can detect quantitatively modest, but nevertheless significant, abnormalities even when patients are asymptomatic and under dietary treatment. Confirmatory testing for many of the FAO disorders is also available. For more information see FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture and HFAOP / Fatty Acid Oxidation Gene Panel, Varies. Peroxisomal Disorders: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle, and single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy, resulting in elevated concentrations of VLCFA in serum or plasma. POXP / Fatty Acid Profile, Peroxisomal (C22-C26), Plasma or POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum is the preferred screening test for evaluating patients with possible peroxisomal disorders, single-enzyme defects of peroxisomal metabolism such as X-linked adrenoleukodystrophy, or peroxisomal biogenesis disorders (Zellweger syndrome spectrum). Confirmatory testing for X-linked adrenoleukodystrophy via molecular genetic analysis is available; see XALDZ / X-Linked Adrenoleukodystrophy, Full Gene Analysis, Varies.

Useful For: Monitoring patients undergoing diet therapy for mitochondrial or peroxisomal disorders (possibly inducing essential fatty acid deficiency in response to restricted fat intake) using plasma specimens Monitoring treatment of essential fatty acid deficiency Monitoring the response to provocative tests (fasting tests, loading tests)

Interpretation: An increased triene:tetraene ratio is consistent with essential fatty acid deficiency. Fatty acid oxidation disorders are recognized on the basis of disease-specific patterns that are correlated to the results of other investigations in plasma (carnitine, acylcarnitines) and urine (organic acids, acylglycines). Increased concentrations of very long-chain fatty acids (VLCFA) C24:0 and C26:0 are seen in peroxisomal disorders, X-linked adrenoleukodystrophy, adrenomyeloneuropathy, and Zellweger syndrome (cerebrohepatorenal syndrome). Increased concentrations of phytanic acid (along with normal pristanic acid concentrations) are seen in Refsum disease (phytanase deficiency). Phytanic acid concentration also may be increased in other peroxisomal disorders and, when combined with the VLCFA, pristanic acid, and pipecolic acid, allows differential diagnosis of peroxisomal disorders.

Reference Values:

Octanoic Acid, C8:0
<1 year: 7-63 nmol/mL
1-17 years: 9-41 nmol/mL
> or =18 years: 8-47 nmol/mL

Decenoic Acid, C10:1
<1 year: 0.8-4.8 nmol/mL
1-17 years: 1.6-6.6 nmol/mL
> or =18 years: 1.8-5.0 nmol/mL

Decanoic Acid, C10:0
<1 year: 2-62 nmol/mL
1-17 years: 3-25 nmol/mL
> or =18 years: 2-18 nmol/mL

Lauroleic Acid, C12:1
<1 year: 0.6-4.8 nmol/mL
1-17 years: 1.3-5.8 nmol/mL
> or =18 years: 1.4-6.6 nmol/mL

Lauric Acid, C12:0
<1 year: 6-190 nmol/mL
1-17 years: 5-80 nmol/mL
> or =18 years: 6-90 nmol/mL

Tetradecadienoic Acid, C14:2
<1 year: 0.3-6.5 nmol/mL
1-17 years: 0.2-5.8 nmol/mL
> or =18 years: 0.8-5.0 nmol/mL

Myristoleic Acid, C14:1
<1 year: 1-46 nmol/mL
1-17 years: 1-31 nmol/mL
> or =18 years: 3-64 nmol/mL

Myristic Acid, C14:0
<1 year: 30-320 nmol/mL
1-17 years: 40-290 nmol/mL

> or =18 years: 30-450 nmol/mL

Hexadecadienoic Acid, C16:2
<1 year: 4-27 nmol/mL
1-17 years: 3-29 nmol/mL
> or =18 years: 10-48 nmol/mL

Hexadecenoic Acid, C16:1w9
<1 year: 21-69 nmol/mL
1-17 years: 24-82 nmol/mL
> or =18 years: 25-105 nmol/mL

Palmitoleic Acid, C16:1w7
<1 year: 20-1,020 nmol/mL
1-17 years: 100-670 nmol/mL
> or =18 years: 110-1,130 nmol/mL

Palmitic Acid, C16:0
<1 year: 720-3,120 nmol/mL
1-17 years: 960-3,460 nmol/mL
> or =18 years: 1,480-3,730 nmol/mL

Gamma-Linolenic Acid, C18:3w6
<1 year: 6-110 nmol/mL
1-17 years: 9-130 nmol/mL
> or =18 years: 16-150 nmol/mL

Alpha-Linolenic Acid, C18:3w3
<1 year: 10-190 nmol/mL
1-17 years: 20-120 nmol/mL
> or =18 years: 50-130 nmol/mL

Linoleic Acid, C18:2w6
< or =31 days: 350-2,660 nmol/mL
32 days-11 months: 1,000-3,300 nmol/mL
1-17 years: 1,600-3,500 nmol/mL
> or =18 years: 2,270-3,850 nmol/mL

Oleic Acid, C18:1w9
<1 year: 250-3,500 nmol/mL
1-17 years: 350-3,500 nmol/mL
> or =18 years: 650-3,500 nmol/mL

Vaccenic Acid, C18:1w7
<1 year: 140-720 nmol/mL
1-17 years: 320-900 nmol/mL
> or =18 years: 280-740 nmol/mL

Stearic Acid, C18:0
<1 year: 270-1,140 nmol/mL
1-17 years: 280-1,170 nmol/mL
> or =18 years: 590-1,170 nmol/mL

EPA, C20:5w3

<1 year: 2-60 nmol/mL
1-17 years: 8-90 nmol/mL
> or =18 years: 14-100 nmol/mL

Arachidonic Acid, C20:4w6
<1 year: 110-1,110 nmol/mL
1-17 years: 350-1,030 nmol/mL
> or =18 years: 520-1,490 nmol/mL

Mead Acid, C20:3w9
< or =31 days: 8-60 nmol/mL
32 days-11 months: 3-24 nmol/mL
> or =1 year: 7-30 nmol/mL

Homo-Gamma-Linolenic Acid, C20:3w6
<1 year: 30-170 nmol/mL
1-17 years: 60-220 nmol/mL
> or =18 years: 50-250 nmol/mL

Arachidic Acid, C20:0
<1 year: 30-120 nmol/mL
1-17 years: 30-90 nmol/mL
> or =18 years: 50-90 nmol/mL

DHA, C22:6w3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
> or =18 years: 30-250 nmol/mL

DPA, C22:5w6
<1 year: 3-70 nmol/mL
1-17 years: 10-50 nmol/mL
> or =18 years: 10-70 nmol/mL

DPA, C22:5w3
<1 year: 6-110 nmol/mL
1-17 years: 30-270 nmol/mL
> or =18 years: 20-210 nmol/mL

DTA, C22:4w6
<1 year: 2-50 nmol/mL
1-17 years: 10-40 nmol/mL
> or =18 years: 10-80 nmol/mL

Docosenoic Acid, C22:1
<1 year: 2-20 nmol/mL
> or =1 year: 4-13 nmol/mL

Docosanoic Acid, C22:0
0.0-96.3 nmol/mL

Nervonic Acid, C24:1
<1 year: 30-150 nmol/mL
1-17 years: 50-130 nmol/mL

> or =18 years: 60-100 nmol/mL

Tetracosanoic Acid, C24:0
0.0-91.4 nmol/mL

Hexacosenoic Acid, C26:1
<1 year: 0.2-2.1 nmol/mL
> or =1 year: 0.3-0.7 nmol/mL

Hexacosanoic Acid, C26:0
0.00-1.30 nmol/mL

Pristanic Acid, C15:0(CH3)4
< or =4 months: 0.00-0.60 nmol/mL
5-8 months: 0.00-0.84 nmol/mL
9-12 months: 0.00-0.77 nmol/mL
13-23 months: 0.00-1.47 nmol/mL
> or =2 years: 0.00-2.98 nmol/mL

Phytanic Acid, C16:0(CH3)4
< or =4 months: 0.00-5.28 nmol/mL
5-8 months: 0.00-5.70 nmol/mL
9-12 months: 0.00-4.40 nmol/mL
13-23 months: 0.00-8.62 nmol/mL
> or =2 years: 0.00-9.88 nmol/mL

Triene/Tetraene Ratio
< or =31 days: 0.017-0.083
32 days-17 years: 0.013-0.050
> or =18 years: 0.010-0.038

Total Saturated Acid
<1 year: 1.2-4.6 mmol/L
1-17 years: 1.4-4.9 mmol/L
> or =18 years: 2.5-5.5 mmol/L

Total Monounsaturated Acid
<1 year: 0.3-4.6 mmol/L
1-17 years: 0.5-4.4 mmol/L
> or =18 years: 1.3-5.8 mmol/L

Total Polyunsaturated Acid
<1 year: 1.1-4.9 mmol/L
1-17 years: 1.7-5.3 mmol/L
> or =18 years: 3.2-5.8 mmol/L

Total w3
<1 year: 0.0-0.4 mmol/L
1-17 years: 0.1-0.5 mmol/L
> or =18 years: 0.2-0.5 mmol/L

Total w6
<1 year: 0.9-4.4 mmol/L
1-17 years: 1.6-4.7 mmol/L

> or =18 years: 3.0-5.4 mmol/L

Total Fatty Acids
<1 year: 3.3-14.0 mmol/L
1-17 years: 4.4-14.3 mmol/L
> or =18 years: 7.3-16.8 mmol/L

Clinical References: 1. Vannice G, Rasmussen H. Position of the Academy of Nutrition and Dietetics: Dietary fatty acids for healthy adults. J Acad Nutr Diet. 2014;114(1):136-153 2. Rinaldo P, Matern D, Bennett MJ. Fatty acid oxidation disorders. Annu Rev Physiol. 2002;64:477-502 3. Jeppesen PB, Christensen MS, Hoy CE, Mortensen PB. Essential fatty acid deficiency in patients with severe fat malabsorption. Am J Clin Nutr. 1997;65(3):837-843 4. VerHoeven NM, Jakobs C. Human metabolism of phytanic acid and pristanic acid. Prog Lipid Res. 2001;40(6):453-466 5. Luszczki E, Boakye F, Zielinska M, et al. Vegan diet: nutritional components, implementation, and effects on adults' health. Front Nutr. 2023 9;10:1294497. doi:10.3389/fnut.2023.1294497 6. Spector AA, Kim HY. Discovery of essential fatty acids. J. Lipid Res. 2015;56(1):11-21

FAPCP
82042

Fatty Acid Profile, Comprehensive (C8-C26), Serum

Clinical Information: Fatty Acid Deficiency/Excess: Fats are important sources of energy for tissues and for the function and integrity of cellular membranes. Deficiencies are commonly caused by inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids, linoleic and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones. The Academy of Nutrition and Dietetics recommends that dietary fat for the healthy adult population should provide 20% to 35% of energy, with an increased consumption of n-3 polyunsaturated fatty acids and limited intake of saturated and trans fats.(1) Fatty Acid Oxidation Disorders: Mitochondrial beta-oxidation is the main source of energy to skeletal and heart muscle during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue and converted to ketone bodies through a series of steps providing an alternate source of energy. Deficient enzymes at any step in this pathway prevent the production of energy during periods of physiologic stress such as fasting or intercurrent illness. The major clinical manifestations associated with fatty acid oxidation (FAO) disorders include hypoketotic hypoglycemia, liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden unexpected death in early life. Signs and symptoms may vary greatly in severity, combination, and age of presentation. Life-threatening episodes of metabolic decompensation frequently occur after periods of inadequate calorie intake or intercurrent illness. When properly diagnosed, patients with FAO disorders respond favorably to fasting avoidance, diet therapy, and aggressive treatment of intercurrent illnesses, with significant reduction of morbidity and mortality. Disease-specific characteristic patterns of metabolites from FAO disorders are detectable in blood, bile, urine, and cultured fibroblasts of living and many deceased individuals. Quantitative determination of C8-C18 fatty acids is an important element of the work-up and differential diagnosis of candidate patients. Fatty acid profiling can detect quantitatively modest, but nevertheless significant, abnormalities even when patients are asymptomatic and under dietary treatment. Confirmatory testing for many of the FAO disorders is also available. For more information see FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture and HFAOP / Fatty Acid Oxidation Gene Panel, Varies. Peroxisomal Disorders: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry

out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle, and single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy, resulting in elevated concentrations of VLCFA in serum or plasma. POXP / Fatty Acid Profile, Peroxisomal (C22-C26), Plasma or POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum is the preferred screening test for evaluating patients with possible peroxisomal disorders, single-enzyme defects of peroxisomal metabolism such as X-linked adrenoleukodystrophy, or peroxisomal biogenesis disorders (Zellweger syndrome spectrum). Confirmatory testing for X-linked adrenoleukodystrophy via molecular genetic analysis is available; see XALDZ / X-Linked Adrenoleukodystrophy, Full Gene Analysis, Varies.

Useful For: Monitoring patients undergoing diet therapy for mitochondrial or peroxisomal disorders (possibly inducing essential fatty acid deficiency in response to restricted fat intake) using serum specimens Monitoring treatment of essential fatty acid deficiency Monitoring the response to provocative tests (fasting tests, loading tests)

Interpretation: An increased triene:tetraene ratio is consistent with essential fatty acid deficiency. Fatty acid oxidation disorders are recognized on the basis of disease-specific patterns that are correlated to the results of other investigations in plasma (carnitine, acylcarnitines) and urine (organic acids, acylglycines). Increased concentrations of serum very long-chain fatty acids (VLCFA) C24:0 and C26:0 are seen in peroxisomal disorders, X-linked adrenoleukodystrophy, adrenomyeloneuropathy, and Zellweger syndrome (cerebrohepatorenal syndrome). Increased concentrations of serum phytanic acid (along with normal pristanic acid concentrations) are seen in Refsum disease (phytanase deficiency). Serum phytanic acid concentration also may be increased in other peroxisomal disorders and, when combined with the VLCFA, pristanic acid and pipecolic acid allow differential diagnosis of peroxisomal disorders.

Reference Values:

Octanoic Acid, C8:0
<1 year: 7-63 nmol/mL
1-17 years: 9-41 nmol/mL
> or =18 years: 8-47 nmol/mL

Decenoic Acid, C10:1
<1 year: 0.8-4.8 nmol/mL
1-17 years: 1.6-6.6 nmol/mL
> or =18 years: 1.8-5.0 nmol/mL

Decanoic Acid, C10:0
<1 year: 2-62 nmol/mL
1-17 years: 3-25 nmol/mL
> or =18 years: 2-18 nmol/mL

Lauroleic Acid, C12:1
<1 year: 0.6-4.8 nmol/mL
1-17 years: 1.3-5.8 nmol/mL
> or =18 years: 1.4-6.6 nmol/mL

Lauric Acid, C12:0
<1 year: 6-190 nmol/mL
1-17 years: 5-80 nmol/mL
> or =18 years: 6-90 nmol/mL

Tetradecadienoic Acid, C14:2
<1 year: 0.3-6.5 nmol/mL
1-17 years: 0.2-5.8 nmol/mL
> or =18 years: 0.8-5.0 nmol/mL

Myristoleic Acid, C14:1
<1 year: 1-46 nmol/mL
1-17 years: 1-31 nmol/mL
> or =18 years: 3-64 nmol/mL

Myristic Acid, C14:0
<1 year: 30-320 nmol/mL
1-17 years: 40-290 nmol/mL
> or =18 years: 30-450 nmol/mL

Hexadecadienoic Acid, C16:2
<1 year: 4-27 nmol/mL
1-17 years: 3-29 nmol/mL
> or =18 years: 10-48 nmol/mL

Hexadecenoic Acid, C16:1w9
<1 year: 21-69 nmol/mL
1-17 years: 24-82 nmol/mL
> or =18 years: 25-105 nmol/mL

Palmitoleic Acid, C16:1w7
<1 year: 20-1,020 nmol/mL
1-17 years: 100-670 nmol/mL
> or =18 years: 110-1,130 nmol/mL

Palmitic Acid, C16:0
<1 year: 720-3,120 nmol/mL
1-17 years: 960-3,460 nmol/mL
> or =18 years: 1,480-3,730 nmol/mL

Gamma-Linolenic Acid, C18:3w6
<1 year: 6-110 nmol/mL
1-17 years: 9-130 nmol/mL
> or =18 years: 16-150 nmol/mL

Alpha-Linolenic Acid, C18:3w3
<1 year: 10-190 nmol/mL
1-17 years: 20-120 nmol/mL
> or =18 years: 50-130 nmol/mL

Linoleic Acid, C18:2w6
< or =31 days: 350-2,660 nmol/mL
32 days-11 months: 1,000-3,300 nmol/mL
1-17 years: 1,600-3,500 nmol/mL
> or =18 years: 2,270-3,850 nmol/mL

Oleic Acid, C18:1w9
<1 year: 250-3,500 nmol/mL

1-17 years: 350-3,500 nmol/mL
> or =18 years: 650-3,500 nmol/mL

Vaccenic Acid, C18:1w7
<1 year: 140-720 nmol/mL
1-17 years: 320-900 nmol/mL
> or =18 years: 280-740 nmol/mL

Stearic Acid, C18:0
<1 year: 270-1,140 nmol/mL
1-17 years: 280-1,170 nmol/mL
> or =18 years: 590-1,170 nmol/mL

EPA, C20:5w3
<1 year: 2-60 nmol/mL
1-17 years: 8-90 nmol/mL
> or =18 years: 14-100 nmol/mL

Arachidonic Acid, C20:4w6
<1 year: 110-1,110 nmol/mL
1-17 years: 350-1,030 nmol/mL
> or =18 years: 520-1,490 nmol/mL

Mead Acid, C20:3w9
< or =31 days: 8-60 nmol/mL
32 days-11 months: 3-24 nmol/mL
> or =1 year: 7-30 nmol/mL

Homo-Gamma-Linolenic Acid, C20:3w6
<1 year: 30-170 nmol/mL
1-17 years: 60-220 nmol/mL
> or =18 years: 50-250 nmol/mL

Arachidic Acid, C20:0
<1 year: 30-120 nmol/mL
1-17 years: 30-90 nmol/mL
> or =18 years: 50-90 nmol/mL

DHA, C22:6w3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
> or =18 years: 30-250 nmol/mL

DPA, C22:5w6
<1 year: 3-70 nmol/mL
1-17 years: 10-50 nmol/mL
> or =18 years: 10-70 nmol/mL

DPA, C22:5w3
<1 year: 6-110 nmol/mL
1-17 years: 30-270 nmol/mL
> or =18 years: 20-210 nmol/mL

DTA, C22:4w6

<1 year: 2-50 nmol/mL
1-17 years: 10-40 nmol/mL
> or =18 years: 10-80 nmol/mL

Docosenoic Acid, C22:1
<1 year: 2-20 nmol/mL
> or =1 year: 4-13 nmol/mL

Docosanoic Acid, C22:0
0.0-96.3 nmol/mL

Nervonic Acid, C24:1
<1 year: 30-150 nmol/mL
1-17 years: 50-130 nmol/mL
> or =18 years: 60-100 nmol/mL

Tetracosanoic Acid, C24:0
0.0-91.4 nmol/mL

Hexacosenoic Acid, C26:1
<1 year: 0.2-2.1 nmol/mL
> or =1 year: 0.3-0.7 nmol/mL

Hexacosanoic Acid, C26:0
0.00-1.30 nmol/mL

Pristanic Acid, C15:0(CH3)4
< or =4 months: 0.00-0.60 nmol/mL
5-8 months: 0.00-0.84 nmol/mL
9-12 months: 0.00-0.77 nmol/mL
13-23 months: 0.00-1.47 nmol/mL
> or =2 years: 0.00-2.98 nmol/mL

Phytanic Acid, C16:0(CH3)4
< or =4 months: 0.00-5.28 nmol/mL
5-8 months: 0.00-5.70 nmol/mL
9-12 months: 0.00-4.40 nmol/mL
13-23 months: 0.00-8.62 nmol/mL
> or =2 years: 0.00-9.88 nmol/mL

Triene/Tetraene Ratio
< or =31 days: 0.017-0.083
32 days-17 years: 0.013-0.050
> or =18 years: 0.010-0.038

Total Saturated Acid
<1 year: 1.2-4.6 mmol/L
1-17 years: 1.4-4.9 mmol/L
> or =18 years: 2.5-5.5 mmol/L

Total Monounsaturated Acid
<1 year: 0.3-4.6 mmol/L
1-17 years: 0.5-4.4 mmol/L
> or =18 years: 1.3-5.8 mmol/L

Total Polyunsaturated Acid
<1 year: 1.1-4.9 mmol/L
1-17 years: 1.7-5.3 mmol/L
> or =18 years: 3.2-5.8 mmol/L

Total w3
<1 year: 0.0-0.4 mmol/L
1-17 years: 0.1-0.5 mmol/L
> or =18 years: 0.2-0.5 mmol/L

Total w6
<1 year: 0.9-4.4 mmol/L
1-17 years: 1.6-4.7 mmol/L
> or =18 years: 3.0-5.4 mmol/L

Total Fatty Acids
<1 year: 3.3-14.0 mmol/L
1-17 years: 4.4-14.3 mmol/L
> or =18 years: 7.3-16.8 mmol/L

Clinical References: 1. Vannice G, Rasmussen H. Position of the Academy of Nutrition and Dietetics: Dietary fatty acids for healthy adults. J Acad Nutr Diet. 2014;114(1):136-153. doi:10.1016/j.jand.2013.11.001 2. Rinaldo P, Matern D, Bennett MJ. Fatty acid oxidation disorders. Ann Rev Physiol. 2002;64:477-502 3. Jeppesen PB, Christensen MS, Hoy CE, Mortensen PB. Essential fatty acid deficiency in patients with severe fat malabsorption. Am J Clin Nutr. 1997;65(3):837-843 4. Spector AA, Kim HY. Discovery of essential fatty acids. J. Lipid Res. 2015;56(1):11-215. VerHoeven NM, Jakobs C. Human metabolism of phytanic acid and pristanic acid. Prog in Lipid Res. 2001;40(6):453-466 6. Luszczki E, Boakye F, Zielinska M, Deren K, et al. Vegan diet: nutritional components, implementation, and effects on adults' health. Front Nutr. 2023 9;10:1294497. doi:10.3389/fnut.2023.1294497

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Fatty Acid Profile, Essential, Plasma

Clinical Information: Fats are important sources of energy for tissues and for the function and integrity of cellular membranes. Deficiencies are commonly caused by inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids, linoleic and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones. The Academy of Nutrition and Dietetics recommends that dietary fat for the healthy adult population should provide 20% to 35% of energy, with an increased consumption of n-3 polyunsaturated fatty acids and limited intake of saturated and trans fats.(1)

Useful For: Evaluating the nutritional intake and intestinal absorption of essential fatty acids using plasma specimens Identifying deficiency of essential and other nutritionally beneficial fatty acids Monitoring treatment of patients with essential fatty acid deficiencies who are receiving linoleic acid (C18:2w6) and alpha-linolenic acid (C18:3w3)

Interpretation: Concentrations below the stated reference ranges are consistent with fatty acid deficiencies. An increased triene:tetraene ratio is consistent with essential fatty acid deficiency

Reference Values:

Lauric Acid, C12:0
<1 year: 6-190 nmol/mL
1-17 years: 5-80 nmol/mL
> or =18 years: 6-90 nmol/mL

Myristic Acid, C14:0
<1 year: 30-320 nmol/mL
1-17 years: 40-290 nmol/mL
> or =18 years: 30-450 nmol/mL

Hexadecenoic Acid, C16:1w9
<1 year: 21-69 nmol/mL
1-17 years: 24-82 nmol/mL
> or =18 years: 25-105 nmol/mL

Palmitoleic Acid, C16:1w7
<1 year: 20-1,020 nmol/mL
1-17 years: 100-670 nmol/mL
> or =18 years: 110-1,130 nmol/mL

Palmitic Acid, C16:0
<1 year: 720-3,120 nmol/mL
1-17 years: 960-3,460 nmol/mL
> or =18 years: 1,480-3,730 nmol/mL

Gamma-Linolenic Acid, C18:3w6
<1 year: 6-110 nmol/mL
1-17 years: 9-130 nmol/mL
> or =18 years: 16-150 nmol/mL

Alpha-Linolenic Acid, C18:3w3
<1 year: 10-190 nmol/mL
1-17 years: 20-120 nmol/mL
> or =18 years: 50-130 nmol/mL

Linoleic Acid, C18:2w6
< or =31 days: 350-2,660 nmol/mL
32 days-11 months: 1,000-3,300 nmol/mL
1-17 years: 1,600-3,500 nmol/mL
> or =18 years: 2,270-3,850 nmol/mL

Oleic Acid, C18:1w9
<1 year: 250-3,500 nmol/mL
1-17 years: 350-3,500 nmol/mL
> or =18 years: 650-3,500 nmol/mL

Vaccenic Acid, C18:1w7
<1 year: 140-720 nmol/mL
1-17 years: 320-900 nmol/mL
> or =18 years: 280-740 nmol/mL

Stearic Acid, C18:0
<1 year: 270-1,140 nmol/mL
1-17 years: 280-1,170 nmol/mL
> or =18 years: 590-1,170 nmol/mL

EPA, C20:5w3
<1 year: 2-60 nmol/mL
1-17 years: 8-90 nmol/mL
> or =18 years: 14-100 nmol/mL

Arachidonic Acid, C20:4w6
<1 year: 110-1,110 nmol/mL
1-17 years: 350-1,030 nmol/mL
> or =18 years: 520-1,490 nmol/mL

Mead Acid, C20:3w9
< or =31 days: 8-60 nmol/mL
32 days-11 months: 3-24 nmol/mL
1-17 years: 7-30 nmol/mL
> or =18 years: 7-30 nmol/mL

Homo-Gamma-Linolenic C20:3w6
<1 year: 30-170 nmol/mL
1-17 years: 60-220 nmol/mL
> or =18 years: 50-250 nmol/mL

Arachidic Acid, C20:0
<1 year: 30-120 nmol/mL
1-17 years: 30-90 nmol/mL
> or =18 years: 50-90 nmol/mL

DHA, C22:6w3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
> or =18 years: 30-250 nmol/mL

DPA, C22:5w6
<1 year: 3-70 nmol/mL
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Docosenoic Acid, C22:1
<1 year: 2-20 nmol/mL

1-17 years: 4-13 nmol/mL
> or =18 years: 4-13 nmol/mL

Nervonic Acid, C24:1w9
<1 year: 30-150 nmol/mL
1-17 years: 50-130 nmol/mL
> or =18 years: 60-100 nmol/mL

Triene/Tetraene Ratio
< or =31 days: 0.017-0.083
32 days-17 years: 0.013-0.050
> or =18 years: 0.010-0.038

Total Saturated Acid
<1 year: 1.2-4.6 mmol/L
1-17 years: 1.4-4.9 mmol/L
> or =18 years: 2.5-5.5 mmol/L

Total Monounsaturated Acid
<1 year: 0.3-4.6 mmol/L
1-17 years: 0.5-4.4 mmol/L
> or =18 years: 1.3-5.8 mmol/L

Total Polyunsaturated Acid
<1 year: 1.1-4.9 mmol/L
1-17 years: 1.7-5.3 mmol/L
> or =18 years: 3.2-5.8 mmol/L

Total w3
<1 year: 0.0-0.4 mmol/L
1-17 years: 0.1-0.5 mmol/L
> or =18 years: 0.2-0.5 mmol/L

Total w6
<1 year: 0.9-4.4 mmol/L
1-17 years: 1.6-4.7 mmol/L
> or =18 years: 3.0-5.4 mmol/L

Total Fatty Acids
<1 year: 3.3-14.0 mmol/L
1-17 years: 4.4-14.3 mmol/L
> or =18 years: 7.3-16.8 mmol/L

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FAPEP 82426 Fatty Acid Profile, Essential, Serum

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Interpretation: Concentrations below the stated reference ranges are consistent with fatty acid deficiencies. An increased triene:tetraene ratio is consistent with essential fatty acid deficiency.

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> or =18 years: 6-90 nmol/mL

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<1 year: 30-320 nmol/mL
1-17 years: 40-290 nmol/mL
> or =18 years: 30-450 nmol/mL

Hexadecenoic Acid, C16:1w9
<1 year: 21-69 nmol/mL
1-17 years: 24-82 nmol/mL
> or =18 years: 25-105 nmol/mL

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<1 year: 720-3,120 nmol/mL
1-17 years: 960-3,460 nmol/mL
> or =18 years: 1,480-3,730 nmol/mL

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<1 year: 6-110 nmol/mL
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1-17 years: 320-900 nmol/mL
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1-17 years: 280-1,170 nmol/mL
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EPA, C20:5w3
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1-17 years: 8-90 nmol/mL
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Arachidonic Acid, C20:4w6
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1-17 years: 350-1,030 nmol/mL
> or =18 years: 520-1,490 nmol/mL

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32 days-11 months: 3-24 nmol/mL
1-17 years: 7-30 nmol/mL
> or =18 years: 7-30 nmol/mL

Homo-Gamma-Linolenic C20:3w6
<1 year: 30-170 nmol/mL
1-17 years: 60-220 nmol/mL
> or =18 years: 50-250 nmol/mL

Arachidic Acid, C20:0
<1 year: 30-120 nmol/mL
1-17 years: 30-90 nmol/mL
> or =18 years: 50-90 nmol/mL

DHA, C22:6w3
<1 year: 10-220 nmol/mL

1-17 years: 30-160 nmol/mL
> or =18 years: 30-250 nmol/mL

DPA, C22:5w6
<1 year: 3-70 nmol/mL
1-17 years: 10-50 nmol/mL
> or =18 years: 10-70 nmol/mL

DPA, C22:5w3
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DTA, C22:4w6
<1 year: 2-50 nmol/mL
1-17 years: 10-40 nmol/mL
> or =18 years: 10-80 nmol/mL

Docosenoic Acid, C22:1
<1 year: 2-20 nmol/mL
1-17 years: 4-13 nmol/mL
> or =18 years: 4-13 nmol/mL

Nervonic Acid, C24:1w9
<1 year: 30-150 nmol/mL
1-17 years: 50-130 nmol/mL
> or =18 years: 60-100 nmol/mL

Triene/Tetraene Ratio
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> or =18 years: 0.010-0.038

Total Saturated Acid
<1 year: 1.2-4.6 mmol/L
1-17 years: 1.4-4.9 mmol/L
> or =18 years: 2.5-5.5 mmol/L

Total Monounsaturated Acid
<1 year: 0.3-4.6 mmol/L
1-17 years: 0.5-4.4 mmol/L
> or =18 years: 1.3-5.8 mmol/L

Total Polyunsaturated Acid
<1 year: 1.1-4.9 mmol/L
1-17 years: 1.7-5.3 mmol/L
> or =18 years: 3.2-5.8 mmol/L

Total w3
<1 year: 0.0-0.4 mmol/L
1-17 years: 0.1-0.5 mmol/L
> or =18 years: 0.2-0.5 mmol/L

Total w6

<1 year: 0.9-4.4 mmol/L
1-17 years: 1.6-4.7 mmol/L
> or =18 years: 3.0-5.4 mmol/L

Total Fatty Acids
<1 year: 3.3-14.0 mmol/L
1-17 years: 4.4-14.3 mmol/L
> or =18 years: 7.3-16.8 mmol/L

Clinical References: 1. Vannice G, Rasmussen H. Position of the Academy of Nutrition and Dietetics: Dietary fatty acids for healthy adults. J Acad Nutr Diet. 2014;1(114):136-153 2. Jeppesen PB, Chistensen MS, Hoy CE, Mortensen PB. Essential fatty acid deficiency in patients with severe fat malabsorption. Am J Clin Nutr. 1997;65(3):837-843 3. Spector AA, Kim HY. Discovery of essential fatty acids. J. Lipid Res. 2015;56(1):11-21 4. Luszczki E, Boakye F, Zielinska M, Deren K, et al. Vegan diet: nutritional components, implementation, and effects on adults' health. Front Nutr. 2023;10:1294497. doi:10.3389/fnut.2023.1294497

FAPM
81939

Fatty Acid Profile, Mitochondrial (C8-C18), Serum

Clinical Information: Mitochondrial beta-oxidation is the main source of energy to skeletal and heart muscle during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue and converted to ketone bodies through a series of steps providing an alternate source of energy. Deficient enzymes at any step in this pathway prevent the production of energy during periods of physiologic stress such as fasting or intercurrent illness. The major clinical manifestations associated with fatty acid oxidation (FAO) disorders include hypoketotic hypoglycemia, liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden unexpected death in early life. Signs and symptoms may vary greatly in severity, combination, and age of presentation. Life-threatening episodes of metabolic decompensation frequently occur after periods of inadequate calorie intake or intercurrent illness. When properly diagnosed, patients with FAO disorders respond favorably to fasting avoidance, diet therapy, and aggressive treatment of intercurrent illnesses, with significant reduction of morbidity and mortality. Disease-specific characteristic patterns of metabolites from FAO disorders are detectable in blood, bile, urine, and cultured fibroblasts of living and many deceased individuals. Quantitative determination of C8-C18 fatty acids is an important element of the workup and differential diagnosis of candidate patients. Fatty acid profiling can detect quantitatively modest, but nevertheless significant, abnormalities even when patients are asymptomatic and under dietary treatment. Confirmatory testing for many of the FAO disorders is also available. For more information see FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture and HFAOP / Fatty Acid Oxidation Gene Panel, Varies

Useful For: Biochemical diagnosis of inborn errors of mitochondrial fatty acid oxidation, including deficiencies of medium-chain acyl-Co-A dehydrogenase, long-chain 3-hydroxyacyl-Co-A dehydrogenase, very long-chain acyl-Co-A dehydrogenase, and glutaric acidemia type 2

Interpretation: Fatty acid oxidation disorders are recognized on the basis of disease-specific metabolite patterns that are correlated to the results of other investigations in plasma (carnitine, acylcarnitines) and urine (organic acids, acylglycines).

Reference Values:
Octanoic Acid, C8:0
<1 year: 7-63 nmol/mL
1-17 years: 9-41 nmol/mL
> or =18 years: 8-47 nmol/mL

Decenoic Acid, C10:1
<1 year: 0.8-4.8 nmol/mL
1-17 years: 1.6-6.6 nmol/mL
> or =18 years: 1.8-5.0 nmol/mL

Decanoic Acid, C10:0
<1 year: 2-62 nmol/mL
1-17 years: 3-25 nmol/mL
> or =18 years: 2-18 nmol/mL

Lauroleic Acid, C12:1
<1 year: 0.6-4.8 nmol/mL
1-17 years: 1.3-5.8 nmol/mL
> or =18 years: 1.4-6.6 nmol/mL

Lauric Acid, C12:0
<1 year: 6-190 nmol/mL
1-17 years: 5-80 nmol/mL
> or =18 years: 6-90 nmol/mL

Tetradecadienoic Acid, C14:2
<1 year: 0.3-6.5 nmol/mL
1-17 years: 0.2-5.8 nmol/mL
> or =18 years: 0.8-5.0 nmol/mL

Myristoleic Acid, C14:1
<1 year: 1-46 nmol/mL
1-17 years: 1-31 nmol/mL
> or =18 years: 3-64 nmol/mL

Myristic Acid, C14:0
<1 year: 30-320 nmol/mL
1-17 years: 40-290 nmol/mL
> or =18 years: 30-450 nmol/mL

Hexadecadienoic Acid, C16:2
<1 year: 4-27 nmol/mL
1-17 years: 3-29 nmol/mL
> or =18 years: 10-48 nmol/mL

Palmitoleic Acid, C16:1w7
<1 year: 20-1,020 nmol/mL
1-17 years: 100-670 nmol/mL
> or =18 years: 110-1,130 nmol/mL

Palmitic Acid, C16:0
<1 year: 720-3,120 nmol/mL
1-17 years: 960-3,460 nmol/mL
> or =18 years: 1,480-3,730 nmol/mL

Linoleic Acid, C18:2w6
< or =31 days: 350-2,660 nmol/mL
32 days-11 months: 1,000-3,300 nmol/mL

1-17 years: 1,600-3,500 nmol/mL
> or =18 years: 2,270-3,850 nmol/mL

Oleic Acid, C18:1w9
<1 year: 250-3,500 nmol/mL
1-17 years: 350-3,500 nmol/mL
> or =18 years: 650-3,500 nmol/mL

Stearic Acid, C18:0
<1 year: 270-1,140 nmol/mL
1-17 years: 280-1,170 nmol/mL
> or =18 years: 590-1,170 nmol/mL

Clinical References: 1. Rinaldo P, Matern D, Bennett MJ. Fatty acid oxidation disorders. Ann Rev Physiol. 2002;64:477-502 2. Kang E, Kim YM, Kang, M, et al. Clinical and genetic characteristics of patients with fatty acid oxidation disorders identified by newborn screening. BMC Pediatr. 2018;18(1):103

POXP
60468

Fatty Acid Profile, Peroxisomal (C22-C26), Plasma

Clinical Information: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions, including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle, and single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy (X-ALD), resulting in elevated concentrations of VLCFA in plasma or serum. Peroxisomal biogenesis disorders (PBD) include Zellweger syndrome spectrum disorders, which are clinically diverse and range in severity from neonatal lethal (Zellweger syndrome) to more variable clinical courses in neonatal adrenoleukodystrophy and infantile Refsum disease. Affected children typically have hypotonia, poor feeding, distinctive facial features, seizures, and liver dysfunction. Other features can include retinal dystrophy, hearing loss, developmental delays, and bleeding episodes. Rhizomelic chondrodysplasia punctata is another PBD. It is characterized by rhizomelic shortening, chondrodysplasia punctata, cataracts, intellectual disability, and seizures, although it can have a milder phenotype with only cataracts and chondrodysplasia. The typical biochemical profile shows normal VLCFA and elevated phytanic acid. X-ALD is a neurologic disorder affecting the white matter and adrenal cortex. It can present between ages 4 and 8 years as a childhood cerebral form with behavioral and cognitive changes, associated with neurologic decline. Other forms include an "Addison disease only" phenotype with adrenocortical insufficiency without initial neurologic abnormality and adrenomyeloneuropathy associated with later-onset progressive paraparesis. X-ALD is an X-linked condition that primarily affects male patients; however, some female patients who are carriers can develop later-onset neurologic manifestations. In 2016, X-ALD was added to the US Recommended Uniform Screening Panel, a list of conditions that are nationally recommended for newborn screening by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. Refsum disease is a peroxisomal disorder characterized by anosmia, retinitis pigmentosa, neuropathy, deafness, ataxia, ichthyosis, and cardiac abnormalities. The classic biochemical profile of Refsum disease is an elevated plasma or serum phytanic acid level. Biochemical abnormalities in peroxisomal disorders include accumulations of VLCFA, phytanic acid, and pristanic acid. The differential diagnosis of these disorders is based on recognition of clinical phenotypes combined with a series of biochemical tests to assess peroxisomal function and structure. These include measurements and ratios of VLCFA, pipecolic acid (PIPA / Pipecolic Acid, Serum; PIPU / Pipecolic Acid, Random, Urine), phytanic acid and its metabolite pristanic acid. In addition, confirmatory testing for X-ALD (XALDZ / X-Linked

Adrenoleukodystrophy, Full Gene Analysis, Varies) via molecular genetic analysis is available.

Useful For: Evaluating patients with possible peroxisomal disorders, including peroxisomal biogenesis disorders, X-linked adrenoleukodystrophy, and Refsum disease using plasma specimens Aiding in the assessment of peroxisomal function

Interpretation: Reports include concentrations of C22:0, C24:0, C26:0 species, phytanic acid and pristanic acid, and calculated C24:0/C22:0, C26:0/C22:0 and phytanic acid:pristanic acid ratios. When no significant abnormalities are detected, a simple descriptive interpretation is provided. A profile of elevated phytanic acid, low-normal pristanic acid, and normal very long-chain fatty acids is suggestive of Refsum disease (phytanic acid oxidase deficiency); however, phytanic acid concentration may also be increased in disorders of peroxisomal biogenesis and should be considered in the differential diagnosis of peroxisomal disorders. If results are suggestive of hemizygosity for X-linked adrenoleukodystrophy, the calculated value of a discriminating function that more accurately segregates hemizygous individuals from normal controls is included in the report. Positive test results could be due to a genetic or nongenetic condition. Additional confirmatory testing would be required to differentiate between these causes.

Reference Values:

C22:0
< or =96.3 nmol/mL

C24:0
< or =91.4 nmol/mL

C26:0
< or =1.30 nmol/mL

C24:0/C22:0 RATIO
< or =1.39

C26:0/C22:0 RATIO
< or =0.023

PRISTANIC ACID
0-4 months: < or =0.60 nmol/mL
5-8 months: < or =0.84 nmol/mL
9-12 months: < or =0.77 nmol/mL
13-23 months: < or =1.47 nmol/mL
> or =24 months: < or =2.98 nmol/mL

PHYTANIC ACID
0-4 months: < or =5.28 nmol/mL
5-8 months: < or =5.70 nmol/mL
9-12 months: < or =4.40 nmol/mL
13-23 months: < or =8.62 nmol/mL
> or =24 months: < or =9.88 nmol/mL

PRISTANIC/PHYTANIC ACID RATIO
0-4 months: < or =0.35
5-8 months: < or =0.28
9-12 months: < or =0.23
13-23 months: < or =0.24
> or =24 months: < or =0.39

Clinical References: 1. Newborn Screening ACT Sheet [Elevated Lysophosphatidylcholine] X-Linked Adrenoleukodystrophy (X-ALD). American College of Medical Genetics and Genomics; 2023. Revised November 2023. Accessed March 25, 2025. Available at www.acmg.net/PDFLibrary/X-ALD-ACT-Sheet.pdf 2. Moser AB, Kreiter N, Bezman L, et al. Plasma very long chain fatty acid assay in 3,000 peroxisome disease patients and 29,000 controls. Ann Neurol. 1999;45:100-110 3. Turk BR, Theda C, Fatemi A, Moser AB. X-linked adrenoleukodystrophy: Pathology, pathophysiology, diagnostic testing, newborn screening and therapies. Int J Dev Neurosci. 2020;80(1):52-72. doi:10.1002/jdn.10003 4. Waterham HR, Ferdinandusse S, Wanders RJA. Human disorders of peroxisome metabolism and biogenesis. Biochimica et Biophysica Acta. 2016;1863(5):922-933. doi:10.1016/j.bbamcr.2015.11.015

POX
81369

Fatty Acid Profile, Peroxisomal (C22-C26), Serum

Clinical Information: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions, including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle, and single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy (X-ALD), resulting in elevated concentrations of VLCFA in plasma or serum. Peroxisomal biogenesis disorders (PBD) include Zellweger syndrome spectrum disorders, which are clinically diverse and range in severity from neonatal lethal (Zellweger syndrome) to more variable clinical courses in neonatal adrenoleukodystrophy and infantile Refsum disease. Affected children typically have hypotonia, poor feeding, distinctive facial features, seizures, and liver dysfunction. Other features can include retinal dystrophy, hearing loss, developmental delays, and bleeding episodes. Rhizomelic chondrodysplasia punctata is another PBD. It is characterized by rhizomelic shortening, chondrodysplasia punctata, cataracts, intellectual disability, and seizures, although it can have a milder phenotype with only cataracts and chondrodysplasia. The typical biochemical profile shows normal VLCFA and elevated phytanic acid. X-ALD is a neurologic disorder affecting the white matter and adrenal cortex. It can present between ages 4 and 8 years as a childhood cerebral form with behavioral and cognitive changes, associated with neurologic decline. Other forms include an "Addison disease only" phenotype with adrenocortical insufficiency without initial neurologic abnormality and adrenomyeloneuropathy associated with later-onset progressive paraparesis. X-ALD is an X-linked condition that primarily affects male patients; however, some female patients who are carriers can develop later-onset neurologic manifestations. In 2016, X-ALD was added to the US Recommended Uniform Screening Panel, a list of conditions that are nationally recommended for newborn screening by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. Refsum disease is a peroxisomal disorder characterized by anosmia, retinitis pigmentosa, neuropathy, deafness, ataxia, ichthyosis, and cardiac abnormalities. The classic biochemical profile of Refsum disease is an elevated plasma or serum phytanic acid level. Biochemical abnormalities in peroxisomal disorders include accumulations of VLCFA, phytanic acid, and pristanic acid. The differential diagnosis of these disorders is based on recognition of clinical phenotypes combined with a series of biochemical tests to assess peroxisomal function and structure. These include measurements and ratios of VLCFA, pipecolic acid (PIPA / Pipecolic Acid, Serum; PIPU / Pipecolic Acid, Random, Urine), phytanic acid and its metabolite pristanic acid. In addition, confirmatory testing for X-ALD (XALDZ / X-Linked Adrenoleukodystrophy, Full Gene Analysis, Varies) via molecular genetic analysis is available.

Useful For: Evaluating patients with possible peroxisomal disorders, single-enzyme defects of peroxisomal metabolism, such as X-linked adrenoleukodystrophy or peroxisomal biogenesis disorders (Zellweger syndrome spectrum) using serum specimens Aiding in the assessment of peroxisomal function

Interpretation: Reports include concentrations of C22:0, C24:0, C26:0 species, phytanic acid and pristanic acid, and calculated C24:0/C22:0, C26:0/C22:0 and phytanic acid:pristanic acid ratios. When no significant abnormalities are detected, a simple descriptive interpretation is provided. A profile of elevated phytanic acid, low-normal pristanic acid, and normal very long-chain fatty acids is suggestive of Refsum disease (phytanic acid oxidase deficiency); however, serum phytanic acid concentration may also be increased in disorders of peroxisomal biogenesis and should be considered in the differential diagnosis of peroxisomal disorders. If results are suggestive of hemizygosity for X-linked adrenoleukodystrophy, the calculated value of a discriminating function that more accurately segregates hemizygous individuals from normal controls is included in the report. Positive test results could be due to a genetic or nongenetic condition. Additional confirmatory testing would be required to differentiate between these causes.

Reference Values:

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C26:0
< or =1.30 nmol/mL

C24:0/C22:0 RATIO
< or =1.39

C26:0/C22:0 RATIO
< or =0.023

PRISTANIC ACID
0-4 months: < or =0.60 nmol/mL
5-8 months: < or =0.84 nmol/mL
9-12 months: < or =0.77 nmol/mL
13-23 months: < or =1.47 nmol/mL
> or =24 months: < or =2.98 nmol/mL

PHYTANIC ACID
0-4 months: < or =5.28 nmol/mL
5-8 months: < or =5.70 nmol/mL
9-12 months: < or =4.40 nmol/mL
13-23 months: < or =8.62 nmol/mL
> or =24 months: < or =9.88 nmol/mL

PRISTANIC/PHYTANIC ACID RATIO
0-4 months: < or =0.35
5-8 months: < or =0.28
9-12 months: < or =0.23
13-23 months: < or =0.24
> or =24 months: < or =0.39

Clinical References: 1. Newborn Screening ACT Sheet [Elevated Lysophosphatidylcholine] X-Linked Adrenoleukodystrophy (X-ALD). American College of Medical Genetics and Genomics; 2023. Revised November 2023. Accessed March 25, 2025. Available at www.acmg.net/PDFLibrary/X-ALD-ACT-Sheet.pdf 2. Moser AB, Kreiter N, Bezman L, et al. Plasma very long chain fatty acid assay in 3,000 peroxisome disease patients and 29,000 controls. Ann Neurol. 1999;45:100-110 3. Turk BR, Theda C, Fatemi A, Moser AB. X-linked adrenoleukodystrophy: Pathology, pathophysiology, diagnostic testing,

newborn screening and therapies. Int J Dev Neurosci. 2020;80(1):52-72. doi:10.1002/jdn.10003 4. Waterham HR, Ferdinandusse S, Wanders RJA. Human disorders of peroxisome metabolism and biogenesis. Biochimica et Biophysica Acta. 2016;1863(5):922-933. doi:10.1016/j.bbamcr.2015.11.015

MFBNG
617365

FBN1 Full Gene Sequencing with Deletion/Duplication, Varies

Clinical Information: Fibrillin-1 is a 320 kDa, cysteine-rich glycoprotein found in the extracellular matrix. Monomers of fibrillin-1 associate to form microfibrils that provide mechanical stability and elastic properties to connective tissues. Fibrillin-1 is encoded by the FBN1 gene, which contains 65 exons and is located at chromosome 15q21. Disease-causing FBN1 variants are most commonly associated with Marfan syndrome (MFS), an autosomal dominant connective tissue disease involving the ocular, skeletal, and cardiovascular systems. Ocular MFS manifestations most commonly include myopia and ectopia lentis (lens displacement). Skeletal manifestations can include arachnodactyly (abnormally long and slender fingers and toes), dolichostenomelia (long limbs), pectus (chest wall) deformity, and scoliosis. Cardiovascular manifestations, which are the major cause of early morbidity and mortality in MFS, include aortic aneurysm and dissection, as well as mitral valve and tricuspid valve prolapse.(1) The clinical diagnosis of Marfan syndrome is based on the revised Ghent nosology for the Marfan syndrome.(2) There may be significant inter- and intrafamilial variability in the MFS phenotype. Disease-causing FBN1 variants have also been reported in several other rare phenotypes with variable overlap with classic MFS.(3) In some cases, MFS may present in the neonatal period with severe, rapidly progressive disease (previously termed "neonatal Marfan syndrome"). Other FBN1-associated conditions include autosomal dominant ectopia lentis (displacement of the lens of the eye), isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis), Marfan lipodystrophy syndrome, and stiff skin syndrome. Hundreds of disease-causing variants have been identified in FBN1, many of them unique to individual families. There is a wide range of variability, including intrafamilial variability, in expressivity among disease-causing FBN1 variants. Approximately two-thirds of disease-causing FBN1 variants are missense changes, with the majority of these being cysteine substitutions. Approximately 25% to 33% of disease-causing FBN1 variants are de novo, in which an individual has no family history of disease. Disease-causing FBN1 variants have been shown to occur across the gene. Some genotype-phenotype correlations have been observed, including the association with truncating and splicing variants with risk for aortic dissection, cysteine-based variants associated with ectopia lentis, and severe, early onset MFS associated with variants in exons 24 through 32.(4-6) Marfan syndrome has significant clinical overlap with a condition called Loeys-Dietz syndrome (LDS); however, the vascular phenotype of LDS can be more severe, and LDS has disease-causing variants in different genes (TGFBR1, TGFBR2, SMAD2, SMAD3, TGFB2 and TGFB3). When the diagnosis of MFS, LDS, or a related disorder is suspected, the use of genetic testing is important to verify the diagnosis and provide appropriate clinical management. Single gene analysis of the FBN1 gene may be appropriate when there is a very high index of suspicion for Marfan syndrome based on clinical presentation and Ghent diagnostic criteria, while multigene panel-based testing can be more appropriate when the differential diagnosis includes Marfan syndrome and additional, overlapping phenotypes. Confirmation of the genetic diagnosis also allows for preconception, prenatal, and family counseling.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of Marfan syndrome and other FBN1-related conditions Establishing a diagnosis for Marfan syndrome and other FBN1-related conditions

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1 Dietz H: FBN1-related Marfan syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2001. Updated February 17, 2022. Accessed August 1, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1335/ 2. Loeys BL, Dietz HC, Braverman AC, et al: The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010 Jul;47(7):476-485 3. OMIM. 134797 Fibrillin 1; FBN1. Johns Hopkins University; 1991. Updated November 12, 2020. Accessed August 1, 2022. Available at https://omim.org/entry/134797 4. Baudhuin LM, Kotzer KE, Lagerstedt SA: Increased frequency of FBN1 truncating and splicing variants in Marfan syndrome patients with aortic events. Genet Med. 2015 Mar;17(3):177-187. doi: 10.1038/gim.2014.91 5. Baudhuin LM, Kotzer KE, Lagerstedt SA: Decreased frequency of FBN1 missense variants in Ghent criteria-positive Marfan syndrome and characterization of novel FBN1 variants. J Hum Genet. 2015 May;60(5):241-252. doi: 10.1038/jhg.2015.10 6. Faivre L, Collod-Beroud G, Loeys BL, et al: Effect of mutation type and location on clinical outcome of 1,013 probands with Marfan syndrome or related phenotypes and FBN1 mutations: an international study. Am J Hum Genet. 2007;81(3):454-466. doi: 10.1086/520125 7. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424.

FETH2
81880

Feather Panel # 2, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to chicken, duck, goose, and turkey Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

LEU
8046

Fecal Leukocytes, Feces

Clinical Information: Leukocytes are not normally seen in feces in the absence of infection or other inflammatory processes. Fecal leukocytosis is a response to infection with microorganisms that invade tissue or produce toxins, which causes tissue damage. Fecal leukocytes are commonly found in patients with shigellosis and salmonellosis and sometimes in amebiasis. Mononuclear cells are found in typhoid fever. Ulcerative colitis may also be associated with fecal leukocytosis.

Useful For: Suggesting the presence of pathogens such as Salmonella, Shigella, and amebiasis

Interpretation: When fecal leukocytes are found they are reported in a semi-quantitative manner: "few" indicates = 2/100x oil immersion microscopic field (OIF); "moderate" indicates 3-9/100x OIF; "many" indicates =10/100x OIF. Erythrocytes are reported in the same manner. The greater the number of fecal leukocytes, the greater the likelihood that an invasive pathogen such as Salmonella or Shigella is present. The presence of few or no leukocytes and many erythrocytes suggests possible amebiasis. Fecal leukocytes are rarely seen in diarrhea caused by other parasites or viruses.

Reference Values:
An interpretive report will be provided.

Clinical References:

FOBT
607700

Fecal Occult Blood, Colorectal Cancer Screen, Qualitative, Immunochemical, Feces

Clinical Information: Colorectal cancer (CRC) is one of the most commonly diagnosed cancers in the United States, and the second leading cause of cancer-related deaths. CRC almost always develops from adenomatous polyps, yet patients remain asymptomatic until the cancer progresses to a fairly advanced stage. Screening for colorectal cancer is strongly advocated for by the United States

Preventive Services Task Force, the American Cancer Society, the American College of Gastroenterology, and other clinical societies, due to the high incidence of disease and decrease in mortality with medical intervention. Men and women at average risk for colorectal cancer should be screened at regular intervals beginning at age 45 and continuing until age 75. Individuals with certain high-risk factors (age, African-American race, inflammatory intestinal disorders, family history of colon cancer, obesity, diabetes, poor diet) may consider earlier screening strategies. A variety of options are available for colorectal cancer screening including fecal occult blood testing, sigmoidoscopy, colonoscopy, and multimarker Cologuard testing that includes genetic markers of colorectal cancer. Historically occult blood tests utilized guaiac-based tests that were susceptible to dietary interferences, but this test utilizes fecal immunochemical testing (FIT) specific for human hemoglobin, eliminating the need for dietary and medication restrictions. For colorectal cancer screening, only a single collection is required. The specificity of FIT is routinely greater than 95% with reported sensitivities ranging from 40% to 70% based on the patient population. The clinical specificity of FIT is 97% based on internal studies conducted at Mayo Clinic but can be limited by gastrointestinal bleeding from a non-colorectal cancer source. In a recent study of 10,000 average risk participants, Cologuard detected colorectal cancer, precancerous lesions, and polyps with high-grade dysplasia with higher sensitivity than FIT testing.(1) However, Cologuard had slightly lower specificity than FIT testing in that study. Cologuard requires an entire bowel movement for testing versus 1 small sample for FIT. Current societal guidelines endorse the use of FIT and Cologuard interchangeably with 1-year based screening for FIT versus a suggested 3-year DNA based screening for average risk population, recognizing that the testing interval for the latter is uncertain.(2,3)

Useful For: Colorectal cancer screening Screening for gastrointestinal bleeding This test has not been validated for testing of patients with hemoglobinopathies.

Interpretation: This is a quantitative assay, but results are reported qualitatively as negative or positive for the presence of fecal occult blood; the cutoff for positivity is 100 ng/mL hemoglobin. The following comments will be reported with the qualitative result for patients older than 17 years: -Positive results; further testing is recommended if clinically indicated. This test has 97% specificity for detection of lower gastrointestinal bleeding in colorectal cancer. -Negative results; this test will not detect upper gastrointestinal bleeding; HQ / HemoQuant, Feces test should be ordered if clinically indicated.

Reference Values:
Negative

This test has not been validated in a pediatric population, results should be interpreted in the context of the patient's presentation.

Clinical References: 1. Imperiate TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med. 2014;370(14):1287-1297 2. Robertson DJ, Lee JK, Boland CR, et al. Recommendations on fecal immunochemical testing to screen for colorectal neoplasia: A consensus statement by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2017;152(5):1217-1237 3. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: Recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2017;153(1):307-323. doi:10.1053/j.gastro.2017.05.013 4. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin. 2008;58(3):130-160. doi:10.3322/CA.2007.0018 5. Whitlock EP, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;149(9):638-658 6. Hol L, Wilschut JA, van Ballegooijen M, et al. Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. Br J Cancer. 2009;100(7):1103-1110. doi:10.1038/sj.bjc.6604961 7. Levi Z, Rozen P, Hazazi R, et al. A quantitative immunochemical fecal occult blood test for colorectal

neoplasia. Ann Intern Med. 2007;146(4):244-255 8. Tannous B, Lee-Lewandrowski E, Sharples C, et al. Comparison of conventional guaiac to four immunochemical methods for fecal occult blood testing: implications for clinical practice in hospital and outpatient settings. Clin Chem Acta. 2009;400(1-2):120-122. doi:10.1016/j.cca.2008.10.023

FELBA
80782

Felbamate (Felbatol), Serum

Clinical Information: Felbamate is an anticonvulsant drug approved for treatment of partial seizures with or without secondary generalization in persons 14 years and older. It is also approved for Lennox-Gastout syndrome in children 2 years and older. Felbamate is well absorbed (>90%) and is metabolized by the hepatic cytochrome P450 system. Metabolites lack anticonvulsant activity. The elimination half-life of felbamate ranges from 16 to 22 hours. Optimal response to felbamate is seen with serum concentrations between 30 mcg/mL to 80 mcg/mL. Patients who are older adults or have kidney dysfunction may require reduced dosing; felbamate should not be given to individuals with hepatic disease. Toxicity can be severe, including life-threatening aplastic anemia or liver failure; toxic concentration has been established at concentrations greater than 100 mcg/mL. Coadministration of felbamate increases the concentration of phenytoin and valproic acid, decreases carbamazepine concentration, and increases carbamazepine-10,11-epoxide (its active metabolite). Conversely, coadministration of phenytoin or carbamazepine causes a decrease in felbamate concentration.

Useful For: Determining whether a poor therapeutic response is attributable to noncompliance or lack of drug effectiveness Monitoring changes in serum concentrations resulting from interactions with coadministered drugs such as barbiturates and phenytoin

Interpretation: Optimal response to felbamate is associated with serum concentrations of 30 mcg/mL to 80 mcg/mL. Toxic serum concentrations for felbamate have been established at concentrations greater than 100 mcg/mL.

Reference Values:
30.0-80.0 mcg/mL

Clinical References: 1. Johannessen SI, Tomson T. Pharmacokinetic variability of newer antiepileptic drugs: when is monitoring needed? Clin Pharmacokinet. 2006;45(11):1061-1075 2. Schmidt D. Felbamate: successful development of a new compound for the treatment of epilepsy. Epilepsia. 1996;34(Suppl 7):S30-S33 3. Patsalos PN: Antiepileptic drugs-best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239-1276 4. Rifai N, Horwath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018 5. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62

FENR
63061

Fentanyl Screen with Reflex, Random, Urine

Clinical Information: This test uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate due to the antibody's ability to cross-react with different drugs in the class being screened for.

Useful For: Screening for drug abuse or use involving fentanyl and confirmation of fentanyl if present in the screen

Interpretation: If the screen result is negative, fentanyl concentrations above 0.20 ng/mL were not detected. If the screen result is positive, then confirmation by liquid chromatography tandem mass spectrometry will be performed. The presence of fentanyl above 0.20 ng/mL or norfentanyl above 1.0 ng/mL is a strong indicator that the patient has used fentanyl.

Reference Values:
Negative
Screening cutoff concentration: 2 ng/mL

Clinical References: 1. Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds: Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Companies; 2006:chap 21 2. Kerrigan S, Goldberger BA. Opioids. In: Levine ZB, eds. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:187-205 3. DURAGESIC (fentanyl transdermal system). Package insert. Janssen Pharmaceutical Products. LP; 2006 4. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 8th ed. Biomedical Publications; 2008:616-619 5. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

FENS
63060

Fentanyl Screen, Random, Urine

Clinical Information: This test uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate due to the antibody's ability to cross react with different drugs in the class being screened.

Useful For: Screening for drug abuse or use involving fentanyl

Interpretation: This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography tandem mass spectrometry) must be used to obtain a confirmed analytical result.

Reference Values:
Negative
Screening cutoff concentration: 2 ng/mL

Clinical References: 1. Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds: Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill; 2006:chap 21 2. Kerrigan S, Goldberger BA. Opioids. In: Levine ZB, ed. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:187-205 3. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 8th ed. Biomedical Publications; 2008:616-619 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

FENTX
62726

Fentanyl with Metabolite Confirmation, Chain of Custody, Random, Urine

Clinical Information: Fentanyl is an extremely fast-acting synthetic opioid related to the phenylpiperidines.(1,2) It is available in injectable as well as transdermal formulations.(1) The analgesic effects of fentanyl are similar to those of morphine and other opioids(1): it interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissue.(1,3) Fentanyl is approximately 80% to 85% protein bound. In plasma, the protein binding capacity of fentanyl decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system (CNS). The average volume of distribution for fentanyl is 6 L/kg (range 3-8).(3,4) In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug.(3,4) The mean elimination half-life is(1-3): -IV: 2 to 4 hours -Iontophoretic transdermal system (Ionsys) terminal half-life: 16 hours -Transdermal patch: 17 hours (13-22 hours; half-life is influenced by absorption rate) -Transmucosal: -Lozenge: 7 hours -Buccal tablet -100 mcg to 200 mcg: 3 to 4 hours -400 mcg to 800 mcg: 11 to 12 hours In clinical settings, fentanyl exerts its principal pharmacologic effects on the CNS. In addition to analgesia, alterations in mood (euphoria, dysphoria) and drowsiness commonly occur.(1,3) Because the biological effects of fentanyl are similar to those of heroin and other opioids, fentanyl has become a popular drug of abuse. Chain of custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detection and confirmation of illicit drug use involving fentanyl Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of fentanyl above 0.20 ng/mL or norfentanyl above 1.0 ng/mL is a strong indicator that the patient has used fentanyl.

Reference Values:

Negative

Positive results are reported with a quantitative result.

Cutoff concentrations:

Immunoassay screen: 2 ng/mL

Liquid chromatography-tandem mass spectrometry:
Fentanyl: 0.2 ng/mL
Norfentanyl: 1.0 ng/mL

Clinical References: 1. Gutstein HB, Akil H. Opioid analgesics. In: Hardman JG LL, Gilman AG, eds: Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill; 2006:chap 21 2. Kerrigan S, Goldberger BA. Opioids. In: Levine ZB, ed. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:187-205 3. DURAGESIC (fentanyl transdermal system). Package insert. Janssen Pharmaceutical Products. LP; 2006 4. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 8th ed. Biomedical Publications; 2008:616-619 5. Langman LJ, Bechtel LK, Meier BM, Holstege C. Clinical toxicology. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 7th ed. Elsevier; 2023:chap 43

FENTU
89655

Fentanyl with Metabolite Confirmation, Random, Urine

Clinical Information: Fentanyl is an extremely fast acting synthetic opioid related to the phenylpiperidines.(1,2) It is available in injectable as well as transdermal formulations.(1) The analgesic effects of fentanyl is similar to those of morphine and other opioids(1): it interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissue.(1,3) Fentanyl is approximately 80% to 85% protein bound. In plasma, the protein binding capacity of fentanyl decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system (CNS). The average volume of distribution for fentanyl is 6 L/kg (range 3-8).(3,4) In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug.(3,4) The mean elimination half-life is(1-3): -IV: 2 to 4 hours -Iontophoretic transdermal system (Ionsys) terminal half-life: 16 hours -Transdermal patch: 17 hours (13-22 hours, half-life is influenced by absorption rate) -Transmucosal: -Lozenge: 7 hours -Buccal tablet -100 to 200 mcg: 3 to 4 hours -400 to 800 mcg: 11 to 12 hours In clinical settings, fentanyl exerts its principal pharmacologic effects on the CNS. In addition to analgesia, alterations in mood (euphoria, dysphoria) and drowsiness commonly occur.(1,3) Because the biological effects of fentanyl are similar to those of heroin and other opioids, fentanyl has become a popular drug of abuse.

Useful For: Detection and confirmation of illicit drug use involving fentanyl

Interpretation: The presence of fentanyl above 0.20 ng/mL or norfentanyl above 1.0 ng/mL is a strong indicator that the patient has used fentanyl.

Reference Values:
Negative
Positive results are reported with a quantitative result.

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Fentanyl: 0.2 ng/mL
Norfentanyl: 1.0 ng/mL

Clinical References: 1. Gutstein HB, Akil H. Opioid analgesics. In: Hardman JG LL, Gilman AG, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill; 2006:chap 21 2. Kerrigan S, Goldberger BA. Opioids. In: Levine ZB, ed. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:187-205 3. DURAGESIC (fentanyl transdermal system). Package insert. Janssen Pharmaceutical Products. LP; 2006 4. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 8th ed. Biomedical Publications; 2008:616-619 5. Langman LJ, Bechtel LK, Meier BM, Holstege C. Clinical toxicology. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 7th ed. Elsevier; 2023:chap 43

FENTS
89654

Fentanyl, Serum

Clinical Information: Fentanyl is an extremely fast-acting synthetic opioid related to the phenylpiperidines.(1,2) It is available in injectable as well as transdermal formulations.(1) The analgesic effects of fentanyl are similar to those of morphine and other opioids(1), as it interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues.(1,3) Fentanyl is approximately 80% to 85% protein bound.(1) Fentanyl plasma protein-binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system (CNS). The average volume of distribution

for fentanyl is 6 L/kg (range 3-8).(3,4) In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug.(3,4) The mean elimination half-life is:(1-3) -IV: 2 to 4 hours -Iontophoretic transdermal system (Ionsys), terminal half-life: 16 hours -Transdermal patch: 17 hours (range 13-22 hours, half-life is influenced by absorption rate) -Transmucosal: -Lozenge: 7 hours -Buccal tablet -100 to 200 mcg: 3 to 4 hours -400 to 800 mcg: 11 to 12 hours In clinical settings, fentanyl exerts its principal pharmacologic effects on the CNS. In addition to analgesia, alterations in mood (euphoria, dysphoria) and drowsiness commonly occur.(1,3) Because the biological effects of fentanyl are similar to those of heroin and other opioids, fentanyl has become a popular drug of abuse.

Useful For: Monitoring fentanyl therapy

Interpretation: Both fentanyl and norfentanyl are reported. Tolerant individuals may require many-fold increases in dose to achieve the same level of analgesia, which can greatly complicate interpretation of therapeutic drug monitoring results and establishment of a therapeutic window. Concentration at which toxicity occurs varies and should be interpreted in light of clinical situation.

Reference Values:

Fentanyl:

Average serum fentanyl concentrations 24 hours after application of transdermal patch:
25 mcg/hour: 0.3-1.2 ng/mL
50 mcg/hour: 0.6-1.8 ng/mL
75 mcg/hour: 1.1-2.6 ng/mL
100 mcg/hour: 1.9-3.8 ng/mL
(Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020)

Norfentanyl:
Reference range: Not established

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Fentanyl: 0.05 ng/mL
Norfentanyl: 0.25 ng/mL

Clinical References: 1. Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Companies; 2006:chap 21 2. Kerrigan S, Goldberger BA. Opioids. In: Levine B, eds. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:187-205 3. DURAGESIC (fentanyl transdermal system). Package insert: Janssen Pharmaceutica Products, LP; 2006 4. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 12th ed. Biomedical Publications; 2020 5. Yaksh T, Wallace M. Opioids, Analgesia, and Pain Management. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 13th ed. McGraw-Hill Education; 2017 6. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 7. Fentanyl. In: Merative Micromedex (electronic version). Merative US 2024. Accessed April 7, 2025. Available at www.micromedexsolutions.com

FEEP
82143

Ferret Epithelium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are

caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to ferret epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FERR1
619953

Ferritin, Serum

Clinical Information: Ferritin is a large spherical protein consisting of 24 noncovalently linked subunits with a molecular weight of approximately 450,000 Da. The subunits form a shell surrounding a central core containing variable amounts of ferric hydroxyphosphate. One molecule of ferritin is capable of binding between 4000 and 5000 atoms of iron, making ferritin the major iron storage protein for the

body. Ferritin is found mainly in the cytoplasm of cells of the reticuloendothelial system and is a constituent of normal human serum. The concentration of ferritin is directly proportional to the total iron stores in the body, resulting in serum ferritin concentrations becoming a common diagnostic tool in the evaluation of iron status. In most normal adults, serum ferritin concentrations vary with age and sex. There is a sharp rise in serum ferritin concentrations in the first month of life, coinciding with the depression of bone marrow erythropoiesis. Within 2 or 3 months, erythropoiesis becomes reactivated and there is a drop in the concentration of serum ferritin. By 6 months, the concentration is reduced to fairly low levels, where they remain throughout childhood. There is no sex difference until the onset of puberty, at which time ferritin concentrations rise, particularly in male patients. There is a significant positive correlation between age and serum ferritin concentrations in female patients but not in male patients. Patients with iron deficiency anemia have serum ferritin concentrations approximately one-tenth of normal subjects, while patients with iron overload conditions (hemochromatosis, hemosiderosis) have serum ferritin concentrations much higher than normal. Studies also suggest that serum ferritin provides a sensitive means of detecting iron deficiency at an early stage. Serum ferritin concentrations may serve as a tool to monitor the effects of iron therapy, but results should be interpreted with caution as these cases may not always reflect the true state of iron stores. Ferritin is a positive acute phase reactant in both adults and children, whereby chronic inflammation results in a disproportionate increase in ferritin in relation to iron reserves. Elevated ferritin is also observed in acute and chronic liver disease, chronic kidney failure, and in some types of neoplastic disease. Evaluating body iron stores may include serum iron determination, total iron binding capacity, and percent saturation of transferrin, however, these are subject to diurnal variations and may be less precise. Additionally, they do not discriminate between depleted iron stores (iron deficiency) and conditions associated with defective iron release (eg, anemia of chronic disease).

Useful For: Aiding in the diagnosis of iron deficiency and iron overload conditions Differentiating iron deficiency anemia and anemia of chronic disease

Interpretation: Hypoferritinemia is associated with increased risk for developing iron deficiency where iron deficiency is sufficient to reduce erythropoiesis causing hemoglobin concentrations to fall. Latent iron deficiency occurs when serum ferritin is low without low hemoglobin. Hyperferritinemia is associated with iron overload conditions including hereditary hemochromatosis where concentrations may exceed 1000 mcg/L. Non-iron overload hyperferritinemia may be caused by common liver disorders, neoplasms, acute or chronic inflammation, and hereditary hyperferritinemia-cataract syndrome. For more information about hereditary hemochromatosis testing, see Hereditary Hemochromatosis Algorithm.

Reference Values:

Males:
0 days-4 weeks: 150-973 mcg/L
5 weeks-5 months: 9-580 mcg/L
6 months-9 years: 6-111 mcg/L
10-17 years: 15-201 mcg/L
> or =18 years: 31-409 mcg/L

Females:
0 days-4 weeks: 150-973 mcg/L
5 weeks-5 months: 9-580 mcg/L
6 months-17 years: 8-115 mcg/L
18-50 years: 6-175 mcg/L
> or =51 years: 11-328 mcg/L

Clinical References: 1. McPherson RA, Pincus MR: Henry's Clinical Diagnosis and Management by Laboratory Methods. 21st ed. Elsevier Saunders; 2007:506 2. Burtis CA, Ashwood ER, Bruns DE: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. Elsevier Saunders; 2012:985-1030 3.

Cappellinin MD, Lo SF, Swickels DW: Hemoglobin, iron, bilirubin. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier Saunders; 2018:719-775

FMB
88841

Fetomaternal Bleed, Flow Cytometry, Blood

Clinical Information: In hemolytic disease of the newborn, fetal red blood cells become coated with IgG alloantibody of maternal origin, which is directed against an antigen on the fetal cells that is of paternal origin and is absent on maternal cells. The IgG-coated cells undergo accelerated destruction, both before and after birth. The clinical severity of the disease can vary from intrauterine death to hematological abnormalities detected only if blood from an apparently healthy infant is subject to serologic testing. Pregnancy causes immunization when fetal red blood cells possessing a paternal antigen foreign to the mother enter the maternal circulation, an event described as fetomaternal hemorrhage (FMH). FMH occurs in up to 75% of pregnancies, usually during the third trimester and immediately after delivery. Delivery is the most common immunizing event, but fetal red blood cells can also enter the mother's circulation after amniocentesis, spontaneous or induced abortion, chorionic villus sampling, cordocentesis, or rupture of an ectopic pregnancy, as well as blunt trauma to the abdomen.(1) Rh immune globulin (RhIG, anti-D antibody) is given to Rh-negative mothers who are pregnant with a Rh-positive fetus. Anti-D antibody binds to fetal D-positive red blood cells, preventing development of the maternal immune response. RhIG can be given either before or after delivery. The volume of FMH determines the dose of RhIG to be administered.

Useful For: Determining the volume of fetal-to-maternal hemorrhage for the purposes of recommending an increased dose of the Rh immune globulin

Interpretation: Greater than 15 mL of fetal red blood cells (RBC) (30 mL of fetal whole blood) is consistent with significant fetomaternal hemorrhage (FMH). A recommended dose of Rh immune globulin (RhIG) will be reported for all specimens. One 300 mcg dose of RhIG protects against a FMH of 30 mL of D-positive fetal whole blood or 15 mL of D-positive fetal RBC. Recommended standard of practice is to administer RhIG within 72 hours of the fetomaternal bleed for optimal protective effects. The effectiveness of RhIG decreases beyond 72 hours post exposure but may still be clinically warranted. This assay has been validated out to 5 days post collection.

Reference Values:
< or =3.75 mL of fetal red blood cells in normal adults

Clinical References: 1. Roback J, Combs MR, Grossman B, Hillyer C, eds. In: Technical manual. 16th ed. AABB Press; 2008:625-637, 888 2. Iyer R, McElhinney B, Heasley N, Williams M, Morris K. False positive Kleihauer tests and unnecessary administration of anti-D immunoglobulin. Clin Lab Haematol. 2003;25(6):405-408 3. Cohn CS, Delaney M, Johnson ST, Katz LM, eds. Technical Manual. 20th ed. AABB Press; 2020

FMBNY
30320

Fetomaternal Bleed, New York, Blood

Clinical Information: In hemolytic disease of the newborn, fetal red blood cells become coated with IgG alloantibody of maternal origin, which is directed against an antigen on the fetal cells that is of paternal origin and is absent on maternal cells. The IgG-coated cells undergo accelerated destruction, both before and after birth. The clinical severity of the disease can vary from intrauterine death to hematological abnormalities detected only if blood from an apparently healthy infant is subject to serologic testing. Pregnancy causes immunization when fetal red blood cells possessing a paternal antigen foreign to the mother enter the maternal circulation, an event described as fetomaternal hemorrhage

(FMH). FMH occurs in up to 75% of pregnancies, usually during the third trimester and immediately after delivery. Delivery is the most common immunizing event, but fetal red blood cells can also enter the mother's circulation after amniocentesis, spontaneous or induced abortion, chorionic villus sampling, cordocentesis, or rupture of an ectopic pregnancy, as well as blunt trauma to the abdomen.(1) Rh immune globulin (RhIG, anti-D antibody) is given to Rh-negative mothers who are pregnant with a Rh-positive fetus. Anti-D antibody binds to fetal D-positive red blood cells, preventing development of the maternal immune response. RhIG can be given either before or after delivery. The volume of FMH determines the dose of RhIG to be administered.

Useful For: Determining the volume of fetal-to-maternal hemorrhage for the purposes of recommending an increased dose of the Rh immune globulin This test is used only for specimens collected in New York state.

Interpretation: Greater than 15 mL of fetal red blood cells (RBC) (30 mL of fetal whole blood) is consistent with significant fetomaternal hemorrhage (FMH). A recommended dose of Rh immune globulin (RhIG) will be reported for all specimens. One 300-mcg dose of RhIG protects against a FMH of 30 mL of D-positive fetal whole blood or 15 mL of D-positive fetal RBC. Recommended standard of practice is to administer RhIG within 72 hours of the fetomaternal bleed for optimal protective effects. The effectiveness of RhIG decreases beyond 72 hours postexposure but may still be clinically warranted. This assay has been validated out to 5 days post collection.

Reference Values:
< or =3.75 mL of fetal red blood cells in normal adults

Clinical References: 1. Roback J, Combs MR, Grossman B, Hillyer C, eds. In: Technical manual. 16th ed. AABB Press; 2008:625-637, 888 2. Iyer R, McElhinney B, Heasley N, Williams M, Morris K. False positive Kleihauer tests and unnecessary administration of anti-D immunoglobulin. Clin Lab Haematol. 2003;25(6):405-408 3. Cohn CS, Delaney M, Johnson ST, Katz LM, eds. Technical Manual. 20th ed. AABB Press; 2020

FGF1F 58124 FGFR1 (8p11.2) Amplification, FISH, Tissue

Clinical Information:

Useful For: Providing prognostic information and guiding treatment primarily for patients with squamous cell carcinoma of the lung, breast, esophagus, thymus, and other locations

Interpretation: FGFR1 will be clinically interpreted as positive or negative. The FGFR1 locus is reported as amplified (positive) when the FGFR1:D8Z2 ratio is greater than 2.0 or an average of 6 or more copies of the FGFR1 probe are observed per tumor nucleus. A tumor with an FGFR1:D8Z2 ratio less than or equal to 2.0 and having an average of less than 6 copies of FGFR1 per tumor nucleus is considered negative for amplification of the FGFR1 locus. A negative result does not exclude the presence of a neoplastic disorder.?

Reference Values:
An interpretive report will be provided.

Clinical References:

FGFR2 63432 FGFR2 (10q26.1) Rearrangement, FISH, Tissue

Clinical Information: Cholangiocarcinoma is a malignancy arising from the biliary tract epithelium. These tumors are often clinically advanced at the time of presentation, and the prognosis is very poor with a short overall survival. Treatment is generally limited to surgical resection, which is associated with a high degree of morbidity, and palliative chemotherapy regimens. Therefore, additional treatment options are eagerly sought. Rearrangement of the FGFR2 gene region has been identified in a subset of cholangiocarcinomas. These rearrangements result in overexpression of FGFR2, which offers the possibility of using targeted FGFR2-inhibitor therapy for treatment. FGFR2 rearrangements have also been identified in a number of other cancers including bladder, thyroid, oral cavity, and brain.

Useful For: Providing prognostic information and guiding treatment for patients with cholangiocarcinomas and other tumor types including bladder, thyroid, oral cavity, and brain

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the FGFR2 fluorescence in situ hybridization (FISH) probe set. A positive result is consistent with the presence of an FGFR2 rearrangement and likely reflects FGFR2 fusion with a partner gene. The significance of this FISH result is dependent on additional clinical and pathologic features. A negative result does not exclude the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Mitesh BJ, Champion MD, Egan JB, et al. Integrated Genomic Characterization Reveals Novel, Therapeutically Relevant Drug Targets in FGFR and EGFR Pathways in Sporadic Intrahepatic Cholangiocarcinoma. PLOS Genetics. 2014;10(2):e1004135 2. Graham RP, Barr Fritcher EG, Pestova E, et al. Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. Hum Pathol. 2014;45(8):1630-1638 3. Arai Y, Totoki Y, Hosoda F, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. Hepatology. 2014;59(4):1427-1434 4. Wu YM, Su F, Kalyana-Sundaram S, et al. Identification of targetable FGFR gene fusions in diverse cancers. Cancer Discov. 2013;3(6):636-647 5. Zou Y, Zhu K, Pang Y, et al. Molecular detection of FGFR2 rearrangements in resected intrahepatic cholangiocarcinomas: FISH could be an ideal method in patients with histological small duct subtype. J Clin Transl Hepatol. 2023;11(6):1355-1367

TFH
619658

FH Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information: Disease-causing alterations of the fumarate hydratase (FH) gene have been implicated in renal cell carcinoma, uterine/cutaneous leiomyoma, and pheochromocytoma/paraganglioma. While these tumors can occur in the sporadic setting, germline alterations of the FH gene have been associated with renal cell carcinoma, and uterine/cutaneous leiomyoma in hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. The 5th edition of the World Health Organization Classification of Tumours recognizes fumarate hydratase-deficient renal cell carcinoma as a molecularly defined entity.(1) This single gene assay, performed using formalin-fixed paraffin-embedded tissue or cytology material, is therefore helpful in documenting an underlying disease-causing alteration of the FH gene and is diagnostically significant. It is important to note that this assay does not distinguish between germline and somatic alterations.

Useful For: Identifying specific mutations within the FH gene to assist in tumor diagnosis/classification, including renal cell carcinoma, uterine/cutaneous leiomyoma, and pheochromocytoma/paraganglioma

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board, eds. Urinary and male genital tumours. 5th ed. World Health Organization; 2022. WHO Classification of Tumours. Vol 8 2. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 3. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 4. Trpkov K, Hes O, Williamson SR, et al: New developments in existing WHO entities and evolving molecular concepts: The Genitourinary Pathology Society (GUPS) update on renal neoplasia. Mod Pathol. 2021;34(7):1392-1424 5. Forde C, Lim DHK, Alwan Y, et al: Hereditary leiomyomatosis and renal cell cancer: Clinical, molecular, and screening features in a cohort of 185 affected individuals. Eur Urol Oncol. 2020;3(6):764-772 6. Gupta S, Swanson AA, Chen YB, et al. Incidence of succinate dehydrogenase and fumarate hydratase-deficient renal cell carcinoma based on immunohistochemical screening with SDHA/SDHB and FH/2SC. Hum Pathol. 2019;91:114-122 7. Carlo MI, Hakimi AA, Stewart GD, et al: Familial kidney cancer: Implications of new syndromes and molecular insights. Eur Urol. 2019;76(6):754-764 8. Nguyen KA, Syed JS, Espenschied CR, et al: Advances in the diagnosis of hereditary kidney cancer: Initial results of a multigene panel test. Cancer. 2017;123(22):4363-4371

MSFGN
620248

Fibrillary Glomerulonephritis Confirmation, Mass Spectrometry, Paraffin Tissue

Clinical Information: Fibrillary glomerulonephritis (FGN) is a rare kidney disease with fibrillary deposits in the glomeruli that contain polyclonal IgG and complement, indicating immune complex deposition. Although usually Congo-red negative, recently cases with weak Congo-red positivity have been observed, making the distinction from amyloid more challenging. Liquid chromatography tandem mass spectrometry (LC-MS/MS) performed on microdissected glomeruli from patients with FGN demonstrates a unique proteomic profile including the protein DNAJB9 (Mayo Clinic unpublished observations). The presence of DNAJB9 was found to be highly sensitive and specific for FGN, distinguishing it from other glomerular diseases, including amyloid, immunotactoid glomerulopathy, and immune complex-mediated proliferative glomerulonephritis. The presence of DNAJB9, in the appropriate clinical and pathological context, can be useful to establish a diagnosis of FGN.

Useful For: Diagnosing fibrillary glomerulonephritis

Interpretation: An interpretation will be provided.

Clinical References: 1. Said SM, Sethi S, Valeri AM, et al. Renal amyloidosis: origin and clinicopathologic correlations of 474 recent cases. Clin J Am Soc Nephrol. 2013;8(9):1515-1523 2. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR 3rd, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009;114(24):4957-4959 3. Rosenstock JL, Markowitz GS, Valeri AM, Sacchi G, Appel GB, D'Agati VD. Fibrillary and immunotactoid glomerulonephritis: Distinct entities with different clinical and pathologic features. Kidney Int. 2003;63(4):1450-1461 4. Casanova S, Donini U, Zucchelli P, Mazzucco G, Monga G, Linke RP. Immunohistochemical distinction between amyloidosis and fibrillar glomerulopathy. Am J Clin Pathol. 1992;97(6):787-795 5. Rosenmann E, Eliakim M. Nephrotic syndrome associated with amyloid-like glomerular deposits. Nephron. 1977;18(5):301-308 6. Nasr SH, Vrana JA, Dasari S, et al. DNAJB9 is a specific immunohistochemical marker for fibrillary glomerulonephritis. Kidney Int Rep. 2017;3(1):56-64 7. Dasari S, Alexander MP, Vrana JA, et al. DnaJ Heat Shock Protein Family B Member 9 is a Novel Biomarker for Fibrillary GN. J Am Soc Nephrol. 2018;29(1):51-56

FIBAG
606887

Fibrinogen Antigen, Plasma

Clinical Information: Fibrinogen (clotting factor I) is an essential protein responsible for blood clot formation. In the final step of the coagulation cascade, thrombin converts soluble fibrinogen into insoluble fibrin strands that crosslink and form a clot. Fibrinogen is synthesized in the liver and has a biological half-life of 3 to 5 days in the circulating plasma. Fibrinogen deficiencies can be congenital or acquired and lead to prolonged coagulation times. Isolated fibrinogen deficiency is an extremely rare inherited coagulation disorder. Acquired fibrinogen deficiency is most commonly caused by, acute or decompensated intravascular coagulation and fibrinolysis. Other causes of fibrinogen deficiency include advanced liver disease, L-asparaginase therapy, or fibrinolytic agents (eg, streptokinase, urokinase, tissue plasminogen activator).

Useful For: Evaluation of fibrinogen deficiency Measuring fibrinogen in patients with elevated plasma levels of fibrin degradation products, patients receiving heparin, and in patients with antibodies to thrombin (following surgical use of topical bovine thrombin) Identifying afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia when ordered in combination with fibrinogen activity (FIBTP / Fibrinogen, Plasma)

Interpretation: This method measures the total amount of fibrinogen protein (ie, fibrinogen antigen) present in the plasma. Adequate fibrinogen antigen levels in a context of low fibrinogen activity suggests a dysfibrinogenemia. Fibrinogen antigen levels lower than 100 mg/dL are associated with an increased risk of bleeding.

Reference Values:
> or =18 years: 196-441 mg/dL
Reference values have not been established for patients that are less than 18 years of age.

Clinical References: 1. de Moerloose P, Casini A, Neerman-Arbez M. Congenital fibrinogen disorders: an update. Semin Thromb Hemost. 2013;39(6):585-595 2. Mackie I, Casini A, Pieters M, Purthi R, Reilly-Stitt C, Suzuki A. International council for standardisation in haematology recommendations on fibrinogen assays, thrombin clotting time and related tests in the investigation of bleeding disorders. Int J Lab Hematol. 2024;46(1): 20-32. doi:10.1111/ijlh.14201

CLFIB
602173

Fibrinogen, Clauss, Plasma

Clinical Information: Fibrinogen, also known as factor 1, is a plasma protein that can be transformed by thrombin into a fibrin gel ("the clot"). Fibrinogen is synthesized in the liver and circulates in the plasma as a disulfide-bonded dimer of 3 subunit chains. The biological half-life of plasma fibrinogen is 3 to 5 days. An isolated deficiency of fibrinogen may be inherited as an autosomal recessive trait (afibrinogenemia or hypofibrinogenemia) and is one of the rarest of the inherited coagulation factor deficiencies. Acquired causes of decreased fibrinogen levels include acute or decompensated intravascular coagulation and fibrinolysis (disseminated intravascular coagulation), advanced liver disease, L-asparaginase therapy, and therapy with fibrinolytic agents (eg, streptokinase, urokinase, tissue plasminogen activator). Fibrinogen function abnormalities, dysfibrinogenemias, may be inherited (congenital) or acquired. Patients with dysfibrinogenemia are generally asymptomatic. However, the congenital dysfibrinogenemias are more likely than the acquired to be associated with bleeding or thrombotic disorders. While the dysfibrinogenemias are generally not associated with clinically significant hemostasis problems, they characteristically produce a prolonged thrombin time clotting test. Congenital dysfibrinogenemias usually are inherited as autosomal codominant traits. Acquired dysfibrinogenemias mainly occur in association with liver disease (eg, chronic hepatitis, hepatoma) or kidney diseases associated with elevated fibrinogen levels. Fibrinogen is an acute-phase reactant, so a number of acquired conditions can result in an increase in its plasma level: -Acute or chronic

inflammatory illnesses -Nephrotic syndrome -Liver disease and cirrhosis -Pregnancy or estrogen therapy -Compensated intravascular coagulation The finding of an increased level of fibrinogen in a patient with obscure symptoms suggests an organic rather than a functional condition. Chronically increased fibrinogen has been recognized as a risk factor for development of arterial and venous thromboembolism.

Useful For: Detecting increased or decreased fibrinogen (factor 1) concentration of acquired or congenital origin Monitoring severity and treatment of disseminated intravascular coagulation and fibrinolysis

Interpretation: This test assesses levels of functional (clottable) fibrinogen (see Cautions). Fibrinogen may be decreased in acquired conditions such as liver disease and acute intravascular coagulation and fibrinolysis and disseminated intravascular coagulation. Fibrinogen may be decreased in rare conditions including congenital afibrinogenemia or hypofibrinogenemia. Fibrinogen may be elevated with acute or chronic inflammatory conditions.

Reference Values:
Only orderable as part of a profile or reflex. For more information, see:
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
APROL / Prolonged Clot Time Profile, Plasma
AATHR / Thrombophilia Profile, Plasma and Whole Blood
ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma
ALUPP / Lupus Anticoagulant Profile, Plasma

Males: 200-500 mg/dL
Females: 200-500 mg/dL
In normal full-term newborns and in healthy premature infants (30-36 weeks gestation) fibrinogen is near adult levels (>150) and reaches adult levels by less than 21 days postnatal.

Clinical References: Favaloro EJ, Lippi G. eds. Hemostasis and Thrombosis: Methods and Protocols. 1st ed. Humana Press; 2017

FIBTP
40937

Fibrinogen, Plasma

Clinical Information: Fibrinogen, also known as factor I, is a plasma protein that can be transformed by thrombin into a fibrin gel ("the clot"). Fibrinogen is synthesized in the liver and circulates in the plasma as a disulfide-bonded dimer of 3 subunit chains. The biological half-life of plasma fibrinogen is 3 to 5 days. An isolated deficiency of fibrinogen may be inherited as an autosomal recessive trait (afibrinogenemia or hypofibrinogenemia) and is one of the rarest of the inherited coagulation factor deficiencies. Acquired causes of decreased fibrinogen levels include acute or decompensated intravascular coagulation and fibrinolysis (disseminated intravascular coagulation: DIC), advanced liver disease, L-asparaginase therapy, and therapy with fibrinolytic agents (eg, streptokinase, urokinase, tissue plasminogen activator). Fibrinogen function abnormalities, dysfibrinogenemias, may be inherited (congenital) or acquired. Patients with dysfibrinogenemia are generally asymptomatic. However, the congenital dysfibrinogenemias are more likely to be associated with bleeding or thrombotic disorders than the acquired dysfibrinogenemias are. While the dysfibrinogenemias are generally not associated with clinically significant hemostasis problems, they characteristically produce a prolonged thrombin time clotting test. Acquired dysfibrinogenemias mainly occur in association with liver disease (eg, chronic hepatitis, hepatoma) or kidney diseases (eg, chronic glomerulonephritis, hypernephroma) and usually are associated with elevated fibrinogen levels. Fibrinogen is an acute phase reactant, so a number of acquired conditions can result in an increase in its

plasma concentration: -Acute or chronic inflammatory illnesses -Nephrotic syndrome -Liver disease and cirrhosis -Pregnancy or estrogen therapy -Compensated intravascular coagulation -Diabetes -Obesity The finding of an increased level of fibrinogen in a patient with obscure symptoms suggests an organic rather than a functional condition. Chronically increased fibrinogen has been recognized as a risk factor for development of arterial thromboembolism.

Useful For: Detecting increased or decreased fibrinogen (factor I) concentration of acquired or congenital origin Monitoring severity and treatment of disseminated intravascular coagulation and fibrinolysis

Interpretation: Fibrinogen may be decreased in acquired conditions such as liver disease and acute intravascular coagulation and fibrinolysis and disseminated intravascular coagulation. Fibrinogen may be decreased in rare conditions, including congenital afibrinogenemia or hypofibrinogenemia. Fibrinogen may be elevated with acute or chronic inflammatory conditions.

Reference Values:
200-393 mg/dL

Clinical References: 1. Mackie IJ, Kitchen S, Machin SJ, Lowe GD: Haemostais and Thrombosis Task Force of the British Committee for standards in Haematology. Guidelines for fibrinogen assays. Br J Haemotol. 2003 May;121(3):396-304 2. Boender J, Kruip MJ, Leebeek FW: A diagnostic approach to mild bleeding disorders. J Thromb Haemost. 2016 Aug;14(8):1507-1516

CULFB
35257

Fibroblast Culture for Biochemical or Molecular Testing, Chorionic Villi/Products of Conception/Tissue

Clinical Information: Cultured cells may be used to perform a wide range of laboratory tests. Prior to testing, the tissue may need to be cultured to obtain adequate numbers of cells.

Useful For: Producing cell cultures that can be used for enzymatic or molecular genetic analysis

Reference Values:
Not applicable

Clinical References: Arsham MS, Barch MJ, Lawce HJ, eds. The AGT Cytogenetics Laboratory Manual. 4th ed. John Wiley and Sons Inc; 2017

FGFRC
71483

Fibroblast Growth Factor Receptor 1, Immunostain, Technical Component Only

Clinical Information: Fibroblast growth factor receptor 1 (FGFR1) is a receptor tyrosine kinase that belongs to the fibroblast growth factor family. FGFR1 amplification is seen in 13% to 22% of lung squamous cell carcinoma and has been associated with a worse prognosis.

Useful For: Classification of a subset of lung squamous cell carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate

immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Nguyen PT, Tsunematsu T, Yanagisawa S, et al. The FGFR1 inhibitor PD173074 induces mesenchymal-epithelial transition through the transcription factor AP-1. Br J Cancer. 2013;109(8):2248-2258 2. Kohler LH, Mireskandari M, Knosel T, et al. FGFR1 expression and gene copy numbers in human lung cancer. Virchows Arch. 2012;461(1):49-57 3. Kim HR, Kim DJ, Kang DR, et al: Fibroblast growth factor receptor 1 gene amplification is associated with poor survival and cigarette smoking dosage in patients with resected squamous cell lung cancer. J Clin Oncol. 2013;31(6):731-737 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

23FBG 620249 Fibroblast Growth Factor-23 (FGF23), In Situ Hybridization

Clinical Information: Fibroblast growth factor-23 (FGF23) is a phosphaturic hormone that acts on the proximal renal tubules to block phosphate reuptake. Production of FGF23 by a particular mesenchymal tumor, phosphaturic mesenchymal tumor, is responsible for the great majority of cases of tumor-induced osteomalacia.

Useful For: Assessing fibroblast growth factor-23 (FGF23) expression

Interpretation: This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

Clinical References: 1. Carter JM, Caron BL, Dogan A, Folpe AL. A novel chromogenic in situ hybridization assay for FGF23 mRNA in phosphaturic mesenchymal tumors. AM J Surg Pathol. 2015;39:(1)75-83 2. Bhattacharyya N, Chong WH, Gafni RI, Collins MT. Fibroblast growth factor 23: State of the field and future directions. Trends Endocrinol Metab. 2012;23(12):610-618 3. Graham RP, Hodge JC, Folpe AL, et al. A cytogenetic analysis of 2 cases of phosphaturic mesenchymal tumor of mixed connective tissue type. Hum Pathol. 2012;43(8):1334-1338 4. Graham R, Krishnamurthy S, Oliveira A, Inwards C, Folpe AL. Frequent expression of fibroblast growth factor-23 (FGF23) mRNA in aneurysmal bone cysts and chondromyxoid fibromas. J Clin Pathol. 2012;65(10):907-909 5. Bahrami A, Weiss SW, Montgomery E, et al. RT-PCR analysis for FGF23 using paraffin sections in the diagnosis of phosphaturic mesenchymal tumors with and without known tumor induced osteomalacia. Am J Surg Pathol. 2009;33(9):1348-1354 6. Folpe AL, Fanburg-Smith JC, Billings SD, et al. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity-an analysis of 32 cases and a comprehensive review of the literature. Am J Surg Pathol. 2004;28(1):1-30

PRKAF 64777 Fibrolamellar Carcinoma, 19p13.1 (PRKACA) Rearrangement, FISH, Tissue

Clinical Information: DNAJB1-PRKACA fusion has been associated with a distinct subtype of hepatocellular carcinoma called fibrolamellar carcinoma. A break-apart strategy FISH probe has been developed to detect the rearrangement event that occurs in the DNAJB1-PRKACA fusion, specifically the loss of the 5' region labeled in red and retention of the 3' region labeled in green.

Useful For: Aid in the diagnosis of identifying PRKACA gene rearrangements of patients with fibrolamellar carcinoma

Interpretation: A positive result with the PRKACA probe is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result of PRKACA suggests fusion of the PRKACA and DNAJB1 genes at 19p13.1. A negative result suggests no fusion of the PRKACA and DNAJB1 genes has occurred.

Reference Values:
An interpretive report will be provided.

Clinical References: R Graham, L Jin, D Knutson, S Kloft-Nelson, et al: DNAJB1-PRKACA is specific for fibrolamellar carcinoma. Mod Path 2015;28:822-829

MSFNG
615305

Fibronectin Glomerulopathy Confirmation, Mass Spectrometry

Clinical Information: Fibronectin glomerulopathy, also called glomerulopathy with fibronectin deposits 2 (GFND2), is a rare kidney disease characterized by large amounts of fibronectin deposits in the mesangium and subendothelial space of renal glomeruli. Liquid chromatography tandem mass spectrometry performed on microdissected glomeruli from patients with GFND2 demonstrates a unique proteomic profile. The presence of abnormal fibronectin deposits, in the appropriate clinical and pathological context, can be useful to establish a diagnosis of GFND2.

Useful For: Aiding in the diagnosis of fibronectin glomerulopathy

Interpretation: An interpretation will be provided.

Clinical References: 1. Lusco MA, Chen Y, Cheng H, et al. AJKD atlas of renal pathology: Fibronectin glomerulopathy. Am J Kidney Dis. 2017;70(5):e21-e22. doi:10.1053/j.ajkd.2017.09.001 2. Ishimoto I, Sohara E, Ito E, Okado T, Rai T, Uchida S. Fibronectin glomerulopathy. Clin Kidney J. 2013;6(5):513-515. doi:10.1093/ckj/sft097 3. Satoskar AA, Shapiro JP, Bott CN, et al. Characterization of glomerular diseases using proteomic analysis of laser capture microdissected glomeruli. Mod Path. 2012;25(5):709-721. doi:10.1038/modpathol.2011.205 4. Castelletti F, Donadelli R, Banterla F, et al. Mutations in FN1 cause glomerulopathy with fibronectin deposits. Proc Natl Acad Sci U S A. 2008;105(7):2538-2543. doi:10.1073/pnas.0707730105

FIBRO
38292

FibroTest-ActiTest, Serum

Clinical Information: Fibrosis and inflammatory activity are the 2 main causes of liver disease. FibroTest-ActiTest estimates the levels of fibrosis and cirrhosis in the liver as well as the level of necroinflammatory activity. The estimation is made by measuring 6 standard serum biomarkers (gamma-glutamyl transferase, total bilirubin, alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, and alanine aminotransferase). The activity score is a measure of liver inflammation caused by disease. Results from these tests are combined with the patient's age and sex to estimate hepatic fibrosis and inflammatory activity scores. Hepatic fibrosis is typically compared to a form of scar tissue that progresses throughout the liver. The most serious stage of fibrosis is known as cirrhosis.

Useful For: Evaluating hepatic fibrosis in chronic hepatitis C patients Diagnosing fibrosis in carriers of chronic hepatitis B virus Evaluating hepatic fibrosis in co-infected HIV carriers Providing access to new-generation non-interferon treatment for hepatitis Evaluating fibrosis in patients suffering from metabolic conditions (nonalcoholic fatty liver disease) and patients who consume excess alcohol

Interpretation: FibroTest-ActiTest provides a score that assesses hepatic fibrosis (F0-F4) and a score

that assesses hepatic inflammatory activity (A0-A3). Interpretation of the score is provided in the report. Individual results from the 6 component tests are also provided with institution-specific reference intervals. Fibrosis is reported relative to a scale ranging from F0-F4 (F0=no fibrosis, F1=minimal fibrosis, F2=moderate fibrosis, F3=advanced fibrosis, F4=severe fibrosis). Fibrosis scores may overlap (eg, F0/F1, F1/F2). Activity is reported relative to a scale ranging from A0-A3 (A0=no activity, A1=minimal activity, A2=significant activity, A3=severe activity). Activity scores may overlap (eg, A0/A1, A1/A2).

Reference Values:

FibroTest-ActiTest, Interpretation FibroTest Score	Stage	Interpretation
0.00-0.21*	F0	No fibrosis
0.21-0.27*	F0-F1	No fibrosis
0.27-0.31*	F1	Minimal fibrosis
0.31-0.48*	F1-F2	Minimal fibrosis
0.48-0.58*	F2	Moderate fibrosis
0.58-0.72*	F3	Advanced fibrosis
0.72-0.74*	F3-F4	Advanced fibrosis
0.74-1.00	F4	Severe fibrosis (Cirrhosis)
*Boundary values can apply to 2 stages based on rounding. For example, a FibroTest score of 0.305 will round up to 0.31 and be staged F1. A FibroTest score of 0.314 will round down to 0.31 and be staged F1-F2. ActiTest Score	Grade	Interpretation
0.00-0.17*	A0	No activity
0.17-0.29*	A0-A1	No activity
0.29-0.36*	A1	Minimal activity
0.36-0.52*	A1-A2	Minimal activity
0.52-0.60*	A2	Significant activity
0.60-0.62*	A2-A3	Significant activity
0.62-0.100	A3	Severe activity

Clinical References:

3FBLN 609271 Fibulin 3 Immunostain, Technical Component Only

Clinical Information: Immunohistochemical staining for fibulin 3 (FBLN3), also known as epidermal growth factor-containing fibulin-like extracellular matrix protein 1 (EFEMP1), is useful in confirming amyloid type. Antibodies to FBLN3 stain the amyloid deposits in patients with FBLN3 amyloidosis. FBLN3 amyloidosis typically involves the venous walls in the gastrointestinal tract.

Useful For: Identification and classification of amyloid types in tissue

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Dao LN, Kurtin PJ, Smyrck TC, et al. The novel form of amyloidosis derived from EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1) preferentially affects the lower gastrointestinal tract of elderly females. Histopath. 2020 Oct 5. doi: 10.1111/his.14276 Epub ahead of print 2. Tasaki M, Ueda M, Hoshii Y, et al. A novel age-related venous amyloidosis derived from EGF-containing fibulin-like extracellular matrix protein 1. J Pathol. 2019;247(4):444-455 3. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FIGE
57916

Fig (Ficus carica) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal/Borderline 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 49.99 Very High Positive 5 50.00 – 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

FACT
61620

Filamentous-Actin (F-actin) Antibody, IgG, Serum

Clinical Information: Autoimmune hepatitis (AIH) is a chronic disease resulting from immune-mediated liver injury with varied clinical manifestations.(1,2) The precise factors leading to disease initiation and perpetuation are unknown, but likely reflect a combination of genetic predisposition relating to defects in immunological control of autoreactivity, as well as environmental triggers, which precipitate a persistent breakdown in self-tolerance.(2) Initially, patients with AIH may be clinically asymptomatic and are usually identified only through an incidental finding of abnormal liver function tests.(1-4) At a more advanced stage, patients may manifest with symptoms such as jaundice, pruritus, or ascites, which are secondary to the more extensive liver damage. As implied by the name, AIH has many characteristics of an autoimmune disease, including female predominance, hypergammaglobulinemia, association with specific HLA alleles, responsiveness to immunosuppression, and the presence of autoantibodies.(1-3) The clinical features of AIH are nonspecific and can be seen in variety of liver diseases (drug/alcohol-associated hepatitis, viral hepatitis, primary sclerosing cholangitis, etc), the diagnosis can be challenging. A set of diagnostic criteria for AIH has been published and includes the presence of various autoantibodies, elevated total IgG, evidence of hepatitis on liver histology, and absence of viral markers.(1,3,4) Based on the specific autoantibodies present, AIH can be placed into one of three categories.(4) The most prevalent is AIH type 1, linked to the presence of smooth muscle autoantibodies (SMA), antinuclear antibodies (ANA) and perinuclear anti-neutrophil cytoplasmic antibodies. SMA are generally identified by indirect immunofluorescence using a smooth muscle substrate. The antigen

specificity of SMA in the context of AIH has been identified as filamentous-actin (F-actin).(3) The combination of autoantibody serology, specifically SMA and anti-F-actin antibodies with liver histology and thorough clinical evaluation are useful in the evaluation of patients with suspected autoimmune hepatitis. SMAs are detected in up to 85% of patients with AIH, either alone or in conjunction with ANA.(1,4,5) The SMA titer can also contribute to International Autoimmune Hepatitis Group diagnostic score in patients with a probable or definite diagnosis of AIH.(1,4,5) These antibodies have also been reported in 33% to 65% of cases of primary biliary cholangitis/AIH overlap syndrome,(6) the concomitant presence of SMA and antimitochondrial antibodies being highly suggestive in this setting. For more information see First-Line Screening for Autoimmune Liver Disease Algorithm.

Useful For: Evaluation of patients with hepatitis of unknown origin associated with hypergammaglobulinemia and/or abnormal liver enzymes This test may also be useful for confirming positivity for smooth muscle antibodies.

Interpretation: Positivity for anti-filamentous-actin (F-actin) antibodies may help support a diagnosis of autoimmune hepatitis (AIH) following exclusion of other causes of hepatitis. A negative result for anti-F-actin antibodies does not exclude a diagnosis of AIH. In a study conducted at Mayo Clinic, the F-actin enzyme-linked immunosorbent assay (ELISA) had a clinical sensitivity of 92.9% when using the manufacturer's recommended cutoff of 20.0 U. In addition, the F-actin ELISA had a clinical specificity of 76.7% when using the aforementioned cutoffs. See Supportive Data.

Reference Values:
Negative: <20.0 U
Weak Positive: 20.0-30.0 U
Positive: >30.0 U

Clinical References: 1. European Association for the Study of the Liver. EASL clinical practice guidelines: autoimmune hepatitis. J Hepatol. 2015;63(4):971-1004 2. Mieli-Vergani G, Vergani D, Czaja AJ, et al. Autoimmune hepatitis. Nat Rev Dis Primers. 2018;4:18017 3. Sebode M, Weiler-Normann C, Liwinski T, Schramm C. Autoantibodies in autoimmune liver disease-clinical and diagnostic relevance. Front Immunol. 2018;9:609 4. Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D. Autoimmune hepatitis: serum autoantibodies in clinical practice. Clin Rev Allergy Immunol. 2022;63(2):124-137 5. Bogdanos DP, Invernizzi P, Mackay IR, Vergani D. Autoimmune liver serology: current diagnostic and clinical challenges. World J Gastroenterol. 2008;14(21):3374-3387 6. Muratori P, Granito A, Pappas G, et al. The serological profile of the autoimmune hepatitis/primary biliary cirrhosis overlap syndrome. Am J Gastroenterol. 2009;104(6):1420-1425.

FFAG4 — Filaria Antibody (IgG4)
57875

Reference Values:

FIL — Filaria, Blood
9232

Clinical Information: The filariae are parasitic nematodes (roundworms) that cause significant human morbidity in tropical regions worldwide. The macroscopic adults live in the human host and release microscopic offspring (microfilariae) into the blood or skin. The microfilariae of Wuchereria bancrofti, Brugia malayi, Brugia timori, Loa loa, Mansonella perstans, and Mansonella ozzardi are found in the blood, while the microfilariae of Onchocerca volvulus and Mansonella streptocerca are found in the skin. If microfilariae are taken up by a biting insect vector (mosquitos, blackflies, midges, and deer flies), they undergo further development in the insect and can then be transmitted to other

humans. W bancrofti and the Brugia species cause a serious condition called lymphatic filariasis. The adults live in the lymphatics and cause inflammation and scarring of the lymph vessels. Over time, the lymphatic channels are obstructed, and fluid cannot drain back to the heart resulting in massive lymphedema (elephantiasis) of the affected limb or groin. W bancrofti is found in the tropics worldwide, while Brugia species are found in parts of Asia and Southeast Asia. Loa loa causes migratory subcutaneous angioedema referred to as "calabar swellings" as the adult worm migrates throughout the body. The adult occasionally migrates across the surface of the eye, giving it the moniker "the African eye worm." Loa loa is only found in Africa. Finally, M perstans and M ozzardi cause a relatively mild form of filariasis. Patients are often asymptomatic. When present, symptoms include fever, angioedema, headache, myalgias, arthralgias, pruritus, and neurologic manifestations. M perstans is found in parts of Africa and South America, while M ozzardi is only found in Mexico and Central and South America. The microfilariae of these filarial worms can be seen on conventional thick and thin blood films, which allows for their definitive identification. However, microfilariae may be in low numbers, and therefore, use of concentration methods, such as the Knott's technique, improves the detection sensitivity. Some microfilariae are released into the blood at certain times of the day; W bancrofti and Brugia species are usually released between 10 p.m. and 2 a.m. (nocturnal periodicity), while L loa is released mostly from 10 a.m. and 2 p.m. (diurnal periodicity). It is therefore important to collect blood during these time periods for optimal detection sensitivity. Mansonella species microfilariae do not exhibit any periodicity and, therefore, a random blood collection is acceptable. Since the levels of parasitemia may fluctuate, multiple smears may be needed to detect the filarial worms. Blood should be obtained and examined every 8 to 12 hours for 2 to 3 days before excluding infection.

Useful For: Detecting microfilariae in peripheral blood

Interpretation: Positive results are provided with the genus and species of the microfilariae, if identifiable.

Reference Values:
Negative
If positive, organism is identified.

Clinical References:

FINCH
82146

Finch Feathers, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to finch feathers Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical

sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FANT
82698

Fire Ant, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to fire ant Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FBSH
82735

Firebush (Kochia), IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to firebush (Kochia) Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the

concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FFSPG
57927

Fish and Shellfish Panel IgG

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

FLEC
9243

Flecainide, Serum

Clinical Information: Flecainide (Tambocor) is a Class I cardiac antiarrhythmic agent indicated for treatment of paroxysmal supraventricular dysrhythmia, paroxysmal atrial fibrillation/flutter, and life-threatening ventricular dysrhythmias. After oral administration, flecainide is almost completely absorbed and peak concentrations are attained in approximately 3 hours. The half-life averages approximately 20 hours but is widely variable (12 to 27 hours), and steady-state concentrations are typically achieved in approximately 5 days. Flecainide is eliminated from blood by hepatic metabolism, as well as renal clearance; significant changes in either organ system will cause impaired clearance. Common adverse effects include dizziness, visual disturbances, and dyspnea. Mild-to-moderate toxicity is associated with dizziness, visual disturbances, headache, nausea, fatigue, palpitations, and chest pain. Visual hallucinations and dysarthria may occur at toxic serum concentrations. Death can occur from hypotension, respiratory failure, and asystole.

Useful For: Optimizing flecainide dosage Assessing flecainide toxicity Monitoring compliance

Interpretation: Flecainide is most effective in premature ventricular contractions suppression at serum concentrations in the range of 0.2 to 1.0 mcg/mL. Serum concentrations above 1.0 mcg/mL are associated with a high rate of cardiac adverse experiences such as conduction defects or bradycardia.

Reference Values:
Trough Value
0.2-1.0 mcg/mL: Therapeutic concentration
>1.0 mcg/mL: Toxic concentration

Clinical References: 1. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453 2. Josephson ME, Buxton AE, Marchlinski FE. The tachyarrhythmias: tachycardias. In: Wilson JD, Braunwald E, Isselbacher KJ, et al, eds. Harrison's Principles of Internal Medicine. 12th ed. McGraw-Hill Book Company; 1991:915 3. Valdes R Jr, Jortani SA, Gheorghiade M. Standards of laboratory practice: cardiac drug monitoring. National Academy of Clinical Biochemistry. Clin Chem. 1998;44(5):1096-1099

FLI1
70432

FLI-1 Immunostain, Technical Component Only

Clinical Information: Friend leukemia integration 1 (FLI1) transcription factor is a member of the erythroblast transformation specific (ETS) family of transcription factors. It has anti-apoptotic activity and interferes with nuclear hormone receptors. A chromosomal translocation between the FLI1 gene and EWS gene is found in most Ewing sarcomas. In normal tissues, nuclear staining is seen in endothelial cells, a subset of T cells, megakaryocytes, and normal breast epithelium. FLI1 expression occurs in endothelial-derived tumors, Ewing sarcoma, Merkel cell carcinoma, lung adenocarcinoma, melanoma, and erythroleukemia.

Useful For: Aiding in phenotyping endothelial-derived tumors, Ewing sarcoma, Merkel cell carcinoma, lung adenocarcinoma, melanoma, and erythroleukemia

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Lee AF, Hayes MM, Lebrun D, et al. FLI-1 distinguishes Ewing sarcoma from small cell osteosarcoma and mesenchymal chondrosarcoma. Appl Immunohistochem Mol Morphol. 2011;19(3):233-238 2. Stockman DL, Hornick JL, Deavers MT, Lev DC, Lazar AJ, Wang WL. ERG and FLI1 protein expression in epithelioid sarcoma. Mod Pathol. 2014;27(4):496-501 3. Nunes Rosado FG, Itani DM, Coffin CM, Cates JM. Utility of immunohistochemical staining with FLI1, D2-40, CD31, and CD34 in the diagnosis of acquired immunodeficiency syndrome-related and non-acquired immunodeficiency syndrome-related Kaposi sarcoma. Arch Pathol Lab Med. 2012;136(3):301-304 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FLNDR
57895

Flounder (Bothidae/Pleuronectidae Fam) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal/Borderline 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 49.99 Very High Positive 5 50.00 – 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

FLT
19739

FLT3 Mutation Analysis, Varies

Clinical Information: The FMS-like tyrosine gene (FLT3) codes for a transmembrane receptor/signaling protein (FLT3) of the tyrosine kinase group. Binding of FLT3 ligand to the FLT3 receptor ultimately leads to production of proteins that cause cell growth and inhibit cell death through apoptosis. Recently, variants in FLT3 have been found in some hematopoietic neoplasms and are particularly common in adult acute myeloid leukemia (AML) with an overall incidence of approximately 20% to 30%. The highest genetic variant rates are seen in adult patients with AML and normal- or intermediate-risk cytogenetics and in patients with acute promyelocytic leukemia. The most common FLT3 variant consists of internal tandem duplication (ITD) of DNA sequences found in exons 14 or 15. In some subgroups of adults with AML, the presence of an FLT3 ITD variant has been found to be an adverse prognostic indicator. The second most common variant is a point alteration in the codon for an aspartate residue (D835) that resides in the activation loop of the FLT3 protein. D835 alterations have been identified in approximately 7% of AML cases but, at this time, it is not clear if the presence of this alteration has any prognostic significance. It is thought that both types of FLT3 variants lead to constitutive (always present, independent of internal or external stimuli) FLT3 activation. Identification of an FLT3 variant in AML is clinically useful, not only because of the prognostic information it provides, but also because FLT3-inhibitory drugs have shown promise as useful therapeutic agents.

Useful For: Prognostic indication for some patients with acute myeloid leukemia This test should not be used to monitor residual disease following treatment.

Interpretation: An interpretive report will be issued indicating whether the FLT3 internal tandem duplication (ITD), D835 alteration, or both were detected. Variant status will be indicated as positive or negative. If ITD positive, an allelic ratio will be reported.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Levis M, Small D. FLT3: ITDoes matter in leukemia. Leukemia. 2003;17:1738-1752 2. Gilliland DG, Griffin JD. The roles of FLT3 in hematopoiesis and leukemia. Blood. 2002;100(5):1532-1542 3. He R, Devine DJ, Tu ZJ, et al. Hybridization capture-based next generation sequencing reliably detects FLT3 mutations and classifies FLT3-internal tandem duplication allelic ratio in acute myeloid leukemia: a comparative study to standard fragment analysis. Mod Pathol. 2019;33:334-34

FFLRO
91795

Flunitrazepam Confirmation, Serum

Reference Values:
Units: Flunitrazepam ng/mL
7-Aminoflunitrazepam ng/mL

Peak plasma Flunitrazepam concentrations in patients receiving chronic, recommended dosages: 10-20 ng/mL.

Note: Flunitrazepam is not legally marketed in the United States.

FL
8641

Fluoride, Plasma

Clinical Information: Fluoride induces bone formation by stimulating osteoblasts. Because fluorides increase bone density, they are used in dental preparations and as an antiosteoporotic agent. However, prolonged high exposure to fluoride produces changes in bone morphology consistent with osteomalacia, including prolonged mineralization lag time and increased osteoid thickness. The adverse skeletal effects of fluoride are associated with plasma fluoride greater than 4 mcmol/L. Chronic fluorosis may produce osteosclerosis, periostitis, calcification of ligaments and tendons, and crippling deformities. Prolonged exposure to the fluoride-containing antifungal agent voriconazole can produce high plasma fluoride concentrations and bone changes (periostitis). Several other medicines also contain fluoride are used for treating skin diseases (eg, flucytosine, an antifungal) and some cancers (eg, fluorouracil, an antimetabolite).

Useful For: Assessing accidental fluoride ingestion Monitoring patients receiving sodium fluoride for bone disease or patients receiving voriconazole therapy

Interpretation: Humans exposed to fluoride-treated water typically have plasma fluoride in the range of 1 to 4 mcmol/L. Those who are not drinking fluoride-treated water have plasma fluoride less than 1 mcmol/L. Plasma fluoride values greater than 4 mcmol/L indicate excessive exposure and are associated with periostitis.

Reference Values:
<4.1 mcmol/L

Clinical References: 1. Cardos VES, Whitford GH, Aoyama H, et al. Daily variations in human plasma fluoride concentrations. J Fluorine Chem. 2008:129;1193-1198 2. Wermers RA, Cooper K, Razonable RR, et al. Fluoride excess and periostitis in transplant patients receiving long-term voriconazole therapy. Clin Infect Dis. 2011 1;52(5):604-611 3. Agency for Toxic Substances and Disease Registry: Toxicological profile for fluorides, hydrogen fluoride, and fluorine. US Department of Health and Human Services 2003. Accessed February 09, 2024. Available at www.atsdr.cdc.gov/ToxProfiles/tp11.pdf 4. Sodi R: Vitamins and trace elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 39

FLUOX
80228

Fluoxetine, Serum

Clinical Information: Fluoxetine is a selective serotonin reuptake inhibitor approved for treatment of bulimia, obsessive-compulsive behavior, panic disorders, premenstrual dysphoria, and major depressive disorder, with a variety of off-label uses. Both fluoxetine and its major metabolite, norfluoxetine, are pharmacologically active and are reported together in this assay. Most individuals respond optimally when combined serum concentrations for both parent and metabolite are in the therapeutic range (120-500 ng/mL) at steady state. Due to the long half-life of the parent and metabolite (1-6 days), it may take several weeks for patients to reach steady-state concentrations. Fluoxetine is a potent inhibitor of the metabolic enzyme cytochrome P450 (CYP) 2D6, with lesser inhibitory effects on CYP2C19 and CYP3A. Therapy with fluoxetine is, therefore, subject to numerous drug interactions, which are compounded by wide interindividual variability in fluoxetine pharmacokinetics. Measurement of the drug is useful for managing comedications, dose or formulation changes, and in assessing compliance. Side effects are milder for fluoxetine than for older antidepressants, such as tricyclic antidepressants. The most common side effects of fluoxetine therapy include nausea, nervousness, anxiety, insomnia, and drowsiness. Anticholinergic and cardiovascular side effects are markedly reduced compared to tricyclic antidepressants. Fatalities from fluoxetine overdose are extremely rare.

Useful For: Monitoring serum concentration of fluoxetine during therapy Evaluating potential toxicity Evaluating patient compliance

Interpretation: Most individuals display optimal response to fluoxetine when combined serum levels of fluoxetine and norfluoxetine are between 120 and 500 ng/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; therefore, interpretation should include clinical evaluation. A toxic range has not been well established.

Reference Values:
Fluoxetine + Norfluoxetine: 120-500 ng/mL

Clinical References: 1. Hiemke C, Bergemann N, Clement HW, et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62 2. Westanmo AD, Gayken J, Haight R: Duloxetine. A balanced and selective norepinephrine- and serotonin-reuptake inhibitor. Am J Health-Syst Pharm. 2005;62(23):2481-2490 3. Waldschmitt C, Vogel F, Pfuhlmann B, Hiemke C. Duloxetine serum concentrations and clinical effects. Data from a therapeutic drug monitoring (TDM) survey. Pharmacopsychiatry. 2009;42(5):189-193 4. Feighner JP, Cohn JB. Double-blind comparative trials of fluoxetine and doxepin in geriatric patients with major depressive disorder. J Clin Psychiatry. 1985;46(3 Pt 2):20-25 5. Kelly MW, Perry PJ, Holstad SG, Garvey MJ. Serum fluoxetine and norfluoxetine concentrations and antidepressant response. Ther Drug Monit. 1989;11:165-170 6. Benfield P, Heel RC, Lewis SP. Fluoxetine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. Drugs. 1986;32(6):481-508 7. Wille SM, Cooreman SG, Neels, et al. Relevant issues in the monitoring and toxicology of antidepressants. Crit Rev Clin Lab Sci. 2008;45(1):25-89

PROLX 80458 Fluphenazine (Prolixin), Serum

Reference Values:
Reference Range: 1.0 - 10 ng/mL

FFLUR 90091 Flurazepam (Dalmane) and Desalkylflurazepam

Reference Values:
Flurazepam:
Reference Range: 0 - 30 ng/mL

Desalkylflurazepam:
Reference Range: 30 - 150 ng/mL

Flurazepam + Desalkyflurazepam:
Reference Range: 30 - 180 ng/mL

FFVOX 57731 Fluvoxamine (Luvox)

Reference Values:
Units: ng/mL

Expected fluvoxamine concentrations on recommended daily dosage regimens:
50-900 ng/mL

IAPC
113345

FNA Immediate Adequacy (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IAAPC
113346

FNA Immediate Adequacy Add'l (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

RFSGS
618114

Focal Segmental Glomerulosclerosis (FSGS) and Nephrotic Syndrome Gene Panel, Varies

Clinical Information: Nephrotic syndrome (NS) is a kidney disorder characterized by proteinuria, hypoalbuminemia, and edema. Many conditions can cause NS, including diseases that only affect the kidney and other more systemic disorders such as diabetes or lupus. Focal segmental glomerulosclerosis (FSGS), a histologic finding characterized by sclerosis involving part of the kidney glomeruli, is commonly found in patients with NS.(1) Approximately 85% of nephrotic syndrome is steroid sensitive, while the remaining 15% is steroid resistant (SRNS). SRNS may be genetic or nongenetic. Nongenetic causes of NS/FSGS may be due to a circulating factor causing generalized injury to podocytes, structural renal abnormalities, viral or drug-induced causes, or other stress on the kidney such as obesity, congenital heart disease, malignancy, or hypertension.(2) Genetic SRNS may result from disease-causing variants in genes encoding renal-specific proteins (renal-limited) or syndromic conditions with extrarenal features.(2) Autosomal recessive forms of nonsyndromic SRNS typically present in childhood and are caused by disease-causing variants in nephrin (NPHS1), podocin (NPHS2), CD2AP, PLCE1, MYO1E, and multiple other genes. Autosomal dominant SRNS is typically adult onset and may be caused by disease-causing variants in TRPC6, ACTN4, INF2, and other genes. Variants in type IV collagen genes, known to cause Alport syndrome, may also be identified in patients with familial or sporadic SNRS and present later in adolescence or adulthood. In syndromic forms of SRNS, extrarenal manifestations may be prominent and diagnostic, but in some cases, extrarenal features may be subtle or develop later in the disease course, such as in Denys-Drash syndrome (DDS) and Frasier syndrome caused by disease-causing variants in WT1. Other genes included on this panel cover a broad spectrum of conditions that may display proteinuria, NS, or FSGS, either as an isolated feature or as part of a more systemic presentation, including genes associated with congenital disorders of glycosylation, Alport syndrome, coenzyme Q10 deficiency, and others. This test also includes assessment of the G1 and G2 alleles of the APOL1 gene. The G1 and G2 alleles have been associated with increased risk for development or progression of nondiabetic chronic kidney diseases, including nonsyndromic SRNS.(3) Despite some clinical and histologic overlap among the various categories of NS, management and prognosis may differ based on the underlying etiology. In particular, steroid sensitive NS may respond to treatment with corticosteroids, while SRNS, including those due to genetic causes, typically does not.(2) Therefore, identification of a genetic form of SRNS may impact evaluation for extra-renal manifestations, treatment decisions including transplantation, and genetic counselling.(4)

Useful For: Providing a genetic evaluation for patients with a personal or family history of steroid resistant nephrotic syndrome (SRNS) Establishing a diagnosis of hereditary SRNS Guiding treatment decisions in individuals with nephrotic syndrome

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or

possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Chen YM, Liapis H: Focal segmental glomerulosclerosis: molecular genetics and targeted therapies. BMC Nephrol. 2015 Jul 9;16:101 2. De Vriese AS, Sethi S, Nath KA, et al: Differentiating primary, genetic, and secondary FSGS in adults: A clinicopathologic approach. J Am Soc Nephrol. 2018 Mar;29(3):759-774 3. Parsa A, Kao WH, Xie D, et al: APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med. 2013;369(23):2183-2196. doi: 10.1056/NEJMoa13103454 4. Rood IM, Deegens JKJ, Wetzels JFM: Genetic causes of focal segmental glomerulosclerosis: implications for clinical practice. Nephrol Dial Transplant. 2012 Mar;27(3):882-890 5. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

ADPKP
618002

Focused Autosomal Dominant Polycystic Kidney Disease Gene Panel, Varies

Clinical Information: Autosomal dominant polycystic kidney disease (ADPKD) typically manifests in adulthood and is primarily characterized by bilateral kidney cysts, liver cysts, and an increased risk for intracranial aneurysm.(1) Less commonly, symptoms of ADPKD can manifest in childhood or adolescence.(2) Two genes, PKD1 and PKD2, account for the majority of cases of ADPKD, with approximately 78% of cases being attributed to disease-causing variants in the PKD1 gene and approximately 15% of cases being attributed to disease-causing variants in the PKD2 gene.(1) Disease-causing variants in 2 other genes, DNAJB11 and GANAB, are estimated to account for less than 1% of ADPKD cases. The lifetime penetrance of bilateral cysts is close to 100% in individuals with ADPKD, but disease manifestation is typically age-dependent and gene-dependent.(3) ADPKD can have significant clinical overlap with other autosomal dominant conditions in which bilateral kidney cysts are a common feature, including autosomal dominant tubulointerstitial kidney diseases due to disease-causing variants in the HNF1B or UMOD genes.(1) Rarer causes of autosomal dominant conditions with overlapping ADPKD features are emerging. The ALG8 gene is most commonly associated with polycystic liver disease, however case reports have identified isolated, bilateral kidney cysts in a small number of individuals.(4) The ALG9 gene is primarily associated with autosomal recessive congenital disorder of glycosylation, type I, but recent studies have identified isolated, bilateral kidney cysts in heterozygous carriers.(5)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of autosomal dominant polycystic kidney disease Establishing a diagnosis of autosomal dominant polycystic kidney disease

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Harris PC, Torres VE: Polycystic kidney disease, autosomal dominant. In:

Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated July 19, 2018. Accessed June 7, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1246/ 2. Gimpel C, Bergmann C, Bockenhauer D, et al: International consensus statement on the diagnosis and management of autosomal dominant polycystic kidney disease in children and young people. Nat Rev Nephrol. 2019 Nov;15(11):713-726 3. Lanktree MB, Haghighi A, Guiard E, et al. Prevalence estimates of polycystic kidney and liver disease by population sequencing. J Am Soc Nephrol. 2018;29(10):2593-2600 4. Besse W, Dong K, Choi J, et al: Isolated polycystic liver disease genes define effectors of polycystin-1 function. J Clin Invest. 2017 May 1;127(5):1772-1785. doi: 10.1172/JCI90129. Erratum in: J Clin Invest. 2017 Sep 1;127(9):3558 5. Besse W, Chang AR, Luo JZ, et al: ALG9 mutation carriers develop kidney and liver cysts. J Am Soc Nephrol. 2019 Nov;30(11):2091-2102. doi: 10.1681/ASN.2019030298 6. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

PGXQP
610057

Focused Pharmacogenomics Panel, Varies

Clinical Information: This panel provides a comprehensive analysis for multiple genes with strong drug phenotype associations. Each sample is tested for specific variations with known functional impact. Pharmacogenomic data for the following specific variants are reviewed and reported (if present): -CYP1A2 *1F, *1K, *6, and *7 -CYP2C9 *2, *3, *4, *5, *6, *8, *9, *11, *12, *13, *14, *15, *16, *17, *18, *25, *26, *28, *30, *33, and *35 -CYP2C19 *2, *3, *4, *5, *6, *7, *8, *9, *10, *17, and *35 -CYP2D6 *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A (now known as *114), *14B (now known as *14), *15, *17, *29, *35, *36, *41, *59, *68, and CYP2D6 gene duplication; additional CYP2D6 variants may be detected through the reflex testing process -CYP3A4 *8, *11, *12, *13, *16, *17, *18, *22, and *26 -CYP3A5 *3, *6, *7, *8, and *9 -CYP4F2 *3 -rs12777823G>A -SLCO1B1 rs4149056 (*5) -VKORC1 c. -1639G>A, c.85G>T, c.106G>T, c.121G>T, c.134T>C, c.172A>G, c.196G>A, c.358C>T, and c.383T>G Based on the results of each assay, a genotype is assigned, and a phenotype is predicted for each gene. Assessment of multiple genes may assist the ordering clinician with personalized drug recommendations, avoidance of adverse drug reactions, and optimization of drug treatment.

Useful For: Preemptive or reactive genotyping of patients for pharmacogenomic purposes Providing an assessment for genes with strong drug-gene associations

Interpretation: An interpretive report will be provided, which focuses on only drugs and genes with published pharmacogenomic practice guidance by the Clinical Pharmacogenetics Implementation Consortium, other professional organizations or where strong US Food and Drug Administration guidance has been issued in drug labels. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Ji Y, Skierka JM, Blommel JH, et al. Preemptive pharmacogenomic testing for precision medicine: A comprehensive analysis of five actionable pharmacogenomic genes using next-generation DNA sequencing and a customized CYP2D6 genotyping cascade. J Mol Diagn. 2016;18(3):438-445. doi:10.1016/j.jmoldx.2016.01.003 2. Samwald M, Xu H, Blagec K, et al. Incidence of exposure of patients in the United States to multiple drugs for which pharmacogenomic guidelines are available. PLoS One. 2016;11(10):e0164972. doi:10.1371/journal.pone.0164972 3. Clinical Pharmacogenetic Implementation Committee (CPIC): Genes-Drugs. CPIC; Accessed November 14, 2024.

Available at https://cpicpgx.org/genes-drugs/ 4. Pharmacogenomics Knowledgebase (PharmGKB). Accessed November 14, 2024. Available at www.pharmgkb.org/ 5. Crews KR, Monte AA, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther. 2021;110(4):888-896. doi:10.1002/cpt.2149

AFOLR
620731

Folate Receptor Alpha (FOLR1), Semi-Quantitative Immunohistochemistry, Manual

Clinical Information: Folate receptor 1 protein (FOLR1), also known as folate receptor alpha (FRa), is expressed in approximately 90% of ovarian carcinomas and serves as a predictive biomarker for FOLR1-targeted therapy for epithelial ovarian cancer. FOLR1 is a member of the folate receptor family that is reported to be highly expressed in various tumors of epithelial origin but has restricted expression in normal epithelial cells. Positivity for FOLR1 is expressed on greater or equal to 75% of viable tumor cells with moderate and/or strong membrane staining, while less than 75% of viable tumor cells with moderate and/or strong membrane staining is considered negative for FOLR1.

Useful For: Diagnosis of epithelial ovarian cancer that may be eligible for treatment with an anti-folate receptor 1 protein antibody

Interpretation: Folate receptor 1 protein (FOLR1) is a biomarker that, when positive (at least moderate membranous staining) in greater than or equal to 75% of tumor cells, predicts response to treatment with Elahere (mirvetuximab soravtansine) and has been approved for epithelial ovarian, fallopian tube, or primary peritoneal cancer.(1) This result should be interpreted in the appropriate clinical context.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. VENTANA FOLR1 (FOR-2.1) RxDx Assay. US Package Insert. Roche Diagnostics; 2022 2. Scaranti M, Cojocaru E, Banerjee S, et al. Exploiting the folate receptor alpha in oncology. Nat Rev Clin Oncol. 2020;17(6):349-359 3. Necela B, Crozier J, Andorfer C, et al. Folate receptor-alpha (FOLR1) expression and function in triple negative tumors. PLoS One. 2015;10(3):e0122209 4. Kobel M, Madore J, Ramus S, et al. Evidence for a time-dependent association between FOLR1 expression and survival from ovarian carcinoma: implications for clinical testing. An Ovarian Tumour Tissue Analysis consortium study. Br J Cancer. 2014;111:2297-2307

FOL
9198

Folate, Serum

Clinical Information: The term folate refers to all derivatives of folic acid. For practical purposes, serum folate is almost entirely in the form of N-(5)-methyl tetrahydrofolate.(1) Approximately 20% of the folate absorbed daily is derived from dietary sources; the remainder is synthesized by intestinal microorganisms. Serum folate levels typically fall within a few days after dietary folate intake is reduced and may be low in the presence of normal tissue stores. Red blood cell folate levels are less subject to short-term dietary changes. Significant folate deficiency is characteristically associated with macrocytosis and megaloblastic anemia. Lower than normal serum folate has also been reported in patients with neuropsychiatric disorders, in pregnant women whose fetuses have neural tube defects, and in women who have recently had spontaneous abortions.(2) Folate deficiency is most commonly due to insufficient dietary intake and is most frequently encountered in pregnant women or in alcoholics. Other causes of low serum folate concentration include: -Excessive utilization (eg, liver

disease, hemolytic disorders, and malignancies) -Rare inborn errors of metabolism (eg, dihydrofolate reductase deficiency, formiminotransferase deficiency, 5,10-methylenetetrahydrofolate reductase deficiency, and tetrahydrofolate methyltransferase deficiency)

Useful For: Investigation of suspected folate deficiency

Interpretation: Serum folate is a relatively nonspecific test.(3) Low serum folate levels may be seen in the absence of deficiency, and normal levels may be seen in patients with macrocytic anemia, dementia, neuropsychiatric disorders, and pregnancy disorders. Results below 4 mcg/L are suggestive of folate deficiency. The cutoff is based on consensus and was derived from the US NHANES III data.(4) Evaluation of macrocytic anemias commonly requires measurement of the serum concentration of both vitamin B12 and folate; ideally, they should be measured simultaneously. Serum folate measurement is preferred over red blood cell (RBC) folate measurement due to considerable analytic variability (coefficient of variation) of assays. Both results give the same interpretation (internal Mayo study), therefore, RBC folate quantitation is not recommended. Additional serum testing for homocysteine and methylmalonic acid (MMA) determinations may help distinguish between vitamin B12 and folate deficiency states. In folate deficiency, homocysteine levels are elevated and MMA levels are normal. In vitamin B12 deficiency, the analytic variability of both serum and RBC folate assays is considerable. Homocysteine and MMA levels are alternate determinates of folate deficiency. For more information see Vitamin B12 Deficiency Evaluation.

Reference Values:
> or =4.0 mcg/L
<4.0 mcg/L suggests folate deficiency

Clinical References: 1. Fairbanks VF, Klee GG. Biochemical aspects of hematology. In: Burtis CA, Ashwood ER, eds: Tietz Textbook of Clinical Chemistry. Saunders Company; 1999:1690-1698 2. George L, Mills JL, Johansson AL, et al. Plasma folate levels and risk of spontaneous abortion. JAMA. 2002;288(15):1867-1873 3. Klee GG. Cobalamin and folate evaluation: measurement of methylmalonic acid and homocysteine vs vitamin B12 and folate. Clin Chem. 2000;46(8 Pt 2):1277-1283 4. de Benoist B. Conclusions of a WHO Technical Consultation on folate and vitamin B12 deficiencies. Food Nutr Bull. 2008;29(2 Suppl):S238-S244 5. Roberts NB, Taylor A, Sodi R: Vitamins and trace elements. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:chap 37

FSHB
70433

Follicle Stimulating Hormone, Beta Subunit (Beta FSH) Immunostain, Technical Component Only

Clinical Information: Follicle stimulating hormone (FSH) stimulates maturation of ovarian follicles and estrogen secretion in female individuals. Sparse population of cells stain positively in normal pituitary gland (approximately 10% of cells). This population of gonadotrophs also produces luteinizing hormone. Immunohistochemical detection of beta FSH may be useful in the classification of pituitary adenomas.

Useful For: Classification of pituitary adenomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Hamid Z, Mrak RE, Ijaz MT, Faas FH. Sensitivity and specificity of immunohistochemistry in pituitary adenomas. The Endocrinologist. 2009;19(1):38-43 2. Osamura RY, Kajiya H, Takei M, et al. Pathology of the human pituitary adenomas. Histochem Cell Biol. 2008;130(3):495-507 3. Osamura RY, Watanabe K. Immunohistochemical studies of human FSH producing pituitary adenomas. Virchows Archiv A Pathol Anat Histopathol. 1988;413(1):61-68 4. Pawlikowski M, Pisarek H, Kubiak R, et al. Immunohistochemical detection of FSH receptors in pituitary adenomas and adrenal tumors. Folia Histochem Cytobiol. 2012;50(3):325-330 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FSH
602753

Follicle-Stimulating Hormone (FSH), Serum

Clinical Information: Luteinizing hormone (LH) is a glycoprotein hormone consisting of 2 noncovalently bound subunits (alpha and beta). Gonadotropin-releasing hormone from the hypothalamus controls the secretion of the gonadotropins, follicle-stimulating hormone (FSH) and LH, from the anterior pituitary. The menstrual cycle is divided by a midcycle surge of both FSH and LH into a follicular phase and a luteal phase. FSH appears to control gametogenesis in both male and female individuals.

Useful For: An adjunct in the evaluation of menstrual irregularities Evaluating patients with suspected hypogonadism Predicting ovulation Evaluating infertility Diagnosing pituitary disorders

Interpretation: In both male and female patients, primary hypogonadism results in an elevation of basal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. FSH and LH are generally elevated in: -Primary gonadal failure -Complete testicular feminization syndrome -Precocious puberty (either idiopathic or secondary to a central nervous system lesion) -Menopause (postmenopausal FSH levels are generally >40 IU/L) -Primary ovarian hypofunction in female patients -Primary hypogonadism in male patients Normal or decreased FSH in: -Polycystic ovary disease in female patients FSH and LH are both decreased in failure of the pituitary or hypothalamus.

Reference Values:

Males
<12 months: < or =3.3 IU/L
12 months-5 years: < or =1.9 IU/L
>5 years-10 years: < or =2.3 IU/L
>10 years-15 years: 0.6-6.9 IU/L
>15 years-18 years: 0.7-9.6 IU/L
>18 years: 1.2-15.8 IU/L

TANNER STAGES*
Stage l: <1.5 IU/L
Stage ll: <3.0 IU/L
Stage lll: 0.4-6.2 IU/L
Stage lV: 0.6-5.1 IU/L
Stage V: 0.8-7.2 IU/L
*Puberty onset occurs for boys at a median age of 11.5 (+/- 2) years. For boys, there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

Females
<12 months: 1.2-12.5 IU/L
12 months-10 years: 0.5-6.0 IU/L

>10 years-15 years: 0.9-8.9 IU/L
>15 years-18 years: 0.7-9.6 IU/L
Premenopausal:
Follicular: 2.9-14.6 IU/L
Midcycle: 4.7-23.2 IU/L
Luteal: 1.4-8.9 IU/L
Postmenopausal: 16.0-157.0 IU/L

TANNER STAGES*
Stage l: 0.6-4.1 IU/L
Stage ll: 0.3-5.8 IU/L
Stage lll: 0.1-7.2 IU/L
Stage lV: 0.3-7.0 IU/L
Stage V: 0.4-8.6 IU/L
*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

Clinical References: 1. Saint Paul LP, Debruyne D, Bernard D, Mock DM, Defer GL: Pharmacokinetics and pharmacodynamics of MD1003 (high-dose biotin) in the treatment of progressive multiple sclerosis. Expert Opin Drug Metab Toxicol. 2016;12(3):327-344. doi: 10.1517/17425255.2016.1136288 2. Grimsey P, Frey N, Bendig G, et al: Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. Int J Pharmacokinet. 2017 Sep;2(4):247-256. doi: 10.4155/ipk-2017-0013 3. Holmes DT, Bertholf RL, Winter WE: Pituitary function and pathophysiology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:767-804 4. Nerenz RD, Boh B: Reproductive endocrinology and related disorders. In: Rifai N, Chiu RWK, Young I, Burnham CAD, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:846-884

FDP1
86207

Food Panel #2, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cabbage, paprika, spinach, and tomato Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FFPG4
58090

Food Panel IgG4 (532)

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

FFPII
57850

Food Panel II IgG

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

FOOD6
81874

Food Panel, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to codfish, cow's milk, egg white, peanut, soybean, and wheat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FOOD2 81869 Food-Fruit Panel, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an

allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to apple, banana, peach, and pear Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FOOD4
81872

Food-Grain Panel, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations.

In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to barley, rice, rye, and wheat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FOOD8
81876

Food-Nut Panel # 1, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by

respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to almond, brazil nut, coconut, hazelnut, and peanut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FOOD1
81868

Food-Nut Panel # 2, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cashew, pecan, pistachio, and walnut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FOOD7
81875

Food-Seafood Panel, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mussel, codfish, salmon, shrimp, and tuna Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy

-To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FRMH
82869

Formaldehyde, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to formaldehyde Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend

upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FORAC
75402

Formic Acid, Serum

Interpretation: Formic acid is also a metabolite of methanol, formaldehyde, and methyl formate among others. Values may vary depending on environmental and occupational exposures, diet, nutritional condition, and pregnancy status.

Reference Values:
Reporting limit determined each analysis
Units: mcg/mL
Normal plasma formic acid range is 1 - 9 mcg/mL
(in pregnant women, 0.5 - 44 mcg/mL).

BFOS
603419

FosB, Immunostain, Technical Component Only

Clinical Information: FosB is a member of the Fos transcription factor family and a component of the activator protein-1 (AP-1) protein complex. Expressed in the nucleus, FosB is useful in the diagnosis of pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma and may be helpful to distinguish it from its histologic mimics. FosB is also found in a subset of epithelioid hemangiomas.

Useful For: Diagnosing pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma and epithelioid hemangiomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Hung YP, Fletcher CD, Hornick JL. FOSB is a useful diagnostic marker for pseudomyogenic hemangioendothelioma. Am J Surg Pathol. 2017;41(5):596-606 2. Sugita S, Hirano H, Kikuchi N, et al. Diagnostic utility of FOSB immunohistochemistry in pseudomyogenic hemangioendothelioma and its histological mimics. Diagn Pathol. 2016;11(1):75. doi:10.1186/s13000-016-0530-2 3. Huang SC, Zhang L, Sung YS, et al. Frequent FOS gene rearrangements in epithelioid hemangioma: A molecular study of 58 cases with morphologic reappraisal. Am J Surg Pathol. 2015;39(10):1313-1321 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

XL2T 616501 FOXL2 Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information: Granulosa cell tumors (GCT) represent approximately 5% to 10% of all ovarian malignancies and are the most common type of malignant ovarian sex-cord stromal tumors. The majority of GCT (95%) are adult type and 5% are juvenile type. Adult GCT can occur at any age but most commonly occur in perimenopausal women, whereas juvenile GCT arise in the first 3 decades of life. FOXL2 (forkhead box L2) gene is involved in ovarian development and function. The FOXL2 gene point mutation c.402C>G in exon 1 (p.C134W) has been reported in the majority of adult GCT (>90%), one molecular subtype of Sertoli-Leydig cell tumor, and rarely also in thecomas. In cases with challenging histopathology, detection of a FOXL2 mutation can aid in the clinical diagnosis of adult GCT. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for the common somatic hotspot mutations in the FOXL2 gene. The results of this test can be useful for supporting a diagnosis of adult GCT.

Useful For: Assisting in the clinical diagnosis of adult granulosa cell tumor by assessing gene targets with in the FOXL2 gene

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. Shah SP, Kobel M, Senz J, et al. Mutation of FOXL2 in granulosa-cell tumors of the ovary. N Engl J Med. 2009;360(26):2719-2729 4. Kim MS, Hur SY, Yoo NJ, Lee SH. Mutational analysis of FOXL2 codon 134 in granulosa cell tumour of ovary and other human cancers. J Pathol. 2010;221(2):147-152 5. Schrader KA, Gorbatcheva B, Senz J, et al. The specificity of the FOXL2 c.402C>G somatic mutation: a survey of solid tumors. PLoS One. 2009;4(11):e7988 6. Benayoun BA, Kalfa N, Sultan C, Veitia RA. The forkhead factor FOXL2: a novel tumor suppressor?

Biochim Biophys Acta. 2010;1805(1):1-5 7. WHO Classification of Tumours Editorial Board: Female genital tumours. 5th ed. World Health Organization; 2021. WHO Classification of Tumours. Vol 4.

FOXP1
70435

FOXP1 Immunostain, Technical Component Only

Clinical Information: Forkhead box protein 1 (FOXP1) is a member of the forkhead box family of transcription factors that have a variety of functions in different cell and tissue types. Gene expression profiling and immunophenotypic studies showed that FOXP1 is expressed in normal activated B cells and overexpressed in a subset of diffuse large B-cell lymphomas with a predominantly nongerminal center phenotype.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Choi WW, Weisenburger DD, Greiner TC, et al. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. Clin Cancer Res. 2009;15(17):5494-5502 2. Hoeller S, Schneider A, Haralambieva E, Dirnhofer S, Tzankov A. FOXP1 protein overexpression is associated with inferior outcome in nodal diffuse large B-cell lymphomas with non-germinal centre phenotype, independent of gains and structural aberrations at 3p14.1. Histopathology. 2010;57(1):73-80 3. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004;103(1):275-282 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FOXP3
70436

FOXP3 Immunostain, Technical Component Only

Clinical Information: Forkhead box P3 (FOXP3) is a transcription factor implicated in T-cell regulation, activation, and differentiation. FOXP3 has been shown to be a master control gene for the development and function of CD4+/CD25+ regulatory T cells. In normal lymphoid tissues, a T-cell subset in interfollicular areas shows nuclear staining. FOXP3 is a specific marker for adult T-cell leukemia/lymphoma.

Useful For: Classification of leukemias and lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Song JJ, Zhao SJ, Fang J, et al: Foxp3 overexpression in tumor cells predicts poor survival in oral squamous cell carcinoma. BMC Cancer. 2016;16:530. doi:10.1186/s12885-016-2419-6 2. Zhang L, Xu J, Zhang X, et al. The role of tumoral FOXP3 on cell proliferation, migration, and invasion in gastric cancer. Cell Physiol Biochem. 2017;42(5):1739-1754.

doi:10.1159/000479442 3. Luo Q, Zhang S, Wei H, Pang X, Zhang H. Roles of Foxp3 in the occurrence and development of cervical cancer. Int J Clin Exp Pathol. 2015;8(8):8717-8730 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FMIL
82832

Foxtail Millet, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Foxtail millet Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier;

FXS 35428 Fragile X Syndrome, Molecular Analysis, Varies

Clinical Information:

Useful For: Confirming a diagnosis of fragile X syndrome, fragile X tremor/ataxia syndrome, or premature ovarian insufficiency caused by expansions in the FMR1 gene Determining carrier status for individuals with a family history of fragile X syndrome or X-linked intellectual disability Prenatal diagnosis of fragile X syndrome when there is a documented FMR1 expansion in the family

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:

Normal alleles: 5-44 CGG repeats
Intermediate (grey zone) alleles: 45-54 CGG repeats
Premutation alleles: 55-200 CGG repeats
Full mutation alleles: >200 CGG repeats
An interpretive report will be provided.

Methylation status:
Unmethylated: < or =20%
Partially methylated: 21-69%
Fully methylated: > or =70%

Clinical References: 1. Jacquemont S, Hagerman RJ, Hagerman PJ, Leehey MA. Fragile-X syndrome and fragile X-associated tremor/ataxia syndrome: two faces of FMR1. Lancet Neurol. 2007;6(1):45-55 2. Finucane B, Abrams L, Cronister A, Archibald AD, Bennett RL, McConkie-Rosell A. Genetic counseling and testing for FMR1 gene mutations: practice guidelines of the National Society of Genetic Counselors. J Genet Couns. 2012;21(6):752-760 3. Spector E, Behlmann A, Kronquist K, Rose NC, Lyon E, Reddi HV. Laboratory testing for fragile X, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(5):799-812 4. Hunter JE, Berry-Kravis E, Hipp H, et al. FMR1 Disorders. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated May 16, 2024. Accessed January 28, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1384/

FUFXS 35427 Fragile X, Follow-up Analysis

Clinical Information: Note: Where applicable, verbiage refers to sex assigned at birth. Fragile X syndrome (FXS) is an X-linked disorder with variable expression in male and female patients. In greater than 99% of affected individuals, it is caused by an expansion of the CGG trinucleotide repeat in the 5'UTR (untranslated region) of the FMR1 gene located on the X chromosome. This trinucleotide repeat is polymorphic in the general population, with the number of repeats ranging from 5 to 44. These normal alleles are passed from generation to generation, with the number of repeats remaining constant. Small expansions, called premutations, range from 55 to 200 CGG repeats. Individuals with a premutation do not exhibit features of FXS but are at risk for other FMR1-related disorders, such as fragile X tremor/ataxia syndrome (FXTAS) and primary ovarian insufficiency (POI). Transmission of a premutation by a man to his female child usually results in little or no change in the CGG repeat number. Transmission of a premutation by a woman to her child usually results in further expansion, either to a larger premutation or a full mutation. The risk for a woman with a premutation to have a child affected

with FXS by expansion to a full mutation increases with the number of CGG repeats in the premutation. Full mutations are typically greater than 200 repeats long and are generally associated with abnormal methylation of a region adjacent to the FMR1 gene. This is thought to interfere with normal FMR1 gene expression, resulting in FXS. There are multiple clinical phenotypes associated with expansion (premutations and full mutations) in the FMR1 gene. Fragile X Syndrome: Approximately 1 in 4000 individuals are affected with FXS. Most affected male patients exhibit moderate intellectual disability with affected female patients having milder, if any, cognitive deficiency. Neuropsychiatric diagnoses, such as autism spectrum and anxiety disorders, are common. Characteristic physical features include a long face with a prominent jaw, protruding ears, connective tissue abnormalities, and large testicles in postpubertal male patients. Fragile X Tremor/Ataxia Syndrome: Fragile X tremor/ataxia syndrome is a neurodegenerative disorder that is clinically distinct from FXS. Both male and female patients with a premutation are at risk for FXTAS. However, the disorder is much less common and milder in clinical presentation than FXS and shows a later age of onset in female patients. Clinical hallmarks of the disorder include intention tremor, gait ataxia, dementia, and neuropsychiatric symptoms. The risk for FXTAS increases as the number of CGG repeats increases, and the majority of individuals with FXTAS have CGG repeat expansions of 70 or more. Penetrance of clinical symptoms is associated with increasing age, with the majority of affected male patients showing symptoms between age 70 and 90 years. Premature Ovarian Insufficiency: Female patients with a premutation are at risk for increased follicular stimulating hormone levels, early menopause, and POI. Penetrance and early onset of female reproductive symptoms correlate with increasing size of the CGG repeat and reaches its highest penetrance at approximately 80 to 90 repeats. Of note, penetrance remains stable or may even decrease at approximately 100 repeats. There is no risk for increased penetrance of the POI phenotype due to maternal or paternal inheritance of the expanded CGG repeat.

Useful For: Confirming the methylation status of the repeat expansion allele in the FMR1 gene, to aid the diagnosis of FMR1-related disorders

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
Only orderable as a reflex. For more information see FXS / Fragile X Syndrome, Molecular Analysis, Varies.

Clinical References: 1. Jacquemont S, Hagerman RJ, Hagerman PJ, Leehey MA. Fragile-X syndrome and fragile X-associated tremor/ataxia syndrome: two faces of FMR1. Lancet Neurol. 2007;6(1):45-55 2. Finucane B, Abrams L, Cronister A, Archibald AD, Bennett RL, McConkie-Rosell A. Genetic counseling and testing for FMR1 gene mutations: practice guidelines of the National Society of Genetic Counselors. J Genet Couns. 2012;21(6):752-60 3. Spector E, Behlmann A, Kronquist K, Rose NC, Lyon E, Reddi HV. Laboratory testing for fragile X, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(5):799-812 4. Hunter JE, Berry-Kravis E, Hipp H, et al. FMR1 Disorders. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated May 16, 2024. Accessed January 6, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1384/

TULG
605952

Francisella tularensis Antibody, IgG, ELISA, Serum

Clinical Information: Francisella tularensis is a small, intracellular, coccobacillary gram-negative bacterium and is an obligate pathogen in animals and humans, primarily maintained in rabbits, hares, cats, ticks, and deerflies. F tularensis is found throughout North America and parts of Asia and, similar to Brucella species, is considered a potential agent of bioterrorism. Human infection with F tularensis usually occurs through inhalation of infected aerosols, ingestion of contaminated meat or water,

handling of diseased or sick animals, or through the bite of an infected arthropod (eg, tick, deerflies). Following a 3- to 5-day incubation period, the clinical manifestations of infection with F tularensis differ primarily depending on the site and route of infection. The most common form of disease is ulceroglandular (45%-80% of cases), which is associated with an arthropod (or animal) bite or another cause of skin barrier compromise. This leads to development of a painful papule that ultimately ulcerates allowing the bacterium to enter the lymphatic system. Glandular tularemia is similar in presentation to ulceroglandular disease; however, it lacks the ulceration and, more frequently, causes septicemia. Other, less frequent clinical manifestations include oculoglandular (Parinaud syndrome), oropharyngeal and gastrointestinal disease, and pneumonic or typhoidal tularemia. Diagnostic testing options for F tularensis primarily include culture and serology. Providers suspecting tularemia should collect appropriate specimens (eg, skin lesion biopsy, lymph node aspirates) promptly and send for culture. The microbiology laboratory should be alerted to the possibility of F tularensis to ensure that appropriate safety measures are taken to protect the laboratory technologists. Growth on culture is a definitive means of making a diagnosis of tularensis. Serologic testing may be used to support a diagnosis of current or recent tularensis in patients who are IgM positive, who seroconvert to IgM, or who are IgG positive in paired sera collected 2 to 3 weeks apart.

Useful For: Evaluating the presence of IgG antibodies in patients with suspected tularemia caused by Francisella tularensis This test should not be used as a test of cure as it is not quantitative. Patients may remain seropositive for months to years following resolution of disease.

Interpretation: IgM result IgG result Interpretation Negative Negative No antibodies to Francisella tularensis detected. Antibody response may be negative in samples collected too soon following infection/exposure. Repeat testing on a new sample in 1 to 2 weeks if clinically indicated. Positive Negative IgM class antibodies to F tularensis detected, suggesting current or recent infection. Repeat testing in 1 to 2 weeks to detect seroconversion of IgG may be considered to confirm the diagnosis. Positive Borderline Borderline Negative Questionable presence of IgM antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Borderline Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Borderline Borderline Questionable presence of IgM and IgG class antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Positive Positive IgM and IgG class antibodies to F tularensis detected suggesting current, recent or past infection. Cross-reactions may occur in patients with a current or prior Brucella infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Borderline Questionable presence of IgG antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks.

Reference Values:
Only orderable as part of a profile. For more information see TULAB / Francisella tularensis Antibody, IgM and IgG, ELISA, Serum.

Negative
Reference values apply to all ages.

Clinical References: 1. Petersen JM, Schriefer ME, Araj GE. Francisella and Brucella. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. AMS Press; 2019 2. Nigrovic LE, Wingerter SL. Tularemia. Infect Dis Clin North Am. 2008;22(3):489-504. doi:10.1016/j.idc.2008.03.004

TULAB 605950 Francisella tularensis Antibody, IgM and IgG, ELISA, Serum

Clinical Information: Francisella tularensis is a small, intracellular, coccobacillary gram-negative bacterium and is an obligate pathogen in animals and humans, primarily maintained in rabbits, hares, cats, ticks, and deerflies. F tularensis is found throughout North America and parts of Asia and, similar to Brucella species, is considered a potential agent of bioterrorism. Human infection with F tularensis usually occurs through inhalation of infected aerosols, ingestion of contaminated meat or water, handling of diseased or sick animals, or through the bite of an infected arthropod (eg, tick, deerflies). Following a 3- to 5-day incubation period, the clinical manifestations of infection with F tularensis differ primarily depending on the site and route of infection. The most common form of disease is ulceroglandular (45%-80% of cases), which is associated with an arthropod (or animal) bite or another cause of skin barrier compromise. This leads to development of a painful papule that ultimately ulcerates allowing the bacterium to enter the lymphatic system. Glandular tularemia is similar in presentation to ulceroglandular disease; however, it lacks the ulceration and, more frequently, causes septicemia. Other, less frequent clinical manifestations include oculoglandular (Parinaud syndrome), oropharyngeal and gastrointestinal disease, and pneumonic or typhoidal tularemia. Diagnostic testing options for F tularensis primarily include culture and serology. Providers suspecting tularemia should collect appropriate specimens (eg, skin lesion biopsy, lymph node aspirates) promptly and send for culture. The microbiology laboratory should be alerted to the possibility of F tularensis to ensure that appropriate safety measures are taken to protect the laboratory technologists. Growth on culture is a definitive means of making a diagnosis of tularensis. Serologic testing may be used to support a diagnosis of current or recent tularensis in patients who are IgM positive, who seroconvert to IgM, or who are IgG positive in paired sera collected 2 to 3 weeks apart.

Useful For: Aiding in the diagnosis of tularemia caused by Francisella tularensis This test should not be used as a test of cure as it is not quantitative. Patients may remain seropositive for months to years following resolution of disease.

Interpretation: IgM result IgG result Interpretation Negative Negative No antibodies to Francisella tularensis detected. Antibody response may be negative in samples collected too soon following infection/exposure. Repeat testing on a new sample in 1 to 2 weeks if clinically indicated. Positive Negative IgM class antibodies to F tularensis detected, suggesting current or recent infection. Repeat testing in 1 to 2 weeks to detect seroconversion of IgG may be considered to confirm the diagnosis. Positive Borderline Borderline Negative Questionable presence of IgM antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Borderline Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Borderline Borderline Questionable presence of IgM and IgG class antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Positive Positive IgM and IgG class antibodies to F tularensis detected suggesting current, recent or past infection. Cross-reactions may occur in patients with a current or prior Brucella infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Borderline Questionable presence of IgG antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks.

Reference Values:
IgG: Negative
IgM: Negative

Reference values apply to all ages.

Clinical References: 1. Petersen JM, Schriefer ME, Araj GE. Francisella and Brucella. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. AMS Press; 2019 2. Nigrovic LE, Wingerter SL. Tularemia. Infect Dis Clin North Am. 2008;22(3):489-504. doi:10.1016/j.idc.2008.03.004

TULI
605953

Francisella tularensis Antibody, IgM and IgG, Technical Interpretation, Serum

Clinical Information: Francisella tularensis is a small, intracellular, coccobacillary gram-negative bacterium and is an obligate pathogen in animals and humans, primarily maintained in rabbits, hares, cats, ticks, and deerflies. F tularensis is found throughout North America and parts of Asia and, similar to Brucella species, is considered a potential agent of bioterrorism. Human infection with F tularensis usually occurs through inhalation of infected aerosols, ingestion of contaminated meat or water, handling of diseased or sick animals, or through the bite of an infected arthropod (eg, tick, deerflies). Following a 3- to 5-day incubation period, the clinical manifestations of infection with F tularensis differ primarily depending on the site and route of infection. The most common form of disease is ulceroglandular (45%-80% of cases), which is associated with an arthropod (or animal) bite or another cause of skin barrier compromise. This leads to development of a painful papule that ultimately ulcerates allowing the bacterium to enter the lymphatic system. Glandular tularemia is similar in presentation to ulceroglandular disease; however, it lacks the ulceration and, more frequently, causes septicemia. Other, less frequent clinical manifestations include oculoglandular (Parinaud syndrome), oropharyngeal and gastrointestinal disease, and pneumonic or typhoidal tularemia. Diagnostic testing options for F tularensis primarily include culture and serology. Providers suspecting tularemia should collect appropriate specimens (eg, skin lesion biopsy, lymph node aspirates) promptly and send for culture. The microbiology laboratory should be alerted to the possibility of F tularensis to ensure that appropriate safety measures are taken to protect the laboratory technologists. Growth on culture is a definitive means of making a diagnosis of tularensis. Serologic testing may be used to support a diagnosis of current or recent tularensis in patients who are IgM positive, who seroconvert to IgM, or who are IgG positive in paired sera collected 2 to 3 weeks apart.

Useful For: Interpretation to aid in the diagnosis of tularemia caused by Francisella tularensis

Interpretation: IgM result IgG result Interpretation Negative Negative No antibodies to Francisella tularensis detected. Antibody response may be negative in samples collected too soon following infection/exposure. Repeat testing on a new sample in 1 to 2 weeks if clinically indicated. Positive Negative IgM class antibodies to F tularensis detected, suggesting current or recent infection. Repeat testing in 1 to 2 weeks to detect seroconversion of IgG may be considered to confirm the diagnosis. Positive Borderline Borderline Negative Questionable presence of IgM antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Borderline Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Borderline Borderline Questionable presence of IgM and IgG class antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Positive Positive IgM and IgG class antibodies to F tularensis detected suggesting current, recent or past infection. Cross-reactions may occur in patients with a current or prior Brucella infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Borderline Questionable presence of IgG antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks.

Reference Values:
Only orderable as part of a profile. For more information see TULAB / Francisella tularensis Antibody, IgM and IgG, ELISA, Serum.

IgM: Negative
IgG: Negative

Reference values apply to all ages.

Clinical References: 1. Petersen JM, Schriefer ME, Araj GE. Francisella and Brucella. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. AMS Press; 2019 2. Nigrovic LE, Wingerter SL. Tularemia. Infect Dis Clin North Am. 2008;22(3):489-504. doi:10.1016/j.idc.2008.03.004

TULM
605951

Francisella tularensis Antibody, IgM, ELISA, Serum

Clinical Information: Francisella tularensis is a small, intracellular, coccobacillary gram-negative bacterium and is an obligate pathogen in animals and humans, primarily maintained in rabbits, hares, cats, ticks, and deerflies. F tularensis is found throughout North America and parts of Asia and, similar to Brucella species, is considered a potential agent of bioterrorism. Human infection with F tularensis usually occurs through inhalation of infected aerosols, ingestion of contaminated meat or water, handling of diseased or sick animals, or through the bite of an infected arthropod (eg, tick, deerflies). Following a 3- to 5-day incubation period, the clinical manifestations of infection with F tularensis differ primarily depending on the site and route of infection. The most common form of disease is ulceroglandular (45%-80% of cases), which is associated with an arthropod (or animal) bite or another cause of skin barrier compromise. This leads to development of a painful papule that ultimately ulcerates allowing the bacterium to enter the lymphatic system. Glandular tularemia is similar in presentation to ulceroglandular disease; however, it lacks the ulceration and, more frequently, causes septicemia. Other, less frequent clinical manifestations include oculoglandular (Parinaud syndrome), oropharyngeal and gastrointestinal disease, and pneumonic or typhoidal tularemia. Diagnostic testing options for F tularensis primarily include culture and serology. Providers suspecting tularemia should collect appropriate specimens (eg, skin lesion biopsy, lymph node aspirates) promptly and send for culture. The microbiology laboratory should be alerted to the possibility of F tularensis to ensure that appropriate safety measures are taken to protect the laboratory technologists. Growth on culture is a definitive means of making a diagnosis of tularensis. Serologic testing may be used to support a diagnosis of current or recent tularensis in patients who are IgM positive, who seroconvert to IgM, or who are IgG positive in paired sera collected 2 to 3 weeks apart.

Useful For: Evaluating the presence of IgM antibodies in patients with suspected tularemia caused by Francisella tularensis This test should not be used as a test of cure as it is not quantitative. Patients may remain seropositive for months to years following resolution of disease.

Interpretation: IgM result IgG result Interpretation Negative Negative No antibodies to Francisella tularensis detected. Antibody response may be negative in samples collected too soon following infection/exposure. Repeat testing on a new sample in 1 to 2 weeks if clinically indicated. Positive Negative IgM class antibodies to F tularensis detected, suggesting current or recent infection. Repeat testing in 1 to 2 weeks to detect seroconversion of IgG may be considered to confirm the diagnosis. Positive Borderline Borderline Negative Questionable presence of IgM antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Borderline Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Borderline Borderline Questionable presence of IgM and IgG class antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks. Positive Positive IgM and IgG class antibodies to F tularensis detected suggesting current, recent or past infection. Cross-reactions may occur in patients with a current or prior Brucella infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Positive IgG class antibodies to F tularensis detected suggesting recent or past infection. Clinical correlation alongside presentation, exposure history and other laboratory findings required. Negative Borderline Questionable presence of IgG antibodies to F tularensis. Consider repeat testing in 1 to 2 weeks.

Reference Values:
Only orderable as part of a profile. For more information see TULAB / Francisella tularensis Antibody,

IgM and IgG, ELISA, Serum.

Negative

Reference values apply to all ages.

Clinical References: 1. Petersen JM, Schriefer ME, Araj GE. Francisella and Brucella. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. AMS Press; 2019 2. Nigrovic LE, Wingerter SL. Tularemia. Infect Dis Clin North Am. 2008;22(3):489-504. doi:10.1016/j.idc.2008.03.004

NEFA
606892

Free Fatty Acids, Total, Serum

Clinical Information: Elevated serum concentrations of nonesterified fatty acids (NEFA) are associated with cardiovascular disease, metabolic syndrome, obesity, and type 2 diabetes mellitus. NEFA are causally linked with insulin resistance and inflammation of vascular endothelium.

Useful For: Evaluation of metabolic status of patients with endocrinopathies Monitoring of control of diabetes mellitus Monitoring the effects of therapeutic diet/exercise lifestyle changes

Interpretation: Abnormally high levels of free fatty acids are associated with uncontrolled diabetes mellitus and with conditions that involve excessive release of a lipoactive hormone such as epinephrine, norepinephrine, glucagon, thyrotropin, and adrenocorticotropin.

Reference Values:
> or =18 years: 0.00-0.72 mmol/L
Reference values have not been established for patients who are <18 years of age.

Clinical References: 1. Boden G. Obesity and free fatty acids. Endocrinol Metab Clin North Am. 2008;37(3):635-646, viii-ix. doi:10.1016/j.ecl.2008.06.007 2. Haus JM, Soloman TP, Marchetti CM, Edmison JM, Gonzalez F, Kirwan JP. Free fatty acid-induced hepatic insulin resistance is attenuated following lifestyle intervention in obese individuals with impaired glucose tolerance. J Clin Endocrinol Metab. 2010;95(1):323-327. doi: 10.1210/jc.2009-1101 3.Imrie H, Abbas A, Kearney M. Insulin resistance, lipotoxicity and endothelial dysfunction. Biochim Biophys Acta. 2010;1801 (3):320-326. doi:10.1016/j.bbalip.2009.09.025 4. Marusic M, Paic M, Knobloch M, Liberati Prso AM. NAFLD, Insulin Resistance, and Diabetes Mellitus Type 2. Can J Gastroenterol Hepatol. 2021;2021:6613827. doi:10.1155/2021/6613827

FRTUP
62583

Free Thyroxine Index (FTI), Serum

Clinical Information: The determination of the total thyroxine (T4) concentration is of importance in laboratory diagnostics for differentiating between euthyroid, hyperthyroid, and hypothyroid conditions. As the major fraction of the total T4 is bound to transport proteins (thyroxine-binding globulin [TBG], prealbumin, and albumin), the determination of total T4 only provides correct information when the thyroxine-binding capacity (TBC) in serum is normal. The free thyroid hormones are in equilibrium with the hormones bound to the carrier proteins. The TBC or T-uptake assay provides a measure of the available thyroxine-binding sites. Determination of the free thyroxine index (FTI) from the quotient of total T4 and thyroxine-binding index (ie, result of the T-uptake determination) takes into account changes in the thyroid hormone carrier proteins and the thyroxine level. While total T4 is a relatively reliable indicator of T4 levels in the presence of normal binding proteins, it is not a reliable indicator when binding proteins are abnormal. For example, increases in thyroxine-binding proteins may cause increased

total T4 levels despite normal free T4 levels and normal thyroid function. Results are changed by drugs or physical conditions that alter the patient's TBG levels or drugs that compete with endogenous T4 and T3 for protein-binding sites. Direct measurement of free thyroxine (FRT4 / T4 [Thyroxine], Free, Serum) has replaced the FTI test in most clinical situations.

Useful For: Estimating the amount of circulating free thyroxine (free thyroxine index) using the total thyroxine and thyroid binding capacity (T-uptake)

Interpretation: The free thyroxine index (FTI) is determined by the following calculation: FTI =thyroxine (T4)/thyroid binding capacity The FTI is a normalized determination that remains relatively constant in healthy individuals and compensates for abnormal levels of binding proteins. Hyperthyroidism causes increased FTI, and hypothyroidism causes decreased values.

Reference Values:

THYROXINE BINDING CAPACITY (units are in Thyroxine Binding Index: TBI):
0-19 years: 0.8-1.2 TBI
> or =20 years: 0.8-1.3 TBI

T4 TOTAL (T4):
0-5 days: 5.0-18.5 mcg/dL
6 days-2 months: 5.4-17.0 mcg/dL
3-11 months: 5.7-16.0 mcg/dL
1-5 years: 6.0-14.7 mcg/dL
6-10 years: 6.0-13.8 mcg/dL
11-19 years: 5.9-13.2 mcg/dL
> or =20 years: 4.5-11.7 mcg/dL

FREE THYROXINE INDEX:
0-5 days: 5.1-20.8 mcg/dL
6 days-2 months: 5.5-18.0 mcg/dL
3-11 months: 5.7-16.8 mcg/dL
1-5 years: 5.9-15.0 mcg/dL
6-10 years: 6.0-13.9 mcg/dL
11-19 years: 5.9-13.2 mcg/dL
> or =20 years: 4.8-12.7 mcg/dL

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Whitley RJ, Meikle AW, Watts NB. Thyroid function. In: Burtis CA, Ashwood, ER, eds. Tietz Fundamentals of Clinical Chemistry. 4th ed. WB Saunders Company; 1996:645-646 2. Wilson JD, Foster DW, Kronenburg MD, et al. Williams Textbook of Endocrinology. 9th ed. WB Saunders Company; 1998:407-477 3. Freedman DB, Halsall D, Marshall WJ, Ellervik C. Thyroid disorders. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1572-1616 4. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26(10):1343-1421 5. Persani L, Cangiano B, Bonomi M. The diagnosis and management of central hypothyroidism in 2018. Endocr Connect. 2019;8(2):R44-R54. doi: 10.1530/EC-18-0515

FLARP 64718 Free-Living Amebae, Molecular Detection, PCR, Varies

Clinical Information: Several free-living amebae can infect the central nervous system (CNS) and cause devastating, usually fatal, disease. The route of entry and clinical course of infection varies with the type of ameba involved. Naegleria fowleri typically causes rapidly progressive primary amebic meningoencephalitis (PAM) in previously healthy children or adults. Infection is acquired during contact with contaminated water, including swimming and diving in warm stagnant freshwater lakes and by nasal irrigation with nonsterile water. During contact, the amebae enter the nasal sinuses and travel along the olfactory nerve through the cribriform plate of the skull and into the CNS. PAM is almost uniformly fatal within several days of exposure. Because of the rarity of the infection and difficulty in initial detection, about 75% of diagnoses are made after the death of the patient. In contrast, Acanthamoeba species and Balamuthia mandrillaris usually cause a subacute CNS illness, usually in adults who are immunocompromised, called granulomatous amebic encephalitis (GAE). The presentation of GAE can mimic a brain abscess, aseptic or chronic meningitis, or CNS malignancy. The amebae usually disseminate to the CNS from the lungs or a primary skin lesion. These amebae are usually identified by microscopic examination of cerebrospinal fluid or brain tissue and agar culture. Culture is more sensitive than microscopy alone but takes up to 7 days to produce a positive result. Also, B mandrillaris will not grow in routine culture. Real-time polymerase chain reaction assays offer a rapid and sensitive alternative to microscopy and culture.

Useful For: Aids in the diagnosis of primary amebic meningoencephalitis and granulomatous amebic encephalitis in spinal fluid and tissue in conjunction with clinical and radiologic findings This test should not be used to screen asymptomatic patients.

Interpretation: A positive result indicates the presence of free-living amoeba DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with symptoms and clinical findings of primary amebic meningoencephalitis and granulomatous amebic encephalitis.

Reference Values:
Negative

Clinical References: 1. Cope JR, Ali KM, Visvesvara GS: Pathogenic and opportunistic free-living amebae. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th Ed. ASM Press; 2019:chap142 2. Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED): Parasites - Acanthamoeba - Granulomatous Amebic Encephalitis (GAE); Keratitis. CDC; Updated December 29, 2021. Accessed March 28, 2023. Available at www.cdc.gov/parasites/acanthamoeba/health_professionals/acanthamoeba_keratitis_hcp.html 3 Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED): Naegleria fowleri - Primary Amebic Meningoencephalitis (PAM) - Amebic Encephalitis. Updated July 7, 2022. Accessed February 19, 2023. Available at www.cdc.gov/parasites/naegleria/health_professionals.html

FFRWB
60477

Friedreich Ataxia, Frataxin, Quantitative, Blood

Clinical Information: Friedreich ataxia (FA) is an autosomal recessive disease affecting approximately 1:50,000 individuals in the white population. The disease is clinically characterized by progressive spasticity, ataxia, dysarthria, absent lower limb reflexes, sensory loss, and scoliosis. Cardiac involvement occurs with the development of myocardial fibrosis due to mitochondrial proliferation and loss of contractile proteins. It tends to be correlated with the clinical neurologic age of onset and the GAA triplet repeat length, but not the duration of disease or the severity of neurologic symptoms. Although most individuals begin experiencing initial symptoms between 10 and 15 years of age, atypical late-onset forms with initial symptoms presenting after age 25 do occur. FA is caused by variants in the FXN gene

encoding a mitochondrial protein, frataxin. Variants in this gene lead to a reduced expression of frataxin, which causes the clinical manifestations of the disease. Approximately 96% of individuals with FA have a homozygous expansion of the GAA trinucleotide repeat in intron 1 of FXN. The remaining 4% of FA patients have the trinucleotide expansion on 1 allele and a point alteration or deletion on the second allele. Normal alleles contain between 5 to 33 GAA repeats. Disease-causing alleles typically range from 66 to 1700 repeats, although the majority of individuals with FA have repeats ranging from 600 to 1200. Historically, FA has been diagnosed by use of a DNA-based molecular test to detect the presence of the GAA expansion. Unfortunately, testing for the triplet repeat expansion will miss patients with point alterations or deletions. Moreover, a molecular-based analysis is not able to effectively monitor treatment. In contrast, this protein-based assay measuring concentration of frataxin is suitable for both diagnosis as well as treatment monitoring in individuals with FA. For patients with a low frataxin level, molecular repeat expansion analysis of the FXN gene (AFXN / Friedreich Ataxia, Repeat Expansion Analysis, Varies) allows for detection of disease-causing expansion alleles.

Useful For: Diagnosing individuals with Friedreich ataxia in whole blood specimens Monitoring frataxin levels in patients with Friedreich ataxia This test is not useful for carrier detection.

Interpretation: Normal results (> or =19 ng/mL for pediatric and > or =23 ng/mL for adult patients) in properly submitted specimens are not consistent with Friedreich ataxia. For results outside the normal reference range an interpretative comment will be provided.

Reference Values:
Pediatric (<18 years) normal frataxin: > or =19 ng/mL
Adults (> or =18 years) normal frataxin: > or =21 ng/mL

Clinical References: 1. Oglesbee D, Kroll C, Gakh O, et al. High-throughput immunoassay for the biochemical diagnosis of Friedreich ataxia in dried blood spots and whole blood. Clin Chem. 2013;59(10):1461-1469. doi:10.1373/clinchem.2013.207472 2. Deutsch EC, Oglesbee D, Greeley NR, Lynch DR. Usefulness of frataxin immunoassays for the diagnosis of Friedreich ataxia. J Neurol Neurosurg Psychiatry. 2014;85(9):994-1002 3. Delatycki MB, Bidichandani SI. Friedreich ataxia-pathogenesis and implications for therapies. Neurobiol Dis. 2019;132:104606. doi:10.1016/j.nbd.2019.104606 4. Boehm T, Scheiber-Mojdehkar B, Kluge B, Goldenberg H, Laccone F, Sturm B. Variations of frataxin protein levels in normal individuals. Neurol Sci. 2011;32(2):327-330. doi:10.1007/s10072-010-0326-1 5. Hanson E, Sheldon M, Pacheco B, Alkubeysi M, Raizada V. Heart disease in Friedreich's ataxia. World J Cardiol. 2019;11(1):1-12. doi:10.4330/wjc.v11.i1.1

FFRBS
60476

Friedreich Ataxia, Frataxin, Quantitative, Blood Spot

Clinical Information: Friedreich ataxia (FA) is an autosomal recessive disease affecting approximately 1:50,000 individuals in the white population. The disease is clinically characterized by progressive spasticity, ataxia, dysarthria, absent lower limb reflexes, sensory loss, and scoliosis. Cardiac involvement occurs with the development of myocardial fibrosis due to mitochondrial proliferation and loss of contractile proteins. It tends to be correlated with the clinical neurologic age of onset and the GAA triplet repeat length, but not the duration of disease or the severity of neurologic symptoms. Although most individuals begin experiencing initial symptoms between 10 and 15 years of age, atypical late-onset forms with initial symptoms presenting after age 25 do occur. FA is caused by variants in the FXN gene encoding a mitochondrial protein, frataxin. Variants in this gene lead to a reduced expression of frataxin, which causes the clinical manifestations of the disease. Approximately 96% of individuals with FA have a homozygous expansion of the GAA trinucleotide repeat in intron 1 of FXN. The remaining 4% of FA patients have the trinucleotide expansion on 1 allele and a point alteration or deletion on the second allele. Normal alleles contain between 5 to 33 GAA repeats. Disease-causing alleles typically range from 66 to 1700 repeats, although the majority of individuals with FA

have repeats ranging from 600 to 1200. Historically, FA has been diagnosed by use of a DNA-based molecular test to detect the presence of the GAA expansion. Unfortunately, testing for the triplet repeat expansion will miss those with point alterations or deletions. Moreover, a molecular-based analysis is not able to effectively monitor treatment. In contrast, this protein-based assay measuring concentration of frataxin is suitable for both diagnosis as well as treatment monitoring in individuals with FA. For patients with a low frataxin level, molecular repeat expansion analysis of the FXN gene (AFXN / Friedreich Ataxia, Repeat Expansion Analysis, Varies) allows for detection of disease-causing expansion alleles.

Useful For: Diagnosing individuals with Friedreich ataxia in blood spot specimens Monitoring frataxin levels in patients with Friedreich ataxia This test is not useful for carrier detection.

Interpretation: Normal results (> or =15 ng/mL for pediatric and > or =23 ng/mL for adult patients) in properly submitted specimens are not consistent with Friedreich ataxia. For results outside the normal reference range an interpretative comment will be provided.

Reference Values:

Pediatric (<18 years) normal frataxin: > or =15 ng/mL
Adults (> or =18 years) normal frataxin: > or =21 ng/mL

Clinical References: 1. Oglesbee D, Kroll C, Gakh O, et al. High-throughput immunoassay for the biochemical diagnosis of Friedreich ataxia in dried blood spots and whole blood. Clin Chem. 2013;59(10):1461-1469. doi:10.1373/clinchem.2013.207472 2. Deutsch EC, Oglesbee D, Greeley NR, Lynch DR. Usefulness of frataxin immunoassays for the diagnosis of Friedreich ataxia. J Neurol Neurosurg Psychiatry. 2014;85(9):994-1002 3. Delatycki MB, Bidichandani SI. Friedreich ataxia-pathogenesis and implications for therapies. Neurobiol Dis. 2019;132:104606. doi:10.1016/j.nbd.2019.104606 4. Boehm T, Scheiber-Mojdehkar B, Kluge B, Goldenberg H, Laccone F, Sturm B. Variations of frataxin protein levels in normal individuals. Neurol Sci. 2011;32(2):327-330. doi:10.1007/s10072-010-0326-1 5. Hanson E, Sheldon M, Pacheco B, Alkubeysi M, Raizada V. Heart disease in Friedreich's ataxia. World J Cardiol. 2019;11(1):1-12. doi:10.4330/wjc.v11.i1.1

AFXN
609751

Friedreich Ataxia, Repeat Expansion Analysis, Varies

Clinical Information: Friedreich ataxia (FA) is one of the most common hereditary ataxias and is characterized by progressive gait and limb ataxia, dysarthria, dysphagia, and sensory loss. The phenotypic spectrum includes non-neurologic manifestations, particularly cardiomyopathy and diabetes mellitus. Onset typically occurs between the ages of 10 to 16 years; however, late-onset and early-onset variants have been reported. Friedreich ataxia is inherited in an autosomal recessive manner. The majority of affected individuals (96%) have homozygous GAA trinucleotide repeat expansions in intron 1 of the FXN gene. The remaining affected individuals have a heterozygous GAA trinucleotide repeat expansion and another disease-causing FXN variant detectable by sequencing or deletion and duplication analysis (order CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies and note the Gene List ID NEUROLOGY-P9CYQH). Correlation exists between the size of the GAA repeat and disease onset and severity, with larger alleles associated with earlier onset and more severe disease presentation. GAA expansions may demonstrate instability during meiosis and mitosis. The GAA repeat size may expand or contract during transmission to offspring, and GAA repeat size may vary in different tissues. The GAA trinucleotide repeat is polymorphic in the general population, with the number of nondisease-associated repeats ranging from 5 to 33. Repeats of 66 or greater are fully penetrant disease-associated alleles; however, the majority of affected individuals have repeat sizes in the 600 to 1200 repeat range. Repeat sizes of 34 to 65 fall within a borderline range. Borderline alleles are of unclear significance and may be associated with clinical symptoms of FA and/or a risk for expansion to a full penetrance allele when transmitted to offspring.

Useful For: Molecular confirmation of clinically suspected Friedreich ataxia

Interpretation: The interpretive report will include assay information, background information, and conclusions based on the test results.

Reference Values:
FXN
Normal alleles: <34 GAA repeats
Borderline alleles: 34-65 GAA repeats
Expanded alleles: >65 GAA repeats

An interpretive report will be provided.

Clinical References: 1. Campuzano V, Montermini L, Molto MD, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science. 1996;271(5254):1423-1427 2. Corben LA, Collins V, Milne S, et al. Clinical Management Guidelines Writing Group. Clinical management guidelines for Friedreich ataxia: best practice in rare diseases. Orphanet J Rare Dis. 2022;17(1):415. doi:10.1186/s13023-022-02568-3 3. Lynch DR, Schadt K, Kichula E, McCormack S, Lin KY. Friedreich ataxia: Multidisciplinary clinical care. J Multidiscip Healthc. 2021;14:1645-1658. doi:10.2147/JMDH.S292945 4. Montermini L, Richter A, Morgan K, et al. Phenotypic variability in Friedreich ataxia: role of the associated GAA triplet repeat expansion. Ann Neurol. 1997;41(5):675-682 5. Pilotto F, Chellapandi DM, Puccio H. Omaveloxolone: a groundbreaking milestone as the first FDA-approved drug for Friedreich ataxia. Trends Mol Med. 2024;30(2):117-125. doi:10.1016/j.molmed.2023.12.002 6. Rummey C, Corben LA, Delatycki M, et al. Natural history of Friedreich ataxia: heterogeneity of neurologic progression and consequences for clinical trial design. Neurology. 2022;99(14):e1499-e1510. doi:10.1212/WNL.0000000000200913 7. Sharma R, De Biase I, Gomez M, Delatycki MB, Ashizawa T, Bidichandani SI. Friedreich ataxia in carriers of unstable borderline GAA triplet-repeat alleles. Ann Neurol. 2004;56(6):898-901

PCIFS
113333

Frozen Section, 1st Block (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

PCAFS
113334

Frozen Section, Additional Blocks (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

FRUCT
81610

Fructosamine, Serum

Clinical Information: Fructosamine is a general term, which applies to any glycated protein. It is formed by the nonenzymatic reaction of glucose with the alpha- and epsilon-amino groups of proteins to form intermediate compounds called aldimines. These aldimines may dissociate or undergo an Amadori rearrangement to form stable ketoamines called fructosamines. This nonenzymatic glycation of specific proteins in vivo is proportional to the prevailing glucose concentration during the lifetime of the protein. Therefore, glycated protein measurement in a patient with diabetes is felt to be a better monitor of long-

term glycemic control than individual or sporadic glucose determinations. The best known of these proteins is glycated hemoglobin, which is often measured as hemoglobin A1c, and reflects glycemic control over the past 6 to 8 weeks. In recognition of the need for a measurement that reflects intermediate-term glycemic control and was easily automated, a nonspecific test, termed fructosamine, was developed. Since albumin is the most abundant serum protein, it accounts for 80% of the glycated serum proteins, and thus, a high proportion of the fructosamine. Although a large portion of the color generated in the reaction is contributed by glycated albumin, the method will measure all proteins, each with a different half-life and different levels of glycation.

Useful For: Monitoring intermediate (1-3 weeks) glycemic control Monitoring glycemic control in patients with shortened red blood cell survival

Interpretation: In general, fructosamine reflects glycemic control in diabetic patients over the previous 1 to 3 weeks. High values indicate poor control. All glycated proteins are measured by this method, with glycated albumin contributing a large portion.

Reference Values:
200-285 mcmol/L

Clinical References:

FROS2
92187

Fructose, Qualitative, Semen

Clinical Information: Fructose is produced in the male reproductive tract by the seminal vesicles and is released into the semen during ejaculation. Fructose is the energy source for sperm motility.

Useful For: Establishing the origin of azoospermia in patients with azoospermia and low volume ejaculates

Interpretation: A positive (indicated by color change) fructose is considered normal. A semen specimen that contains no sperm (azoospermia) and is fructose negative may indicate an absence of the seminal vesicles, absence of the vas deferens in the area of the seminal vesicles, or an obstruction at the level of the seminal vesicles.

Reference Values:
Positive

Clinical References: 1. Lipshultz LI, Howards SS, Niederberger CS, eds: In: Infertility in the Male. 4th ed. Cambridge University Press 2009 2. Risz B, Agarwal A, Sabanegh ES, eds: Male Infertility in Reproductive Medicine: Diagnosis and Management. CRC Press; 2019

FFPG
57932

Fruit Panel IgG

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

IHCFH
606334

Fumarate Hydratase Immunostain, Technical Component Only

Clinical Information: A ubiquitously expressed mitochondrial enzyme fumarate hydratase (FH) catalyzes the reversible hydration of fumaric acid to yield I-malic acid during the Krebs cycle. Germline alterations in the FH gene cause a predisposition to renal defects like hereditary leiomyomatosis and renal cell carcinoma (HLRCC). While morphologic features are characteristic enough that they can be suspected, FH deficiency or germline DNA testing are necessary for its diagnosis. HLRCC can be associated with multiple cutaneous leiomyomas, uterine leiomyomas, and an aggressive variant of renal cell carcinoma that occurs frequently in young patients.

Useful For: Identifying fumarate hydratase-deficient neoplasms Supporting the diagnosis of an atypical smooth muscle tumor over leiomyosarcoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Carter CS, Skala SL, Chinnaiyan AM, et al. Immunohistochemical characterization of fumarate hydratase (FH) and succinate dehydrogenase (SDH) in cutaneous leiomyomas for detection of familial cancer syndromes. Am J Surg Pathol. 2017;41(6):801-809 2. Trpkov K, Hes O, Agaimy A, et al. Fumarate hydratase-deficient renal cell carcinoma is strongly correlated with fumarate hydratase mutation and hereditary leiomyomatosis and renal cell carcinoma syndrome. Am J Surg Pathol. 2016;40(7):865-875 3. Harrison WJ, Andrici J, Maclean F, et al. Fumarate hydratase-deficient uterine leiomyomas occur in both the syndromic and sporadic settings. Am J Surg Pathol. 2016;40(5):599-607 4. Llamas-Velasco M, Requena L, Kutzner H, et al. Fumarate hydratase immunohistochemical staining may help to identify patients with multiple cutaneous and uterine leiomyomatosis (MCUL) and hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome. J Cutan Pathol. 2014;41(11):859-865 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FBL
50022

Fungal Culture, Blood

Clinical Information: Due to the high mortality rate from fungemia, the expeditious detection and identification of fungi from the patient's blood can have great diagnostic prognostic importance. Risk factors for fungemia include, but are not limited to, extremes of age, immunosuppression, and those individuals with burns or indwelling intravascular devices.

Useful For: Diagnosis and treatment of the etiologic agents of fungemia

Interpretation: Positive cultures of yeast and filamentous fungi are reported with the organism identification. Positive cultures are usually an indication of infection and are reported as soon as detected. Correlation of culture results and the clinical situation is required for optimal patient management. A final negative report is issued after 42 days of incubation.

Reference Values:
Negative
If positive, notification is made as soon as the positive culture is detected or identified.

Clinical References: 1. Procop GW, Church DL, Hall GS, et al. Mycology. In: Koneman's Color Atlas and Textbook of Diagnostic Microbiology. 7th ed. Walters Kluwer; 2017:1322-1416 2. Zheng S, Ng TY, Li H, Tan AL, Tan TT, Tan BH. A dedicated fungal culture medium is useful in the diagnosis of fungemia: a retrospective cross-sectional study. PLoS One. 2016;11(10):e0164668. doi:10.1371/journal.pone.0164668 3. Magallon A, Basmaciyan L, Chapuis A, et al. Evaluation of the relevance of use of the BD-BACTEC MycosisIC/F, BD-BACTEC PlusAerobic/F, BD-BACTEC Lytic/10 anaerobic/F and BD-BACTEC PedsPlus/F culture bottle system for fungemia detection: A 4-year retrospective study at the Dijon university hospital, France. J Mycol Med. 2022;32(4):101295. doi:10.1016/j.mycmed.2022.101295

FDERM
87283

Fungal Culture, Dermal

Clinical Information: Fungal infections of keratinized tissues (hair, skin, nails) can be caused by dermatophytic fungi belonging to the genera Epidermophyton, Microsporum, and Trichophyton. Opportunistic superficial infections resembling dermatophytoses may be caused by yeasts or by unrelated filamentous fungi that are normally saprobes or plant pathogens. Dermatophytes are usually unable to penetrate deeper tissues. Infection may range from mild to severe.

Useful For: Recovery and identification of dermatophyte fungi from hair, skin, and nail infected specimens

Interpretation: Positive cultures are reported with organism identification. Negative reports are issued after 30 days incubation.

Reference Values:
Negative
If positive, fungus or yeast will be identified.

Clinical References: Borman AM, Summerbell RC: Trichophyton, Microsporum, Epidermophyton and agents of superficial mycoses. In: Carroll KC, Pfaller MA, Landry ML, et al. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:2208-2233

FGEN
84389

Fungal Culture, Routine

Clinical Information: Many fungi in the environment cause disease in immunocompromised human hosts. Accordingly, the range of potential pathogenic fungi has increased as the number of immunosuppressed individuals (persons with AIDS, patients receiving chemotherapy or transplant rejection therapy, etc) has increased. Isolation and identification of the infecting fungus in the clinical laboratory can help guide patient care.

Useful For: Diagnosing fungal infections from specimens other than blood, skin, hair, nails, and vagina (separate tests are available for these specimen sites)

Interpretation: Positive cultures of yeast and filamentous fungi are reported with the organism identification. The clinician must determine whether the presence of an organism is significant or not. A final negative report is issued after 24 days of incubation.

Reference Values:
Negative
If positive, fungus will be identified.

Clinical References: Ashbee HR. General approaches for direction detection and identification of fungi. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. Vol 1. ASM Press; 2019:2035-2055

FVAG
5184

Fungal Culture, Vaginal

Clinical Information: Candidal vulvovaginitis is believed to be the most frequent or second most frequent vaginal infection. Depending on the geographical area, its prevalence in women is estimated to be in the range of 5% to 20%. Besides Candida albicans, Candida glabrata, and Candida tropicalis are the most frequently isolated Candida species both from vulvo-vaginitis patients and from healthy carriers.

Useful For: Monitoring therapy for vulvovaginitis Managing chronic recurring disease Determining the etiology of infectious vaginitis when other tests have been uninformative

Interpretation: Meaningful diagnosis of vaginal candidiasis requires that 1) yeast are demonstrable in the affected area and 2) clinical symptoms and signs are consistent with the disease. Since in up to 20% of healthy women, yeast cells are part of the normal vaginal flora, the presence of Candida on culture may be meaningless or misleading unless other clinical factors are considered.

Reference Values:
Negative

If positive, yeast will be identified.

Clinical References: 1. Abdallah M, Augenbraun MH, McCormack W: Vulvovaginitis and cervicitis. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:1462-1476 2. Ashbee HR: General approaches for direction detection and identification of fungi. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. Vol 1. ASM Press; 2019:2035-2055

FUNA
45196

Fungal Ident Panel A (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

FUNB
45205

Fungal Ident Panel B (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

D2F
45079

Fungal Sequencing Identification (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

FS
84390

Fungal Smear, Varies

Clinical Information: Many fungi in the environment cause disease in severely compromised human hosts. Accordingly, the range of potential pathogenic fungi has increased as the number of immunosuppressed individuals (persons with AIDS, patients receiving chemotherapy or transplant rejection therapy, etc) has increased. Few fungal diseases can be diagnosed clinically; most are diagnosed by isolating and identifying the infecting fungus in the clinical laboratory.

Useful For: Detection of fungi in clinical specimens

Interpretation: Positive slides are reported as one or more of the following: fungal elements seen, yeast, yeast and psuedohyphae, hyphae, organism resembling Blastomyces species complex, organism resembling Coccidioides species, hyphae resembling Mucorales, or organism resembling Malassezia species.

Reference Values:
Negative

Clinical References:

FUNBL
57873

Fungitell, BAL

Clinical Information: The Fungitell Beta – D Glucan assay detects (1,3) – Beta-D-glucan from the following pathogens: Candida spp., Acremonium, Aspergillus spp., Coccidioides immitis, Fusarium spp., Histoplasma capsulatum, Trichosporon spp., Sporothrix schenckii, Saccharomyces cerevisiae, and Pneumocystis jiroveci. The Fungitell Beta-D Glucan assay does not detect certain fungal species such as the genus Cryptococcus, which produces very low levels of (1,3) – Beta-D-glucan, nor the Zygomycetes, such as Absidia, Mucor, and Rhizopus, which are not known to produce (1,3) – Beta-D-glucan. Studies indicate Blastomyces dermatitidis is usually not detected due to little (1,3) – Beta-D-glucan produced in the yeast phase.

Interpretation: The performance characteristics of the Fungitell assay in BAL have been determined by Viracor-Eurofins; there are no established criteria for the interpretation of Fungitell results from BAL fluid. Research studies have evaluated the use of the Fungitell assay in BAL in both immunocompromised patients (Mycopathologia (2013) 175:33-41) and acute eosinophilic pneumonia (Chest (2003) 123:1302-1307).

Reference Values:
A reference range for specimens other than serum has not been established.

FUNBW
57872

Fungitell, bronch wash

Clinical Information: The Fungitell Beta – D Glucan assay detects (1,3) – Beta-D-glucan from the following pathogens: Candida spp., Acremonium, Aspergillus spp., Coccidioides immitis, Fusarium spp., Histoplasma capsulatum, Trichosporon spp., Sporothrix schenckii, Saccharomyces cerevisiae, and Pneumocystis jiroveci. The Fungitell Beta-D Glucan assay does not detect certain fungal species such as the genus Cryptococcus, which produces very low levels of (1,3) – Beta-D-glucan, nor the Zygomycetes, such as Absidia, Mucor, and Rhizopus, which are not known to produce (1,3) – Beta-D-glucan. Studies indicate Blastomyces dermatitidis is usually not detected due to little (1,3) – Beta-D-glucan produced in the yeast phase.

Interpretation: The performance characteristics of the Fungitell assay in bronchial wash have been determined by Viracor-IBT Laboratories; there are no established criteria for the interpretation of Fungitell results from bronchial wash fluid. Research studies have evaluated the use of the Fungitell assay in BAL in both immunocompromised patients (Mycopathologia (2013) 175:33-41) and acute eosinophilic pneumonia (Chest (2013) 123:1302-1307).

Reference Values:
A reference range for specimens other than serum has not been established.

FUNSF
57871

Fungitell, CSF

Clinical Information: The Fungitell Beta-D Glucan assay is indicated for the presumptive diagnosis of invasive fungal disease through detection of elevated levels of (1,3)- Beta-D-glucan in serum. Normal human serum contains low levels of (1,3)- Beta-D glucan, typically 10 to 40 pg/mL, presumably from commensal yeasts present in the alimentary canal and gastrointestinal tract. However, (1,3)- Beta-D-glucan is sloughed from the cell walls during the life cycle of most pathogenic fungi. Thus, monitoring serum for evidence of elevated and rising levels of (1,3)- Beta-D-glucan provides a convenient surrogate marker for invasive fungal disease. The Fungitell Beta - D Glucan assay detects (1,3) - Beta-D-glucan from the following pathogens: Candida spp., Acremonium, Aspergillus spp., Coccidioides immitis, Fusarium spp., Histoplasma capsulatum, Trichosporon spp., Sporothrix schenckii, Saccharomyces cerevisiae, and Pneumocystis jiroveci. The Fungitell Beta-D Glucan assay does not detect certain fungal species such as the genus Cryptococcus, which produces very low levels of (1,3) - Beta-D-glucan, nor the Zygomycetes, such as Absidia, Mucor, and Rhizopus, which are not known to produce (1,3) - Beta-D-glucan. Studies indicate Blastomyces dermatitidis is usually not detected due to little (1,3) - Beta-D-glucan produced in the yeast phase.

Interpretation: The performance characteristics of the Fungitell assay in CSF have been determined by Eurofins Viracor; there are no established criteria for the interpretation of Fungitell results from CSF. Research studies have evaluated the use of the Fungitell assay in CSF during a fungal meningitis outbreak (J. Clin. Microbiol. 2013, 51(4):1285-1287).

Reference Values:
A reference range for specimens other than serum has not been established.

FFURO
91119

Furosemide (Lasix)

Reference Values:
Expected serum furosemide concentration in patients on usual daily dosages: Up to 5.0 ug/mL

Toxic: greater than 50.0 ug/mL

FUSI
70434

FUS Immunostain, Technical Component Only

Clinical Information: Fused in sarcoma (FUS), also known as translated in liposarcoma (TLS), protein is a multifunctional DNA- and RNA-binding protein. Studies have shown the cause of familial amyotrophic lateral sclerosis to be an alteration in the gene encoding the FUS protein. FUS has been linked to other neurodegenerative diseases including frontotemporal lobar dementia and neuronal intermediate filament inclusion disease.

Useful For: Identification of frontotemporal lobar dementia

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Armstrong RA. Neuronal cytoplasmic inclusions in tau, TDP-43, and FUS molecular subtypes of frontotemporal lobar degeneration share similar spatial patterns. Folia Neuropathol. 2017;55(3):185-192. doi:10.5114/fn.2017.70482 2. Armstrong RA, Gearing M, Bigio EH, et al. Spatial patterns of FUS-immunoreactive neuronal cytoplasmic inclusions (NCI) in neuronal intermediate filament inclusion disease (NIFID). J Neural Transm. 2011;118(11):1651-1657. doi:10.1007/s00702-011-0690-x 3. Irwin DJ, Cairns NJ, Grossman M, et al. Frontotemporal lobar degeneration: defining phenotypic diversity through personalized medicine. Acta Neuropathol. 2015;129(4):469-491. doi:10.1007/s00401-014-1380-1 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FUSM
82750

Fusarium moniliforme, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Fusarium moniliforme Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FCDX1
75841

Gabapentin Confirmation (Qualitative), Umbilical Cord Tissue

Reference Values:
Reporting limit determined each analysis.
Units: ng/g

Only orderable as a reflex test.

GABA
80826

Gabapentin, Serum

Clinical Information: Gabapentin is an antiepileptic drug that is effective in treating seizures, neuropathies, and a variety of neurological and psychological maladies. Although designed as a gamma-aminobutyric acid (GABA) analogue, gabapentin does not bind to GABA receptors, nor does it affect the neuronal uptake or degradation of GABA. In fact, the precise mechanism by which it exerts its analgesic and anticonvulsant effects is unknown. After oral administration and absorption, gabapentin circulates essentially unbound to serum proteins. In addition, gabapentin does not undergo hepatic metabolism, unlike most other antiepileptic drugs, and is eliminated almost entirely by renal excretion with a clearance that approximates the glomerular filtration rate. The elimination half-life is 5 to 7 hours in patients with normal kidney function. Since gabapentin does not bind to serum proteins, it does not exhibit pharmacokinetic variability and interactions with other highly protein-bound medications (eg, phenytoin). In addition, the lack of hepatic metabolism eliminates the interactions with other hepatically cleared medications, which can induce/inhibit hepatic drug metabolizing enzyme systems (eg, cytochrome P450 enzymes). Therefore, gabapentin serum concentration is not changed following the addition or discontinuation of other common anticonvulsants (ie, phenobarbital, phenytoin, carbamazepine, or valproic acid), nor are their serum concentrations altered upon the addition or discontinuation of gabapentin. In general, adverse effects with gabapentin are infrequent and usually resolve with continued treatment. The most common side effects include somnolence, dizziness, ataxia, and fatigue. Experience to date indicated that gabapentin is safe and relatively nontoxic.

Useful For: Monitoring serum gabapentin concentrations Assessing compliance Adjusting dosage in

patients

Interpretation: Therapeutic ranges are based on specimens collected immediately before the next dose (ie, trough). Most epileptic patients show a response to the drug when the trough concentration is in the range of 2 to 20 mcg/mL. Therapeutic drug monitoring may be useful due to inter-individual variation in pharmacokinetics and dose-dependent bioavailability; specimens for measurements should be collected before the morning dose since the short half-life may affect the interpretation of the concentration.

Reference Values:
2.0-20.0 mcg/mL

Toxic Range: > or =25.0 mcg/mL

Clinical References: 1. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62 2. Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs-best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239-1276 3. Johannessen SI, Tomson T. Pharmacokinetic variability of newer antiepileptic drugs: when is monitoring needed? Clin Pharmacokinetics. 2006;45(11):1061-1075 4. Milone MC, Shaw LM: Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

FCDUE
75840

Gabapentin, Umbilical Cord Tissue

Reference Values:
Reporting limit determined each analysis.
Units: ng/g

Only orderable as part of a profile-see FCDSU

FGABA
51115

Gabapentin, Urine

Reference Values:
Reference Range: Not Established

Units: ug/mL

GDU
89301

Gadolinium, 24 Hour, Urine

Clinical Information: Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media (gadolinium-based contrast agents: GBCA) for magnetic resonance imaging and computer tomography scanning. Gadolinium is primarily eliminated via the kidneys, so exposure can be prolonged in patients with kidney insufficiency. Patients with reduced kidney function and some patients with normal kidney function may exhibit a prolonged gadolinium elimination half-life. To date the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF). NSF is a relatively uncommon condition in which fibrous plaques develop in the dermis and often in deeper connective tissues. Reported cases have

occurred almost exclusively in patients with severe kidney disease, and almost all have been associated with prior use of GBCA. NSF is a painful skin disease characterized by thickening of the skin, which can involve the joints and cause significant limitation of motion within weeks to months. Over the past decade, changes in clinical practice guidelines have almost eliminated the incidence of NSF. However, the association of NSF and observed elevated gadolinium concentrations is still not fully understood.

Useful For: Assessing chronic exposure and monitoring effectiveness of dialysis in a 24-hour urine collection

Interpretation: Elevated urine gadolinium results from a specimen collected more than 96 hours after administration of a gadolinium-based contrast agent confirms past exposure or continued exposure through anthropogenic sources and prolonged elimination of gadolinium. Gadolinium also has been shown to be present in some municipal water sources, which may contribute to the observation of low concentrations of gadolinium in patients who never have been exposed to gadolinium-based contrast agents. Elevated gadolinium in a specimen collected more than 96 hours after contrast media infusion does not indicate risk of nephrogenic systemic fibrosis.

Reference Values:
0-17 years: Not established
> or =18 years: <1.1 mcg/24 hours

Clinical References: 1. Othersen JB, Maize JC, Woolson RF, Budisavljevic MN. Nephrogenic systemic fibrosis after exposure to gadolinium in patients with renal failure. Nephrol Dial Transplant. 2007;22:3179-3185 2. Christensen KN, Lee CU, Hanley MM, et al. Quantification of gadolinium in fresh skin and serum samples from patients with nephrogenic systemic fibrosis. J Am Acad Dermatol. 2011;64(1):91-96 3. Telgmann L, Sperling M, Karst U. Determination of gadolinium-based MRI contrast agents in biological and environmental samples: A review. Analytica Chimica Acta. 2013;764:1-16 4. Daftari Besheli L, Aran S, Shaqdan K, et al. Current status of nephrogenic systemic fibrosis. Clin Radiol. 2014;69(7):661-668 5. Aime S, Caravan P. Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. J Magn Reson Imaging. 2009;30(6):1259-1267 6. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology. 2015;275:772-782 7. Attari H, Cao Y, Elmholdt TR, Zhao Y, Prince MR. A systematic review of 639 patients with biopsy-confirmed nephrogenic systemic fibrosis. Radiology. 2019;292(2):376-386 8. Woolen SA, Shankar PR, Gagnier JJ, MacEachern MP, Singer L, Davenport MS. Risk of nephrogenic systemic fibrosis in patients with stage 4 or 5 chronic kidney disease receiving a group II gadolinium-based contrast agent: A systematic review and meta-analysis. JAMA Intern Med. 2020;180(2):223-230 9. Bornhorst J, Wegwerth P, Day P, et al. Urinary reference intervals for gadolinium in individuals without recent exposure to gadolinium-based contrast agents. Clin Chem Lab Med. 2020;58(3):e87-e90 10. Alwasiyah D, Murphy C, Jannetto P, Hogg M, Beuhler MC. Urinary Gadolinium Levels After Contrast-Enhanced MRI in Individuals with Normal Renal Function: a Pilot Study. J Med Toxicol. 2019;15(2):121-127

GDS
89299

Gadolinium, Serum

Clinical Information: Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media (gadolinium-based contrast agents: GBCA) for magnetic resonance imaging and computer tomography scanning. Gadolinium is primarily eliminated via the kidneys, so exposure can be prolonged in patients with kidney insufficiency. Patients with reduced kidney function and some patients with normal kidney function may exhibit a prolonged gadolinium elimination half-life. To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF). NSF is a relatively uncommon

condition in which fibrous plaques develop in the dermis and often in deeper connective tissues. Reported cases have occurred almost exclusively in patients with severe kidney disease, and almost all have been associated with prior use of GBCA. NSF is a painful skin disease characterized by thickening of the skin, which can involve the joints and cause significant limitation of motion within weeks to months. Over the past decade, changes in clinical practice guidelines have almost eliminated completely the incidence of NSF. However, the association of NSF and observed elevated gadolinium concentrations is still not fully understood.

Useful For: Aiding in documenting previous exposure to gadolinium-based contrast agents using serum specimens

Interpretation: Elevated gadolinium observed in serum specimens drawn more than 96 hours after administration of gadolinium-containing contrast media is not typical of most patients with normal kidney function and may indicate prolonged elimination of gadolinium and exposure to anthropogenic sources.

Reference Values:
<0.5 ng/mL

Clinical References: 1. Othersen JB, Maize JC, Woolson RF, Budisavljevic MN. Nephrogenic systemic fibrosis after exposure to gadolinium in patients with renal failure. Nephrol Dial Transplant. 2007;22:3179-3185 2. Christensen KN, Lee CU, Hanley MM, et al. Quantification of gadolinium in fresh skin and serum samples from patients with nephrogenic systemic fibrosis. J Am Acad Dermatol. 2011;64(1):91-96 3. Telgmann L, Sperling M, Karst U. Determination of gadolinium-based MRI contrast agents in biological and environmental samples: A review. Analytica Chimica Acta. 2013;764:1-16 4. Daftari Besheli L, Aran S, Shaqdan K, et al. Current status of nephrogenic systemic fibrosis. Clin Radiol. 2014;69(7):661-668 5. Aime S, Caravan P. Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. J Magn Reson Imaging 2009;30(6):1259-1267 6. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology. 2015;275(3):772-782 7. Attari H, Cao Y, Elmholdt TR, Zhao Y, Prince MR. A systematic review of 639 patients with biopsy-confirmed nephrogenic systemic fibrosis. Radiology. 2019;292(2):376-386 8. Woolen SA, Shankar PR, Gagnier JJ, MacEachern MP, Singer L, Davenport MS. Risk of nephrogenic systemic fibrosis in patients with stage 4 or 5 chronic kidney disease receiving a group II gadolinium-based contrast agent: A systematic review and meta-analysis. JAMA Intern Med. 2020;180(2):223-230 11. Bornhorst J, Wegwerth P, Day P, et al. Urinary reference intervals for gadolinium in individuals without recent exposure to gadolinium-based contrast agents. Clin Chem Lab Med. 2020;58(3):e87-e90 12. Alwasiyah D, Murphy C, Jannetto P, Hogg M, Beuhler MC. Urinary Gadolinium Levels After Contrast-Enhanced MRI in Individuals with Normal Renal Function: a Pilot Study. J Med Toxicol. 2019;15(2):121-127

GDUCR
615338

Gadolinium/Creatinine Ratio, Random, Urine

Clinical Information: Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media (gadolinium-based contrast agents: GBCA) for magnetic resonance imaging and computer tomography scanning. Gadolinium is primarily eliminated via the kidneys, so exposure can be prolonged in patients with renal insufficiency. Patients with reduced kidney function and some patients with normal kidney function may exhibit a prolonged gadolinium elimination half-life. To date the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF). NSF is a relatively uncommon condition in which fibrous plaques develop in the dermis and often in deeper connective tissues. Reported cases have occurred almost exclusively in patients with severe kidney disease, and almost all have been associated with prior use of GBCA. NSF is a painful skin disease characterized by thickening of the skin, which can

involve the joints and cause significant limitation of motion within weeks to months. Over the past decade, changes in clinical practice guidelines have almost completely eliminated the incidence of NSF. However, the association of NSF and observed elevated gadolinium concentrations is still not fully understood.

Useful For: Assessing chronic exposure and monitoring effectiveness of dialysis in a random urine collection

Interpretation: Although much of the gadolinium associated with the administration of gadolinium-based contrast agents (GBCA) is cleared in the urine in the first 96 hours, lower concentrations of gadolinium may persist in the urine for months after GBCA exposure. Elevated urine gadolinium results collected after administration of a GBCA confirm past exposure, prolonged elimination of gadolinium, and/or continued exposure through anthropogenic sources. Gadolinium also has been shown to be present in some municipal water sources, which may contribute to the observation of low concentrations of gadolinium in patients who never have been exposed to GBCA. Elevated gadolinium in a specimen collected more than 96 hours after contrast media infusion does not indicate risk of nephrogenic systemic fibrosis.

Reference Values:
0-17 years: Not established
> or =18 years: <0.8 mcg/g creatinine

Clinical References: 1. Othersen JB, Maize JC, Woolson RF, Budisavljevic MN. Nephrogenic systemic fibrosis after exposure to gadolinium in patients with renal failure. Nephrol Dial Transplant. 2007;22(11):3179-3185 2. Christensen KN, Lee CU, Hanley MM, et al. Quantification of gadolinium in fresh skin and serum samples from patients with nephrogenic systemic fibrosis. J Am Acad Dermatol. 2011;64(1):91-96 3. Girardi M, Kay J, Elston DM, et al. Nephrogenic systemic fibrosis: Clinicopathological definition and workup recommendations. J Am Acad Dermatol. 2011;65(6):1095-1106 4. Telgmann L, Sperling M, Karst U. Determination of gadolinium-based MRI contrast agents in biological and environmental samples: A review. Analytica Chimica Acta. 2013;764:1-16 5. Daftari Besheli L, Aran S, Shaqdan K, et al. Current status of nephrogenic systemic fibrosis. Clin Radiol. 2014;69(7):661-668 6. Aime S, Caravan P. Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. J. Magn Reson Imaging. 2009;30(6):1259-1267 7. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology. 2015;275:772-782 8. Bornhorst J, Wegwerth P, Day P, et al. Urinary reference intervals for gadolinium in individuals without recent exposure to gadolinium-based contrast agents. Clin Chem Lab Med. 2020;58(3):e87-e90. doi: 10.1515/cclm-2019-0607 9. Alwasiyah D, Murphy C, Jannetto P, Hogg M, Beuhler MC. Urinary Gadolinium Levels After Contrast-Enhanced MRI in Individuals with Normal Renal Function: a Pilot Study. J Med Toxicol. 2019;15(2):121-127

GDCU
615339

Gadolinium/Creatinine Ratio, Urine

Clinical Information: Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media (gadolinium-based contrast agents: GBCA) for magnetic resonance imaging and computer tomography scanning. Gadolinium is primarily eliminated via the kidneys, so exposure can be prolonged in patients with renal insufficiency. In healthy subjects with normal kidney function, the plasma half-life of gadolinium is approximately 90 minutes (1.5 hours). Patients with reduced kidney function and some patients with normal kidney function may exhibit a prolonged gadolinium elimination half-life. To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF). NSF is a relatively uncommon condition in which fibrous plaques develop in the dermis and, often, in deeper

connective tissues. Reported cases have occurred almost exclusively in patients with severe kidney disease, and almost all have been associated with prior use of GBCA. NSF is a painful skin disease characterized by thickening of the skin, which can involve the joints and cause significant limitation of motion within weeks to months. Over the past decade, changes in clinical practice guidelines have almost completely eliminated the incidence of NSF. However, the association of NSF and observed elevated gadolinium concentrations is still not fully understood.

Useful For: Measurement of gadolinium concentration for assessing chronic exposure and monitoring effectiveness of dialysis using a random urine collection

Interpretation: Although much of the gadolinium associated with the administration of gadolinium-based contrast agents (GBCA) is cleared in the urine in the first 96 hours, lower concentrations of gadolinium may persist in the urine for months after GBCA exposure. Elevated urine gadolinium results collected after administration of a GBCA confirm past exposure, prolonged elimination of gadolinium, and/or continued exposure through anthropogenic sources. Gadolinium also has been shown to be present in some municipal water sources, which may contribute to the observation of low concentrations of gadolinium in patients who never have been exposed to GBCA. Elevated gadolinium in a specimen collected more than 96 hours after contrast media infusion does not indicate risk of nephrogenic systemic fibrosis.

Reference Values:
Only orderable as part of a profile. For more information see GDUCR / Gadolinium/Creatinine Ratio, Random, Urine.

0-17 years: Not established
> or =18 years: <0.8 mcg/g creatinine

Clinical References: 1. Othersen JB, Maize JC, Woolson RF, Budisavljevic MN. Nephrogenic systemic fibrosis after exposure to gadolinium in patients with renal failure. Nephrol Dial Transplant 2007;22(11):3179-3185 2. Christensen KN, Lee CU, Hanley MM, et al. Quantification of gadolinium in fresh skin and serum samples from patients with nephrogenic systemic fibrosis. J Am Acad Dermatol. 2011;64(1):91-96 3. Girardi M, Kay J, Elston DM, et al. Nephrogenic systemic fibrosis: Clinicopathological definition and workup recommendations. J Am Acad Dermatol. 2011;65(6):1095-1106 4. Telgmann L, Sperling M, Karst U. Determination of gadolinium-based MRI contrast agents in biological and environmental samples: A review. Analytica Chimica Acta. 2013;764:1-16 5. Daftari Besheli L, Aran S, Shaqdan K, et al. Current status of nephrogenic systemic fibrosis. Clin Radiol. 2014;69(7):661-668 6. Aime S, Caravan P. Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. J. Magn Reson Imaging 2009;30(6):1259-1267 7. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology. 2015;275:772-782 8. Bornhorst J, Wegwerth P, Day P, et al. Urinary reference intervals for gadolinium in individuals without recent exposure to gadolinium-based contrast agents. Clin Chem Lab Med. 2020;58(3):e87-e90. doi: 10.1515/cclm-2019-0607 9. Alwasiyah D, Murphy C, Jannetto P, Hogg M, Beuhler MC. Urinary Gadolinium Levels After Contrast-Enhanced MRI in Individuals with Normal Renal Function: a Pilot Study. J Med Toxicol. 2019;15(2):121-127

GATOL
62440

Galactitol, Quantitative, Urine

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of 1 of the 4 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase, uridine diphosphate galactose-4-epimerase, and galactose mutarotase. GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near complete deficiency of the GALT enzyme is life threatening.

If left untreated, complications include liver failure, sepsis, cognitive and intellectual disabilities, and death. Galactosemia is treated with a galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, abnormalities of motor function, and female patients are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000. Galactose levels may be continuously elevated in individuals affected with galactosemia even with a galactose-restricted diet regimen due to an endogenous production of galactose. The reduction of galactose to galactitol is an alternate pathway of galactose disposition when galactose metabolism is impaired. The excretion of abnormal quantities of galactitol in the urine of patients is characteristic of this disorder, and patients may have abnormal levels of galactitol even with dietary compliance. Daily consumption of galactose may cause urine levels to rise thus providing information on effectiveness of or compliance with treatment, but unlike erythrocyte galactose-1-phosphate and plasma galactose, urine galactitol levels usually do not provide insight into acute and transient effects of galactose intake.

Useful For: Monitoring effectiveness of treatment in patients with galactosemia Establishing a baseline level prior to initiating treatment for galactosemia

Interpretation: The concentration of galactitol is provided along with reference ranges for patients with galactosemia and normal controls.

Reference Values:
0-11 months: <109 mmol/mol creatinine
1-3 years: <52 mmol/mol creatinine
4-17 years: <16 mmol/mol creatinine
> or =18 years: <13 mmol/mol creatinine

Clinical References: 1. Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated March 11, 2021. Accessed October 24, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1518/ 2. Walter JH, Fridovich-Keil JL. Galactosemia. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed October 24, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225081023&bookid=2709 3. OMIM entry 618881 Galactose mutarotase deficiency. Johns Hopkins University; 2020. Updated August 20, 2020. Available at https://omim.org/entry/618881 4. Pasquali M, Yu C, Coffee B. Laboratory diagnosis of galactosemia: a technical standard and guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018;20(1):3-11. doi:10.1038/gim.2017.172

GALCR
606280

Galactocerebrosidase Reflex, Leukocytes

Clinical Information: Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of the enzyme, galactocerebrosidase (GALC). GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates (galactosylceramide, lactosylceramide, and lactosylsphingosine) causing severe demyelination throughout the brain. Krabbe disease is caused by variants in the GALC gene, and it has an estimated frequency of 1 in 100,000 births. Although rare, a few infants with an infantile Krabbe disease-like phenotype due to deficiency of saposin A have been found. Saposin-A is a sphingolipid activator protein that assists galactocerebrosidase in its action on galactosylceramide. Severely affected infants typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows, with death usually occurring by 2

years of age. Some individuals have later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression presenting anywhere from age 6 months to the seventh decade of life. The clinical course of Krabbe disease can be variable, even within the same family. Newborn screening for Krabbe disease has been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed early, prior to onset of neurologic damage. Reduced or absent galactocerebrosidase in leukocytes can indicate a diagnosis of Krabbe disease; however, a number of alterations in the GALC gene have been identified that result in reduced galactocerebrosidase activity in vitro but do not cause disease. The biomarker, psychosine (PSY / Psychosine, Blood Spot or PSYR / Psychosine, Whole Blood or PSYCF / Psychosine, Spinal Fluid), has been shown to be elevated in patients with active Krabbe disease. Molecular sequencing of the GALC gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, Varies) is necessary for differentiating alternations from disease-causing variants in affected patients and for carrier detection in family members.

Useful For: Diagnosis of Krabbe disease as a confirmatory reflex of the six-enzyme panel Follow-up testing for evaluation of an abnormal newborn screening result for Krabbe disease This test is not recommended for carrier detection because of the wide range of enzymatic activities observed in carriers and noncarriers.

Interpretation: When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

Only orderable as a reflex. For more information see LSD6W / Lysosomal Storage Disorders, Six-Enzyme Panel, Leukocytes.

> or =0.300 nmol/hour/mg protein

Clinical References: 1. Elliott S, Buroker N, Cournoyer JJ, et al: Pilot study of newborn screening for six lysosomal storage diseases using Tandem Mass Spectrometry. Mol Genet Metab. 2016 Aug;118(4):304-309 2. Matern D, Gavrilov D, Oglesbee D, Raymond K, Rinaldo P, Tortorelli S: Newborn screening for lysosomal storage disorders. Semin Perinatol. 2015 Apr;39(3):206-216 3. Orsini JJ, Escolar ML, Wasserstein MP, et al: Krabbe disease. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated October 11, 2018. Accessed April 5, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1238/ 4. Liao HC, Spacil Z, Ghomashchi F, et al: Lymphocyte galactocerebrosidase activity by LC-MS/MS for post-newborn screening evaluation of Krabbe disease. Clin Chem. 2017 Aug;63(8):1363-1369 5. Lin N, Huang J, Violante S, et al: Liquid chromatography-tandem mass spectrometry assay of leukocyte acid alpha-glucosidase for post-newborn screening evaluation of Pompe disease. Clin Chem. 2017 Apr;63(4):842-851

GALCW
606270

Galactocerebrosidase, Leukocytes

Clinical Information: Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of the enzyme, galactocerebrosidase (GALC). GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates (galactosylceramide, lactosylceramide, and lactosylsphingosine causing severe demyelination throughout the brain. Krabbe

disease is caused by variants in the GALC gene, and it has an estimated frequency of 1 in 100,000 births. Although rare, a few infants with an infantile Krabbe disease-like phenotype due to deficiency of saposin A have been found. Saposin-A is a sphingolipid activator protein that assists galactocerebrosidase in its action on galactosylceramide. Severely affected infants typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows, with death usually occurring by age 2 years. Some individuals have later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression presenting anywhere from age 6 months to the seventh decade of life. The clinical course of Krabbe disease can be variable, even within the same family. Newborn screening for Krabbe disease has been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed early, prior to onset of neurologic damage. Reduced or absent galactocerebrosidase in leukocytes can indicate a diagnosis of Krabbe disease; however, a number of alterations in the GALC gene have been identified that result in reduced galactocerebrosidase activity in vitro but do not cause disease. The biomarker, psychosine (PSY / Psychosine, Blood Spot or PSYR / Psychosine, Whole Blood or PSYCF / Psychosine, Spinal Fluid), has been shown to be elevated in patients with active Krabbe disease. Molecular sequencing of the GALC gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, Varies) is necessary for differentiating alterations from disease-causing variants in affected patients and for carrier detection in family members.

Useful For: Diagnosis of Krabbe disease Follow-up testing for evaluation of an abnormal newborn screening result for Krabbe disease This test is not intended for carrier detection.

Interpretation: When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
> or =0.300 nmol/hour/mg protein
An interpretative report will be provided.

Clinical References: 1. Newborn Screening ACT Sheet [Decreased galactocerebrosidase, elevated psychosine] Krabbe Disease (infantile form). American College of Medical Genetics and Genomics; 2021. Updated May 2022. Accessed June 10, 2024. Available at www.acmg.net/PDFLibrary/Krabbe-Infantile.pdf 2. Newborn Screening ACT Sheet [Decreased galactocerebrosidase, mildly elevated psychosine] Krabbe Disease (late-onset form). American College of Medical Genetics and Genomics; 2021. Updated May 2022. Accessed June 10, 2024. Available www.acmg.net/PDFLibrary/Krabbe-Later-Onset.pdf 3. Elliott S, Buroker N, Cournoyer JJ, et al: Pilot study of newborn screening for six lysosomal storage diseases using Tandem Mass Spectrometry. Mol Genet Metab. 2016 Aug;118(4):304-309 4. Matern D, Gavrilov D, Oglesbee D, Raymond K, Rinaldo P, Tortorelli S: Newborn screening for lysosomal storage disorders. Semin Perinatol. 2015 Apr;39(3):206-216 5. Orsini JJ, Escolar ML, Wasserstein MP, et al: Krabbe disease. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated October 11, 2018. Accessed April 5, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1238/ 6. Liao HC, Spacil Z, Ghomashchi F, et al: Lymphocyte galactocerebrosidase activity by LC-MS/MS for post-newborn screening evaluation of Krabbe disease. Clin Chem. 2017 Aug;63(8):1363-1369 7. Kwon JM, Matern DM, Kurtzberg J, et al: Consensus guidelines for newborn screening, diagnosis and treatment of infantile Krabbe disease. Orphanet J Rare Dis. 2018;13:30 doi: 10.1186/s13023-018-0766-x

GALK
8628

Galactokinase, Blood

Clinical Information: Galactokinase (GALK) deficiency is a very rare autosomal recessive disorder in the first step of galactose metabolism. Prevalence is unknown but is estimated to be approximately 1 in 50,000-1 in 100,000 live births, with a higher frequency in the Romani population. Individuals with GALK deficiency have a milder clinical presentation than that seen in patients with classic galactosemia, galactose-1-phosphate uridyltransferase deficiency. The major clinical manifestation is bilateral juvenile cataracts. GALK deficiency is treated with a galactose-restricted diet. Early treatment may prevent or reverse the formation of cataracts. In GALK deficiency, erythrocyte galactose-1-phosphate levels are generally normal, and plasma or urine galactose levels are generally elevated. The diagnosis is established by demonstrating deficient GALK enzyme activity in erythrocytes. Testing for GALK deficiency should be performed when there is a suspicion of galactosemia, either based upon the patient's clinical presentation or laboratory studies and GALT deficiency has been excluded. Specimens sent for GALT analysis may be used for GALK testing if the original specimen was received in the laboratory within the stability parameters listed in Specimen Stability Information. GALK deficiency is caused by variants in the GALK1 gene. Molecular analysis of the GALK1 gene is available; order CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies and specify Gene List ID: IEMCP-C2DU1U. For more information see Galactosemia Testing Algorithm.

Useful For: Diagnosis of galactokinase deficiency Evaluation of children with unexplained bilateral congenital or juvenile onset cataracts

Interpretation: An interpretive report will be provided. Deficient galactokinase enzyme activity in erythrocytes is diagnostic for galactokinase deficiency.

Reference Values:
> or =0.7 nmol/h/mg of hemoglobin

Clinical References: 1. Pasquali M, Yu C, Coffee B. Laboratory diagnosis of galactosemia: a technical standard and guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018;20(1):3-11. doi:10.1038/gim.2017.172 2. Hennermann JB, Schadewaldt P, Vetter B, Shin YS, Monch E, Klein J. Features and outcome of galactokinase deficiency in children diagnosed by newborn screening. J Inherit Metab Dis. 2011;34(2):399-407. doi:10.1007/s10545-010-9270-8 3. Ramani PK, Arya K. Galactokinase deficiency. In: StatPearls [Internet]. StatPearls Publishing; 2021. Updated July 31, 2023. Accessed September 12, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK560683/ 4. Walter JH, Fridovich-Keil JL. Galactosemia. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019 Accessed September 12, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=%20225081023

KM55
621066

Galactose Deficient IgA1 (KM55) Immunostain, Technical Component Only

Clinical Information:

Useful For: Identification of Galactose deficient IgA1 by KM55, useful in the diagnosis of IgA nephropathy

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate

immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Bu L, Ye B, Kouri AM, Kim Y. Diagnostic Utility of Galactose-Deficient Immunoglobulin A1 Immunostaining in the Differentiation of Lupus Nephritis and Immunoglobulin A Nephropathy. Glomerular Dis. 2021;1(1):34-39. Published 2021 Mar 10. doi:10.1159/000511056 2. Suzuki H, Yasutake J, Makita Y, et al. IgA nephropathy and IgA vasculitis with nephritis have a shared feature involving galactose-deficient IgA1-oriented pathogenesis. Kidney Int. 2018;93(3):700-705. doi:10.1016/j.kint.2017.10.019 3. Raj R, Sharma A, Barwad A, et al. KM55 in the Evaluation of IgA-Containing Glomerular Diseases. Glomerular Dis. 2021;2(2):59-74. Published 2021 Nov 2. doi:10.1159/000520640 4. Zhang K, Li Q, Zhang Y, et al. Clinical Significance of Galactose-Deficient IgA1 by KM55 in Patients with IgA Nephropathy. Kidney Blood Press Res. 2019;44(5):1196-1206. doi:10.1159/000502579

GALP
83638

Galactose, Quantitative, Plasma

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 4 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), uridine diphosphate galactose-4-epimerase (GALE), and galactose mutarotase (GALM). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Female patients with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. A comparison of plasma and urine galactose and blood galactose-1-phosphate (Gal1P) levels may be useful in distinguishing among the 4 forms of galactosemia. Deficiency Galactose (plasma/urine) Gal1P (blood) GALK Elevated Normal GALT Elevated Elevated GALE Normal-Elevated Elevated GALM Elevated Normal-Elevated For more information see Galactosemia Testing Algorithm.

Useful For: Screening for galactosemia

Interpretation: Additional testing is required to investigate the cause of abnormal results. In patients with galactosemia, elevated galactose in plasma or urine may suggest ineffective dietary restriction or compliance; however, the concentration of galactose-1-phosphate in erythrocytes (GAL1P / Galactose-1-Phosphate, Erythrocytes) is the most sensitive index of dietary control for patients with galactose-1-phosphate uridyltransferase and uridine diphosphate galactose-4-epimerase deficiencies. Increased concentrations of galactose may also be suggestive of severe hepatitis, biliary atresia of the newborn, and, in rare cases, galactose intolerance. If results are outside the normal range and galactosemia is suspected, additional testing to identify the specific enzymatic defect is required. Results should be correlated with clinical presentation and confirmed by specific enzyme or molecular analysis. For follow-up of abnormal newborn screening results, comprehensive diagnostic testing, and carrier testing see Galactosemia Testing Algorithm. For more information see Ordering Guidance.

Reference Values:
< or =7 days: <5.4 mg/dL
8-14 days: <3.6 mg/dL
> or =15 days: <2.0 mg/dL

Clinical References: 1. Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated March 11, 2021. Accessed September 12, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1518/ 2. Walter JH, Fridovich-Keil JL. Galactosemia. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 12, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=%20225081023 3. Wada Y, Kikuchi A, Arai-Ichinoi N, et al. Biallelic GALM pathogenic variants cause a novel type of galactosemia. Genet Med. 2019;21(6):1286-1294. doi:10.1038/s41436-018-0340-x 4. Timson DJ. Type IV galactosemia. Genet Med. 2019;21(6):1283-1285. doi:10.1038/s41436-018-0359-z

GALTP
80341

Galactose-1-Phosphate Uridyltransferase Biochemical Phenotyping, Erythrocytes

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 4 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), uridine diphosphate galactose-4-epimerase (GALE), and galactose mutarotase (GALM). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Female patients with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. Duarte-variant galactosemia (compound heterozygosity for the Duarte variant, N314D, and a classic variant) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Previously, it was unknown whether children with Duarte-variant galactosemia were at an increased risk for adverse developmental outcomes due to milk exposure and were often treated with a low galactose diet during infancy. More recently, the outcomes data suggest a lack of evidence for developmental complications due to milk exposure, therefore treatment recommendations remain controversial. The Los Angeles variant, which consists of N314D and a second variant, L218L, is associated with higher levels of GALT enzyme activity than the Duarte-variant allele. In general, molecular genetic analysis (GALZ / Galactosemia, GALT Gene, Full Gene Analysis, Varies) is typically performed to determine the specific genotype. If the enzymatic and molecular results are incongruent, biochemical phenotyping may be beneficial to help clarify results to determine a treatment strategy and recurrence risks. For more information see Galactosemia Testing Algorithm.

Useful For: Determining the biochemical phenotype for galactosemia when enzymatic and molecular results are incongruent

Interpretation: Different banding patterns obtained by isoelectric focusing of galactose-1-phosphate uridyltransferase (GALT) can be consistent with classic galactosemia, carrier status for a disease-causing GALT variant, compound heterozygosity, or a normal biochemical phenotype. The banding pattern is interpretated in the context of the separately measured GALT activity.

Reference Values:
An interpretative report will be provided.

Clinical References: 1. Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam

MP, Feldman J, Mirzaa GM, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated March 11, 2021. Accessed September 12, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1518/ 2. Walter JH, Fridovich-Keil JL. Galactosemia. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 12, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=%20225081023 3. Carlock G, Fischer ST, Lynch ME, et al. Developmental outcomes in Duarte galactosemia. Pediatrics. 2019;143(1):e20182516. doi:10.1542/peds.2018-2516 4. Anderson S. GALT deficiency galactosemia. MCN Am J Matern Child Nurs. 2018;43(1):44-51. doi:10.1097/NMC.0000000000000388

GALT
8333

Galactose-1-Phosphate Uridyltransferase, Blood

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 4 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), uridine diphosphate galactose-4-epimerase (GALE), and galactose mutarotase (GALM). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Female patients with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. Galactose-1-phosphate (Gal1P) accumulates in the erythrocytes of patients with galactosemia. The quantitative measurement of Gal1P (GAL1P / Galactose-1-Phosphate, Erythrocytes) is useful for monitoring compliance with dietary therapy. Gal1P is thought to be the causative factor for development of liver disease in these patients and, because of this, patients should maintain low levels and be monitored on a regular basis. Duarte-variant galactosemia (compound heterozygosity for the Duarte variant, N314D and a classic variant) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Previously, it was unknown whether children with Duarte-variant galactosemia were at an increased risk for adverse developmental outcomes due to milk exposure and were often treated with a low galactose diet during infancy. More recently, the outcomes data suggest a lack of evidence for developmental complications due to milk exposure, therefore treatment recommendations remain controversial. The Los Angeles variant, which consists of N314D and a second variant, L218L, is associated with higher levels of GALT enzyme activity than the Duarte-variant allele. Newborn screening for galactosemia is performed in all 50 US states, though the method by which potentially affected individuals are detected varies from state to state and may include the measurement of total galactose (galactose and Gal1P) and/or determining the activity of the GALT enzyme. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene (GALZ / Galactosemia, GALT Gene, Full Gene Analysis, Varies) is available to identify private variations. For more information see Galactosemia Testing Algorithm.

Useful For: Diagnosis of galactose-1-phosphate uridyltransferase deficiency, the most common cause of galactosemia Confirmation of abnormal state newborn screening results

Interpretation: Results below 24.5 nmol/h/mg of hemoglobin in properly submitted specimens have different causes from carrier status for a disease-causing variant in the GALT gene (typically reduced galactose-1-phosphate uridyltransferase [GALT] activity close to the normal activity range) to "Classic Galactosemia" due to biallelic disease-causing variants in the GALT gene that abolish GALT activity.

Further differentiation requires additional biochemical and molecular genetic analyses as well as correlation with clinical signs and symptoms. Normal results (> or =24.5 nmol/hour/mg of hemoglobin) are not consistent with galactosemia due to GALT deficiency. For more information see Galactosemia Testing Algorithm.

Reference Values:
> or =24.5 nmol/h/mg of hemoglobin

Clinical References: 1. Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, Feldman J, Mirzaa GM, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated March 11, 2021. Accessed September 12, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1518/ 2. Walter JH, Fridovich-Keil JL. Galactosemia. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 12, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=%20225081023 3. Carlock G, Fischer ST, Lynch ME, et al. Developmental outcomes in Duarte galactosemia. Pediatrics. 2019;143(1):e20182516. doi:10.1542/peds.2018-2516 4. Anderson S. GALT deficiency galactosemia. MCN Am J Matern Child Nurs. 2018;43(1):44-51. doi:10.1097/NMC.0000000000000388

GAL1P
80337

Galactose-1-Phosphate, Erythrocytes

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 4 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), uridine diphosphate galactose-4-epimerase (GALE), and galactose mutarotase (GALM). Galactose-1-phosphate (Gal1P) accumulates in the erythrocytes of patients with galactosemia due to GALT or GALE deficiency or in neonates with GALM deficiency. The quantitative measurement of Gal1P is useful for monitoring compliance with dietary therapy for either GALT or GALE deficiency. Gal1P is thought to be the causative factor for development of liver disease in these patients and, because of this, patients should maintain low levels and be monitored on a regular basis. The concentration of Gal1P in erythrocytes is the most sensitive index of dietary control. GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death. Galactosemia due to GALT deficiency is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Female patients with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. Epimerase deficiency galactosemia can be categorized into 3 types: generalized, peripheral, and intermediate. Generalized epimerase deficiency galactosemia results in profoundly decreased enzyme activity in all tissues, whereas peripheral epimerase deficiency galactosemia results in decreased enzyme activity in red and white blood cells but normal enzyme activity in all other tissues. This is compared with intermediate epimerase deficiency galactosemia, which results in decreased enzyme activity in red and white blood cells and less than 50% of normal enzyme levels in other tissues. Clinically, infants with generalized epimerase deficiency galactosemia develop symptoms such as liver and kidney dysfunction and mild cataracts when on a normal milk diet, while infants with peripheral or intermediate epimerase deficiency galactosemia do not develop any symptoms. Generalized epimerase deficiency galactosemia is treated by a galactose- and lactose-restricted diet, which can improve or prevent the symptoms of kidney and liver dysfunction and mild cataracts. Despite adequate treatment from an early age, individuals with generalized epimerase deficiency galactosemia remain at increased risk for developmental delay and intellectual disability. Unlike patients with classic galactosemia resulting from a GALT deficiency, female patients with generalized epimerase deficiency galactosemia experience normal puberty and are not at

increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of epimerase deficiency galactosemia in the United States ranges from approximately 1 in 6700 African American infants to 1 in 70,000 infants of European ancestry. GALM deficiency is a rare form of galactosemia that is due to a deficiency of galactose mutarotase, which may manifest clinically with bilateral cataracts. Infants with GALM deficiency have increased blood galactose concentrations with levels of galactose 1-phosphate ranging from 0.3 to 10.8 mg/dL.(1) Neonates with GALM deficiency have elevated galactose-1-phosphate, but Gal1P decreases rapidly in early infancy. To date, only pediatric patients have been described in the literature, and so the long-term, adult consequences of GALM deficiency remain unknown. The incidence of GALM deficiency has been reported as 1 in 10,000 in African populations and close to 1 in 80,000 in the Japanese population, with an overall estimation of about 1:228,411 in all populations.(2) For more information see Galactosemia Testing Algorithm.

Useful For: Monitoring dietary therapy of patients with galactosemia due to deficiency of galactose-1-phosphate uridyltransferase or uridine diphosphate galactose-4-epimerase

Interpretation: The concentration of galactose-1-phosphate (Gal1P) is provided along with reference values for patients with galactosemia and normal controls. The recommended Gal1P goal for patients with galactosemia is 4.9 mg/dL or less.

Reference Values:
Reference interval (normal range): < or =0.9 mg/dL
Therapeutic range: < or =4.9 mg/dL

Clinical References: 1. Wada Y, Kikuchi A, Arai-Ichinoi N, et al. Biallelic GALM pathogenic variants cause a novel type of galactosemia. Genet Med. 2019;21(6):1286-1294. doi:10.1038/s41436-018-0340-x 2. Iwasawa S, Kikuchi A, Wada Y, et al. The prevalence of GALM mutations that cause galactosemia: A database of functionally evaluated variants. Mol Genet Metab. 2019;126(4):362-367. doi:10.1016/j.ymgme.2019.01.018 3. Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, Feldman J, Mirzaa GM, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated March 11, 2021. Accessed September 12, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1518/ 4. Walter JH, Fridovich-Keil JL. Galactosemia. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed July 26, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=%20225081023 5. Timson DJ. Type IV galactosemia. Genet Med. 2019;21(6):1283-1285. doi:10.1038/s41436-018-0359-z 6. Fridovich-Keil J, Bean L, He M, et al. Epimerase deficiency galactosemia. In: Adam MP, Feldman J, Mirzaa GM, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 1993-2024. Updated March 4, 2021. Accessed September 12, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK51671/

APGAL
609738

Galactose-Alpha-1,3-Galactose (Alpha-Gal) Mammalian Meat Allergy Profile, Serum

Clinical Information: Immunoglobulin E antibodies to galactose-alpha-1,3-galactose (alpha-gal), a carbohydrate commonly expressed on non-primate mammalian proteins, are capable of eliciting allergenic reactions. Sensitization may occur through tick bites or exposure to the drug cetuximab. In the United States, individuals bitten by Amblyomma americanum, also known as the Lone Star tick, may develop IgE antibodies to alpha-gal, although sensitization to alpha-gal through other tick species has also been implicated.(1) The Lone Star tick was historically localized to the southern and southeastern United States but has now expanded its range into the central Midwest and northwards along the eastern seaboard. It is thought to be responsible for most cases of alpha-gal sensitization in the United States. The tick species that appears to be responsible for these responses in France is Ixodes

ricinus, while in Australia it is Ixodes holocyclus.(2,3,4) Signs and symptoms of an alpha-gal allergic reaction are often delayed compared with other food allergies. Upon exposure of sensitized subjects to non-primate mammalian meat (eg, beef, pork, venison) or meat-derived product such as gelatin, a delayed allergic response may ensue, often 3 to 6 hours after ingestion. Symptoms can include urticaria, angioedema, difficulty breathing, abdominal pain, vomiting, and even anaphylactic shock. Individuals who have antibodies produced against alpha-gal following a tick bite or previous exposure to the drug cetuximab may experience anaphylaxis when given cetuximab. Cetuximab is a monoclonal antibody, which contains an alpha-gal epitope on the antigen binding fragment (Fab fragment) of the monoclonal drug. Unlike the delayed onset anaphylaxis associated with red meat consumption, individuals with IgE antibody response to alpha-gal can experience immediate onset anaphylaxis upon intravenous cetuximab administration. Although most sensitizations to alpha-gal occur later in life, children who develop IgE antibodies to alpha-gal may also experience anaphylaxis and urticaria 3 to 6 hours after eating mammalian meat. Unlike their adult counterparts, who frequently present with anaphylaxis, the majority of children with this syndrome present with urticaria. Alpha-gal can also be found in mammalian milk, including cow and goat milk. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease.

Useful For: As an aid in diagnosis of an IgE mediated hypersensitivity allergy to non-primate mammalian red meat, such as beef, pork, venison, and meat-derived products, such as gelatin, via allergen profile testing This test is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists. This test is not useful for patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Berg EA, Platts-Mills TAE, Commins SP: Drug allergens and food--the cetuximab and galactose-alpha-1,3-galactose story. Ann Allergy Asthma Immunol. 2014 Feb;112(2):97-101 2. Commins SP, Platts-Mills TAE: Delayed anaphylaxis to red meat in patients with IgE specific for galactose alpha-1,3-galactose (alpha-gal). Curr Allergy Asthma Rep. 2013 Feb;13(1):72-77 3. Commins SP, James HR, Kelly LA, et al: The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-alpha-1,3-galactose. J Allergy Clin Immunol. 2011 May;127(5):1286-1293 4. Wolver SE, Sun DR, Commins SP, Schwartz LB: A peculiar

cause of anaphylaxis: no more steak? The journey to discovery of a newly recognized allergy to galactose-alpha-1,3-galactose found in mammalian meat. J Gen Intern Med. 2013 Feb;28(2):322-325 5. Commins SP, Platts-Mills TAE: Tick bites and red meat allergy. Curr Opin Allergy Clin Immunol. 2013 Aug;13(4):354-359 6. Hamsten C, Starkhammar M, Tran TA, et al: Identification of galactose-alpha-1,3-galactose in the gastrointestinal tract of the tick Ixodes ricinus; possible relationship with red meat allergy. Allergy. 2013 Apr;68(4):549-552 7. Steinke JW, Platts-Mills TAE, Commins SP: The alpha-gal story: lessons learned from connecting the dots. J Allergy Clin Immunol. 2015 Mar;135(3):589-597 8. Crispell G, Commins SP, Archer-Hartman SA, Choudhary S, Dharmarajan G, Azadi P, Karim S: Discovery of alpha-gal-containing antigens in North American tick species believed to induce red meat allergy. Front Immunol. 2019 May 17;10:1056 9. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070

ALGAL
609737

Galactose-Alpha-1,3-Galactose (Alpha-Gal), IgE, Serum

Clinical Information: Immunoglobulin E antibodies to galactose-alpha-1,3-galactose (alpha-gal), a carbohydrate commonly expressed on non-primate mammalian proteins, are capable of eliciting allergenic reactions. Sensitization may occur through tick bites or exposure to the drug cetuximab. In the United States, individuals bitten by Amblyomma americanum, also known as the Lone Star tick, may develop IgE antibodies to alpha-gal, although sensitization to alpha-gal through other tick species has also been implicated.(1) The Lone Star tick was historically localized to the southern and southeastern United States but has now expanded its range into the central Midwest and northwards along the eastern seaboard. It is thought to be responsible for most cases of alpha-gal sensitization in the United States. The tick species that appears to be responsible for these responses in France is Ixodes ricinus, while in Australia it is Ixodes holocyclus.(2,3,4) Signs and symptoms of an alpha-gal allergic reaction are often delayed compared with other food allergies. Upon exposure of sensitized subjects to non-primate mammalian meat (eg, beef, pork, venison) or meat-derived product such as gelatin, a delayed allergic response may ensue, often 3 to 6 hours after ingestion. Symptoms can include urticaria, angioedema, difficulty breathing, abdominal pain, vomiting, and even anaphylactic shock. Individuals who have antibodies produced against alpha-gal following a tick bite or previous exposure to the drug cetuximab may experience anaphylaxis when given cetuximab. Cetuximab is a monoclonal antibody, which contains an alpha-gal epitope on the antigen binding fragment (Fab fragment) of the monoclonal drug. Unlike the delayed onset anaphylaxis associated with red meat consumption, individuals with IgE antibody response to alpha-gal can experience immediate onset anaphylaxis upon intravenous cetuximab administration. Although most sensitizations to alpha-gal occur later in life, children who develop IgE antibodies to alpha-gal may also experience anaphylaxis and urticaria 3 to 6 hours after eating mammalian meat. Unlike their adult counterparts, who frequently present with anaphylaxis, the majority of children with this syndrome present with urticaria. Alpha-gal can also be found in mammalian milk, including cow and goat milk. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease.

Useful For: As an aid in diagnosis of an IgE mediated hypersensitivity allergy to non-primate mammalian red meat, such as beef, pork, venison, and meat-derived products (eg, gelatin) This test is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists. This test is not useful for patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Berg EA, Platts-Mills TAE, Commins SP: Drug allergens and food--the cetuximab and galactose-alpha-1,3-galactose story. Ann Allergy Asthma Immunol. 2014 Feb;112(2):97-101 2. Commins SP, Platts-Mills TAE: Delayed anaphylaxis to red meat in patients with IgE Specific for Galactose alpha-1,3-Galactose (alpha-gal). Curr Allergy Asthma Rep. 2013 Feb;13(1):72-77 3. Commins SP, James HR, Kelly LA, et al: The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-alpha-1,3-galactose. J Allergy Clin Immunol. 2011 May;127(5):1286-1293 4. Wolver SE, Sun DR, Commins SP, Schwartz LB: A peculiar cause of anaphylaxis: no more steak? The journey to discovery of a newly recognized allergy to galactose-alpha-1,3-galactose found in mammalian meat. J Gen Intern Med. 2013 Feb;28(2):322-325 5. Commins SP, Platts-Mills TAE: Tick bites and red meat allergy. Curr Opin Allergy Clin Immunol. 2013 Aug;13(4):354-359 6. Hamsten C, Starkhammar M, Tran TA, et al: Identification of galactose-alpha-1,3-galactose in the gastrointestinal tract of the tick Ixodes ricinus; possible relationship with red meat allergy. Allergy. 2013 Apr;68(4):549-552 7. Steinke JW, Platts-Mills TAE, Commins SP: The alpha-gal story: lessons learned from connecting the dots. J Allergy Clin Immunol. 2015 Mar;135(3):589-597 8. Crispell G, Commins SP, Archer-Hartman SA, Choudhary S, Dharmarajan G, Azadi P, Karim S: Discovery of alpha-gal-containing antigens in North American tick species believed to induce red meat allergy. Front Immunol. 2019 May 17;10:1056 9. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070

GCT
84360

Galactosemia Reflex, Blood

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 4 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase, uridine diphosphate galactose-4-epimerase, and galactose mutarotase. GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and motor function abnormalities. Female patients with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1

in 60,000 live births. Galactose-1-phosphate (Gal1P) accumulates in the erythrocytes of patients with galactosemia. The quantitative measurement of Gal1P is useful for monitoring compliance with dietary therapy. Gal1P is thought to be the causative factor for development of liver disease in these patients. Because of this, patients should maintain low levels and be monitored on a regular basis. Duarte-variant galactosemia (compound heterozygosity for the Duarte variant, N314D, and a classic variant) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Previously, it was unknown whether children with Duarte-variant galactosemia were at an increased risk for adverse developmental outcomes due to milk exposure and were often treated with a low galactose diet during infancy. More recently, the outcomes data suggest a lack of evidence for developmental complications due to milk exposure, therefore treatment recommendations remain controversial. The Los Angeles variant, which consists of N314D and a second genetic variant, L218L, is associated with higher levels of GALT enzyme activity than the Duarte-variant allele. Newborn screening for galactosemia is performed in all 50 US states, though the method by which potentially affected individuals are detected varies from state to state and may include the measurement of total galactose (galactose and Gal1P) and/or determining the activity of the GALT enzyme. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme level is less than 24.5 nmol/h/mg of hemoglobin, sequencing of the GALT gene is performed. For more information see Galactosemia Testing Algorithm.

Useful For: Preferred test for diagnosis, carrier detection, and determination of genotype of galactose-1-phosphate uridyltransferase deficiency, the most common cause of galactosemia Differentiating Duarte variant galactosemia from classic galactosemia Confirming results of newborn screening programs

Interpretation: The laboratory provides an interpretation of the results, including galactose-1-phosphate uridyltransferase enzyme activity and genotype, if necessary. This interpretation provides an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional testing. In any specimen where enzyme activity is less than 24.5 nmol/h/mg of hemoglobin GALT full gene sequencing will be performed. For testing algorithm and more information, see Galactosemia Testing Algorithm. The GALT gene maps to chromosome 9p13. Several disease-causing variants are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R classic variant. This alteration accounts for 60% to 70% of classic galactosemia alleles. The S135L variant is the most frequently observed in African Americans and accounts for approximately 50% of the altered alleles in this population. The K285N variant is common in those of eastern European descent and accounts for 25% to 40% of the alleles in this population. The L195P variant is observed in 5% to 7% of classical galactosemia. The 5-kilobase deletion is common in individuals of Ashkenazi Jewish descent. The Duarte variant (N314D and -119_-116delGTCA) is observed in 5% of the general US population.

Reference Values:
> or =24.5 nmol/h/mg of hemoglobin

Clinical References: 1. Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated March 11, 2021. Accessed September 10, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1518/ 2. Walter JH, Fridovich-Keil JL. Galactosemia. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. Eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 10, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=%20225081023 3. Carlock G, Fischer ST, Lynch ME, et al. Developmental outcomes in Duarte galactosemia. Pediatrics. 2019;143(1):e20182516. doi:10.1542/peds.2018-2516

GALZ
608016

Galactosemia, GALT Gene, Full Gene Analysis, Varies

Clinical Information: Classic galactosemia is an autosomal recessive disorder of galactose metabolism caused by variants in the galactose-1-phosphate uridyltransferase (GALT) gene. The complete or near complete deficiency of the GALT enzyme is life threatening. If left untreated, complications include liver failure, sepsis, intellectual disability, and death. Galactosemia is treated by a galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. The prevalence of classic galactosemia is approximately 1 in 30,000. Duarte variant galactosemia (compound heterozygosity for the Duarte variant, N314D and a classic variant) is generally associated with higher levels of GALT activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte variant galactosemia have a milder phenotype but are often treated with a low galactose diet during infancy. The LA variant, consisting of N314D and a second change, L218L, is associated with higher levels of GALT activity than the Duarte variant alone. Newborn screening, which identifies potentially affected individuals by measuring total galactose (galactose and galactose-1-phosphate) or determining the activity of the GALT enzyme, varies from state to state. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT activity. If enzyme activity levels are indicative of carrier or affected status, molecular testing for common GALT variants may be performed. If 1 or both disease-causing variants are not detected by targeted variant analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is available to identify private variants. The GALT gene maps to 9p13 and more than 180 variants have been identified. Several disease-causing variants are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R variant, which accounts for 60% to 70% of classic galactosemia alleles. The S135L variant is the most frequently observed variant in the African American population and accounts for approximately 50% of the altered alleles in this population. The K285N variant is common in those of eastern European descent and accounts for 25% to 40% of the alleles in this population. The L195P variant is observed in 5% to 7% of classic galactosemia. The Duarte variant (N314D) is found in 5% of the general United States population. The above variants, plus the LA variant, are included in GCT / Galactosemia Reflex, Blood, which is the preferred test for the diagnosis of galactosemia or for follow-up to positive newborn screening results. These variants are also included in GALMP / Galactosemia, GALT Gene, Variant Panel, Varies. Full sequencing of the GALT gene can be useful for the identification of variants when 1 or no variants are found with these tests in an individual with demonstrated GALT activity deficiency. Full sequencing of the GALT gene identifies over 95% of the sequence variants in the coding region and splice junctions. For more information see Galactosemia Testing Algorithm.

Useful For: Identifying variants in individuals who test negative for the common variants and who have a biochemical diagnosis of galactosemia or galactose-1-phosphate uridyltransferase activity levels indicative of carrier status

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Elsas LJ 2nd, Lai K. The molecular biology of galactosemia. Genet Med.

1998;1(1):40-48 3. Novelli G, Reichardt JK. Molecular basis of disorders of human galactose metabolism: past, present, and future. Mol Genet Metab. 2000;71(1-2):62-65 4. Bosch AM, Ijlst L, Oostheim W, et al. Identification of novel variants in classical galactosemia. Hum Mutat. 2005;25(5):502 5. Welling L, Bernstein LE, Berry GT, et al. International clinical guideline for the management of classical galactosemia; diagnosis, treatment, and follow-up. J Inherit Metab Dis. 2017;40(2):171-176

GALMP
606343

Galactosemia, GALT Gene, Variant Panel, Varies

Clinical Information: Classical galactosemia is an autosomal recessive disorder of galactose metabolism caused by genetic variants in the galactose-1-phosphate uridyltransferase (GALT) gene. The complete or near complete deficiency of the GALT enzyme is life threatening. If left untreated, complications include liver failure, sepsis, intellectual disability, and death. Galactosemia is treated by a galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Women with galactosemia are at increased risk for premature ovarian failure. The prevalence of classic galactosemia is approximately 1 in 30,000. Duarte variant galactosemia (compound heterozygosity for the Duarte variant, N314D and -119_-116delGTCA in cis [on the same chromosome], and a classic variant in trans [on the opposite chromosome]) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte variant galactosemia have a milder phenotype but are also often treated with a low-galactose diet during infancy. The Los Angeles (LA) variant, which consists of N314D without the presence of -119_-116delGTCA, is associated with normal levels of GALT enzyme activity. Newborn screening, which identifies potentially affected individuals by measuring total galactose (galactose and galactose-1-phosphate) and/or determining the activity of the GALT enzyme, varies from state to state. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are indicative of carrier or affected status, molecular testing for common GALT variants may be performed. If one or both disease-causing variants are not detected by targeted variant analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is available to identify private variants. The GALT gene maps to 9p13. Several disease-causing variants are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R classic variant. This variant accounts for 60% to 70% of classical galactosemia alleles. The S135L variant is the most frequently observed variant in African Americans and accounts for approximately 50% of the altered alleles in this population. The K285N variant is common in those of eastern European descent and accounts for 25% to 40% of the alleles in this population. The L195P variant is observed in 5% to 7% of classical galactosemia. The 5 kilobase deletion is common in individuals of Ashkenazi Jewish descent. The Duarte variant (N314D and -119_-116delGTCA) is observed in 5% of the general United States population. The rest of the variants detected by this method are all uncommon but known to be recurrent in the general population. These variants, in addition to the LA variant, are included in this test and in GCT / Galactosemia Reflex, Blood. For more information see Galactosemia Testing Algorithm. Table. Targeted Variants Associated phenotype Gene (transcript) Variants Galactosemia GALT (NM_000155) c.-119_-116del*, c.136_140del, c.221T>C*, c.253-2A>G*, c.292G>A*, c.404C>T*, c.413C>T*, c.425T>A*, c.443G>A*, c.505C>A, c.512T>C*, c.563A>G*, c.584T>C*, c.607G>A*, c.626A>G*, c.855G>T*, c.940A>G*, c.958G>A*, c.997C>G*, c.997C>T*, c.1018G>T, c.1030C>A*, c.1138T>C* Deletion analysis of exon 1-11 *Previously detected in a known positive sample

Useful For: Second-tier test for confirming a diagnosis of galactosemia as indicated by enzymatic testing or newborn screening Carrier testing family members of an affected individual of known genotype (has variants included in the panel) Resolution of Duarte variant and Los Angeles (LA) variant genotypes

Interpretation: An interpretative report will be provided. Results should be interpreted in the context of biochemical results. If results of the galactose-1-phosphate uridyltransferase enzyme analysis and this test are discordant, then consider GALZ / Galactosemia, GALT Gene, Full Gene Analysis, Varies.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424. doi: 10.1038/gim.2015.30 2. Elsas LJ 2nd, Lai K: The molecular biology of galactosemia. Genet Med. 1998 Nov-Dec;1(1):40-48. doi: 10.1097/00125817-199811000-00009 3. Kaye CI, Committee on Genetics, Accurso F, et al: Newborn screening fact sheets. Pediatrics. 2006 Sep;118(3):e934-e963. doi: 10.1542/peds.2006-1783 4. Novelli G, Reichardt JK: Molecular basis of disorders of human galactose metabolism: past, present, and future. Mol Genet Metab. 2000 Sep-Oct;71(1-2):62-65. doi: 10.1006/mgme.2000.3073 5. Welling L, Bernstein LE, Berry GT, et al: International clinical guideline for the management of classical galactosemia: diagnosis, treatment, and follow-up. J Inherit Metab Dis. 2017 Mar;40(2):171-176. doi: 10.1007/s10545-016-9990-5 6. Carlock G, Fischer ST, Lynch ME, et al: Developmental outcomes in Duarte galactosemia. Pediatrics. 2019 Jan;143(1):e20182516. doi: 10.1542/peds.2018-2516

GAL1
606832

GALAD Score, Serum

Clinical Information: Biomarkers of hepatocellular carcinoma (HCC) include alpha-fetoprotein (AFP), third electrophoretic form of lentil lectin-reactive AFP (AFP-L3), and des-carboxy-prothrombin (DCP). The GALAD (gender, age, AFP-L3, AFP, des-gamma-carboxy prothrombin) model combines these three biomarkers with the patient's gender and age to estimate the risk of HCC in patients with chronic liver disease based on the following equation: Z = -10.08 + 0.09 x age + 1.67 x sex + 2.34 log(10) (AFP) + 0.04 x AFP - L3 + 1.33 x log(10) (DCP), where sex = 1 for males, 0 for females. The GALAD score is calculated using the lower limit of quantitation (LLOQ) when one or more of the following values are below the LLOQ: %L3, Total AFP, or Des-Gamma-Carboxy Prothrombin.. In the event this occurs, the GALAD score is resulted as (<)GALAD score. The GALAD model has been demonstrated to have higher diagnostic accuracy for the detection of HCC when compared to the use AFP, AFP-L3, and DCP markers alone or in combination. The performance of the GALAD score has also been reported to be superior to ultrasound for HCC detection.

Useful For: Calculation of the GALAD (gender, age, alpha-fetoprotein L3% [AFP-L3], AFP, des-gamma-carboxy prothrombin) model score for hepatocellular carcinoma development in patients with chronic liver disease

Interpretation: Higher GALAD (gender, age, AFP-L3, AFP, des-gamma-carboxy prothrombin) model scores correlate with increased risk of hepatocellular carcinoma (HCC). The area under the curve (AUC) of a receiver operating characteristic (ROC) curve of the GALAD score was 0.95 for all HCC detection and 0.92 for the detection of early-stage HCC. Additionally, the AUC of the GALAD score (0.95) was higher than that of ultrasound alone for all HCC detection (AUC of 0.82, P <0.01). The sensitivity and specificity performance characteristics of the GALAD score for HCC will be influenced by the selected GALAD score cut-off. For example, at an optimal AUC cutoff of -0.76, the GALAD score had 91% sensitivity and 85% specificity for HCC detection. At a more specific GALAD score cutoff of 0.88, the observed sensitivity was 80% for HCC detection, with an observed specificity of 97%. The GALAD model was developed and validated in patient cohorts with a prevalence of HCC ranging from 35% to 49%. The performance of the model may be altered in populations with different HCC prevalence. In addition, the clinical performance of the GALAD score varies by etiology of HCC and, therefore, may be

different in different regions of the world.

Reference Values:
Only orderable as part of a profile. For more information see HCCGS / Hepatocellular Carcinoma Risk Panel with GALAD Score, Serum

Not applicable

Clinical References: 1. Johnson P, Pirrie S, Cox T, et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev. 2014;23(1):144-153 2. Berhane S, Toyota H, Tada T, et al. Role of the GALAD and BALAD-2 serologic models in diagnosis of hepatocellular carcinoma and prediction of survival in patients. Clin Gastroenterol Hepatic. 2016;14(6):875-886 3. Yang JD, Addissie BD, Mara KC, et al. GALAD score for hepatocellular carcinoma detection in comparison with liver ultrasound and proposal of GALADUS score. Cancer Epidemiol Biomarkers Prev. 2019;28(3):531-538. doi:10.1158/1055-9965 4. Leerapun A, Suravarapu S, Bida JP, et al. The utility of serum AFP-L3% in the diagnosis of hepatocellular carcinoma: Evaluation in a U.S. referral population. Clin Gastroenterol Hepatol. 2007;5(3):394-402 5. Durazo FA, Blatt LM, Corey WG, et al. Des-gamma-carboxyprothrombin, alpha-fetoprotein and AFP-L3 in patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma. J Gastroenterol Hepatol. 2008;23(10):1541-1548 6. Chaiteerakij R, Addissie BD, Roberts LR. Update on biomarkers of hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2015;13(2):237-245. doi:10.1016/j.cgh.2013.10.038

GALN3
70438

Galectin-3 Immunostain, Technical Component Only

Clinical Information: Galectin-3 is a member of the beta-galactoside binding lectin family and is involved in cellular adhesion. It is expressed by normal macrophages, neutrophils, and mast cells. It is not expressed in normal or benign thyroid glands but may be expressed in thyroid carcinoma.

Useful For: Distinguishing normal and benign thyroid gland from thyroid carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

GAL3
86202

Galectin-3, Serum

Clinical Information: Heart failure is a complex cardiovascular disorder with a variety of etiologies and heterogeneity with respect to the clinical presentation of the patient. Heart failure is significantly increasing in prevalence with an aging population and is associated with high short- and long-term mortality rate. Over 80% of patients diagnosed and treated for acute heart failure syndromes in the emergency department are re-admitted within the forthcoming year, incurring costly treatments and therapies. The development and progression of heart failure is a clinically silent process until manifestation of the disorder, which typically occurs late and irreversibly into its progression. Mechanistically, heart failure, whether due to systolic or diastolic dysfunction, is thought to progress primarily through adverse cardiac remodeling and fibrosis in response to cardiac injury or stress. Galectin-3 is a biomarker that appears to be actively involved in both the inflammatory and some

fibrotic pathways. Galectin-3 is a carbohydrate-binding lectin whose expression is associated with inflammatory cells, including macrophages, neutrophils, and mast cells. Galectin-3 has been linked to cardiovascular physiological processes including myofibroblast proliferation, tissue repair, and cardiac remodeling in the setting of heart failure. Concentrations of galectin-3 have been used to predict adverse remodeling after a variety of cardiac insults.

Useful For: Aiding in the prognosis for patients diagnosed with heart failure Risk stratification of patients with heart failure An early indication of treatment failure and as a therapeutic target

Interpretation: Clinically, galectin-3 concentrations may be categorized into 3 risk categories, substantiated by results from several large chronic heart failure studies: < or =17.8 ng/mL (low risk) 17.9-25.9 ng/mL (intermediate risk) >25.9 ng/mL (higher risk) Results should be interpreted in the context of the individual patient presentation. Elevated galectin-3 results indicate an increased risk for adverse outcomes and signal the presence of galectin-3-mediated fibrosis and adverse remodeling. Once galectin-3 concentrations are elevated they are relatively stable over time in the absence of intervention. Knowledge of a patient with heart failure's galectin-3 results may assist in risk stratification and lead to more aggressive management. There are no specific galectin-3 inhibitors available at this time, and patients with heart failure and elevated galectin-3 concentrations should be treated and monitored according to established guidelines. Angiotensin receptor blockers and aldosterone antagonists are thought to be particularly effective. A large multicenter, prospective, observational study was conducted to derive the reference intervals for galectin-3 that included 1092 subjects between the ages of 55 and 80 years without any known cardiac disease (520 males, 572 females). The 97.5th percentile of galectin-3 in that cohort was 22.1 ng/mL. Individuals with concentrations greater than 22.1 ng/mL had a significant association with mortality and New York Heart Association classification. However, this was an older population and definitive evidence of cardiac disease was not documented.

Reference Values:
<24 months: Not established
2-17 years: < or =25.0 ng/mL
> or =18 years: < or =22.1 ng/mL

Clinical References: 1. Van der Velde AR, Meijers WC, Van den Heuvel ER, et al. Determinants of temporal changes in galectin-3 level in the general population: Data of PREVEND. Int J Cardiol. 2016;222:385-390. doi:10.1016/j.ijcard.2016.07.241 2. Mueller T, Gegenhuber A, Leitner I, et al. Diagnostic and prognostic accuracy of galectin-3 and soluble ST2 for acute heart failure. Clin Chim Acta. 2016;463:158-164. doi:10.1016/j.cca.2016.10.034 3. Sudharshan S, Novak E, Hock K, et al. Use of biomarkers to predict readmission for congestive heart failure. Am J Cardiol. 2017;119:445-451. doi:10.1016/j.amjcard.2016.10.022 4. Meijers WC, van der Velde AR, Muller Kobold AC, et al. Variability of biomarkers in patients with chronic heart failure and healthy controls. Eur J Heart Fail. 2017;19:357-365. doi:10.1002/ejhf.669 5. Meeusen JW, Johnson JN, Gray A, et al. Soluble ST2 and galectin-3 in pediatric patients without heart failure. Clin Biochem. 2015;48(18):1337-1340. doi:10.1016/j.clinbiochem.2015.08.007

GBACS
620232

Gamma-Amino Butyric Acid Type A (GABA-A) Receptor Antibody, Cell-Binding Assay, Serum

Clinical Information: Gamma-amino butyric acid type A (GABA-A) receptor autoantibodies are highly predictive of GABA-A receptor autoimmune encephalitis. Patients who are seropositive for GABA-A receptor encephalitis have characteristic clinical-radiologic presentations including frequent seizures and multifocal lesions in the white matter. Majority of patients are treatable with immunotherapy.

Useful For: Evaluating patients with suspected autoimmune encephalitis and autoimmune epilepsy

using serum specimens

Interpretation: Seropositivity for gamma-amino butyric acid type A receptor autoantibodies supports the clinical diagnosis of autoimmune encephalitis with neurological presentations including seizures and multifocal lesions in the white matter. A search for thymoma cancer and a trial of immunotherapy should be considered.

Reference Values:
Negative

Clinical References: 1. O'Connor K, Waters P, Komorowski L, et al. GABAA receptor autoimmunity A multicenter experience. Neurol Neuroimmunol Neuroinflamm 2019;6(3):e552. doi:10.1212/NXI.0000000000000552 2. Spatola M, Petit-Pedrol M, Simabukuro MM, et al. Investigations in GABAA receptor antibody-associated encephalitis. Neurology. 2017;88(11):1012-1020. doi:10.1212/WNL.0000000000003713 3. Waters P, Irani S. GABA-A receptor antibodies and their clinical associations. Neurology. 2017; 88:1010-1011 4. Petit-Pedrol M, Armangue T, Peng X, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterization of the antigen, and analysis of the effects of antibodies. Lancet Neurol. 2014;13(3):276-286

GBACC
620231

Gamma-Amino Butyric Acid Type A (GABA-A) Receptor Antibody, Cell-Binding Assay, Spinal Fluid

Clinical Information: Gamma-amino butyric acid type A (GABA-A) receptor autoantibodies are highly predictive of GABA-A receptor autoimmune encephalitis. Patients who are seropositive for GABA-A receptor encephalitis have characteristic clinical-radiologic presentations including frequent seizures and multifocal lesions in the white matter. The majority of patients are treatable with immunotherapy.

Useful For: Evaluating patients with suspected autoimmune encephalitis and autoimmune epilepsy using spinal fluid specimens

Interpretation: Seropositivity for gamma-amino butyric acid type A receptor autoantibodies supports the clinical diagnosis of autoimmune encephalitis with neurological presentations including seizures and multifocal lesions in the white matter. A search for thymoma cancer and a trial of immunotherapy should be considered.

Reference Values:
Negative

Clinical References: 1. O'Connor K, Waters P, Komorowski L, et al. GABAA receptor autoimmunity A multicenter experience. Neurol Neuroimmunol Neuroinflamm. 2019;6(3):e552. doi:10.1212/NXI.0000000000000552 2. Spatola M, Petit-Pedrol M, Simabukuro MM, et al. Investigations in GABAA receptor antibody-associated encephalitis. Neurology. 2017; 88(11):1012-1020. doi:10.1212/WNL.0000000000003713 3. Waters P, Irani S. GABA-A receptor antibodies and their clinical associations. Neurology. 2017;88:1010-1011 4. Petit-Pedrol M, Armangue T, Peng X, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterization of the antigen, and analysis of the effects of antibodies. Lancet Neurol. 2014;13(3):276-286

WGSEQ
62982

Gamma-Globin Full Gene Sequencing, Varies

Clinical Information: Hemoglobin F (HbF) is the dominant hemoglobin at birth but is gradually replaced by adult hemoglobin (HbA) during the year after birth (normal value < or =1% of total hemoglobin after age 2 years). Increased HbF levels may continue after the neonatal period and into adulthood for various reasons. Genetic causes include deletional and nondeletional forms of hereditary persistence of fetal hemoglobin (HPFH) and delta-beta thalassemia variants. Over 100 genetic variants have been described in the gamma genes and, if detectable, the protein expression will vary over time according to the overall HbF expression. Gamma globin variants can manifest either as a quantitative (gamma thalassemia or nondeletional HPFH) or a qualitative (gamma variant) abnormality. Nondeletional HPFH alterations frequently modulate the expected severity of sickling disorders due to the inhibitory properties of HbF on sickle formation. Many gamma chain variants are benign, although some, such as unstable, high- and low-oxygen affinity, or M hemoglobin variants, cause hemolytic anemia/hyperbilirubinemia, erythrocytosis, cyanosis, and methemoglobinemia, respectively. The percentages of gamma variants will vary according to if they are present on the HBG1 or HBG2 genes, as these genes are differentially expressed depending on the age of the patient. Symptoms due to gamma variants are expected to decrease along with the normal decrease in HbF and therefore, most resolve after the first 6 months of life.

Useful For: An adjunct in the interpretation of hemoglobin electrophoresis results Evaluation for suspected gamma variants or nondeletional hereditary persistence of fetal hemoglobin Assessment of unstable gamma chain variants when other tests for causes of hemolysis are unrevealing

Interpretation: An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any variants in the gene. If positive, the alteration will be correlated with clinical significance if known.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Crowley MA, Mollan TL, Abdulmalik OY, et al. A hemoglobin variant associated with neonatal cyanosis and anemia. N Engl J Med. 2011;364(19):1837-1843 2. Cui J, Baysdorfer C, Azimi M, et al. Identification of three novel Hb F variants: Hb F-Hayward [(G)gamma1(NA1)Gly>Asp, GGT>GAT], Hb F-Chori-I [(A)gammaT16(A13)Gly>Asp, GGC>GAC] and Hb F-Chori-II [(A)gammaI29(B11)Gly>Glu, GGA>GAA]. Hemoglobin. 2012;36:305-309 3. Akinsheye I, Alsultan A, Solovieff N, et al. Fetal hemoglobin in sickle cell anemia. Blood. 2011;118(1):19-27 4. Steinberg M, Forget B, Higgs D, Weatherall D, eds. Disorders of Hemoglobin Genetics, Pathophysiology, and Clinical Management. 2nd ed. Cambridge University Press; 2009 5. Provan D, Gribben J, eds. Molecular Hematology. 3rd ed. Blackwell Publishing; 2010 6. Hoyer JD, Kroft SH, eds. Color Atlas of Hemoglobin Disorders: A Compendium Based on Proficiency Testing. College of American Pathologists; 2003 7. Merchant S, Oliveira JL, Hoyer JD, Viswanatha DS. Molecular diagnosis in hematopathology. In: Goldblum J. Hsi E, eds. Hematopathology: A Volume in the Series: Foundations in Diagnostic Pathology. 2nd ed. Churchill Livingstone; 2012:chap 24 8. Semkiu KM, Oliveira JL, Nguyen PL, Porter TR, Wilson DB. Hb F-Wentzville [(G)gamma24(B6)Gly>Glu; HBG2: c.74G>A, p.Gly25Glu]: An unstable (G)gamma-globin variant associated with neonatal hemolytic anemia. Hemoglobin. 2020;44(1):67-69. doi:10.1080/03630269.2020.1716002

GGT
8677

Gamma-Glutamyltransferase (GGT), Serum

Clinical Information: Gamma-glutamyltransferase (GGT) is primarily present in kidney, liver, and pancreatic cells. Small amounts are present in other tissues. Even though renal tissue has the highest level of GGT, the enzyme present in the serum appears to originate primarily from the hepatobiliary system,

and GGT activity is elevated in any and all forms of liver disease. It is highest in cases of intra- or posthepatic biliary obstruction, reaching levels some 5 to 30 times normal. GGT is more sensitive than alkaline phosphatase (ALP), leucine aminopeptidase, aspartate transaminase, and alanine aminotransferase in detecting obstructive jaundice, cholangitis, and cholecystitis; its rise occurs earlier than with these other enzymes and persists longer. Only modest elevations (2-5 times normal) occur in infectious hepatitis, and in this condition, GGT determinations are less useful diagnostically than are measurements of the transaminases. High elevations of GGT are also observed in patients with either primary or secondary (metastatic) neoplasms. Elevated levels of GGT are noted not only in the sera of patients with alcoholic cirrhosis but also in the majority of sera from persons who are heavy drinkers. Studies have emphasized the value of serum GGT levels in detecting alcohol-induced liver disease. Elevated serum values are also seen in patients receiving drugs such as phenytoin and phenobarbital, and this is thought to reflect induction of new enzyme activity. Normal values are observed in various muscle diseases and in renal failure. Normal values are also seen in cases of skeletal disease, children older than 1 year, and in healthy pregnant women-conditions in which ALP is elevated.

Useful For: Diagnosing and monitoring hepatobiliary disease, it is currently the most sensitive enzymatic indicator of liver disease Ascertaining whether observed elevations of alkaline phosphatase are due to skeletal disease (normal gamma-glutamyltransferase: GGT) or reflect the presence of hepatobiliary disease (elevated GGT) A screening test for occult alcoholism

Interpretation: An elevation of gamma-glutamyltransferase (GGT) activity is seen in any and all forms of liver disease, although the highest elevations are seen in intra- or posthepatic biliary obstruction. Elevated values can also indicate alcoholic cirrhosis or individuals who are heavy drinkers. The finding of increased GGT and alkaline phosphatase (ALP) activity is consistent with hepatobiliary disease. The finding of normal GGT activity and increased ALP activity is consistent with skeletal disease.

Reference Values:

Males
0-11 months: <178 U/L
12 months-6 years: <21 U/L
7-12 years: <24 U/L
13-17 years: <43 U/L
> or =18 years: 8-61 U/L

Females
0-11 months: <178 U/L
12 months- 6 years: <21 U/L
7-12 years: <24 U/L
13-17 years: <26 U/L
> or =18 years: 5-36 U/L

Clinical References: 1. Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. WB Saunders Company, Philadelphia, 1994 2. Heiduk M, Page I, Kliem C, et al: Pediatric reference intervals determined in ambulatory and hospitalized children and juveniles. Clin Chim Acta 2009:406:156-161

FGHSP 58034 Gamma-Hydroxybutyric Acid (GHB), Serum/Plasma

Reference Values:

Reference Range: Negative

Screening threshold: 10.0 ug/mL

FGHSU 58036 Gamma-Hydroxybutyric Acid (GHB), Urine

Reference Values:
Reference Range: Negative

Screening threshold: 5.0 ug/mL

FGANP 75518 Ganciclovir, Plasma

Interpretation: Plasma concentrations after 1-hour I.V. infusion of 5 mg/kg were 9.46 +/- 2.02 mcg/mL at 1 hour post-dose and 0.56 +/- 0.66 mcg/mL at 11 hours post-dose. Peak plasma concentrations following chronic oral administration of 1000 mg three times daily ranged from 0.95 - 1.40 mcg/mL.

Reference Values:
Reporting limit determined each analysis.
None Detected mcg/mL

FGAGM 58017 Ganglioside (Asialo-GM1, GM1, GM2, GD1a, GD1b, and GQ1b) Antibodies

Interpretation: Ganglioside antibodies are associated with diverse peripheral neuropathies. Elevated antibody levels to ganglioside-monosialic acid (GM1) and the neutral glycolipid, asialo-GM1 are associated with motor or sensorimotor neuropathies, particularly multifocal motor neuropathy. Anti-GM1 may occur as IgM (polyclonal or monoclonal) or IgG antibodies. These antibodies may also be found in patients with diverse connective tissue diseases as well as normal individuals. GD1a antibodies are associated with different variants of Guillain-Barre syndrome (GBS) particularly acute motor axonal neuropathy while GD1b antibodies are predominantly found in sensory ataxic neuropathy syndrome. Anti-GQ1b antibodies are seen in more than 80 percent of patients with Miller-Fisher syndrome and may be elevated in GBS patients with ophthalmoplegia. The role of isolated anti-GM2 antibodies is unknown. These tests by themselves are not diagnostic and should be used in conjunction with other clinical parameters to confirm disease.

Reference Values:

29 IV or less	Negative
30-50 IV	Equivocal
51-100 IV	Positive
101 IV or greater	Strong Positive

GAES 621108 Ganglioside Antibodies Evaluation, Serum

Clinical Information: Neuropathy patients have variable sensory disturbance (loss or exaggerated sensation including with pain), weakness, and autonomic involvements (sweat abnormalities, gastrointestinal dysfunction, and lightheadedness on standing). These symptoms are a result of injury to the distal nerves, roots, and ganglia or their gathering points (nerve plexus in the thighs and arms). Patients may have symmetric or asymmetric involvement of the extremities, trunk, and head, including extraocular muscles. Subacute onsets and asymmetric involvements favor inflammatory or immune causes over inherited or metabolic forms. Depending on the specific inflammatory or immune-mediated causes, other parts of the nervous system may also be affected (brain, cerebellum, spinal cord). Nerve conduction studies and needle electromyography can help classify the neuropathy as primary axonal, primary demyelinating, or mixed axonal and demyelinating. Among the immune-mediated peripheral neuropathies, autoantibodies to gangliosides represent an important class of noncancer-associated autoimmune peripheral neuropathies. Gangliosides are glycosphingolipids that contain sialic acid and are present in many cell types, most abundantly within neural tissues along their linings (myelin). Depending on the specific ganglioside autoantibody found and the antibody titer, in the appropriate clinical context these findings may be supportive of a specific clinical diagnosis and may also be prognostic for treatment response.(1,2) Specifically, in multifocal motor neuropathy (MMN) and multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy, also known as Lewis-Sumner syndrome or multifocal chronic immune demyelinating polyradiculoneuropathy, the presence ganglioside autoantibodies, particularly high-titer GM1 IgM autoantibodies, may be supportive of the diagnosis in the correct clinical context. Furthermore, ganglioside seropositivity has been associated with favorable response to immunotherapy among patients suspected to have MMN during the initial clinical evaluation.(1) Additionally, the presence of ganglioside antibodies may support a diagnosis of Guillain-Barre syndrome (GBS) in the appropriate clinical context.(3) GBS is a class of autoimmune peripheral neuropathies that comprises a spectrum of disorders, including acute inflammatory demyelinating polyradiculoneuropathy, acute motor axonal neuropathy, and acute motor and sensory axonal neuropathy. This class of autoimmune neuropathies is generally characterized by an acute onset. Although the diagnosis of these disorders is dependent on clinical evaluation and electrophysiologic studies, assessment of ganglioside antibodies can further support the diagnosis.

Useful For: Supporting the diagnosis of an autoimmune neuropathy

Interpretation: High titers (>1:8000) favor the diagnosis of multifocal motor neuropathy or multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy over motor neuron disease. About 30% to 50% of patients with these clinical syndromes or the pure motor variant of chronic inflammatory demyelinating polyneuropathy have ganglioside autoantibodies. High-antibody titers appear to be a specific, but not sensitive, marker of these related disorders.

Reference Values:

GQ1b-IgG ELISA: Negative
IgG Disialo. GD1b: Negative
IgM Disialo. GD1b: Negative
IgG Monos. GM1: Negative
IgM Monos. GM1: Negative

IgG Disialo GD1b Titer: <1:2000
IgM Disialo GD1b Titer: <1:2000
IgG Monos GM1 Titer: <1:2000
IgM Monos GM1 Titer: <1:4000

Clinical References: 1. Martinez JM, Snyder MR, Ettore M, et al. Composite ganglioside autoantibodies and immune treatment response in MMN and MADSAM. Muscle Nerve. 2018;57:1000-1005. doi:10.1002/mus.26051 2. Taylor BV, Gross L, Windebank AJ. The sensitivity and specificity of anti-GM1 antibody testing. Neurology. 1996;47:951-955 3. Kaida K, Ariga T, Yu RK. Antiganglioside antibodies and their pathophysiological effects on Guillain-Barre syndrome and related

disorders-a review. Glycobiology. 2009;19:676-692. doi:10.1093/glycob/cwp027

FGGAG 57812 Ganglioside GD1a Antibody (IgG)

Reference Values:
<1:100 titer

GQ1ES 621107 Ganglioside GQ1b Antibody, IgG, ELISA, Serum

Clinical Information:

Useful For: Evaluating patients with an underlying demyelinating neuropathy Supporting the diagnosis of a ganglioside GQ1b IgG-related disorder

Interpretation: A positive result is consistent with an immune-mediated demyelinating neuropathy and correlation with clinical electrodiagnostic features is recommended. Ganglioside GQ1b (GQ1b) IgG antibodies occur in Miller Fisher syndrome, Bickerstaff brainstem encephalitis, and atypical Guillain-Barre syndromes having variably present demyelinating neuropathy, ophthalmoplegia, ataxia, brainstem features with encephalitis and, less commonly, other neurogenic conditions. A negative result does not exclude an immune-mediated demyelinating neuropathy nor a GQ1b IgG syndrome.

Reference Values:
Negative

Clinical References: 1. Nishimoto Y, Odaka M, Hirata K, Yuki N. Usefulness of anti-GQ1b IgG antibody testing in Fisher syndrome compared with cerebrospinal fluid examination. J Neuroimmunol. 2004;148(1-2):200-205 2. Odaka M, Yuki N, Hirata K. Anti-GQ1b IgG antibody syndrome: clinical and immunological range. J Neurol Neurosurg Psychiatry. 2001;70(1):50-55 3. Shahrizaila N, Yuki N. Bickerstaff brainstem encephalitis and Fisher syndrome: anti-GQ1b antibody syndrome. J Neurol Neurosurg Psychiatry. 2013;84(5):576-583 4. Gwathmey KG, Smith AG. Immune-Mediated Neuropathies. Neurol Clin. 2020;38(3):711-735

FGARG 57634 Garlic IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

GARL 82760 Garlic, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from

IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to garlic Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FPEPA
57838

Gastric Pepsin Assay

Reference Values:

Protein Unit: mg/mL
Pepsin A Unit: ng/mL

Pepsin A Reference Range (ng/mL):

<12.5 negative
12.5-100 weak to moderate positive
>100 strong positive

GASTN
70439

Gastrin Immunostain, Technical Component Only

Clinical Information: Gastrin is a polypeptide hormone produced and secreted by G cells in the antral mucosa of the stomach and in the duodenum and upper jejunum. The hormone is a potent stimulant of acid secretion and also increases gastric motility. Gastrin staining can identify G cells in the antral stomach and help characterize some islet cell tumors and other neuroendocrine tumors.

Useful For: Characterization of islet cell tumors and endocrine tumors of the gastrointestinal tract

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Smith JP, Nadella S, Osborne N. Gastrin and gastric cancer. Cell Mol Gastroenterol Hepatol. 2017;4(1):75-83. doi:10.1016/j.jcmgh.2017.03.004 2. Meng LL, Wang JL, Xu SP, et al. Low serum gastrin associated with ER(+) breast cancer development via inactivation of CCKBR/ERK/P65 signaling. BMC Cancer. 2018;18(1):824. doi:10.1186/s12885-018-4717-7 3. Morgat C, Schollhammer R, Macgrogan G, et al. Comparison of the binding of the gastrin-releasing peptide receptor (GRP-R) antagonist 68Ga-RM2 and 18F-FDG in breast cancer samples. PLoS One. 2019;14(1):e0210905 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

GAST
8512

Gastrin, Serum

Clinical Information: Gastrin is a peptide hormone produced by mucosal G cells of the gastric antrum. It is synthesized as preprogastrin and then cleaved to progastrin, which undergoes several posttranslational modifications, particularly, sulfation. It is finally processed into the mature 34-amino acid, gastrin-34. Gastrin-34 may be cleaved further into the shorter 17-amino acid, gastrin-17. Either may be secreted as a C-terminal amidated or unamidated isoform. A number of additional, smaller gastrin fragments, as well as gastrin molecules with atypical posttranslational modifications (eg, absent sulfation), may also be secreted in small quantities. Gastrin's half-life is short, 5 minutes for amidated gastrin-17, and 20 to 25 minutes for amidated gastrin-34. Elimination occurs through peptidase cleavage and renal excretion. Gastrin-17 I (nonsulfated form) and gastrin-17 II (sulfated) appear equipotent. Their biological effects are chiefly associated with the amidated isoforms and consist of promotion of gastric epithelial cell proliferation and differentiation to acid-secreting cells, direct promotion of acid secretion, and indirect stimulation of acid production through histamine release. In addition, gastrin stimulates gastric motility and release of pepsin and intrinsic factor. Most gastrin isoforms with atypical posttranslational modifications and most small gastrin fragments display reduced or absent bioactivity. This assay measures predominately gastrin-17. Larger precursors and smaller fragments have little or no cross-reactivity in the assay. Intraluminal stomach pH is the main factor regulating gastrin production and secretion. Rising gastric pH levels result in increasing serum gastrin levels, while falling pH levels are associated with mounting somatostatin production in gastric D cells. Somatostatin, in turn, downregulates gastrin synthesis and release. Other weaker factors that stimulate gastrin secretion are gastric distention, protein-rich foods, and elevated secretin or serum calcium levels. Serum gastrin levels may also be

elevated in gastric distention due to gastric outlet obstruction and in a variety of conditions that lead to real or functional gastric hypo- or achlorhydria (gastrin is secreted in an attempted compensatory response to achlorhydria). These include atrophic gastritis with or without pernicious anemia, a disorder characterized by destruction of acid-secreting (parietal) cells of the stomach; gastric dumping syndrome; and surgically excluded gastric antrum. In atrophic gastritis, the chronic cell-proliferative stimulus of the secondary hypergastrinemia may contribute to the increased gastric cancer risk observed in this condition. Gastrin levels are pathologically increased in gastrinoma, a type of neuroendocrine tumor that can occur in the pancreas (20%-40%) or in the duodenum (50%-70%). The triad of non-beta islet cell tumor of the pancreas (gastrinoma), hypergastrinemia, and severe ulcer disease is referred to as the Zollinger-Ellison syndrome. Over 50% of gastrinomas are malignant and can metastasize to regional lymph nodes and the liver. About 25% of gastrinomas occur as part of the multiple endocrine neoplasia type 1 (MEN 1) syndrome and are associated with hyperparathyroidism and pituitary adenomas. These MEN 1-associated tumors have been observed to occur at an earlier age than sporadic tumors and often follow a more benign course. Basal and secretin-stimulated serum gastrin measurements are the best laboratory tests for gastrinoma.

Useful For:

Interpretation: Achlorhydria is the most common cause of elevated serum gastrin levels. The most common cause for achlorhydria is treatment of gastroduodenal ulcers, nonulcer dyspepsia, or gastroesophageal reflux with proton pump inhibitors (substituted benzimidazoles, eg, omeprazole). Other causes of hypo- and achlorhydria include chronic atrophic gastritis with or without pernicious anemia, gastric ulcer, gastric carcinoma, and previous surgical or traumatic vagotomy. If serum B12 levels are significantly low (<150 ng/L), even if the intrinsic factor blocking antibody tests are negative, a serum gastrin level above the reference range makes it likely the patient is suffering from pernicious anemia. Hypergastrinemia with normal or increased gastric acid secretion is suspicious of a gastrinoma (Zollinger-Ellison syndrome). Gastrin levels less than 100 pg/mL are observed so uncommonly in untreated gastrinoma patients with intact upper gastrointestinal anatomy as to virtually exclude the diagnosis. The majority (>60%) of patients with gastrinoma have very significantly elevated serum gastrin levels (>400 pg/mL). Levels above 1000 pg/mL in a gastric- or duodenal-ulcer patient without previous gastric surgery, on no drugs, who has a basal gastric acid output of greater than 15 mmol/hour (>5 mmol/hour in patients with prior acid-reducing surgery) are considered diagnostic of gastrinoma. If there are any doubts about gastric acid output, an infusion of 0.1 M HCl (hydrochloric acid) into the stomach reduces the serum gastrin in patients with achlorhydria but not in those with gastrinoma. Other conditions that may be associated with hypergastrinemia in the face of normal or increased gastric acid secretion include gastric and, rarely, duodenal ulcers, gastric outlet obstruction, bypassed gastric antrum, and gastric dumping. Occasionally, diabetes mellitus, autonomic neuropathy with gastroparesis, pheochromocytoma, rheumatoid arthritis, thyrotoxicosis, and paraneoplastic syndromes can also result in hypergastrinemia with normal acid secretion. None of these conditions tends to be associated with fasting serum gastrin levels above 400 pg/mL, and levels above 1000 pg/mL are virtually never observed. Several provocative tests can be used to distinguish these patients from individuals with gastrinomas. Patients with gastrinoma, who have normal or only mildly to modestly increased fasting serum gastrin levels, respond with exaggerated serum gastrin increases to intravenous infusions of secretin or calcium. Because of its greater safety, secretin infusion is preferred. The best validated protocol calls for a baseline fasting gastrin measurement, followed by an injection of 2 clinical units of secretin per kg body weight (0.4 microgram/kg) over 1 minute and further serum gastrin specimens at 5-, 10-, 15-, 20-, and 30-minutes postinjection. A peak gastrin increase of more than 200 pg/mL above the baseline value has greater than 85% sensitivity and near 100% specificity for gastrinoma. Secretin or calcium infusion tests are not carried out in the clinical laboratory but are usually performed at gastroenterology or endocrine testing units under the supervision of a physician. They are progressively being replaced (or supplemented) by imaging procedures, particularly duodenal and pancreatic endoscopic ultrasound. All patients with confirmed gastrinoma should be evaluated for possible multiple endocrine neoplasia type 1 (MEN 1), which is the underlying cause in approximately 25% of cases. If clinical, biochemical, or genetic testing confirms MEN 1, other family members need to be

screened.

Reference Values:
<100 pg/mL
There is no evidence that fasting serum gastrin levels differ between adults and children. Although 8-hour fasts are difficult or impossible to enforce in small children, serum gastrin levels after shorter fasting periods (3-8 hours) may be 50% to 60% higher than the 8-hour fasting value.

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Ellison EC, Johnson JA. The Zollinger-Ellison syndrome: a comprehensive review of historical, scientific, and clinical considerations. Curr Probl Surg. 2009;46(1):13-106. doi:10.1067/j.cpsurg.2008.09.001 2. McColl KE, Gillen D, El-Omar E. The role of gastrin in ulcer pathogenesis. Ballieres Best Pract Res Clin Gastroenterol. 2000;14(1):13-26. doi:10.1053/bega.1999.0056 3. Dockray GJ, Varro A, Dimaline R, Wang T. The gastrins: their production and biological activities. Annu Rev Physiol. 2001;63:119-139. doi:10.1146/annurev.physiol.63.1.119 4. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for the diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001;86(12):5658-5671. doi:10.1210/jcem.86.12.8070 5. Ward PCJ. Modern approaches to the investigation of vitamin B12 deficiency. Clin Lab Med. 2002;22(2):435-445. doi:10.1016/s0272-2712(01)00003-8 6. Dacha S, Razvi M, Massaad J, Cai Q, Wehbi M. Hypergastrinemia. Gastroenterol Rep (Oxf). 2015;3(3):201-208. doi:10.1093/gastro/gov004 7. Ahmed M, Ahmed S. Functional, diagnostic and therapeutic aspects of gastrointestinal hormones. Gastroenterology Res. 2019;12(5):233-244. doi:10.14740/gr1219

GID2
92120

Gastrointestinal Dysmotility, Autoimmune/Paraneoplastic Evaluation, Serum

Clinical Information: Autoimmune gastrointestinal dysmotility (AGID) is a limited form of dysautonomia (also known as autoimmune autonomic ganglionopathy or neuropathy) that is sometimes a paraneoplastic disorder. Neoplasms most frequently found are lung cancer, thymoma, and miscellaneous adenocarcinomas. Diagnosis is confirmed by objective abnormalities on gastrointestinal (GI) motility studies (eg, gastric, small intestinal, or colonic nuclear transit studies; esophageal, gastroduodenal, or colonic manometry or anorectal manometry with balloon expulsion). These disorders target autonomic postganglionic synaptic membranes and, in some cases, ganglionic neurons and autonomic nerve fibers, and may be accompanied by sensory small fiber neuropathy. Onset may be subacute or insidious. There may be additional manifestations of dysautonomia (eg, impaired pupillary light reflex, anhidrosis, orthostatic hypotension, sicca manifestations, and bladder dysfunction) or signs of other neurologic impairment. Autonomic reflex testing and a thermoregulatory sweat test are valuable aids in the documentation of objective abnormalities. The serological profile of AGID may include autoantibodies specific for onconeural proteins found in the nucleus, cytoplasm, or plasma membrane of neurons or muscle. Some of these autoantibodies are highly predictive of an underlying cancer. A commonly encountered autoantibody marker of AGID is the ganglionic neuronal alpha-3-acetylcholine receptor (alpha-3-AChR) autoantibody. The pathogenicity of this autoantibody was demonstrated in rabbits immunized with a recombinant extracellular fragment of the alpha-3-AChR subunit and in mice injected with IgG from high-titered alpha-3-AChR autoantibody-positive rabbit or human sera. A direct relationship between antibody titer and severity of dysautonomia occurs in both experimental animals and patients. Patients with high alpha-3-AChR autoantibody values (>1.0 nmol/L) generally present with profound pandysautonomia, and those with lower alpha-3-AChR autoantibody values may have limited autoimmune dysautonomia or other neurological signs and symptoms. Importantly, cancer is detected in 30% of patients with alpha-3-AChR autoantibody. Cancer risk factors include the patient's previous or family history of cancer, history of smoking, or social and environmental exposure to carcinogens. Early

diagnosis and treatment of the neoplasm favor less morbidity from the GI dysmotility disorder. The cancers recognized most frequently with alpha-3-AChR autoantibody include lymphoma and adenocarcinomas of breast, lung, prostate, and GI tract. A specific neoplasm is often predictable when a patient's autoantibody profile includes other autoantibodies to onconeural proteins shared by neurons, glia, or muscle. Small-cell lung carcinoma is found in 80% of patients who are antineuronal nuclear antibody-type 1 (ANNA-1, also known as anti-Hu) positive, and 23% of patients who are ANNA-1 positive have GI dysmotility. The most common GI manifestation is gastroparesis but the most dramatic is pseudoobstruction.

Useful For: Investigating unexplained weight loss, early satiety, anorexia, nausea, vomiting, constipation, or diarrhea in a patient with a past or family history of cancer or autoimmunity Directing a focused search for cancer Investigating gastrointestinal symptoms that appear in the course or wake of cancer therapy, not explainable by recurrent cancer, metastasis, or therapy; detection of autoantibodies on this profile helps differentiate autoimmune gastrointestinal dysmotility from the effects of chemotherapy Detecting early evidence of cancer recurrence in previously seropositive patients who have a rising titer of 1 or more autoantibodies

Interpretation: Antibodies directed at onconeural proteins shared by neurons, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects and are usually accompanied by subacute signs and symptoms. It is not uncommon for more than one antibody to be detected. Three classes of antibodies are recognized (the individual antibodies from each class included in the profile are denoted in parentheses): -Antineuronal nuclear autoantibody-type 1 (ANNA-1) -Neuronal and muscle cytoplasmic (collapsin response-mediator protein-5 [CRMP5]) -Plasma membrane cation channel (neuronal ganglionic alpha-3-acetylcholine [ACh] receptor). These autoantibodies are potential effectors of autoimmune gastrointestinal dysmotility.

Reference Values:

Test ID	Reporting Name	Methodology*	Reference Value
AGIDI	GI Dysmotility, Interpretation, S	Medical interpretation	Interpretive report
GANG	AChR Ganglionic Neuronal Ab, S	RIA	< or =0.02 nmol/L
ANN1S	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
APBIS	AP3B2 IFA, S	IFA	Negative
CS2CS	CASPR2-IgG CBA, S	CBA	Negative
CRMS	CRMP-5-IgG, S	IFA	Negative
DPPCS	DPPX Ab CBA, S	CBA	Negative
LG1CS	LGI1-IgG CBA, S	CBA	Negative
PCAB2	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
Reflex Information: Test ID	Reporting Name	Methodology*	Reference Value
AN1BS	ANNA-1 Immunoblot, S	IB	Negative
AN1TS	ANNA-1 Titer, S	IFA	
AN2BS	ANNA-2 Immunoblot, S	IB	Negative

APBCS	AP3B2 CBA, S	CBA	Negative
APBTS	AP3B2 IFA Titer, S	IFA	
CRMTS	CRMP-5-IgG Titer, S	IFA	
CRMWS	CRMP-5-IgG Western Blot, S	WB	Negative
DPPTS	DPPX Ab IFA Titer, S	IFA	
PC2TS	PCA-2 Titer, S	IFA	

Clinical References: 1. Flanagan EP, Saito YA, Lennon VA, et al. Immunotherapy trial as diagnostic test in evaluating patients with presumed autoimmune gastrointestinal dysmotility. Neurogastroenterol Motil. 2014;26(9):1285-1297. doi:10.1111/nmo.12391 2. Dhamija R, Tan KM, Pittock SJ, Foxx-Orenstein A, Benarroch E, Lennon VA. Serologic profiles aiding the diagnosis of autoimmune gastrointestinal dysmotility. Clin Gastroenterol Hepatol. 2008;6(9):988-992. doi:10.1016/j.cgh.2008.04.009 3. Cutsforth-Gregory JK, McKeon A, Coon EA, et al. Ganglionic antibody level as a predictor of severity of autonomic failure. Mayo Clin Proc. 2018;93(10):1440-1447. doi:10.1016/j.mayocp.2018.05.033 4. Tobin WO, Lennon VA, Komorowski L, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. Neurology. 2014;83(20):1797-1803. doi:10.1212/WNL.0000000000000991

GIP
63169

Gastrointestinal Pathogen Panel, PCR, Feces

Clinical Information: Acute diarrheal syndromes are usually self-limiting but may be complicated by dehydration, vomiting, and fever. Diagnostic testing and treatment may be required in some instances. Many bacterial enteric infections in the United States originate within the food supply chain. According to the Centers for Disease Control and Prevention (CDC), in 2012 there were 19,531 laboratory-confirmed cases of infection with pathogens potentially transmitted through food in the United States. The numbers of infections, by pathogen, were as follows: Salmonella species (7800), Campylobacter species (6793), Shigella species (2138), Cryptosporidium species (1234), Shiga toxin-producing Escherichia coli non-O157 (551), Shiga toxin-producing E coli O157 (531), Vibrio species (193), Yersinia species (155), and Cyclospora cayetanensis (15). Giardia may also be transmitted through ingestion of contaminated food and water. There were 15,178 cases of giardiasis reported to the CDC in 2012. Since the clinical presentation may be very similar to many of these bacterial, viral, and parasitic pathogens, laboratory testing is required for definitive identification of the causative agent. Rapid multiplex panel detection of the most common agents of bacterial, viral, and parasitic enteric infections directly from stool specimens is sensitive, specific, and provides same-day results, obviating the need for culture, antigen testing, microscopy, or individual nucleic acid amplification tests. For other diagnostic tests that may be of value in evaluating patients with diarrhea the following are available: -Parasitic Investigation of Stool Specimens Algorithm -Laboratory Testing for Infectious Causes of Diarrhea

Useful For: Rapid detection of gastrointestinal infections caused by: -Campylobacter species (Campylobacter jejuni/Campylobacter coli/Campylobacter upsaliensis) -Clostridioides difficile toxin A/B -Plesiomonas shigelloides -Salmonella species -Vibrio species (Vibrio parahaemolyticus, Vibrio vulnificus, Vibrio cholerae) -Vibrio cholerae -Yersinia species -Enteroaggregative Escherichia coli (EAEC) -Enteropathogenic E coli (EPEC) -Enterotoxigenic E coli (ETEC) -Shiga toxin -E coli O157 -Shigella/Enteroinvasive E coli (EIEC) -Cryptosporidium species -Cyclospora cayetanensis -Entamoeba histolytica -Giardia -Adenovirus F 40/41 -Astrovirus -Norovirus GI/GII -Rotavirus A -Sapovirus This test is not recommended as a test of cure.

Interpretation: A negative result should not rule-out infection in patients with a high pretest probability for gastrointestinal infection. The assay does not test for all potential infectious agents of diarrheal disease. Positive results do not distinguish between a viable or replicating organism and the presence of a nonviable organism or nucleic acid, nor do they exclude the potential for coinfection by organisms not contained within the panel. Results of the panel are intended to aid in the diagnosis of illness and are meant to be used in conjunction with other clinical and epidemiological findings. In some cases, there may be local public health requirements that impact Mayo Clinic Laboratories (MCL) clients and require additional testing on specimens with positive results from this panel. Clients should familiarize themselves with local requirements. MCL recommends clients retain an aliquot of each specimen submitted for this test to perform additional testing themselves, as needed. If necessary, selected add-on tests can be performed by MCL at an additional charge, as detailed below. Call 800-533-1710 within 4 days of specimen collection to request supplemental testing for positive test results: Gastrointestinal pathogen panel positive for Client action Campylobacter species Request add on test CAMPC / Campylobacter Culture, Feces Salmonella species Request add on test SALMC / Salmonella Culture, Feces Shigella/Enteroinvasive E coli Request add on test SHIGC / Shigella Culture, Feces (for the Shigella/Enteroinvasive E coli target, the culture will assess for Shigella species only) Yersinia species Request add on test YERSC / Yersinia Culture, Feces Shiga toxin-producing E coli E coli O157 Request add on test E157C / Escherichia coli O157:H7 Culture, Feces MCL will report results to the client for additional cultures when ordered. If cultures are positive and the client needs the isolated organism (eg, Campylobacter, Salmonella, Shigella, Yersinia or Vibrio species, or E coli O157:H7) for submission to a public health laboratory, the client needs to call MCL and request that the isolates be returned to them (the client). The client will be responsible for submitting the isolates to the appropriate public health department. Positive culture results will also be reported via the Electronic Clinical Laboratory Reporting System. Alternatively (not preferred), clients who want a patient specimen returned from MCL should call 800-533-1710 as soon as possible, at the latest within 96 hours of specimen collection, to request that MCL return an aliquot of the submitted specimen to them. Clients will be responsible for submitting specimens to appropriate public health departments.

Reference Values:
Negative (for all targets)

Clinical References: 1. Khare R, Espy MJ, Cebelinski E, et al. Comparative evaluation of two commercial multiplex panels for detection of gastrointestinal pathogens by use of clinical stool specimens. J Clin Microbiol. 2014;52(10):3667-3673 2. Centers for Disease Control and Prevention (CDC). Incidence and trends of infection with pathogens transmitted commonly through food-foodborne diseases active surveillance network, 10 U.S. sites, 1996-2012. MMWR Morb Mortal Wkly Rep. 2013;62(15):283-287 3. Centers for Disease Control and Prevention. Summary of notifiable diseases-United States, 2012. MMWR Morb Mortal Wkly Rep. 2014;61(53):1-121 4. DuPont HL. Persistent diarrhea: A clinical review. JAMA. 2016;315(24):2712-2723. doi:10.1001/jama.2016.7833 5. Lawson PA, Citron DM, Tyrrell KL, Finegold SM. Reclassification of Clostridium difficile as Clostridioides difficile (Hall and O'Toole 1935) Prevot 1938. Anaerobe. 2016;40:95-99. doi:10.1016/j.anaerobe.2016.06.008 6. Oren A, Garrity GM. Validation List No. 169. List of new names and new combinations previously effectively, but not validly, published. Int J Syst Evol Microbiol. 2016;66(6):2456-2458. doi:10.1099/ijsem.0.001181

GATA3
70440

GATA Binding Protein 3 Immunostain, Technical Component Only

Clinical Information: GATA-binding protein 3 (GATA3) is a transcription factor of the GATA family. GATA3 is involved in the regulation of development and differentiation of a variety of human tissues including T cells, skin, kidney, mammary gland, and the central nervous system. GATA3 has been shown to be a useful in the characterization of carcinomas, including primary bladder and breast

carcinomas, and some types of mesenchymal and neuroectodermal tumors (ie, paragangliomas).

Useful For: Characterizing carcinomas, including primary bladder and breast carcinomas, and some types of mesenchymal and neuroectodermal tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chang A, Amin A, Gabrielson E, et al. Utility of GATA3 immunohistochemistry in differentiating urothelial carcinoma from prostate adenocarcinoma and squamous cell carcinomas of the uterine cervix, anus, and lung. Am J Surg Pathol. 2012;36(10):1472-1476 2. Gruver AM, Amin MB, Luthringer DJ, et al. Selective immunohistochemical markers to distinguish between metastatic high-grade urothelial carcinoma and primary poorly differentiated invasive squamous cell carcinoma of the lung. Arch Pathol Lab Med. 2010;136(11):1339-1346 3. Higgins JPT, Kaygusuz G, Wange L, et al. Placental S100(S100P) and GATA3: Markers for transitional epithelium and urothelial carcinoma discovered by complementary DNA microarray. Am J Surg Pathol. 2007;31(5):673-680 4. Liu H, Shi J, Wilkerson ML, Lin F. Immunohistochemical evaluation of GATA3 expression in tumors and normal tissues. A useful immunomarker for breast and urothelial carcinomas. Am J Clin Pathol. 2012;138(1):57-64 5. Miettinen M, McCue PA, Sarlomo-Rikala M, et al. GATA3: A Multispecific but potentially useful marker in surgical pathology. A systematic analysis of 2500 epithelial and nonepithelial tumors. Am J Surg Pathol. 2014;38(1):13-22 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

GATAS
619802

GATA-Binding Protein 2, GATA2, Full Gene Analysis, Next-Generation Sequencing, Varies

Clinical Information: GATA-binding protein 2 (GATA2) deficiency causes multiple previously distinct clinical entities, including DCML deficiency (dendritic cell, monocyte, B and natural killer [NK] cell lymphocyte deficiency), MonoMAC syndrome (monocytopenia with Mycobacterium avium complex infection), Emberger syndrome (myelodysplastic syndrome [MDS] with lymphedema), NK cell deficiency, and familial MDS/acute myeloid leukemia. As such, there is a wide spectrum of clinical features, including severe viral infections (particularly with human papillomavirus, molluscum contagiosum, herpes simplex virus, Epstein-Barr virus, and cytomegalovirus), warts, fungal infections (particularly histoplasmosis and aspergillosis), mycobacterial infections, pulmonary alveolar proteinosis, bone marrow hypocellularity, neutropenia, sensorineural hearing loss, and congenital lymphedema. Immunological phenotypes include dendritic cell, monocyte, CD4+ T cell, B- and NK- cell deficiencies. Also, the loss of a specific NK-cell subset, CD56 bright NK cells, has been reported in these patients. GATA2 is a zinc finger transcription factor involved in hematopoiesis, maintenance of the hematopoietic stem cell (HSC) pool, and for HSC progenitor differentiation. Disease-causing genetic variants in GATA2 result in loss-of-function and haploinsufficiency and are transmitted in an autosomal dominant manner or arise de novo. Null variants (frameshift, nonsense, splicing, and large deletions) account for most cases, while missense variants account for approximately 30% of cases, and noncoding variants in an intronic enhancer element and synonymous variants that impact splicing account for the remainder of cases. Genotype-phenotype correlations are difficult to make, as there is considerable clinical heterogeneity. Incomplete penetrance has been observed with GATA2 deficiency, and the age at presentation varies; however, by age 60 years, the penetrance is estimated to be 90%. Additionally, there may be a role for environmental factors triggering certain infectious manifestations. The definitive treatment for GATA2 deficiency is HSC transplantation. Early genetic diagnosis of GATA2 deficiency may aid in selecting

management strategies and allow for family screening and counseling.

Useful For: Comprehensive evaluation of the GATA2 gene in patients with clinical or immunological symptoms suggestive of GATA-binding protein 2 (GATA2) deficiency Screening family members of patients with confirmed GATA2 deficiency

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 2. Fabozzi F, Mastronuzzi A, Ceglie G, Masetti R, Leardini D: GATA 2 deficiency: Focus on immune system impairment. Frong Immunol. 2022 Jun 13;13:865773 3. Hsu AP, McReynolds LJ, Holland SM: GATA2 deficiency. Curr Opin Allergy Clin Immunol. 2015 Feb;15(1):104-109 4. Bresnick EH, Jung MM, Katsumura KR: Human GATA2 mutations and hematologic disease: how many paths to pathogenesis? Blood Adv. 2020 Sep 22;4(18):4584-4592 5. Kozyra EJ, Pastor VB, Lefkopoulos S, et al: Synonymous GATA2 mutations result in selective loss of mutated RNA and are common in patients with GATA2 deficiency. 2020 Oct;34(10):2673-2687 6. Tangye SG, Al-Herz W, Bousfiha A, et al: Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022 Oct;42(7):1473-1507. doi: 10.1007/s10875-022-01289-3

GATAB 603213 GATA-Binding Protein 3 Immunostain, Technical Component Only, Bone Marrow,

Clinical Information: GATA-binding protein 3 (GATA3) is a transcription factor of the GATA family. GATA3 is involved in the regulation of development and differentiation of a variety of human tissues including T cells, skin, kidney, mammary gland, and the central nervous system. GATA3 has been shown to be a useful in the characterization of carcinomas, including primary bladder and breast carcinomas, and some types of mesenchymal and neuroectodermal tumors (ie, paragangliomas).

Useful For: Characterizing carcinomas, including primary bladder and breast carcinomas, and some types of mesenchymal and neuroectodermal tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chang A, Amin A, Gabrielson E, et al. Utility of GATA3 immunohistochemistry in differentiating urothelial carcinoma from prostate adenocarcinoma and squamous cell carcinomas of the uterine cervix, anus, and lung. Am J Surg Pathol.

2012;36(10):1472-1476 2. Gruver AM, Amin MB, Luthringer DJ, et al. Selective immunohistochemical markers to distinguish between metastatic high-grade urothelial carcinoma and primary poorly differentiated invasive squamous cell carcinoma of the lung. Arch Pathol Lab Med. 2010;136:1339-1346 3. Higgins JPT, Kaygusuz G, Wange L, et al. Placental S100(S100P) and GATA3: Markers for transitional epithelium and urothelial carcinoma discovered by complementary DNA microarray. Am J Surg Pathol. 2007;31(5):673-680 4. Liu H, Shi J, Wilkerson ML, Lin F. Immunohistochemical evaluation of GATA3 expression in tumors and normal tissues. A useful immunomarker for breast and urothelial carcinomas. Am J Clin Pathol. 2012;138:57-64 5. Miettinen M, McCue PA, Sarlomo-Rikala M, et al. GATA3: A multispecific but potentially useful marker in surgical pathology. A systematic analysis of 2500 epithelial and nonepithelial tumors. Am J Surg Pathol. 2014;38(1):13-22 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

GBAZ
35438

Gaucher Disease, Full Gene Analysis, Varies

Clinical Information: Gaucher disease is a relatively rare lysosomal storage disorder resulting from a deficiency of acid beta-glucocerebrosidase. Reduced or absent activity of this enzyme results in accumulation of its substrate in lysosomes, interfering with cell function. There are 3 major types of Gaucher disease: nonneuropathic (type 1), acute neuropathic (type 2), and subacute neuropathic (type 3). In addition, there are 2 rare presentations of Gaucher disease: a perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, and corneal opacities. Gaucher disease demonstrates large clinical variability, even within families. Type 1 accounts for over 95% of all cases of Gaucher disease and is the presentation commonly found among Ashkenazi Jewish patients. The carrier rate of Gaucher disease in the Ashkenazi Jewish population is 1:18. There is a broad spectrum of disease in type 1 Gaucher disease, with some patients exhibiting severe symptoms and others very mild disease. Type 1 disease does not involve nervous system dysfunction; patients may display anemia, low blood platelet levels, massively enlarged livers and spleens, lung infiltration, and extensive skeletal disease. Type 2 is characterized by early-onset neurologic disease with rapid progression to death by 2 to 4 years of age. Type 3 may have early onset of symptoms, but generally a slower disease progression than type 2. Alterations in the GBA gene cause the clinical manifestations of Gaucher disease. Over 250 variants have been reported to date. The N370S and L444P alterations have the highest prevalence in most populations. N370S is associated with type 1 Gaucher disease, and individuals with at least 1 copy of this alteration do not develop the primary neurologic disease seen in types 2 and 3. Conversely, L444P is associated with neurologic disease. Alterations in the GBA gene have also been reported to cause an increased risk for Parkinson disease. Alterations associated with Parkinson disease, but not Gaucher disease, are not routinely reported for patients under the age of 18, but are available upon request. For carrier screening of the general population, the recommended test is GAUP / Gaucher Disease, Mutation Analysis, GBA, Varies, which tests for the 8 most common GBA alterations. For diagnostic testing (ie, potentially affected individuals), enzyme testing (GBAW / Beta-Glucosidase, Leukocytes) should be performed prior to variant analysis. In individuals with abnormal enzyme activity and 1 or no variants detected by a panel of common alterations, sequence analysis of the GBA gene should be utilized to detect private variants. Additionally, measurement of the glucopsychosine biomarker can aid in diagnosis and ongoing therapeutic monitoring (GPSY / Glucopsychosine, Blood Spot).

Useful For: Confirmation of a diagnosis of Gaucher disease Carrier screening in cases where there is a family history of Gaucher disease, but an affected individual is not available for testing or disease-causing alterations have not been identified

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(2) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Newborn Screening ACT Sheet [Decreased beta-glucocerebrosidase] Gaucher Disease. American College of Medical Genetics and Genomics; 2022. Revised March 2022. Accessed June 10, 2024. Available at www.acmg.net/PDFLibrary/Gaucher.pdf 2. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 3. Guggenbuhl P, Grosbois B, Chales G: Gaucher disease. Joint Bone Spine. 2008 Mar;75(2):116-124 4. Hruska KS, LaMarca ME, Scott CR, Sidransky E: Gaucher disease: mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). Hum Mutat. 2008 May;29(5):567-583 5. O'Regan G, deSouza RM, Balestrino R, Schapira AH: Glucocerebrosidase mutations in Parkinson disease. J Parkinsons Dis. 2017;7(3):411-422

GCDF
70441

GCDFP-15 Immunostain, Technical Component Only

Clinical Information: Immunohistochemical staining with the monoclonal antibody gross cystic disease fluid protein 15 (GCDFP-15) produces diffuse, granular cytoplasmic staining in apocrine sweat glands, normal breast epithelial cells, and breast carcinoma malignant cells. Other neoplasms expressing GCDFP-15 are extramammary Paget disease and carcinomas of the salivary glands, sweat glands, and prostate. A heterogeneous staining pattern, often with paranuclear enhancement, is usually obtained in breast carcinoma.

Useful For: Aiding in the identification of extramammary Paget disease, carcinomas of the salivary glands, sweat glands, and prostate

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Darb-Esfahani S, von Minckwitz G, Denkert C, et al. Gross cystic disease fluid protein 15 (GCDFP-15) expression in breast cancer subtypes. BMC Cancer. 2014;14:546. doi:10.1186/1471-2407-14-546. 2. Huo L, Zhang J, Gilcrease MZ, et al. Gross cystic disease fluid protein-15 and mammaglobin A expression determined by immunohistochemistry is of limited utility in triple-negative breast cancer. Histopathology. 2013;62(2):267-274. doi:10.1111/j.1365-2559.2012.04344.x 3. Wendroth SM, Mentrikoski MJ, Wick MR. GATA3 expression in morphologic subtypes of breast carcinoma: a comparison with gross cystic disease fluid protein 15 and mammaglobin. Ann Diagn Pathol. 2015;19(1):6-9. doi:10.1016/j.anndiagpath.2014.12.001 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FGPE
57919

Gelatin Porcine IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

GELA
86326

Gelatin, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to gelatin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GBETH
607434

General Factor Bethesda Units, Plasma

Clinical Information: Significant bleeding can result from the presence of a coagulation factor inhibitor and could be life threatening. Whether the inhibitor is present due to hemophilia or is of an acquired nature, it greatly complicates the treatment process of a decreased factor level. The titer of the inhibitor may determine the mode of treatment. Bethesda units are a standardization to give a uniform definition of an inhibitor.

Useful For: Detecting and quantifying the presence and titer of a specific factor inhibitor directed against a specific coagulation factor

Interpretation: An interpretive report will be provided when testing is complete.

Reference Values:
Only orderable as a reflex. For more information see:
-ALBLD / Bleeding Diathesis Profile, Limited, Plasma
-ACBL / Bleeding Diathesis Profile, Comprehensive, Plasma
-APROL / Prolonged Clot Time Profile, Plasma
-2INHE / Factor II Inhibitor Evaluation, Plasma
-7INHE / Factor VII Inhibitor Evaluation, Plasma
-10INE / Factor X Inhibitor Evaluation, Plasma
-11INE / Factor XI Inhibitor Evaluation, Plasma

< or =0.5 Bethesda Units

Clinical References: 1. Biggs R, Bidwell E. A method for the study of antihemophiliac globulin inhibitors with reference to six cases. Br J Haematol. 1959;5:379-395 2. Hoyer LW: Factor VIII inhibitors. In: Hoyer LW, eds. Progress in Clinical and Biological Research. Vol 150. R Alan Liss Inc, 1984:87-98 3. Kasper CK, Aledort L, Aronson D, et al. Proceedings: A more uniform measurement of factor VIII inhibitors. Thromb Diath Haemorrh. 1975;34(2):61 4. Kasper C, Ewing N. Acquired inhibitors of plasma coagulation factors. J Med Tech 1986;38:431-439 5. Kottke-Marchant K, ed: Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012 6. Hoffman R, Benz Jr EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018

GENPA
37042

Gentamicin, Peak, Serum

Clinical Information: Gentamicin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Acinetobacter species, Enterobacter species, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A gentamicin minimal inhibitory concentration (MIC) of less than or equal to 4 mcg/mL is considered susceptible for gram-negative bacilli. A MIC of less than or equal to 500 mcg/mL is considered synergistic when combined with appropriate antibiotics for treatment of serious enterococcal infections. Conventional dosing of gentamicin is usually given 2 to 3 times per day by intravenous or intramuscular injections in doses to achieve peak blood concentration between 3.0 and 12.0 mcg/mL depending on the type of infections. Gentamicin also may be administered at higher doses (usually 5-7 mg/kg) once per day to patients with good renal function (known as pulse dosing). Dosing amount or interval must be decreased to accommodate for reduced renal function. Ototoxicity and nephrotoxicity are the primary toxicities associated with gentamicin. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels and symptoms consistent with ototoxicity is important. For longer durations of use, audiology/vestibular testing should be considered at baseline and periodically during therapy.

Useful For: Monitoring adequacy of drug clearance during gentamicin therapy

Interpretation: Goal levels depend on the type of infection being treated. Peak targets are generally between 5.0 and 8.0 mcg/mL for less severe infections and 8.0 and 10.0 mcg/mL for severe infections. Prolonged exposure to peak levels exceeding 12.0 mcg/mL may lead to toxicity.

Reference Values:
Peak: 3.0-12.0 mcg/mL
Toxic peak: >12.0 mcg/mL

Clinical References: 1. Hammett-Stabler CA, Johns T: Laboratory guidelines for monitoring of antimicrobial drugs. Clin Chem 1998;44(5):1129-1140 2. Moyer TP: Therapeutic drug monitoring. In Tietz Textbook of Clinical Chemistry, Fourth edition. Edited by CA Burtis, ER Ashwood, Philadelphia, WB Saunders Company, 2006 3. Wilson JW, Estes LL: Mayo Clinic Antimicrobial Therapy Quick Guide. Mayo Clinic Scientific Press and Informa Healthcare USA, 2008

GENRA
37044

Gentamicin, Random, Serum

Clinical Information: Gentamicin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Acinetobacter species, Enterobacter species, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A gentamicin minimal inhibitory concentration (MIC) of less than or equal to 4.0 mcg/mL is considered susceptible for gram-negative bacilli. A MIC of less than or equal to 500 mcg/mL is considered synergistic when combined with appropriate antibiotics for treatment of serious enterococcal infections. Conventional dosing of gentamicin is usually given 2 to 3 times per day by intravenous or intramuscular injections in doses to achieve peak blood concentration between 3.0 to 12.0 mcg/mL depending on the type of infections. Gentamicin also may be administered at higher doses (usually 5-7 mg/kg) once per day to patients with good renal function (known as pulse dosing). Dosing amount or interval must be decreased to accommodate for reduced renal function. Ototoxicity and nephrotoxicity are the primary toxicities associated with gentamicin. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels and symptoms consistent with ototoxicity is important. For longer durations of use, audiology/vestibular testing should be considered at baseline and periodically during therapy.

Useful For: Monitoring adequacy of serum concentration during gentamicin therapy in specimens for which no collection timing information is provided

Interpretation: Goal peak concentrations levels depend on the type of infection being treated. Goal trough levels should be less than 2.0 mcg/mL. Peak targets are generally between 3.0 and 12.0 mcg/mL for conventional dosing. Prolonged exposure to either peak levels exceeding 12.0 mcg/mL or to trough levels exceeding 2.0 mcg/mL may lead to toxicity.

Reference Values:
Gentamicin, Peak
Therapeutic: 3.0-12.0 mcg/mL
Toxic: >12.0 mcg/mL
Gentamicin, Trough
Therapeutic: <2.0 mcg/mL
Toxic: >2.0 mcg/mL

Clinical References: 1. Hammett-Stabler CA, Johns T: Laboratory Guidelines for Monitoring of Antimicrobial Drugs. Clin Chem 1998;44(5):1129-1140 2. Moyer TP: Therapeutic drug monitoring. In

Tietz Textbook of Clinical Chemistry. Fourth edition. Edited by CA Burtis, ER Ashwood, Philadelphia, WB Saunders Company, 2006 3. Wilson JW, Estes LL: Mayo Clinic Antimicrobial Therapy Quick Guide. Mayo Clinic Scientific Press and Information Healthcare USA, 2008

GENTA
37043

Gentamicin, Trough, Serum

Clinical Information: Gentamicin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Acinetobacter species, Enterobacter species, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A gentamicin minimal inhibitory concentration (MIC) of 4.0 mcg/mL or less is considered susceptible for gram-negative bacilli. A MIC of 500 mcg/mL or less is considered synergistic when combined with appropriate antibiotics for treatment of serious enterococcal infections. Conventional dosing of gentamicin is usually given 2 to 3 times per day by intravenous or intramuscular injections in doses to achieve peak blood concentration between 3.0 to 12.0 mcg/mL depending on the type of infection. Gentamicin also may be administered at higher doses (usually 5-7 mg/kg) once per day to patients with good renal function (known as pulse dosing). Dosing amount or interval must be decreased to accommodate for reduced renal function. Ototoxicity and nephrotoxicity are the primary toxicities associated with gentamicin. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels and symptoms consistent with ototoxicity is important. For longer durations of use, audiology/vestibular testing should be considered at baseline and periodically during therapy.

Useful For: Monitoring adequacy of drug clearance during gentamicin therapy

Interpretation: Goal levels depend on the type of infection being treated. Goal trough levels should be less than 2.0 mcg/mL for conventional dosing. Prolonged exposure to trough levels exceeding 2.0 mcg/mL may lead to toxicity.

Reference Values:
Therapeutic: <2.0 mcg/mL
Toxic: >2.0 mcg/mL

Clinical References: 1. Wilson JW, Estes LL: Mayo Clinic Antimicrobial Therapy Quick Guide, 2008 2. Hammett-Stabler CA, Johns T: Laboratory guidelines for monitoring of antimicrobial drugs. Clin Chem 1998 May;44(5):1129-1140 3. Gonzalez LS III, Spencer JP: Aminoglcosides: a practical review. Am Fam Physician 1998 Nov 15;58(8):1811-1820

GERB
82545

Gerbil Epithelium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to gerbil epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GCTF
35270

Germ Cell Tumor (GCT), Isochromosome 12p, FISH, Tissue

Clinical Information: Germ cell tumors (GCT) comprise a heterogeneous group of solid neoplasms that arise in midline locations including the gonads, retroperitoneum, mediastinum, and central nervous system. GCT are categorized based upon their histologic differentiation and can be separated into 2 classes. Seminomatous GCT include seminoma of the testis, dysgerminoma of the ovaries, and germinoma of the brain. Nonseminomatous GCT include yolk sac tumor, embryonal carcinoma, choriocarcinoma, immature teratoma, and mixed forms. Due to the wide spectrum of histologic features observed in these tumors, distinction from non-GCT can be difficult. GCT are often very responsive to chemotherapy and have a better outcome relative to histologically similar malignancies. Thus, distinguishing GCT from non-GCT is critical to providing the appropriate treatment for the patient. Gain of the short arm of chromosome 12, most commonly as an isochromosome 12p [i(12p)], is a highly nonrandom chromosomal marker seen in a significant percentage of GCT. While i(12p) is not 100% specific for GCT, the literature indicates it has diagnostic and possible therapeutic relevance for patients with these tumors. Testing of i(12p) should be concomitant with histologic evaluation, and positive results may support the diagnosis of GCT.

Useful For: Supporting the diagnosis of germ cell tumors when used conjunction with an anatomic pathology consultation

Interpretation: Testing will be clinically interpreted as positive or negative. A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the i(12p) probe set. A positive result is consistent with an isochromosome 12p. The significance of this finding is dependent on the clinical and pathologic features. A negative result suggests an isochromosome 12p is not present but does not exclude the diagnosis of germ cell tumors.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Wehle D, Yonescu R, Long PP, Gala N, Epstein J, Griffin CA. Fluorescence in situ hybridization of 12p in germ cell tumors using a bacterial artificial chromosome clone 12p probe on paraffin-embedded tissue: clinical test validation. Cancer Genet Cytogenet. 2008;183(2):99-104 2. Poulos C, Cheng L, Zhang S, Gersell DJ, Ulbright TM. Analysis of ovarian teratomas for isochromosome 12p: evidence supporting a dual histogenetic pathway for teratomatous elements. Mod Pathol. 2006;19(6):766-771 3. Chaganti RS, Houldsworth J. Genetics and biology of adult human male germ cell tumors. Cancer Res. 2000;60(6):1475-1482 4. Freitag CE, Sukov WR, Bryce AH, et al. Assessment of isochromosome 12p and 12p abnormalities in germ cell tumors using fluorescence in situ hybridization, single-nucleotide polymorphism arrays, and next-generation sequencing/mate-pair sequencing. Hum Pathol. 2021;112:20-34

GCET
70442

Germinal Center B-cell Expressed Transcript 1 Immunostain, Technical Component Only

Clinical Information: Germinal center B-cell expressed transcript 1 (GCET1), is also known as Centerin and SERPIN9 (serine protease inhibitor). GCET1 is expressed in B cells in the germinal center of normal lymph node and tonsil tissues. Most follicular lymphomas strongly express GCET1. In addition, a proportion of diffuse large B-cell lymphomas (DLBCL) are positive. In the diagnosis of B-cell lymphomas, GCET1 can be useful in an immunohistochemical panel to assign a germinal center phenotype.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Menter T, Gasser A, Juskevicius D, Dirnhofer S, Tzankov A. Diagnostic utility of the germinal center-associated markers GCET1, HGAL, and LMO2 in hematolymphoid neoplasms. Appl Immunohistochem Mol Morph. 2015;23(7):491-498 2. Culpin RE, Sieniawski M, Angus B, et al. Prognostic significance of immunohistochemistry-based markers and algorithms in immunochemotherapy-treated diffuse large B cell lymphoma patients. Histopathology. 2013;63(6);788-801 3. Meyer PN, Fu K, Greiner TC, et al. Immunohistochemical methods for predicting cell of origin and survival in patients with diffuse large B-cell lymphoma treated with rituximab. J Clin Oncol. 2011;29(2):200 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FGHTP
75898

Ghrelin Total (Plasma)

Clinical Information: Ghrelin is a novel 28 amino acid peptide derived by post-translational processes from a preproghrelin consisting of 117 residues, secreted by the stomach with specific receptors in the brain involved in appetite regulation. It conveys information to the brain thereby increasing appetite, food intake and body weight and influences the release of growth hormone. Ghrelin is a growth hormone-releasing peptide which acts as an endogenous ligand of the growth hormone secretagogue receptors (GHS-Rs). Ghrelin levels are inversely correlated with body weight and are higher during weight loss.

Reference Values:
Normal weight/control subjects: 520-700 pg/mL

Obese subjects prior to diet: 340-450 pg/mL
8:00 am-12:00 pm: Up to 420 pg/mL
6:00pm: Up to 480 pg/mL

Obese subjects post induced
Weight loss: 450-600 pg/mL
8:00 am-12:00 pm: Up to 575 pg/mL
6:00 pm: Up to 600 pg/mL

Obese subjects post gastric-bypass surgery: Up to 120 pg/mL

Clinical References: 1. Shiiya T, Nakazato M, Mizuta M, et al. Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. J Clin Endocrinol Metab. 2002;87(1):240-244. doi:10.1210/jcem.87.1.8129 2. Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med. 2002;346(21):1623-1630. doi:10.1056/NEJMoa012908

GRW
82685

Giant Ragweed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to giant ragweed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GIAR
80231

Giardia Antigen, Feces

Clinical Information: Giardia duodenalis (also known as Giardia lamblia, Giardia intestinalis) is a flagellated protozoan parasite found in contaminated natural streams, lakes, and surface water municipal reservoirs. Several animals may serve as a host for G duodenalis, including dogs and beavers. Humans become infected when ingesting the environmentally resistant parasite cysts in water, food, and by the fecal-oral route (eg, on hands or fomites). Following ingestion, each cyst releases two trophozoites, which infect the small intestine by attaching to the mucosa with a ventral sucking disc. Infection may be associated with a variety of outcomes ranging from asymptomatic disease (estimated to occur in 50% of infected individuals) to acute and chronic giardiasis. When present, symptoms generally appear 7 to 14 days after infection and consist of watery diarrhea, malaise, malodorous steatorrhea, flatulence, abdominal cramping, nausea or vomiting, weight loss, and low-grade fever. Less commonly, patients experience constipation and urticaria. Symptoms will resolve in most patients after a period of several weeks. However, approximately 15% to 20% will remain chronically infected without treatment and experience ongoing loose stools, weight loss, malabsorption, steatorrhea, abdominal cramping, flatulence, and burping. Longstanding malabsorption may result in vitamin deficiencies and hypoalbuminemia. Acquired lactose intolerance may also occur and persist for months after successful parasite eradication. Giardiasis is the most common intestinal parasitic infection in the United States reported to the Centers for Disease Control and Prevention and is a common cause of diarrhea in children (especially in daycare centers), travelers, and campers or hikers. It is also responsible for waterborne epidemics. Although Giardia parasites (cysts and trophozoites) may be seen using the microscopy-based stool parasitic exam (OPE / Ova and Parasite, Travel History or Immunocompromised, Feces), this is an insensitive method for detection and requires examination of three or more specimens. Instead, detection of parasite antigen or DNA is recommended for optimal sensitivity. The Giardia antigen test is ideal for settings in which giardiasis is specifically suspected (eg,

outbreak scenarios), whereas the multiplex gastrointestinal polymerase chain reaction panel (GIP / Gastrointestinal Pathogen Panel, PCR, Feces) is better suited for evaluating multiple potential causes of diarrhea, including parasitic, viral, and bacterial pathogens. For more information about diagnostic tests that may be of value in evaluating patients with diarrhea see the following: -Parasitic Investigation of Stool Specimens Algorithm -Laboratory Testing for Infectious Causes of Diarrhea

Useful For: Sensitive screening for the detection of Giardia antigens present in fecal specimens

Interpretation: A positive enzyme-linked immunosorbent assay indicates the presence in a fecal specimen of Giardia antigens. Interpretation of results should be correlated with patient symptoms and clinical picture.

Reference Values:
Negative

Clinical References: 1. Garcia LS, Arrowood M, Kokoskin E, et al. Practical guidance for clinical microbiology laboratories: Laboratory diagnosis of parasites from the gastrointestinal tract. Clin Microbiol Rev. 2017;31(1):e00025-17 2. Hanson KL, Cartwright CP. Use of an enzyme immunoassay does not eliminate the need to analyze multiple stool specimens for sensitive detection of Giardia lamblia. J Clin Microbiol. 2001;39(2):474-477 3. Centers for Disease Control and Prevention (CDC) National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED): Parasites-Giardia. CDC; Updated May 19, 2022. Accessed August 28, 2023. Available at www.cdc.gov/parasites/giardia/index.html

GING
82488

Ginger, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to ginger Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

DGLDN
89031

Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process that occurs in genetically susceptible individuals following ingestion of wheat, rye, or barley proteins.(1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Individuals with family members who have celiac disease are at increased risk of developing the disease.(2) Genetic susceptibility is related to specific human leukocyte antigen (HLA) markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. For this reason, HLA-DQ2 and HLA-DQ8 are considered genetic risk factors for celiac disease and are required, but not sufficient, for the disease process to occur. HLA testing is not required for diagnosis in all cases, but can be useful in situations where histology and serology are discrepant, or for individuals who have started a gluten free diet before evaluation.(3) A definitive diagnosis of celiac disease requires a duodenal biopsy demonstrating villous atrophy.(3) Given the invasive nature and cost of the biopsy, serologic tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, individuals with positive laboratory results may be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm). In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial antibody, tissue transglutaminase (tTG), and deamidated gliadin antibodies.(4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests is tTG IgA

isotype, in individuals who produce sufficient total IgA. For individuals who are IgA deficient, testing for tTG and deamidated gliadin IgG antibodies is required. A recent multi-cohort international study found that a tTG IgA titer of greater than or equal to 10 times the upper limit of normal (ULN) had a positive predictive value of 95% in an adult population.(5) In addition, several prospective studies have shown that a biopsy free approach to celiac disease diagnosis may be possible in children with a tTG titer greater than or equal to 10 times the ULN who meet certain criteria.(6-9) Given this evidence, the American College of Gastroenterology now suggests that a positive tTG IgA result greater than 10 times the upper limit of normal with a positive endomysial antibody in a separate blood sample may be sufficient for a diagnosis celiac disease in children.(3) The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, concentrations of associated autoantibodies decline, which is sometimes accompanied by reconstitution of the small intestinal villi. In most patients, an improvement in clinical symptoms is observed. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease. See Celiac Disease Diagnostic Testing Algorithm for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm.

Useful For: Assessment of deaminated gliadin IgA and IgG antibodies for evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disorder, positivity for HLA DQ2 and/or DQ8) Monitoring response to a gluten-free diet in patients with celiac disease.

Interpretation: Positive test results for deamidated gliadin IgA or IgG antibodies, are consistent with a diagnosis of celiac disease. Negative results for deamidated gliadin IgA or IgG antibodies indicate a decreased likelihood of celiac disease. A decrease in the concentrations of deamidated gliadin IgA or IgG antibodies may begin after initiation of a gluten-free diet and could indicate a response to therapy.

Reference Values:

Negative: <20.0 U
Weak positive: 20.0-30.0 U
Positive: >30.0 U
Reference values apply to all ages.

Clinical References: 1. Rubin JE, Crowe SE. Celiac disease. Ann Intern Med. 2020;172(1):ITC1-ITC16. doi:10.7326/AITC202001070 2. Lebwohl B, Rubio-Tapia A: Epidemiology, presentation, and diagnosis of celiac disease. Gastroenterology. 2021;160(1):63-75. doi:10.1053/j.gastro.2020.06.098 3. Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease [published correction appears in Am J Gastroenterol. 2024 Jul 1;119(7):1441. doi: 10.14309/ajg.0000000000002210.]. Am J Gastroenterol. 2023;118(1):59-76. doi:10.14309/ajg.0000000000002075 4. Penny HA, Raju SA, Sanders DS. Progress in the serology-based diagnosis and management of adult celiac disease. Exp Rev Gastroenterol Heptatol. 2020;14(3):147-154. doi:10.1080/17474124.2020.1725472 5. Penny HA, Raju SA, Lau MS, et.al. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. Gut. 2021;70(5):876-883. doi:10.1136/gutjnl-2020-320913 6. Ylonen V, Lindfors K, Repo M, et al. Non-Biopsy Serology-Based Diagnosis of Celiac Disease in Adults Is Accurate with Different Commercial Kits and Pre-Test Probabilities. Nutrients. 2020;12(9):2736. Published 2020 Sep 8. doi:10.3390/nu12092736 7. Werkstetter KJ, Korponay-Szabo IR, Popp A, et al. Accuracy in Diagnosis of Celiac Disease Without Biopsies in Clinical Practice. Gastroenterology. 2017;153(4):924-935. doi:10.1053/j.gastro.2017.06.002 8. Wolf J, Petroff D, Richter T, et al. Validation of Antibody-Based Strategies for Diagnosis of Pediatric Celiac Disease Without Biopsy. Gastroenterology.

2017;153(2):410-419.e17. doi:10.1053/j.gastro.2017.04.023 9. Ho SS, Keenan JI, Day AS. Role of serological tests in the diagnosis of coeliac disease in children in New Zealand. J Paediatr Child Health. 2020;56(12):1906-1911. doi:10.1111/jpc.15076

DAGL
89029

Gliadin (Deamidated) Antibody, IgA, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process that occurs in genetically susceptible individuals following ingestion of wheat, rye, or barley proteins.(1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific human leukocyte antigen (HLA) markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. For this reason, HLA-DQ2 and HLA-DQ8 are considered genetic risk factors for celiac disease and are required, but not sufficient, for the disease process to occur. HLA testing is not required for diagnosis in all cases, but can be useful in situations where histology and serology are discrepant, or for individuals who have started a gluten free diet before evaluation.(3) A definitive diagnosis of celiac disease requires a duodenal biopsy demonstrating villous atrophy.(3) Given the invasive nature and cost of the biopsy, serologic tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, individuals with positive laboratory results may be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm). In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial antibody, tissue transglutaminase (tTG), and deamidated gliadin antibodies.(4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic test is tTG IgA isotype, in individuals who produce sufficient total IgA. For individuals who are IgA deficient, testing for tTG and deamidated gliadin IgG antibodies is required. A recent multi-cohort international study found that a tTG IgA titer of greater than or equal to 10 times the upper limit of normal (ULN) had a positive predictive value of 95% in an adult population.(5) In addition, several prospective studies have shown that a biopsy free approach to celiac disease diagnosis may be possible in children with a tTG titer greater than or equal to 10 times the ULN who meet certain criteria.(6-9) Given this evidence, the American College of Gastroenterology now suggests that a positive tTG IgA result greater than 10 times the upper limit of normal with a positive endomysial antibody in a separate blood sample may be sufficient for a diagnosis celiac disease in children.(3) The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, concentrations of associated autoantibodies decline, which is sometimes accompanied by reconstitution of the small intestinal villi. In most patients, an improvement in clinical symptoms is observed. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease. See Celiac Disease Diagnostic Testing Algorithm for the recommended approach to a patient suspected of celiac disease. An algorithm is available for

monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm.

Useful For: Assessment of deaminated gliadin IgA antibodies for evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disorder, positivity for HLA DQ2 and/or DQ8) Monitoring response to a gluten-free diet in patients with celiac disease

Interpretation: Positive test results for deamidated gliadin IgA antibodies are consistent with a diagnosis of celiac disease. Negative results for deamidated gliadin IgA antibodies indicate a decreased likelihood of celiac disease. A decrease in the concentration of deamidated gliadin IgA antibodies may begin after initiation of a gluten-free diet and could indicate a response to therapy.

Reference Values:
Negative: <20.0 U
Weak positive: 20.0-30.0 U
Positive: >30.0 U
Reference values apply to all ages.

Clinical References: 1. Rubin JE, Crowe SE. Celiac disease. Ann Intern Med. 2020;172(1):ITC1-ITC16. doi:10.7326/AITC202001070 2. Lebwohl B, Rubio-Tapia A: Epidemiology, presentation, and diagnosis of celiac disease. Gastroenterology. 2021;160(1):63-75. doi:10.1053/j.gastro.2020.06.098 3. Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease [published correction appears in Am J Gastroenterol. 2024 Jul 1;119(7):1441. doi: 10.14309/ajg.0000000000002210.]. Am J Gastroenterol. 2023;118(1):59-76. doi:10.14309/ajg.0000000000002075 4. Penny HA, Raju SA, Sanders DS. Progress in the serology-based diagnosis and management of adult celiac disease. Exp Rev Gastroenterol Heptatol. 2020;14(3):147-154. doi:10.1080/17474124.2020.1725472 5. Penny HA, Raju SA, Lau MS, et.al. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. Gut. 2021;70(5):876-883. doi:10.1136/gutjnl-2020-320913 6. Ylonen V, Lindfors K, Repo M, et al. Non-Biopsy Serology-Based Diagnosis of Celiac Disease in Adults Is Accurate with Different Commercial Kits and Pre-Test Probabilities. Nutrients. 2020;12(9):2736. Published 2020 Sep 8. doi:10.3390/nu12092736 7. Werkstetter KJ, Korponay-Szabo IR, Popp A, et al. Accuracy in Diagnosis of Celiac Disease Without Biopsies in Clinical Practice. Gastroenterology. 2017;153(4):924-935. doi:10.1053/j.gastro.2017.06.002 8. Wolf J, Petroff D, Richter T, et al. Validation of Antibody-Based Strategies for Diagnosis of Pediatric Celiac Disease Without Biopsy. Gastroenterology. 2017;153(2):410-419.e17. doi:10.1053/j.gastro.2017.04.023 9. Ho SS, Keenan JI, Day AS. Role of serological tests in the diagnosis of coeliac disease in children in New Zealand. J Paediatr Child Health. 2020;56(12):1906-1911. doi:10.1111/jpc.15076

DGGL
89030

Gliadin (Deamidated) Antibody, IgG, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process that occurs in genetically susceptible individuals following ingestion of wheat, rye, or barley proteins.(1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with

neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Individuals with family members who have celiac disease are at increased risk of developing the disease.(2) Genetic susceptibility is related to specific human leukocyte antigen (HLA) markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. For this reason, HLA-DQ2 and HLA-DQ8 are considered genetic risk factors for celiac disease and are required, but not sufficient, for the disease process to occur. HLA testing is not required for diagnosis in all cases, but can be useful in situations where histology and serology are discrepant, or for individuals who have started a gluten free diet before evaluation.(3) A definitive diagnosis of celiac disease requires a duodenal biopsy demonstrating villous atrophy.(3) Given the invasive nature and cost of the biopsy, serologic tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, individuals with positive laboratory results may be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm). In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial antibody, tissue transglutaminase (tTG), and deamidated gliadin antibodies.(4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic test is tTG IgA isotype, in individuals who produce sufficient total IgA. For individuals who are IgA deficient, testing for tTG and deamidated gliadin IgG antibodies is required A recent multi-cohort international study found that a tTG IgA titer of greater than or equal to 10 times the upper limit of normal (ULN) had a positive predictive value of 95% in an adult population.(5) In addition, several prospective studies have shown that a biopsy free approach to celiac disease diagnosis may be possible in children with a tTG titer greater that or equal to 10 times the ULN who meet certain criteria.(6-9) Given this evidence, the American College of Gastroenterology now suggests that a positive tTG IgA result greater than 10 times the upper limit of normal with a positive endomysial antibody in a separate blood sample may be sufficient for a diagnosis celiac disease in children.(3) The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, concentrations of associated autoantibodies decline, which is sometimes accompanied by reconstitution of the small intestinal villi. In most patients, an improvement in clinical symptoms is observed. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease. See Celiac Disease Diagnostic Testing Algorithm for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm.

Useful For: Assessment of deaminated gliadin IgG antibodies for evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disorder, positivity for HLA DQ2 and/or DQ8) Monitoring response to a gluten-free diet in patients with celiac disease

Interpretation: Positive test results for deamidated gliadin IgG antibodies, particularly in individuals who are IgA deficient, are consistent with a diagnosis of celiac disease. Negative results for deamidated gliadin IgG antibodies indicate a decreased likelihood of celiac disease. A decrease in the concentration of deamidated gliadin IgG antibodies may begin after the initiation of a gluten-free diet and could indicate a response to therapy.

Reference Values:

Negative: <20.0 U
Weak positive: 20.0-30.0 U
Positive: >30.0 U
Reference values apply to all ages.

Clinical References: 1. Rubin JE, Crowe SE. Celiac disease. Ann Intern Med. 2020;172(1):ITC1-ITC16. doi:10.7326/AITC202001070 2. Lebwohl B, Rubio-Tapia A: Epidemiology, presentation, and diagnosis of celiac disease. Gastroenterology. 2021;160(1):63-75. doi:10.1053/j.gastro.2020.06.098 3. Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease [published correction appears in Am J Gastroenterol. 2024 Jul 1;119(7):1441. doi: 10.14309/ajg.0000000000002210.]. Am J Gastroenterol. 2023;118(1):59-76. doi:10.14309/ajg.0000000000002075 4. Penny HA, Raju SA, Sanders DS. Progress in the serology-based diagnosis and management of adult celiac disease. Exp Rev Gastroenterol Heptatol. 2020;14(3):147-154. doi:10.1080/17474124.2020.1725472 5. Penny HA, Raju SA, Lau MS, et.al. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. Gut. 2021;70(5):876-883. doi:10.1136/gutjnl-2020-320913 6. Ylonen V, Lindfors K, Repo M, et al. Non-Biopsy Serology-Based Diagnosis of Celiac Disease in Adults Is Accurate with Different Commercial Kits and Pre-Test Probabilities. Nutrients. 2020;12(9):2736. Published 2020 Sep 8. doi:10.3390/nu12092736 7. Werkstetter KJ, Korponay-Szabo IR, Popp A, et al. Accuracy in Diagnosis of Celiac Disease Without Biopsies in Clinical Practice. Gastroenterology. 2017;153(4):924-935. doi:10.1053/j.gastro.2017.06.002 8. Wolf J, Petroff D, Richter T, et al. Validation of Antibody-Based Strategies for Diagnosis of Pediatric Celiac Disease Without Biopsy. Gastroenterology. 2017;153(2):410-419.e17. doi:10.1053/j.gastro.2017.04.023 9. Ho SS, Keenan JI, Day AS. Role of serological tests in the diagnosis of coeliac disease in children in New Zealand. J Paediatr Child Health. 2020;56(12):1906-1911. doi:10.1111/jpc.15076

GFATS
605133

Glial Fibrillary Acidic Protein Alpha Subunit Antibody, Immunofluorescence Titer Assay, Serum

Clinical Information: Antibody targeting glial fibrillary acidic protein (GFAP)-IgG is a biomarker of a subacute and progressive autoimmune meningitis, encephalitis, and myelitis that can mimic multiple sclerosis (MS) or other idiopathic inflammatory central nervous system (CNS) disorders such as sarcoidosis. Neurological manifestations include headache, optic neuropathy, transverse myelitis, cognitive decline, and cerebellar ataxia. Cerebrospinal fluid (CSF) is inflammatory. Cranial magnetic resonance (MR) imaging reveals linear perivascular enhancement oriented radially to ventricles. A paraneoplastic neurological context is common. Reported neoplasms accompanying neurological symptoms include adenocarcinomas (prostate and gastroesophageal), myeloma, melanoma, colonic carcinoid, parotid pleomorphic adenoma, and teratoma. If GFAP-IgG is detected by immunofluorescence assay (IFA), it is reflexed to a test for the alpha isoform of GFAP (GFAPalpha-IgG) by cell based assay.

Useful For: Reporting an end titer result in serum specimens Distinguishing autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy from infectious meningoencephalitis and idiopathic inflammatory central nervous system (CNS) disorders such as multiple sclerosis, vasculitis and sarcoidosis, disorders commonly considered in the differential diagnosis Alerting the clinician that the patient has an immune-mediated, steroid-responsive disorder and to search for a malignancy

Interpretation: Seropositivity for autoantibody (positive) is supportive of autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy, a treatable form of meningoencephalomyelitis. A paraneoplastic basis should be considered, according to age, sex, and other risk factors. Patients who are GFAP-IgG positive have increased risk of tumor. GFAP-IgG increases the likelihood of certain malignancies being found within 2 years of symptom onset (34%). The most common malignancy found is ovarian teratoma (22%). GFAP meningoencephalomyelitis is immunotherapy-responsive. GFAP-IgG positive patients have

better outcomes after treatment with corticosteroids. The presence of GFAP-IgG alerts the clinician that the patient has an immune-mediated, steroid-responsive disorder and directs patient care accordingly. It also alerts the clinician to search for a malignancy.

Reference Values:

Only orderable as a reflex. For more information see:
ENS2 / Encephalopathy, Autoimmune Evaluation Serum
DMS2 / Dementia, Autoimmune Evaluation, Serum
EPS2 / Epilepsy, Autoimmune Evaluation, Serum
MAS1 / Autoimmune Myelopathy Evaluation, Serum

<1:240

Clinical References: 1. Fang B, McKeon A, Hinson SR, et al: Autoimmune glial fibrillary acidic protein astrocytopathy: a novel meningoencephalomyelitis. JAMA Neurol 2016;73:1297-1307 2. Flanagan EP, Hinson SR, Lennon VA, et al: Glial fibrillary acidic protein immunoglobulin G as biomarker of autoimmune astrocytopathy: Analysis of 102 patients. Ann Neurol 2017;81:298-309 3. Iorio R, Damato V, Evoli A, et al:Clinical and Immunological characteristics of the spectrum of GFAP autoimmunity: a case series of 22 patients. J Neurol Neurosurg Psychiatry 2018 Feb;89(2):138-146 doi:10.1136/jnnp-2017-316583

GFATC
605134

Glial Fibrillary Acidic Protein Alpha Subunit Antibody, Immunofluorescence Titer Assay, Spinal Fluid

Clinical Information: Antibody targeting glial fibrillary acidic protein (GFAP)-IgG is a biomarker of a subacute and progressive autoimmune meningitis, encephalitis, and myelitis that can mimic multiple sclerosis (MS) or other idiopathic inflammatory central nervous system (CNS) disorders such as sarcoidosis. Neurological manifestations include headache, optic neuropathy, transverse myelitis, cognitive decline, and cerebellar ataxia. Cerebrospinal fluid (CSF) is inflammatory. Cranial magnetic resonance (MR) imaging reveals linear perivascular enhancement oriented radially to ventricles. A paraneoplastic neurological context is common. Reported neoplasms accompanying neurological symptoms include adenocarcinomas (prostate and gastroesophageal), myeloma, melanoma, colonic carcinoid, parotid pleomorphic adenoma and teratoma. If GFAP-IgG is detected by immunofluorescence assay (IFA), it is reflexed to a test for the alpha isoform of GFAP (GFAPalpha-IgG) by cell based assay.

Useful For: Reporting an end titer result in spinal fluid specimens Distinguishing, in spinal fluid, autoimmune GFAP astrocytopathy from infectious meningoencephalitis and idiopathic inflammatory central nervous system (CNS) disorders such as multiple sclerosis, vasculitis and sarcoidosis, disorders commonly considered in the differential diagnosis Alerting the clinician that the patient has an immune-mediated, steroid-responsive disorder and to search for a malignancy

Interpretation: Seropositivity for autoantibody (positive) is supportive of autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy, a treatable form of meningoencephalomyelitis. A paraneoplastic basis should be considered, according to age, sex, and other risk factors. Patients who are GFAP-IgG positive have increased risk of tumor. GFAP-IgG increases the likelihood of certain malignancies being found within 2 years of symptom onset (34%). The most common malignancy found is ovarian teratoma (22%). GFAP meningoencephalomyelitis is immunotherapy-responsive. GFAP-IgG positive patients have better outcomes after treatment with corticosteroids. The presence of GFAP-IgG alerts the clinician the patient has an immune-mediated, steroid-responsive disorder and directs patient care accordingly. It also alerts the clinician to search for a malignancy.

Reference Values:
Only orderable as a reflex. For more information, see:
DMC2 / Dementia Autoimmune Evaluation, Spinal Fluid
ENC2 / Encephalopathy Autoimmune Evaluation, Spinal Fluid
EPC2 / Epilepsy Autoimmune Evaluation, Spinal Fluid
MAC1 / Autoimmune Myelopathy Evaluation, Spinal Fluid

<1:2

Clinical References: 1. Fang B, McKeon A, Hinson SR, et al: Autoimmune glial fibrillary acidic protein astrocytopathy: a novel meningoencephalomyelitis. JAMA Neurol 2016;73:1297-1307 2. Flanagan EP, Hinson SR, Lennon VA, et al: Glial fibrillary acidic protein immunoglobulin G as biomarker of autoimmune astrocytopathy: Analysis of 102 patients. Ann Neurol 2017;81:298-309 3. Iorio R, Damato V, Evoli A, et al:Clinical and Immunological characteristics of the spectrum of GFAP autoimmunity: a case series of 22 patients. J Neurol Neurosurg Psychiatry 2018 Feb;89(2):138-146 doi:10.1136/jnnp-2017-316583

GFAP
70443

Glial Fibrillary Acidic Protein Immunostain, Technical Component Only

Clinical Information: Glial fibrillary acidic protein (GFAP) is an intermediate filament protein of 52 kDa found in glial cells, astrocytes, and ependymal cells. Immunoperoxidase staining for GFAP produces intense cytoplasmic staining of astrocytes, glial cells, and ependymal cells in normal brain. In neoplastic tissues, GFAP is useful for the identification of glial tumors such as astrocytomas and ependymomas.

Useful For: Classification of glial tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Goyal R, Mathur SK, Gupta S, et al. Immunohistochemical expression of glial fibrillary acidic protein and CAM5. 2 in glial tumors and their role in differentiating glial tumors from metastatic tumors of central nervous system. J Neurosci Rural Pract. 2015;6(4):499-503 2. Zhao J, Wang B, Huang T, et al. Glial response in early stages of traumatic brain injury. Neurosci Lett. 2019;708:134335 3. Magaki SD, Williams CK, Vinters HV. Glial function (and dysfunction) in the normal and ischemic brain. Neuropharmacology. 2018 15;134(Pt B):218-225 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FGLIP
91097

Glipizide (Glucotrol)

Reference Values:
Units: ng/mL

Plasma insulin concentrations have been shown to increase only when plasma glipizide concentrations exceeded 200 ng/mL.

Toxic range has not been established.

LGBWB 602351 Globotriaosylsphingosine, Blood

Clinical Information: Fabry disease is an X-linked recessive lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A (alpha-GAL A). Reduced enzyme activity results in accumulation of glycosphingolipids in the lysosomes throughout the body, particularly in the kidney, heart, and brain. Severity and onset of symptoms are dependent on the residual enzyme activity. Symptoms may include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, corneal opacity, kidney insufficiency leading to kidney failure, and cardiac and cerebrovascular disease. There are renal and cardiac variant forms of Fabry disease that may be underdiagnosed. Female patients who are heterozygous for Fabry disease can have clinical presentations ranging from asymptomatic to severely affected, and they may have alpha-GAL A activity in the normal range. The estimated incidence varies from 1 in 3000 infants detected via newborn screening to 1 in 10,000 male patients diagnosed after onset of symptoms. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy has led to significant clinical improvement in affected individuals. For this reason, early diagnosis and treatment are desirable, and in a few US states, early detection of Fabry disease through newborn screening has been implemented. Measurement of alpha-GAL A in leukocytes (AGAW / Alpha-Galactosidase, Leukocytes), serum (AGAS / Alpha-Galactosidase, Serum), or blood spots (AGABS / Alpha-Galactosidase, Blood Spot) can reliably diagnose classic or variant Fabry disease in male patients. Molecular genetic testing is the recommended diagnostic test for female patients as alpha-GAL A may be in the normal range in an affected female patient. Molecular analysis of the GLA gene allows for detection of the disease-causing variant in both male and female patients; order FABRZ / Fabry Disease, Full Gene Analysis, Varies. The glycosphingolipid, globotriaosylsphingosine (LGb3), may be elevated in symptomatic patients and supports a diagnosis of Fabry disease. It may also be helpful as a tool for monitoring disease progression as well as determining treatment response in known patients. In addition, measurement of LGb3, may provide additional diagnostic information in the evaluation of uncertain cases, such as in asymptomatic heterozygous female patients, individuals with novel GLA variants of unclear clinical significance, as well as asymptomatic patients identified by family screening.

Useful For: Screening of patients with Fabry disease when a serum specimen is not available This test should not be used for newborn screening followup.

Interpretation: An elevation of globotriaosylsphingosine is indicative of Fabry disease, however, a normal result does not rule out Fabry disease.

Reference Values:
Cutoff: < or =0.034 nmol/mL

Clinical References: 1. Vardarli I, Rischpler C, Herrmann K, Weidemann F. Diagnosis and screening of patients with Fabry disease. Ther Clin Risk Manag. 2020;16:551-558. doi:10.2147/TCRM.S247814 2. Mehta A, Hughes DA. Fabry disease. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated April 11, 2024. Accessed December 2, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1292/ 3. Nowak A, Mechtler T, Kasper DC, Desnick RJ. Correlation of Lyso-Gb3 levels in dried blood spots and sera from patients with classic and later-onset Fabry disease. Mol Genet Metab. 2017;121(4):320-324. doi:10.1016/j.ymgme.2017.06.006 4. Johnson B, Mascher H, Mascher D, et al. Analysis of lyso-globotriaosylsphingosine in dried blood spots. Ann Lab Med. 2013;33(4):274-278. doi:10.3343/alm.2013.33.4.274

LGBBS
113521

Globotriaosylsphingosine, Blood Spot

Clinical Information: Fabry disease is an X-linked recessive lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A (alpha-GAL A). Reduced enzyme activity results in accumulation of glycosphingolipids in the lysosomes throughout the body, particularly in the kidney, heart, and brain. Severity and onset of symptoms are dependent on the residual enzyme activity. Symptoms may include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, corneal opacity, kidney insufficiency leading to kidney failure, and cardiac and cerebrovascular disease. There are renal and cardiac variant forms of Fabry disease that may be underdiagnosed. Female patients who are heterozygous for Fabry disease can have clinical presentations ranging from asymptomatic to severely affected, and they may have alpha-GAL A activity in the normal range. The estimated incidence varies from 1 in 3000 infants detected via newborn screening to 1 in 10,000 male patients diagnosed after onset of symptoms. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy has led to significant clinical improvement in affected individuals. For this reason, early diagnosis and treatment are desirable, and in a few US states, early detection of Fabry disease through newborn screening has been implemented. Measurement of alpha-GAL A in leukocytes (AGAW / Alpha-Galactosidase, Leukocytes), serum (AGAS / Alpha-Galactosidase, Serum), or blood spots (AGABS / Alpha-Galactosidase, Blood Spot) can reliably diagnose classic or variant Fabry disease in male patients. Molecular genetic testing is the recommended diagnostic test for female patients as alpha-GAL A activity may be in the normal range in an affected female patient. Molecular sequence analysis of the GLA gene allows for detection of the disease-causing variant in both male and female patients, order FABRZ / Fabry Disease, Full Gene Analysis, Varies. The glycosphingolipid, globotriaosylsphingosine (LGb3), may be elevated in symptomatic patients and supports a diagnosis of Fabry disease. It may also be helpful as a tool for monitoring disease progression as well as determining treatment response in known patients. In addition, measurement of LGb3, may provide additional diagnostic information in the evaluation of uncertain cases, such as in asymptomatic heterozygous female patients, individuals with novel GLA variants of unclear clinical significance, as well as asymptomatic patients identified by family screening.

Useful For: Screening of patients with Fabry disease using dried blood spots when a serum specimen is not available This test should not be used for newborn screening followup.

Interpretation: An elevation of globotriaosylsphingosine is indicative of Fabry disease, however a normal result does not rule out Fabry disease.

Reference Values:
Cutoff: < or =0.034 nmol/mL

Clinical References: 1. Vardarli I, Rischpler C, Herrmann K, Weidemann F. Diagnosis and screening of patients with Fabry disease. Ther Clin Risk Manag. 2020;16:551-558. doi:10.2147/TCRM.S247814 2. Mehta A, Hughes DA. Fabry disease. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated April 11, 2024. Accessed December 2, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1292/ 3. Nowak A, Mechtler T, Kasper DC, Desnick RJ. Correlation of Lyso-Gb3 levels in dried blood spots and sera from patients with classic and later-onset Fabry disease. Mol Genet Metab. 2017;121(4):320-324. doi:10.1016/j.ymgme.2017.06.006 4. Johnson B, Mascher H, Mascher D, et al. Analysis of lyso-globotriaosylsphingosine in dried blood spots. Ann Lab Med. 2013;33(4):274-278. doi:10.3343/alm.2013.33.4.274

LGB3S
65532

Globotriaosylsphingosine, Serum

Clinical Information: Fabry disease is an X-linked recessive lysosomal storage disorder caused by a

deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Reduced enzyme activity results in accumulation of glycosphingolipids in the lysosomes throughout the body, in particular, the kidney, heart, and brain. Severity and onset of symptoms are dependent on the residual enzyme activity. Symptoms may include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, corneal opacity, renal insufficiency leading to end-stage kidney disease, and cardiac and cerebrovascular disease. There are renal and cardiac variant forms of Fabry disease that may be underdiagnosed. Female patients who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected, and they may have alpha-Gal A activity in the normal range. The estimated incidence varies from 1 in 3000 infants detected via newborn screening to 1 in 10,000 male patients diagnosed after onset of symptoms. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy leads to significant clinical improvement in affected individuals. For this reason, early diagnosis and treatment are desirable. In a few US states, early detection of Fabry disease through newborn screening has been implemented. Absent or reduced alpha-Gal A in blood spots, leukocytes (AGAW / Alpha-Galactosidase, Leukocytes), or serum (AGAS / Alpha-Galactosidase, Serum) can indicate a diagnosis of classic or variant Fabry disease. Molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis, Varies) allows for detection of the disease-causing variant in male and female patients. Molecular genetic testing is the recommended diagnostic test for female patients as alpha-galactosidase activity may be in the normal range in those affected. The glycosphingolipid, globotriaosylsphingosine (LGb3), may be elevated in symptomatic patients and supports a diagnosis of Fabry disease. It may also be helpful as a tool for monitoring disease progression as well as determining treatment response in known patients. In addition, measurement of LGb3, may provide additional diagnostic information in the evaluation of uncertain cases, such as in asymptomatic heterozygous female patients, individuals with novel GLA variants of unclear clinical significance, as well as asymptomatic patients identified by family screening.

Useful For: Diagnosis and monitoring of Fabry disease

Interpretation: Elevation of globotriaosylsphingosine is diagnostic for Fabry disease.

Reference Values:
< or =1.0 ng/mL

Clinical References: 1. Aerts JM, Groener JE, Kuiper S, et al: Elevated globotriaosylsphingosine is a hallmark of Fabry disease. Proc Natl Acad Sci USA. 2008 Feb 26;105(8)2812-2817 2. Mehta A, Hughes DA: Fabry disease. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated January 27, 2022. Accessed January 17, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1292/ 3. Laney DA, Bennett RL, Clarke V, et al: Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2013 Oct;22(5):555-564 4. Laney DA, Peck DS, Atherton AM, et al: Fabry disease in infancy and early childhood: a systematic literature review. Genet Med. 2015 May;17(5):323-330 5. Weidemann F, Beer M, Kralewski M, Siwy J, Kampmann C: Early detection of organ involvement in Fabry disease by biomarker assessment in conjunction with LGE cardiac MRI: results from the SOPHIA study. Mol Genet Metab. 2019 Feb;126(2):169-182

GBM
8106

Glomerular Basement Membrane Antibodies, IgG, Serum

Clinical Information: Anti-glomerular basement (GBM) disease is a rare autoimmune disease, with an estimated incidence of 0.6-1.79 cases per million population per year.(1) Without prompt treatment, this disease is potentially fatal. Patients may present with rapidly progressive glomerulonephritis, pulmonary hemorrhage, or both.(2,3) The serological hallmark of this disease is the presence of anti-GBM antibodies of the IgG isotype. Anti-GBM antibodies bind to the non-collagenous

domain 1 (NC1) of the alpha3 chain of type IV collagen, which is one of the main components of the kidney and lung basement membranes. Deposition of anti-GBM antibodies in the kidney and lungs triggers complement activation and production of reactive oxygen species, ultimately leading to vascular necrosis and damage to the GBM. The diagnosis of anti-GBM disease in a patient with compatible clinical symptoms is often confirmed by detecting the presence of anti-GBM antibodies. This can be accomplished by a variety of antigen-specific, solid-phase immunoassays. Given the implications of this testing, understanding the diagnostic sensitivity and specificity of anti-GBM antibody methods is critical. In a recent meta-analysis, a pooled sensitivity of 93% (95%CI: 84-97%) and a pooled specificity of 97% (95%CI: 94-99%) was demonstrated across 11 methods.(4) In addition, some studies have suggested a prognostic role for anti-GBM antibodies, with higher titers being associated with increased mortality. However, it appears that this effect can largely be abrogated by prompt and aggressive treatment, particularly plasmapheresis.(1)

Useful For: Evaluating patients with clinical features of anti-glomerular basement disease, including rapidly progressive glomerulonephritis or pulmonary hemorrhage

Interpretation: A positive result for anti-glomerular basement (GBM) antibody is consistent with the diagnosis of anti-GBM disease, in patients with the appropriate clinical presentation.

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References: 1. Kuang H, Jiang N, Jia XY, Cui Z, Zhao MH. Epidemiology, clinical features, risk factors, and outcomes in anti-glomerular basement membrane disease: A systematic review and meta-analysis. Autoimmun Rev. 2024;23(4):103531 2. Ponticelli C, Calatroni M, Moroni G. Anti-glomerular basement membrane vasculitis. Autoimmun Rev. 2023;22(1):103212 3. Reggiani F, L'Imperio V, Calatroni M, Pagni F, Sinico RA. Goodpasture syndrome and anti-glomerular basement membrane disease. Clin Exp Rheumatol. 2023;41(4):964-974 4. Shiroshita A, Oda Y, Takenouchi S, Hagino N, Kataoka Y. Accuracy of anti-GBM antibodies in diagnosing anti-glomerular basement membrane Disease: A systematic review and meta-analysis. Am J Nephrol. 2021;52(7):531-538

GLUCG
70445

Glucagon Immunostain, Technical Component Only

Clinical Information: Glucagon is a polypeptide hormone produced by the alpha cells of the pancreatic islets in response to hypoglycemia or to stimulation by growth hormone. Cytoplasmic staining is seen in pancreatic islet glucagon alpha cells and islet cell tumors. Glucagon is also found in neuroendocrine cells of the small intestine and stomach.

Useful For: Aiding in the study of islet-cell tumors and some endocrine tumors of the gastrointestinal tract

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Gurlo T, Butler PC, Butler AE. Evaluation of immunohistochemical staining for glucagon in human pancreatic tissue. J Histotechnol. 2016;39(1):8-16.

doi:10.1179/2046023615Y.0000000013 2. Hebsgaard JB, Pyke C, Yildirim E, Knudsen LB, Heegaard S, Kvist PH. Glucagon-like peptide-1 receptor expression in the human eye. Diabetes Obes Metab. 2018;20(9):2304-2308. doi:10.1111/dom.13339 3. Mi B, Xu Y, Pan D, et al. Non-invasive glucagon-like peptide-1 receptor imaging in pancreas with (18)F-Al labeled Cys(39)-exendin-4. Biochem Biophys Res Commun. 2016;471(1):47-51. doi:10.1016/j.bbrc.2016.01.184 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

GLP
9358

Glucagon, Plasma

Clinical Information: Glucagon is a single-chain polypeptide of 29 amino acids that is derived from a larger precursor peptide (big plasma glucagon), which is cleaved upon secretion. The main sites of glucagon production are the hypothalamus and pancreatic alpha-islet cells. The function of hypothalamic glucagon is incompletely understood and currently no clinical disorders of hypothalamic glucagon function have been defined. Pancreatic islet glucagon is secreted in response to hypoglycemia, with resultant increases in blood glucose concentration. Glucagon's hyperglycemic effect is produced by stimulating hepatic glycogenolysis and gluconeogenesis; it has no effect on muscle glycogen. Once blood glucose levels have normalized, glucagon secretion ceases. Excessive glucagon secretion can lead to hyperglycemia. Excessive and inappropriate glucagon secretion can sometimes be observed in diabetes, particularly during ketoacidosis, and can complicate management of the disorder. In rare cases, it also can occur in tumors of the pancreatic islets (glucagonoma), hepatocellular carcinomas, carcinoid tumors, and other neuroendocrine neoplasms. Patients with glucagon-secreting tumors may present with classic glucagonoma syndrome, consisting of necrolytic migratory erythema, diabetes, and diarrhea, but can also have more subtle symptoms and signs. Decreased or absent glucagon response to hypoglycemia can be seen in type I diabetes (insulin-dependent diabetes) and can contribute to severe and prolonged hypoglycemic responses. Glucagon is routinely measured along with serum glucose, insulin, and C-peptide levels during the mixed-meal test employed in the diagnostic workup of suspected postprandial hypoglycemia. However, it plays only a minor role in the interpretation of this test.

Useful For: Diagnosis and follow-up of glucagonomas and other glucagon-producing tumors
Assessing diabetic patients with problematic hyper- or hypoglycemic episodes (extremely limited utility)

Interpretation: Elevated glucagon concentrations in the absence of hypoglycemia may indicate the presence of a glucagon-secreting tumor. Successful treatment of a glucagon-secreting tumor is associated with normalization of glucagon levels. Inappropriate elevations in glucagon concentrations in patients who are hyperglycemic and have type I diabetes indicate that paradoxical glucagon release may contribute to disease severity. This can be observed if insulin treatment is inadequate and patients are ketotic. However, glucagon measurement plays little, if any, role in the diagnostic workup of diabetic ketoacidosis. In patients with diabetes, low glucagon concentrations (undetectable or in the lower quartile of the normal range) in the presence of hypoglycemia indicate impairment of hypoglycemic counter regulation. These patients may be particularly prone to recurrent hypoglycemia. This can be a permanent problem due to islet alpha-cell destruction or other, less well understood processes (eg, autonomous neuropathy). It can also be functional, most often due to over-tight blood glucose control and may be reversible after decreasing insulin doses.

Reference Values:
> or =1 year of age: < or =159 pg/mL
<1 year of age: No reference interval established.

For International System of Units (SI) for Reference Values, see www.mayocliniclabs.com/order-

tests/si-unit-conversion.html.

Clinical References: 1. Tomassetti P, Migliori M, Lalli S, Campana D, Tomassetti V, Corinaldesi R. Epidemiology, clinical features and diagnosis of gastroenteropancreatic endocrine tumours. Ann Oncol. 2001;12 Suppl 2:S95-S99 2. Jiang G, Zhang BB. Glucagon and regulation of glucose metabolism. Am J Physiol Endocrinol Metab. 2003;284(4):E671-E678 3. van Beek AP, de Haas ER, van Vloten WA, Lips CJ, Roijers JF, Canninga-van Dijk MR. The glucagonoma syndrome and necrolytic migratory erythema: a clinical review. Eur J Endocrinol. 2004;151(5):531-537 4. Cruz-Bautista I, Lerman I, Perez-Enriquez B, et al. Diagnostic challenge of glucagonoma: case report and literature review. Endocr Pract. 2006;12(4):422-426 5. Falconi M, Eriksson B, Kaltsas G, et al. ENETS Consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology. 2016;103(2):153-171

GPSYW
113430

Glucopsychosine, Blood

Clinical Information: Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme, beta-glucosidase, which facilitates the lysosomal degradation of glucosylceramide (glucocerebroside) and glucopsychosine (glucosylsphingosine: lyso-GL1). Gaucher disease is caused by disease-causing variants in the GBA gene and presents with a markedly variable phenotype, ranging from a perinatal lethal disorder to mildly symptomatic. It has historically been categorized into 3 types (GD1, GD2 and GD3) based on the presence and progression of neuropathic features. All types of Gaucher disease include hepatosplenomegaly and hematological abnormalities. Gaucher disease type I is the most common form, representing more than 90% of cases. It is generally characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, coagulation abnormalities, lung disease, but no central nervous system involvement. Gaucher disease types II and III are characterized by the presence of primary neurologic disease, although in practice, assigning a type in infancy can sometimes be challenging due to overlapping clinical features. In addition, type II typically presents with limited psychomotor development, hepatosplenomegaly, and lung disease, resulting in death usually between 2 and 4 years of age. Individuals with Gaucher disease type III may present prior to 2 years of age, but the progression is not as rapid, and patients may survive into the third and fourth decade. Additional subtypes of Gaucher disease include a perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, corneal opacities, and gaze impairment. Treatment is available in the form of enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) for types I and III. Some patients with chronic and progressive neurologic symptoms despite ERT or SRT may be candidates for bone marrow transplant or a multifaceted approach. Currently, only supportive therapy is available for type II because of the inability of enzyme provided by replacement therapy to cross the blood-brain barrier. The incidence of GD is variable, with a higher occurrence in populations with known founder variants such as the Ashkenazi Jewish population. A diagnostic workup for GD may demonstrate the characteristic finding of Gaucher cells on bone marrow examination, other hematologic abnormalities, and hepatosplenomegaly. The diagnosis can be confirmed by the demonstration of reduced or absent acid beta-glucosidase activity in leukocytes (GBAW / Beta-Glucosidase, Leukocytes) or dried blood spots (PLSD / Lysosomal and Peroxisomal Disorders Screen, Blood Spot) and molecular genetic analysis of the GBA gene (GBAZ / Gaucher Disease, Full Gene Analysis, Varies). Lyso GL-1 is a sensitive and specific biomarker for Gaucher disease, and an elevation of lyso GL-1 in blood supports the diagnosis. Lyso GL-1 has also been shown to be helpful in monitoring mildly symptomatic individuals for disease progression and in determining treatment response.

Useful For: Second-tier test when newborn screening results with reduced beta-glucosidase (GBA) activity are identified Diagnosis and monitoring of patients with Gaucher disease using whole blood specimens Supporting the biochemical diagnosis of Gaucher disease Monitoring a patient's response to treatment This test is not useful for identifying carriers of GBA variants.

Interpretation: An elevation of glucopsychosine (glucosylsphingosine: lyso-GL1) is indicative of Gaucher disease.

Reference Values:
Cutoff: < or =0.040 nmol/mL

Clinical References: 1. Newborn Screening ACT Sheet [Decreased beta-glucocerebrosidase] Gaucher Disease. American College of Medical Genetics and Genomics; 2022. Revised March 2022. Accessed November 14, 2024. Available at www.acmg.net/PDFLibrary/Gaucher.pdf 2. Hughes DA, Pastores GM. Gaucher Disease. In: Adam MP, Feldman J, Mirzaa GM, et al. eds. GeneReviews. [Internet]. University of Washington, Seattle; 2000. Updated December 7, 2023. Accessed November 14, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1269/ 3. Kishnani PS, Al-Hertani W, Balwani M, et al. Screening, patient identification, evaluation, and treatment in patients with Gaucher disease: Results from a Delphi consensus. Mol Genet Metab. 2022;135(2):154-162. doi:10.1016/j.ymgme.2021.12.009 4. Grabowski GA, Petsko GA, Kolodny EH. : Gaucher disease. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Accessed November 14, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225546056&bookid=2709 5. Murugesan V, Chuan WL, Liu J, et al. Glucosylsphingosine is a key biomarker of Gaucher disease. Am J Hematol. 2016;91(11)1082-1089 6. Saville JT, McDermott BK, Chin SJ, Fletcher JM, Fuller M. Expanding the clinical utility of glucosylsphingosine for Gaucher disease. J Inherit Metab Dis. 2020;43(3):558-563 7. Daykin EC, Ryan E, Sidransky E. Diagnosing neuronopathic Gaucher disease: New considerations and challenges in assigning Gaucher phenotypes. Mol Genet Metab. 2021;132(2):49-58. doi:10.1016/j.ymgme.2021.01.002

GPSY
62236

Glucopsychosine, Blood Spot

Clinical Information: Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme, beta-glucosidase, which facilitates the lysosomal degradation of glucosylceramide (glucocerebroside) and glucopsychosine (glucosylsphingosine: lyso-GL1). Gaucher disease is caused by disease-causing variants in the GBA gene and presents with a markedly variable phenotype, ranging from a perinatal lethal disorder to mildly symptomatic. It has historically been categorized into 3 types (GD1, GD2 and GD3) based on the presence and progression of neuropathic features. All types of Gaucher disease include hepatosplenomegaly and hematological abnormalities. Gaucher disease type I is the most common form, representing more than 90% of cases. It is generally characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, coagulation abnormalities, lung disease, but no central nervous system involvement. Gaucher disease types II and III are characterized by the presence of primary neurologic disease, although in practice, assigning a type in infancy can sometimes be challenging due to overlapping clinical features. In addition, type II typically presents with limited psychomotor development, hepatosplenomegaly, and lung disease, resulting in death usually between 2 and 4 years of age. Individuals with Gaucher disease type III may present prior to 2 years of age, but the progression is not as rapid, and patients may survive into the third and fourth decade. Further subtypes of Gaucher disease include a perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, corneal opacities, and gaze impairment. Treatment is available in the form of enzyme replacement therapy (ERT) or substrate reduction therapy (SRT) for types I and III. Some patients with chronic and progressive neurologic symptoms despite ERT or SRT may be candidates for bone marrow transplant or a multifaceted approach. Currently, only supportive therapy is available for type II because of the inability of enzyme provided by replacement therapy to cross the blood-brain barrier. The incidence of GD is variable, with a higher occurrence in populations with known founder variants such as the Ashkenazi Jewish population. A diagnostic workup for GD may demonstrate the characteristic finding of Gaucher cells on bone marrow examination, other hematologic abnormalities, and hepatosplenomegaly. The diagnosis can be

confirmed by the demonstration of reduced or absent acid beta-glucosidase activity in leukocytes (GBAW / Beta-Glucosidase, Leukocytes) or dried blood spots (PLSD / Lysosomal and Peroxisomal Disorders Screen, Blood Spot) and molecular genetic analysis of the GBA gene (GBAZ / Gaucher Disease, Full Gene Analysis, Varies). Lyso GL-1 is a sensitive and specific biomarker for Gaucher disease, and an elevation of lyso GL-1 in blood supports the diagnosis. Lyso GL-1 has also been shown to be helpful in monitoring mildly symptomatic individuals for disease progression and in determining treatment response.

Useful For: Second-tier test when newborn screening results with reduced beta-glucosidase (GBA) activity are identified Diagnosis and monitoring of patients with Gaucher disease using dried blood spot specimens Monitoring a patient's response to treatment This test is not useful for identifying carriers of GBA variants.

Interpretation: An elevation of glucopsychosine (glucosylsphingosine: lyso-GL1) is indicative of Gaucher disease.

Reference Values:
Cutoff: < or =0.040 nmol/mL

Clinical References: 1. Newborn Screening ACT Sheet [Decreased beta-glucocerebrosidase] Gaucher Disease. American College of Medical Genetics and Genomics; 2022. Revised March 2022. Accessed November 14, 2024. Available at www.acmg.net/PDFLibrary/Gaucher.pdf 2. Hughes DA, Pastores GM. Gaucher disease. In: Adam MP, Feldman J, Mirzaa GM, et al. eds. GeneReviews. [Internet]. University of Washington, Seattle; 2000. Updated December 7, 2023. Accessed November 14, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1269/ 3. Kishnani PS, Al-Hertani W, Balwani M, et al. Screening, patient identification, evaluation, and treatment in patients with Gaucher disease: Results from a Delphi consensus. Mol Genet Metab. 2022;135(2):154-162. doi:10.1016/j.ymgme.2021.12.009 4. Grabowski GA, Petsko GA, Kolodny EH. Gaucher disease. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Accessed November 14, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225546056&bookid=2709 5. Murugesan V, Chuan WL, Liu J, et al. Glucosylsphingosine is a key biomarker of Gaucher disease. Am J Hematol. 2016;91(11)1082-1089 6. Saville JT, McDermott BK, Chin SJ, Fletcher JM, Fuller M. Expanding the clinical utility of glucosylsphingosine for Gaucher disease. J Inherit Metab Dis. 2020;43(3):558-563 7. Daykin EC, Ryan E, Sidransky E. Diagnosing neuronopathic Gaucher disease: New considerations and challenges in assigning Gaucher phenotypes. Mol Genet Metab. 2021;132(2):49-58. doi:10.1016/j.ymgme.2021.01.002

GPSYP
65632

Glucopsychosine, Plasma

Clinical Information: Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme, beta-glucosidase, which facilitates the lysosomal degradation of glucosylceramide (glucocerebroside) and glucopsychosine (glucosylsphingosine: lyso-GL1). Gaucher disease is caused by disease-causing variants in the GBA gene and presents with a markedly variable phenotype, ranging from a perinatal lethal disorder to mildly symptomatic. It has historically been categorized into 3 types (GD1, GD2 and GD3) based on the presence and progression of neuropathic features. All types of Gaucher disease include hepatosplenomegaly and hematological abnormalities. Gaucher disease type I is the most common, representing more than 90% of cases. It is generally characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, coagulation abnormalities, lung disease, but no central nervous system involvement. Gaucher disease types II and III are characterized by the presence of primary neurologic disease, although in practice, assigning a type in infancy can sometimes be challenging due to overlapping clinical features. In addition, type II typically

presents with limited psychomotor development, hepatosplenomegaly, and lung disease, resulting in death usually between 2 and 4 years of age. Individuals with Gaucher disease type III may present prior to 2 years of age, but the progression is not as rapid, and patients may survive into the third and fourth decade. Additional subtypes of Gaucher disease include a perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, corneal opacities, and gaze impairment. Treatment is available in the form of enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) for types I and III. Some patients with chronic and progressive neurologic symptoms despite ERT or SRT may be candidates for bone marrow transplant or a multifaceted approach. Currently, only supportive therapy is available for type II because of the inability of enzyme provided by replacement therapy to cross the blood-brain barrier. The incidence of GD is variable, with a higher occurrence in populations with known founder variants such as the Ashkenazi Jewish population. A diagnostic workup for GD may demonstrate the characteristic finding of Gaucher cells on bone marrow examination, other hematologic abnormalities, and hepatosplenomegaly. The diagnosis can be confirmed by the demonstration of reduced or absent acid beta-glucosidase activity in leukocytes (GBAW / Beta-Glucosidase, Leukocytes), or dried blood spots (PLSD / Lysosomal and Peroxisomal Disorders Screen, Blood Spot) and molecular genetic analysis of the GBA gene (GBAZ / Gaucher Disease, Full Gene Analysis, Varies). Lyso-GL1 is a sensitive and specific biomarker for Gaucher disease, and an elevation of lyso GL-1 in blood supports the diagnosis. Lyso GL-1 has also been shown to be helpful in monitoring mildly symptomatic individuals for disease progression and in determining treatment response.

Useful For: Second-tier test when newborn screening results with reduced beta-glucosidase (GBA) activity are identified Diagnosis and monitoring of patients with Gaucher disease using plasma specimens Supporting a biochemical diagnosis of Gaucher disease Monitoring a patient's response to treatment This test is not useful for identifying carriers of GBA variants.

Interpretation: An elevation of glucopsychosine (glucosylsphingosine: lyso-GL1) is indicative of Gaucher disease.

Reference Values:
GLUCOPSYCHOSINE
Cutoff: < or =0.003 nmol/mL

Clinical References: 1. Newborn Screening ACT Sheet [Decreased beta-glucocerebrosidase] Gaucher Disease. American College of Medical Genetics and Genomics; 2022. Revised March 2022. Accessed November 14, 2024. Available at www.acmg.net/PDFLibrary/Gaucher.pdf 2. Hughes DA, Pastores GM. Gaucher disease. In: Adam MP, Feldman J, Mirzaa GM, et al. eds. GeneReviews. [Internet]. University of Washington, Seattle; 2000. Updated December 7, 2023. Accessed November 14, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1269/ 3. Kishnani PS, Al-Hertani W, Balwani M, et al. Screening, patient identification, evaluation, and treatment in patients with Gaucher disease: Results from a Delphi consensus. Mol Genet Metab. 2022;135(2):154-162. doi:10.1016/j.ymgme.2021.12.009 4. Grabowski GA, Petsko GA, Kolodny EH: : Gaucher disease. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Accessed November 14, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225546056&bookid=2709 5. Murugesan V, Chuan WL, Liu J, et al. Glucosylsphingosine is a key biomarker of Gaucher disease. Am J Hematol. 2016;91(11)1082-1089 6. Saville JT, McDermott BK, Chin SJ, Fletcher JM, Fuller M. Expanding the clinical utility of glucosylsphingosine for Gaucher disease. J Inherit Metab Dis. 2020;43(3):558-563 7. Daykin EC, Ryan E, Sidransky E. Diagnosing neuronopathic Gaucher disease: New considerations and challenges in assigning Gaucher phenotypes. Mol Genet Metab. 2021;132(2):49-58. doi:10.1016/j.ymgme.2021.01.002

G6PDC
608417

Glucose 6 Phosphate Dehydrogenase Enzyme Activity, Blood

Clinical Information: Hemolytic anemia may be associated with deficiency of erythrocyte enzymes. The most common enzyme defect worldwide is a deficiency of glucose-6-phosphate dehydrogenase (G6PD). As an enzyme in the hexose monophosphate pathway, G6PD plays a key role in the generation of reduced nicotinamide adenine dinucleotide phosphate (NADPH). Because red blood cells lack the citric acid cycle, this NADPH generation is critical for protection against oxidative stress. Normal conditions require approximately 2% of capacity, leaving 98% reserve for stressor events. More than 400 molecular variants of G6PD are known, and the clinical and laboratory features of G6PD deficiency vary according to the degree to which enzyme reserve is decreased. G6PD deficiency (OMIM 300908, X-linked) therefore results in various forms of anemia and is classified by World Health Organization (WHO) criteria according to enzyme activity and chronic versus acute episodic clinical course.(1-3) In 2022, the WHO Malaria Policy Advisory Group panel proposed updated guidance for the classification of G6PD variants.(3) This revised guidance is based on the median residual enzyme activity (per allele) and seeks to resolve problems identified with the WHO G6PD classification system that has been in place since 1985 (See Table in Interpretation). The G6PD locus is located on the X chromosome and, therefore, G6PD deficiency is a sex-linked disorder. Most people with G6PD deficiency are asymptomatic until a stressor event occurs resulting in acute hemolytic anemia that resolves after stimulus removal. Symptoms can include neonatal jaundice (presents at 1-4 days of age) or acute hemolysis triggered by medications (antimalarials, sulfonamides, dapsone, nitrofurantoin, and naphthalene), infection (hepatitis, cytomegalovirus, typhoid), or fava bean ingestion. Hemolysis and jaundice begin 24 to 72 hours after a triggering stimulus, with accompanying dark urine/hemoglobinuria. Anemia worsens for approximately one week and begins to recover ten days after cessation. Splenomegaly, gallstones, and recurrent jaundice are additional clinical symptoms. Because it is X-linked, male patients are usually more severely affected but homozygous female patients are seen due to the prevalence of genetic variants. Heterozygous female patients (carriers) range from asymptomatic to severe anemia due to mosaicism/lyonization. Acquired G6PD may occur due to increasing X inactivation in aging women.(4) Acute episodic G6PD deficiency (WHO class B, formerly class II and III) is not expected to affect length or quality of life. Less commonly seen are genetic variants that result in chronic nonspherocytic hemolytic anemia which manifest similarly to other enzyme deficiencies (WHO class A, formerly class I). The major G6PD variants occur in specific ethnic groups. Thus, knowledge of the ethnic background of the patient is helpful. G6PD deficiency has very high frequency in persons of southeast Asian, African, southern European, and Middle Eastern descent. Rasburicase therapy is contraindicated in patients with G6PD deficiency. US Food and Drug Administration (FDA) guidelines state to screen patients at higher risk for G6PD deficiency (eg, patients of African or Mediterranean ancestry) prior to starting therapy.(5) Deficiency can be assessed by enzymatic and/or genetic assays. Due to limitations of genetic testing, in most cases it is preferential to perform G6PD enzyme testing to assign G6PD status. However, enzyme activity can be affected by recent red blood cell transfusion, marked reticulocytosis and very high white blood cell count. In these settings, genotyping may be useful for correlation with the red blood cell enzyme level.(6,7) Due to historic issues with other similar antimalarial medications, questions arise if hydroxychloroquine (HCQ) or chloroquine (CQ) therapy may trigger acute hemolytic episodes in some G6PD subtypes. Data is limited in this regard. Available published data did not find hemolytic episodes associated with HCQ therapy in G6PD deficient African American (8) or CQ therapy in G6PD deficient African (9) patients. Both studied populations were assumed to have mild forms of the disorder. Data regarding these medications in populations with more severe G6PD phenotypes is lacking. While patients receiving HCQ do not routinely need G6PD levels checked before initiating therapy, testing may be considered in patients who are from ethnic backgrounds with high G6PD variant rates, such as those from Mediterranean, African, or Asian descent. Although specific details are not described, hemolysis has been reported in at least one individual with G6PD deficiency during the post-approval use of hydroxychloroquine sulfate tablets, United States Pharmacopeia (USP) per FDA label information.(10)

Useful For: Evaluation of individuals with episodic or chronic Coombs-negative nonspherocytic hemolytic anemia Rapid testing to assess glucose-6-phosphate dehydrogenase (G6PD) enzyme capacity prior to rasburicase or other therapies that may cause hemolysis or methemoglobinemia in G6PD deficient

patients May aid in the creation of a comprehensive patient profile and can ensure appropriate patient monitoring for developing anemia

Interpretation: The World Health Organization (WHO) classification of glucose-6-phosphate dehydrogenase (G6PD) deficiency is historically based on enzyme activity level and in most cases enzyme activity level is sufficient. Accurate classification requires correlation with clinical, and in certain cases, genetic data. The revised WHO classification (2022) has updated classification subtypes from classes I, II, III, IV and V to class A, B, C and U. The Advisory Group panel concluded: (3)"In future, G6PD variants should be classified based on the median residual enzyme activity expressed as a percentage of normal activity. It should be emphasized that this system is for classifying genetic variants of G6PD and should not be used to classify individual patients with G6PD deficiency. Currently, no variants have been identified in homozygous deficient females or hemizygous deficient males that have median G6PD enzyme activity falling between 45% and 60%. Therefore, a gap has been left between Classes B and C. If new variants are found with median G6PD enzyme activity in this range, these should be included in the "U" class and studied until solid evidence is found that they induce acute haemolytic anaemia (= Class B) or do not pose a haemolytic risk (= Class C). Based on new evidence, the thresholds may then need to be revisited" Table. Updated (2022) and Legacy G6PD Variant WHO Classification and Associated G6PD Deficiency Phenotype 2022 WHO class Median* G6PD activity Hemolysis Legacy** WHO class Level of residual enzyme activity (% of normal) A <20% Chronic (CNSHA) I <10% B <45% Acute, triggered II <10% III 10%-60% C 60-150% No hemolysis IV Normal U Any Uncertain clinical significance *The activity is per variant (ie, per allele) and most straightforward to assess in hemizygous male patients and homozygous female patients. Compound heterozygous female patients are more complex and rely on clinical and familial correlation. **Legacy WHO Class V: Increased activity (enzyme activity >150%) has been discontinued in the 2022 recommendations. It was originally created due to a single variant that has not been corroborated and is not deemed clinically relevant. Although G6PD deficiency is an X-linked recessive disorder and most often seen in hemizygous male patients, some female patients are affected. In addition, older women who are heterozygous can develop deficiency due to differential X-skewing with age.(4) It is important to note that clinically significant G6PD deficiency can be masked in the setting of significant reticulocytosis, markedly elevated white blood cell count or recent red blood cell transfusion. If any of these are present in the setting of a history of neonatal, chronic or episodic jaundice or anemia, genotyping for G6PD genetic alterations is recommended. If desired, order G6PDZ / Glucose-6-Phosphate Dehydrogenase (G6PD) Full Gene Sequencing, Varies.

Reference Values:

Only orderable as part of a profile. For more information see:
-HAEV1 / Hemolytic Anemia Evaluation, Blood
-EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation, Blood

> or =12 months of age: 8.0-11.9 U/g Hb

Reference values have not been established for patients who are less than12 months of age.

Clinical References:

G6PD1 Glucose 6-Phosphate Dehydrogenase Enzyme Activity, Blood

607460

Clinical Information: Hemolytic anemia may be associated with deficiency of erythrocyte enzymes. The most common enzyme defect worldwide is a deficiency of glucose 6-phosphate dehydrogenase (G6PD). As an enzyme in the hexose monophosphate pathway, G6PD plays a key role in the generation of reduced nicotinamide adenine dinucleotide phosphate (NADPH). Because red blood cells lack the citric acid cycle, this NADPH generation is critical for protection against oxidative stress.

Normal conditions require approximately 2% of capacity, leaving 98% reserve for stressor events. More than 400 molecular variants of G6PD are known, and the clinical and laboratory features of G6PD deficiency vary according to the degree to which enzyme reserve is decreased. G6PD deficiency (OMIM 300908, X-linked) therefore results in various forms of anemia and is classified by World Health Organization (WHO) criteria according to enzyme activity and chronic versus acute episodic clinical course.(1-3) In 2022, the WHO Malaria Policy Advisory Group panel proposed updated guidance for the classification of G6PD variants.(3) This revised guidance is based on the median residual enzyme activity (per allele) and seeks to resolve problems identified with the WHO G6PD classification system that has been in place since 1985 (see Table in Interpretation). The G6PD locus is located on the X chromosome and, therefore, G6PD deficiency is a sex-linked disorder. Most people with G6PD deficiency are asymptomatic until a stressor event occurs resulting in acute hemolytic anemia that resolves after stimulus removal. Symptoms can include neonatal jaundice (presents at 1-4 days of age) or acute hemolysis triggered by medications (antimalarials, sulfonamides, dapsone, nitrofurantoin, and naphthalene), infection (hepatitis, CMV, typhoid), or fava bean ingestion. Hemolysis and jaundice begin 24 to 72 hours after a triggering stimulus, with accompanying dark urine/hemoglobinuria. Anemia worsens for approximately 1 week and begins to recover 10 days after cessation. Splenomegaly, gallstones, and recurrent jaundice are additional clinical symptoms. Because it is X-linked, male patients are usually more severely affected, but homozygous female patients are seen due to the prevalence of genetic variants. Heterozygous female patients (carriers) range from asymptomatic to severe anemia due to mosaicism/lyonization. Acquired G6PD may occur due to increasing X inactivation in aging women.(4) Acute episodic G6PD deficiency (WHO class B, formerly class II and III) is not expected to affect length or quality of life. Less commonly seen are genetic variants that result in chronic nonspherocytic hemolytic anemia, which manifests similarly to other enzyme deficiencies (WHO class A, formerly class I). The major G6PD variants occur in specific ethnic groups. Thus, knowledge of the ethnic background of the patient is helpful. G6PD deficiency has very high frequency in persons of southeast Asian, African, southern European, and Middle Eastern descent. Rasburicase therapy is contraindicated in patients with G6PD deficiency. US Food and Drug Administration (FDA) guidelines state to screen patients at higher risk for G6PD deficiency (eg, patients of African or Mediterranean ancestry) prior to starting therapy.(5) Deficiency can be assessed by enzymatic and/or genetic assays. Due to limitations of genetic testing, in most cases it is preferential to perform G6PD enzyme testing to assign G6PD status. However, enzyme activity can be affected by recent red blood cell transfusion, marked reticulocytosis, and very high white blood cell count. In these settings, genotyping may be useful for correlation with the red blood cell enzyme level.(6,7) Due to historic issues with other similar antimalarial medications, questions arise if hydroxychloroquine (HCQ) or chloroquine (CQ) therapy may trigger acute hemolytic episodes in some G6PD subtypes. Data is limited in this regard. Available published data did not find hemolytic episodes associated with HCQ therapy in G6PD deficient African American (8) or CQ therapy in G6PD deficient African (9) patients. Both studied populations were assumed to have mild forms of the disorder. Data regarding these medications in populations with more severe G6PD phenotypes is lacking. While patients receiving HCQ do not routinely need G6PD levels checked before initiating therapy, testing may be considered in patients who are from ethnic backgrounds with high G6PD variant rates, such as those from Mediterranean, African, or Asian descent. Although specific details are not described, hemolysis has been reported in at least one individual with G6PD deficiency during the post-approval use of HCQ sulfate tablets, United States Pharmacopeia (USP) per FDA label information.(10)

Useful For: Evaluation of individuals with episodic or chronic Coombs-negative nonspherocytic hemolytic anemia Rapid testing to assess glucose 6-phosphate dehydrogenase (G6PD) enzyme capacity prior to rasburicase or other therapies that may cause hemolysis or methemoglobinemia in G6PD deficient patients May aid in the creation of a comprehensive patient profile and can ensure appropriate patient monitoring for developing anemia

Interpretation: The World Health Organization (WHO) classification of glucose 6-phosphate dehydrogenase (G6PD) deficiency is historically based on enzyme activity level, and, in most cases, enzyme activity level is sufficient. Accurate classification requires correlation with clinical, and in certain cases, genetic data. The revised WHO classification (2022) has updated classification subtypes from

classes I, II, III, IV and V to class A, B, C and U. The Advisory Group panel concluded:(3) "In future, G6PD variants should be classified based on the median residual enzyme activity expressed as a percentage of normal activity. It should be emphasized that this system is for classifying genetic variants of G6PD and should not be used to classify individual patients with G6PD deficiency. Currently, no variants have been identified in homozygous deficient females or hemizygous deficient males that have median G6PD enzyme activity falling between 45% and 60%. Therefore, a gap has been left between Classes B and C. If new variants are found with median G6PD enzyme activity in this range, these should be included in the "U" class and studied until solid evidence is found that they induce acute haemolytic anaemia (= Class B) or do not pose a haemolytic risk (= Class C). Based on new evidence, the thresholds may then need to be revisited." Table. Updated (2022) and Legacy G6PD Variant WHO Classification and Associated G6PD Deficiency Phenotype 2022 WHO class Median* G6PD activity Hemolysis Legacy** WHO class Level of residual enzyme activity (% of normal) A <20% Chronic (CNSHA) I <10% B <45% Acute, triggered II <10% III 10%-60% C 60-150% No hemolysis IV Normal U Any Uncertain clinical significance *The activity is per variant (ie, per allele) and most straightforward to assess in hemizygous male patients and homozygous female patients. Compound heterozygous female patients are more complex and rely on clinical and familial correlation. **Legacy WHO Class V: increased activity (enzyme activity >150%) has been discontinued in the 2022 recommendations. It was originally created due to a single variant that has not been corroborated and is not deemed clinically relevant. Although G6PD deficiency is an X-linked recessive disorder and most often seen in hemizygous male patients, some female patients are affected. In addition, older women who are heterozygous can develop deficiency due to differential X-skewing with age.(4) It is important to note that clinically significant G6PD deficiency can be masked in the setting of significant reticulocytosis, markedly elevated white blood cell count, or recent red blood cell transfusion. If any of these are present in the setting of a history of neonatal, chronic, or episodic jaundice or anemia, genotyping for G6PD genetic alterations is recommended. If desired, order G6PDZ / Glucose-6-Phosphate Dehydrogenase (G6PD) Full Gene Sequencing, Varies.

Reference Values:

> or =12 months of age: 8.0-11.9 U/g Hb

Reference values have not been established for patients who are less than 12 months of age.

Clinical References: 1. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008;371(9606):64-74 2. Glucose-6-phosphate dehydrogenase deficiency. WHO Working Group. Bull World Health Organ. 1989;67(6):601-611 3. Global Malaria Programme, Malaria Policy Advisory Group. Meeting report of the technical consultation to review the classification of glucose-6-phosphate dehydrogenase (G6PD). World Health Organization; 2022. Accessed October 10, 2023. Available at www.who.int/publications/m/item/WHO-UCN-GMP-MPAG-2022.01 4. Au WY, Ma ES, Lam VW, et al. 6-phosphate dehydrogenase (G6PD) deficiency in elderly Chinese women heterozygous for G6PD variants. Am J Med Genet A. 2004;129A(2):208-211 5. ELITEK (rasburicase). Package insert: Sanofi-aventis; Updated December 2019. Accessed October 22, 2020; Available at products.sanofi.us/elitek/Elitek.html 6. Relling MV, McDonagh EM, Chang T, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of G6PD deficiency genotype. Clin Pharmacol Ther. 2014;96(2):169-174 7. Robinson KM, Yang W, Haider CE, et al. Concordance between glucose-6-phosphate dehydrogenase (G6PD) genotype and phenotype and rasburicase use in patients with hematologic malignancies. Pharmacogenomics J. 2019;19(3):305-314. doi:10.1038/s41397-018-0043-3 8. Mohammad S, Clowse MEB, Eudy AM, Criscione-Schreiber LG. Examination of hydroxychloroquine use and hemolytic anemia in G6PDH-deficient patients. Arthritis Care Res (Hoboken). 2018;70(3):481-485. doi:10.1002/acr.23296 9. Mandi G, Witte S, Meissner P, et al. Safety of the combination of chloroquine and methylene blue in healthy adult men with G6PD deficiency from rural Burkina Faso. Trop Med Int Health. 2005;10(1):32-38 10. PLAQUENIL Hydroxychloroquine Sulfate Tablets, USP. Package insert: Concordia Pharmaceuticals Inc; 2015 Updated January 2017. Accessed October 20, 2023. Available at www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf 11. Minucci A,

Moradkhani K, Hwang MJ, et al. Glucose-6-phosphate dehydrogenase (G6PD) mutations database: Review of the "old" and update of the new mutations. Blood Cells Mol Dis. 2012;48(3):154-165 12. Beutler E. Glucose-6-phosphate dehydrogenase deficiency. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ. Hematology. 5th ed. McGraw-Hill Book Company; 1995:564-586 13. Mehta A, Mason PJ, Vulliamy TJ. Glucose-6-phosphate dehydrogenase deficiency. Baillieres Best Pract Res Clin Haematol. 2000;13(1):21-38 14. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia-pathophysiology, clinical aspects and laboratory diagnosis. Int J Lab Hematol. 2014;36:388-397 15. Luzzatto L, Ally M, Notaro R. Glucose-6-phosphate dehydrogenase deficiency. Blood. 2020;136(11):1225-1240. doi:10.1182/blood.2019000944

GPIC
608419

Glucose Phosphate Isomerase Enzyme Activity, Blood

Clinical Information: The glucose 6-phosphate isomerase (GPI) enzyme interconverts glucose 6-phosphate and fructose 6-phosphate in the second step of glycolysis. GPI deficiency (OMIM 613470) is a cause of nonspherocytic hemolytic anemia and has been reported in patients from varied ethnic backgrounds. As investigational methods have improved, the number of confirmed diagnoses has increased, although the disorder remains rare. Inheritance is autosomal recessive. Clinically significant GPI deficiency manifests in variable severity ranging from mild to severe anemia, with jaundice, gallstones and splenomegaly. Some cases of neonatal death/hydrops fetalis have been reported to be associated with GPI deficiency A subset of patients shows neurologic impairment and granulocyte dysfunction. Heterozygotes are expected to have a normal phenotype.

Useful For: The evaluation of individuals with Coombs-negative chronic hemolysis

Interpretation: Most clinically significant hemolytic anemias due to glucose phosphate isomerase (GPI) deficiency are associated with activity levels less than 30% of mean normal; however, some clinically affected patients can have higher activity due to reticulocytosis. Heterozygotes usually show 40% to 60% of mean normal activity and are hematologically normal. Increased GPI activity is variably seen when young red blood cells are being produced in response to the anemia (reticulocytosis) or in newborns.

Reference Values:
Only available as part of a profile. For more information see:
-HAEV1 / Hemolytic Anemia Evaluation, Blood
-EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation, Blood

> or =12 months of age: 40.0-58.0 U/g Hb
Reference values have not been established for patients who are younger than12 months of age.

Clinical References: 1. Manco L, Bento C, Victor BL, et al. Hereditary nonspherocytic hemolytic anemia caused by red cell glucose-6-phosphate isomerase (GPI) deficiency in two Portuguese patients: Clinical features and molecular study. Blood Cells Mol Dis. 2016;60:18-23 2. Mojzikova R, Koralkova P, Holub D, et al. Two novel mutations (p.(Ser160Pro) and p.(Arg472Cys)) causing glucose-6-phosphate isomerase deficiency are associated with erythroid dysplasia and inappropriately suppressed hepcidin. Blood Cells Mol Dis. 2018;69:23-29 3. Fairbanks VF, Klee GG: Biochemical aspects of hematology. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 3rd ed. WB Saunders Company, 1999; 1642-1646 4. Koralkova P, van Solinge WW, van Wijk R: Rare hereditary red blood cell enzymopathies associated with hemolytic anemia-pathophysiology, clinical aspects and laboratory diagnosis. Int J Lab Hematol. 2014; 36:388-397

GPI1
607463

Glucose Phosphate Isomerase Enzyme Activity, Blood

Clinical Information: The glucose 6-phosphate (G6P) isomerase enzyme interconverts G6P and fructose-6-phosphate in the second step of glycolysis. Glucose phosphate isomerase (GPI) deficiency (OMIM 613470) is a cause of nonspherocytic hemolytic anemia and has been reported in patients from varied ethnic backgrounds. As investigational methods have improved, the number of confirmed diagnoses has increased, although the disorder remains rare. Inheritance is autosomal recessive. Clinically significant GPI deficiency manifests in variable severity ranging from mild to severe anemia, with jaundice, gallstones, splenomegaly. Some cases of neonatal death/hydrops fetalis have been reported to be associated with GPI deficiency. A subset of patients shows neurologic impairment and granulocyte dysfunction. Heterozygotes are expected to have a normal phenotype.

Useful For: The evaluation of individuals with Coombs-negative chronic hemolysis

Interpretation: Most clinically significant hemolytic anemias due to glucose phosphate isomerase (GPI) deficiency are associated with activity levels under 30% of mean normal; however, some clinically affected patients can have higher activity due to reticulocytosis. Heterozygotes usually show 40% to 60% of mean normal activity and are hematologically normal. Increased GPI activity is variably seen when young red blood cells are being produced in response to the anemia (reticulocytosis) or in newborns.

Reference Values:
> or =12 months: 40.0-58.0 U/g Hb
Reference values have not been established for patients who are younger than 12 months of age.

Clinical References: 1. Manco L, Bento C, Victor BL, et al: Hereditary nonspherocytic hemolytic anemia caused by red cell glucose-6-phosphate isomerase (GPI) deficiency in two Portuguese patients: Clinical features and molecular study. Blood Cells Mol Dis. 2016 Sep;60:18-23 2. Mojzikova R, Koralkova P, Holub D, et al: Two novel mutations (p.(Ser160Pro) and p.(Arg472Cys)) causing glucose-6-phosphate isomerase deficiency are associated with erythroid dysplasia and inappropriately suppressed hepcidin. Blood Cells Mol Dis. 2018 Mar;69:23-29 3. Fairbanks VF, Klee GG: Biochemical aspects of hematology. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 3rd ed. WB Saunders Company; 1999:1642-1646 4. Koralkova P, van Solinge WW, van Wijk R: Rare hereditary red blood cell enzymopathies associated with hemolytic anemia-pathophysiology, clinical aspects and laboratory diagnosis. Int J Lab Hematol. 2014;36:388-397

GLBF
606609

Glucose, Body Fluid

Clinical Information: Blood glucose is measured to assess the glycemic state of a patient. Body fluid glucose concentrations that are lower than expected indicate increased cellularity and, therefore, glycolysis within the body fluid space. This serves as an indicator of infection or possibly malignancy. Body fluid glucose concentrations are expected to be lower than that found in serum or plasma. Ideally, they are measured in the fasting state, whereby glucose is able to equilibrate into the space the body fluid is contained within. Pleural fluid: Low pleural fluid glucose concentrations (<40-60 mg/dL) indicate a complicated parapneumonic or malignant effusion.(1) However, low glucose is not specific for infection or malignancy and may be attributed to hemothorax, tuberculosis, or rheumatoid or lupus pleuritis, among other diseases. pH is the preferred test for making this determination when available. Pericardial fluid: Pericardial fluid glucose levels have been investigated on a limited basis. In presumed normal specimens collected during surgery, pericardial fluid-to-serum ratio for glucose was 1.0 (95% CI, 0.8-1.2).(2) Peritoneal fluid: Ascitic fluid glucose should be interpreted in conjunction with serum glucose measurement. In a cohort of noninfected patients with alcohol-related cirrhosis, the mean (SD) ascitic fluid-to-serum glucose ratio was 1.04 (0.25).(3) Ascitic fluid glucose may be helpful in differentiating spontaneous bacterial peritonitis from secondary peritonitis caused by bowel perforation.(4) Secondary peritonitis is likely if 2 of the 3 following criteria are met: 1. Total protein is

greater than 1 g/dL 2. Lactate dehydrogenase is greater than 225 IU/L (or greater than the upper limit of normal for serum) 3. Glucose is less than 50 mg/dL(4) Amniotic fluid: Amniotic fluid is produced by the amnion and placenta, representing a plasma ultrafiltrate. Amniocentesis may be performed to assess fetal distress. Intraamniotic infection or chorioamnionitis is an acute inflammation of the fetal membranes commonly caused by bacterial infection prompting an inflammatory response leading to labor and term or preterm birth.(5) Chorioamnionitis may be symptomatic (clinical) or asymptomatic (histological), occurring most often during prolonged labor or as a consequence of membrane rupture as bacteria have greater opportunity to ascend the lower genital tract to colonize the uterus. Prompt diagnosis and treatment for clinical chorioamnionitis is critical to avoid maternal and fetal morbidity and mortality. Culture and gram stain are often used in the assessment of infection, however, gram stain lacks sensitivity and culture results are not returned in a timely enough manner to make clinical decisions. Low glucose concentrations have been associated with positive culture results and consequently poor outcomes.(6) Synovial fluid: Synovial fluid is present in joint cavities and serves a number of important roles in maintaining joint health and mobility. Symptoms of joint problems include pain, swelling, stiffness, or decreased range of motion. Routine analysis of synovial fluid includes Gram stain, culture, crystal analysis, and cell count with white blood cells differential. In normal synovial fluid, glucose concentrations are similar to those observed in fasting serum. Low synovial fluid glucose has been associated with septic arthritis or inflammation.(7) Pancreatice Cyst: Pancreatic cyst fluid glucose may be useful for differentiating mucinous from non-mucinous cystic lesions.

Useful For: Aiding in the diagnosis of infection using body fluid specimens

Interpretation: Body fluid glucose concentrations may be decreased due to increased cellular metabolism and should be interpreted in the context of blood glucose concentrations and in conjunction with other laboratory and clinical findings.(8, 9) Pleural, peritoneal, and pericardial fluid and serum glucose concentrations are similar in the absence of infection.(3) Transudative pleural fluid glucose concentrations are similar to serum glucose concentrations, while exudates have glucose concentrations less than serum glucose. Glucose levels below 60 mg/dL are typically associated with low fluid pH.(1,10) Amniotic fluid glucose levels below 16 mg/dL is suggestive of infection.(6) Synovial fluid glucose concentrations are similar to fasting blood glucose concentrations or approximately 50% of the nonfasting serum glucose concentration under normal conditions. Values below this can be seen with infection.(7) Pancreatic cyst fluid glucose less than50 mg/dL is associated with mucinous cystic lesions.(13-15)

Reference Values:
An interpretive report will be provided.

Clinical References:

GLURA
89115

Glucose, Random, Serum

Clinical Information: The most common disease related to carbohydrate metabolism is diabetes mellitus, which is characterized by insufficient blood levels of active insulin. Symptoms include polyuria, abnormally elevated blood and urine glucose values, excessive thirst, constant hunger, sudden weight loss, and possibly elevated blood and urine ketones. Complications from diabetes are the third leading cause of death in the United States. There are approximately 16 million diabetics in the United States, and that number is growing. It is estimated that at least 5 million of these people have not been diagnosed. The prevalence in the population age 65 and older is 18.4%, representing 6.3 million cases. The cost of diabetes to the US economy exceeds $92 billion annually. Overproduction or excess administration of insulin causes a decrease in blood glucose to levels below normal. In severe cases, the resulting extreme hypoglycemia is followed by muscular spasm and loss of consciousness, known as insulin shock.

Useful For: Diagnosing and managing diabetes mellitus and other carbohydrate metabolism disorders

including gestational diabetes, neonatal hypoglycemia, idiopathic hypoglycemia, and pancreatic islet cell carcinoma

Interpretation: Any of the following results, confirmed on a subsequent day, can be considered diagnostic for diabetes: -Fasting plasma or serum glucose > or =126 mg/dL after an 8-hour fast -2-Hour plasma or serum glucose > or =200 mg/ dL during a 75-gram oral glucose tolerance test (OGTT) -Random glucose >200 mg/dL, plus typical symptoms Patients with "impaired" glucose regulation are those whose fasting serum or plasma glucose fall between 101 and 126 mg/dL, or whose 2-hour value on oral glucose tolerance test fall between 140 and 199 mg/dL. These patients have a markedly increased risk of developing type 2 diabetes and should be counseled for lifestyle changes and followed up with more testing. Indications for screening and testing include strong family history, marked obesity, history of babies over 9 pounds, and recurrent skin and genitourinary infections. Glucose levels of 25 mg/dL or lower in infants younger than 1 week are considered to be potentially life threatening, as are glucose levels of 40 mg/dL or lower in infants older than 1 week. Glucose levels of 400 mg/dL and higher are considered a critical value.

Reference Values:
0-11 months: not established
> or =1 year: 70-140 mg/dL

Clinical References: Chapter 25: In Tietz Textbook of Clinical Chemistry. Fourth edition. Edited by CA Burtis, ER Ashwood, DE Bruns. WB Saunders Company, Philadelphia, 2006, pp 837-907

GLUR1
609796

Glucose, Random, Urine

Clinical Information: The test is specific for glucose. No other substance excreted in urine is known to give a positive result, including other reducing substances (eg, galactose, fructose, and lactose). This test may be used to determine whether the reducing substance found in urine is glucose. Glucosuria occurs when the renal threshold for glucose is exceeded (typically >180 mg/dL); this is most commonly, although not exclusively, seen in diabetes. However, if the urine glucose is high and the patient is not known to have diabetes mellitus, more specific testing should be considered (fasting blood glucose and/or glycosylated hemoglobin).

Useful For: Limited usefulness for routine screening or management of diabetes mellitus

Interpretation: Small amounts of glucose are normally excreted by the kidney. These amounts are usually below the sensitivity of this test but, on occasion, may produce a color between negative and 100 mg/dL (trace), which is interpreted by the instrument as a positive. Results at the first positive level may be significantly abnormal if found consistently.

Reference Values:
Negative

Clinical References: 1. Brunzel NA: Chemical examination of urine. In: Fundamentals of Urine and Body Fluids. 4th ed. Saunders; 2018:85-125 2. Chen J, Guo H, Yuan S, et al: Efficacy of urinary glucose for diabetes screening: a reconsideration. Acta Diabetol. 2019 Jan;56(1):45-53

GLSF
152

Glucose, Spinal Fluid

Clinical Information: Cerebrospinal fluid (CSF) is secreted by the choroid plexuses, around the

cerebral vessels, and along the walls of the ventricles of the brain, filling the ventricles and cisternae and bathing the spinal cord. CSF is reabsorbed into the blood through the arachnoid villi. CSF turnover is rapid, exchanging about 4 times per day. CSF glucose levels may be decreased due to consumption by microorganisms, impaired glucose transport, or increased glycolysis. Elevated CSF glucose levels are consistent with hyperglycemia.

Useful For: Investigating possible central nervous system infection

Interpretation: Cerebrospinal fluid (CSF) glucose levels may be decreased in any central nervous system infection, although levels are typically normal in viral meningitis, low in bacterial meningitis, and may be normal or low in fungal meningitis. CSF glucose levels are normally about 60% of blood glucose levels.

Reference Values:
Spinal fluid glucose concentration should be approximately 60% of the plasma/serum concentration and should be compared with concurrently measured plasma/serum glucose for adequate clinical interpretation.

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. Edited by CA Burtis, ER Ashwood, DE Bruns, St. Louis, MO, Elsevier Saunders, 2012

G6PDZ
610053

Glucose-6-Phosphate Dehydrogenase (G6PD) Full Gene Sequencing, Varies

Clinical Information: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzymopathy, estimated to affect up to 500 million people worldwide. It is most frequently found in populations where Plasmodium falciparum malaria is (or was) endemic, but G6PD deficiency may be present in any population. G6PD deficiency primarily manifests as episodic acute hemolytic anemia (AHA), chronic non-spherocytic hemolytic anemia (CNSHA), and neonatal jaundice. These clinical manifestations can be triggered in individuals with G6PD deficiency by fava beans, several types of medications (including rasburicase, dapsone-containing combinations of antimalarial drugs, and methylene blue), and infection. G6PD converts glucose-6-phosphate to 6-phosphoglyconolactone in the first step of the pentose phosphate pathway, this reaction also produces nicotinamide adenine dinucleotide phosphate (NADPH) from NADP(+). NADPH, through subsequent enzymatic reactions, protects erythrocytes from damage by detoxifying hydrogen peroxide and other sources of oxidative stress. G6PD is encoded by the gene G6PD, which lies on the X-chromosome. G6PD deficiency is inherited in an X-linked recessive manner; therefore, male patients are more commonly affected than female patients, but due to the high prevalence of G6PD deficiency, homozygous and compound heterozygous female patients are not uncommon. Over 200 G6PD variants have been discovered and are classified based on guidance from the World Health Organization (WHO). In 2022, WHO proposed updated guidance for the classification of G6PD variants (Table). This revised guidance is based on the median residual enzyme activity and seeks to resolve problems identified with the WHO G6PD classification system that has been in place since 1985 (Table). Table. Updated and Legacy G6PD Variant WHO Classification and Associated G6PD Deficiency Phenotype 2022 WHO class Median G6PD activity Hemolysis Legacy WHO class Level of residual enzyme activity (% of normal) A <20% Chronic (CNSHA) I <10% B <45% Acute, triggered II <10% III 10%-60% C 60-150% No hemolysis IV Normal U Any Uncertain clinical significance With the exception of those with CNSHA, individuals with G6PD deficiency are typically asymptomatic until they are challenged with an exogenous factor, such as a drug, infection, or fava beans. The exogenous factor can trigger AHA in individuals with G6PD deficiency. The severity of AHA is highly variable, ranging from mild neonatal jaundice to life-threatening complications, such as

kernicterus. Therefore, determining the G6PD deficiency status is recommended on the US Food and Drug Administration label of several drugs either proven or suspected to cause AHA in patients with G6PD deficiency. For more information on drugs known to cause AHA in individuals with G6PD deficiency, see Pharmacogenomic Associations Tables. Preemptive genotyping allows for the identification of patients at risk for an adverse reaction to drugs known to cause AHA in those with G6PD deficiency. In most cases, genotyping provides sufficient information to avoid the use of contraindicated drugs. In some cases, including heterozygous female patients, the phenotyping assay is necessary to determine if such drugs should be avoided. Skewed X-inactivation in heterozygous female patients has been reported to result in G6PD deficiency, so the phenotyping assay is necessary to determine G6PD activity level.

Useful For: Genetic test for individuals at high risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency Aiding in the diagnosis of G6PD deficiency Determining G6PD deficiency status in individuals with inconclusive or unexpected phenotyping results Differentiation of heterozygotes with skewed X-inactivation from homozygotes and compound heterozygotes Definitive diagnosis of carrier status Evaluation of neonates with unexplained jaundice Identifying individuals at risk of drug-induced acute hemolytic anemia related to G6PD deficiency

Interpretation: All detected alterations will be evaluated according to the latest American College of Medical Genetics and Genomics recommendations and the most recent World Health Organization system for classifying genetic variants of G6PD.(1,2) Variants will be classified based on known, predicted, or possible effect on gene pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;(17):105-423 2. Global Malaria Programme, Malaria Policy Advisory Group. Meeting report of the technical consultation to review the classification of glucose-6-phosphate dehydrogenase (G6PD). World Health Organization; 2022. Accessed July 3, 2023. Available at www.who.int/publications/m/item/WHO-UCN-GMP-MPAG-2022.01 3. Luzzatto L, Ally M, Notaro R. Glucose-6-phosphate dehydrogenase deficiency. Blood. 2020;136(11):1225-1240. doi:10.1182/blood.2019000944 4. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008;371:64-67 5. Luzzatto L, Seneca E. G6PD deficiency: a classic example of pharmacogenetics with on-going clinical implications. Br J Haematol. 2014;164:469-480 4. OMIM. 305900 Glucose-6-phosphate dehydrogenase. Johns Hopkins University; 1987. Updated April 28, 2023. Accessed July 3, 2023. Available at www.omim.org/entry/305900 5. Relling MV, McDonagh EM, Chang T, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of G6PD deficiency genotype. Clin Pharmacol Ther. 2014 Aug;96(2):169-174

HEX4
64174

Glucotetrasaccharides, Random, Urine

Clinical Information: Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme, acid alpha-glucosidase (GAA). This leads to an accumulation of glycogen in the lysosome causing swelling, cell damage, and progressive organ dysfunction. In glycogen storage diseases, excess glycogen is degraded to glucotetrasaccharide (glucose tetrasaccharide: Glc4), which is excreted in urine. Measurement of Glc4 in urine is used for both initial diagnosis and monitoring of patients with Pompe disease and may also

be elevated in other glycogen storage disorders. Pompe disease is caused by deleterious variants in the GAA gene. The classic, early infantile onset form of the disease is characterized by progressive muscle hypotonia, weakness, hypertrophic cardiomyopathy, and death due to either cardiorespiratory or respiratory failure, typically by the end of the first year of life. Juvenile and adult-onset forms of Pompe disease are characterized by later onset and longer survival. Primary symptoms of later-onset Pompe disease include muscle weakness and respiratory insufficiency, with cardiomyopathy only rarely developing. Based on data from newborn screening, the incidence is approximately 1 in 20,000 live births with most patients being affected with later onset forms of Pompe disease. The clinical phenotype depends on residual enzyme activity, with complete loss of activity causing onset in infancy. Enzyme replacement therapy (ERT) improves outcomes in many patients with either classic infantile-onset or later-onset Pompe disease. Early initiation of treatment improves the prognosis and makes early diagnosis of Pompe disease desirable. Because of this, newborn screening for Pompe disease has recently been added to the Recommended Uniform Screening Panel and already been implemented in some states. Historically, diagnostic testing required a skin or muscle biopsy to measure GAA enzyme activity. Today, noninvasive enzyme assays (GAAW / Acid Alpha-Glucosidase, Leukocytes) and molecular genetic analysis of the GAA gene (GAAZ / Pompe Disease, Full Gene Analysis, Varies) are available for testing in blood and dried blood spots. In addition, Glc4 can be measured in urine to support a diagnosis of Pompe disease and other glycogen storage disorders.

Useful For: Diagnosing Pompe disease, when used in conjunction with acid alpha-glucosidase enzyme activity assays and molecular genetic analysis of the GAA gene Monitoring patients with Pompe disease on enzyme replacement therapy May support the diagnosis and monitoring of other glycogen storage disorders; however, glucotetrasaccharide (Glc4) excretion appears to be less consistently elevated in glycogen storage disorders other than Pompe disease This test is not useful for carrier screening.

Interpretation: An elevated excretion of glucotetrasaccharide is indicative of Pompe disease or other glycogen storage disorders. Enzyme or molecular analysis is required to confirm suspected diagnosis.

Reference Values:
< or =14 months: < or =14.9 mmol/mol Cr
> or =15 months: < or =4.0 mmol/mol Cr

Clinical References:

GLUT
70446

GLUT-1 Immunostain, Technical Component Only

Clinical Information: Glucose transporter 1 (GLUT-1) is a ubiquitous facilitative membrane glucose transporter that is activated by hypoxia-sensing cellular pathways and may sustain cellular metabolism via glycolysis when hypoxia is present. It is expressed at high levels on erythrocytes, the endothelium of the blood-brain barrier, and the perineurium. Various carcinomas may show overexpression, including fallopian tube carcinomas.

Useful For: Identification of erythrocytes in various normal and neoplastic tissues

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Zhou JC, Zhang JJ, Zhang W, Ke ZY, Ma LG, Liu M. Expression of GLUT-1 in nasopharyngeal carcinoma and its clinical significance. Eur Rev Med Pharmacol Sci.

2017;21(21):4891-4895 2. Berlth F, Monig S, Pinther B, et al. Both GLUT-1 and GLUT-14 are independent prognostic factors in gastric adenocarcinoma. Ann Surg Oncol. 2015;22 Suppl 3:S822-31. doi:10.1245/s10434-015-4730-x 3. Abdou AG, Eldien MM, Elsakka D. GLUT-1 expression in cutaneous basal and squamous cell carcinomas. Int J Surg Pathol. 2015;23(6):447-453. doi:10.1177/1066896915589968 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

GD65S 81596 Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Serum

GD65C 84221 Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Spinal Fluid

Clinical Information: Glutamic acid decarboxylase (GAD) is a neuronal enzyme involved in the synthesis of the neurotransmitter gamma-aminobutyric acid (GABA). Serum antibodies directed against the 65-kDa isoform of GAD (GAD65) are detected in heightened frequency in a variety of autoimmune neurologic disorders, including autoimmune encephalitis, stiff-person (Moersch-Woltman) syndrome, autoimmune ataxia, and autoimmune epilepsy.

Useful For: Possible use in evaluating patients with autoimmune encephalitis, stiff-person syndrome, autoimmune ataxia, autoimmune epilepsy, and other acquired central nervous system disorders affecting gabaminergic neurotransmission

Interpretation: Intrathecal synthesis of glutamic acid decarboxylase 65 (GAD65) antibody has been demonstrated in patients with stiff-man syndrome, but cerebrospinal fluid (CSF) values are log orders lower than serum. We have not determined the frequency of GAD65 antibodies in CSF of patients with various diagnoses.

Reference Values:
< or =0.02 nmol/L
Reference values apply to all ages.

Clinical References: 1. McKeon A, Tracy JA. GAD65 neurological autoimmunity. Muscle Nerve. 2017;56(1):15-27. doi:10.1002/mus.25565 2. Pittock SJ, Yoshikawa H, Ahlskog JE, et al. Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal and spinal cord dysfunction. Mayo Clin Proc. 2006;81(9):1207-1214 3. McKeon A, Robinson MT, McEvoy KM, et al. Stiff-man syndrome and variants: clinical course, treatments, and outcomes. Arch Neurol. 2012;69(2):230-238 4. Steriade C, Britton J, Dale RC, et al. Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: Conceptual definitions. Epilepsia. 2020;61(7):1341-1351 5. Bingley PJ. Clinical applications of diabetes antibody testing. J Clin Endocrinol Metab. 2010;95(1):25-33

GLUTS 70450 Glutamine Synthetase Immunostain, Technical Component Only

Clinical Information: Glutamine synthetase (GS) is an enzyme that catalyzes the adenosine triphosphate-dependent condensation of glutamate with ammonia to form glutamine. GS can be used with a panel of immunohistochemistry markers (beta-catenin, liver fatty acid binding protein, C-reactive protein, and amyloid A) to distinguish hepatic adenoma from focal nodular hyperplasia and nonneoplastic liver. GS, a target gene of beta-catenin, is expressed in hepatic adenomas with beta-

catenin alterations (type 2), but it is not expressed in hepatic adenomas without beta-catenin alterations. GS is expressed in zone 3 of normal liver and has a characteristic map-like pattern in focal nodular hyperplasia.

Useful For: Classification of hepatic adenomas and the identification of focal nodular hyperplasia

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Bakheet AMH, Zhao C, Chen JN, et al. Improving pathological early diagnosis and differential biomarker value for hepatocellular carcinoma via RNAscope technology. Hepatol Int. 2020;14(1):96-104. doi:10.1007/s12072-019-10006-z 2. Long J, Wang H, Lang Z, Wang T, Long M, Wang B. Expression level of glutamine synthetase is increased in hepatocellular carcinoma and liver tissue with cirrhosis and chronic hepatitis B. Hepatol Int. 2011;5(2):698-706. doi:10.1007/s12072-010-9230-2 3. Margolskee E, Bao F, de Gonzalez AK, et al. Hepatocellular adenoma classification: a comparative evaluation of immunohistochemistry and targeted mutational analysis. Diagn Pathol. 2016;11:27. doi:10.1186/s13000-016-0475-5 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

GA2P
608029

Glutaric Aciduria Type II Gene Panel, Varies

Clinical Information: Glutaric acidemia Type II (GA II), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is caused by defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. This disease can be severe and is often fatal in the first weeks of life, with symptoms including hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA II can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood and muscle weakness in childhood and adulthood. Three genes have been implicated in causing GA II: ETFA, ETFB, and ETFDH. This comprehensive gene panel is a helpful tool to establish a diagnosis for patients with suggestive clinical and biochemical features of GA II.

Useful For: Follow up for abnormal biochemical results suggestive of glutaric acidemia type II Establishing a molecular diagnosis for patients with glutaric acidemia type II Identifying variants within genes known to be associated with glutaric acidemia, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 2. Frerman FE, Goodman SI: Defects of electron transfer flavoprotein and electron

transfer flavoprotein-ubiquinone oxidoreductase: Glutaric acidemia type II. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed December 20, 2019. Available at www.ommbid.com

GSH
608409

Glutathione, Blood

Clinical Information: Hemolytic anemia may be associated with deficiency of erythrocyte enzymes. Red blood cell (RBC) enzymes linked to hemolysis are those important in the energy generation of glycolysis or protection from oxidative stress such as the hexose monophosphate shunt. The hexose monophosphate pathway depends primarily upon the glucose 6-phosphate dehydrogenase (G6PD) enzyme for the generation of reduced nicotinamide-adenine dinucleotide phosphate (NADPH) with 6-phosphogluconate dehydrogenase (6PGD) providing an additive effect. Both reactions require adequate levels of reduced glutathione (GSH). Because RBCs lack the citric acid cycle, this is an important source of NADPH, and a deficiency of G6PD or GSH results in the inability to neutralize oxidative insults. GSH is synthesized from amino acids by two enzymatic steps and is present in liver, kidney, brain, muscle, and RBCs. It plays widely versatile and important roles in the synthesis of proteins and DNA, the processing of medications and toxins, and other redox reactions. Similar to G6PD deficiency, glutathione deficiency can have an episodic acute time course of hemolysis or jaundice, be triggered by fava beans, and cause neonatal hyperbilirubinemia. Five enzymes impact GSH availability and therefore are potential candidates for abnormalities leading to glutathione deficiency: -Two enzymes, gamma-glutamylcysteine synthetase (GCLC) and glutathione synthetase (GSS), are required for GSH synthesis -Two enzymes, glutathione reductase (GSR) and glutathione peroxidase (GPX1), are required for reduction-oxidation cycling of oxidized glutathione (GSSG) to reduced glutathione (GSH) -A family of enzymes, glutathione S-transferases (GSTs), utilizes GSH in the detoxification and preparation of substances for excretion into the bile or urine Enzyme deficiencies have been reported in all of these enzymes, albeit very rarely. The best characterized are GSS and GCLC deficiencies. GSS deficiency is associated with two clinical presentations; a mild form causing isolated chronic hemolytic anemia, and a more severe form marked by urinary excretion of 5-oxoproline, metabolic acidosis, hemolytic anemia, and central nervous system disorders (5-oxoprolinuria). GCLC deficiency is associated with moderate to severe chronic hemolytic anemia present from neonatal or early childhood, or compensated hemolysis with sporadic but recurrent anemia or jaundice. Some cases have shown learning disabilities, severe and progressive ataxia with myopathy and spinocerebellar degeneration. GSR deficiency has been confirmed in three siblings with favism (episodic hemolysis after fava bean ingestion) and cataracts in early adulthood, and an unrelated infant with marked neonatal hyperbilirubinemia. GSR activity can be decreased in riboflavin deficiency, but whether this results in hemolysis is not clear. Although patients have been reported with anemia in the context of decreased GPX1 activity and decreased GST activity was found in a person with hemolytic anemia, splenomegaly, hyperbilirubinemia, and cholelithiasis, neither have been characterized sufficiently as the definitive cause of hemolysis. All described cases have shown autosomal recessive inheritance pattern. A deficiency of either of the synthetic enzymes, GCLC or GSS, results in GSH levels less than 25%, but many show a virtual absence of measurable GSH. Heterozygotes usually show normal GSH levels. Elevated concentrations of GSH are found in patients with myelofibrosis and in those with pyrimidine-5'-nucleotidase deficiency.

Useful For: Evaluation of neonatal hyperbilirubinemia, favism or chronic or episodic hemolysis or jaundice Evaluation for gamma-glutamylcysteine synthetase deficiency Evaluation for glutathione synthetase deficiency causing hemolytic anemia Evaluation for generalized glutathione synthetase deficiency with 5-oxoprolinuria

Interpretation:

Reference Values:

> or =12 months: 46.9-90.1 mg/dL RBC
Reference values have not been established for patients who are younger12 months of age.

Clinical References: 1. Valentine WN, Paglia DE: Syndromes with increased red cell glutathione (GSH). Hemoglobin. 1980;4(5-6):799-804. doi:10.3109/03630268008997748 2. Manu Pereira M, Gelbart T, Ristoff E, et al. Chronic non-spherocytic hemolytic anemia associated with severe neurological disease due to gamma-glutamylcysteine synthetase deficiency in a patient of Moroccan origin. Haematologica. 2007;92(11). doi:10.3324/haematol.11238 3. Ristoff E, Mayatepek E, Larsson A. Long-term clinical outcome in patients with glutathione synthetase deficiency. J Pediatr. 2001;139(1):79-84. doi:10.1067/mpd.2001.114480 4. Konrad PN, Richards F, Valentin WN, et al. Gamma glutamyl cysteine synthetase deficiency. N Engl J Med. 1972;286:557 5. Mehta A, Mason PJ, Vulliamy TJ. Glucose-6-phosphate dehydrogenase deficiency. Baillieres Best Pract Res Clin Haematol. 2000;13(1):21-38 6. Beutler E, Dunning D, Dabe IB, Forman L. Erythrocyte glutathione S-transferase deficiency and hemolytic anemia. Blood. 1988;72:73-77 7. Kamerbeek NM, van Zwieten R, de Boer M, et al. Molecular basis of glutathione reductase deficiency in human blood cells. Blood. 2007;109(8):3560-3566. doi:10.1182/blood-2006-08-042531 8. Tomoda A, Noble NA, Lachant NA, Tanaka KR. Hemolytic anemia in hereditary pyrimidine 5'-nucleotidase deficiency: nucleotide inhibition of G6PD and the pentose phosphate shunt. Blood. 1982;60(5):1212-1218 9. van Solinge WW, van Wijk. Enzymes of the red blood cell. In: Rifai N, Horvath AR, Wittwer CT: eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:chap 30

FGLUT
57559

Gluten IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

GLT
82894

Gluten, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to gluten Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not

useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GLYCS
606972

Glycine Receptor Alpha1 IgG, Cell Binding Assay, Serum

Clinical Information: Inhibitory synaptic transmission is mediated by gamma-aminobutyric acid-ergic (GABA-ergic) and glycinergic spinal interneurons, which regulate motor neuron excitability in the brainstem and spinal cord. Autoimmune central nervous system disorders include classic stiff-man syndrome (also known as stiff-person syndrome), limited stiff-man forms (eg, stiff-limb syndrome) and a severe (and sometimes fatal) encephalomyelitic variant known as progressive encephalomyelitis with rigidity and myoclonus (PERM). These disorders are unified clinically by exaggerated startle, stiffness, and spasms of the axis and/or limbs. Characteristic electrophysiologic findings include continuous motor unit activity by unipolar electromyographic (EMG) recording, and exaggerated and non-habituating acoustic startle responses. Eighty percent of patients are seropositive for antibody targeting the 65 kDa isoform of glutamic acid decarboxylase (GAD65). The alpha-1-subunit of the glycine receptor (GlyRa1), which is enriched in brainstem and spinal cord, has emerged as an antigenic target with specificity for the autoimmune stiff-person spectrum, and is particularly useful for diagnostics among patients seronegative for GAD65-IgG. GlyRa1-IgG has been described among patients with PERM (33%), classic stiff-man syndrome (9%), and limited stiff-man forms (17%). Seropositivity for GlyRa1-IgG is detected in 19% of patients from the stiff-man spectrum who are GAD65-IgG seronegative. The clinical context is usually non-paraneoplastic, though thymoma and lymphomas have been occasionally described. Disease-specific antibodies may be detected in serum only, CSF only, or both. Improvements with immunotherapy (steroids, plasma exchange or intravenous immune globulin) occur more commonly in GlyRa1-IgG seropositive patients than among patients seropositive for

GAD65 antibody only. In one series, improvement was noted in 6/7 GlyRa1-IgG antibody positive patients compared with only 7/25 without these antibodies.

Useful For: Evaluating patients with suspected autoimmune stiff-person spectrum disorders (stiff-person syndrome, stiff-limb, stiff trunk or progressive encephalomyelitis with rigidity and myoclonus [PERM]) using serum specimens

Interpretation: In the appropriate clinical context, this profile is consistent with a stiff-person syndrome spectrum disorder (classical stiff-person, stiff-limb, or progressive encephalomyelitis with rigidity and myoclonus [PERM]). A paraneoplastic cause should be considered.

Reference Values:
Negative

Clinical References: 1. Hutchinson M, Waters P, McHugh J, et al: Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology. 2008;71:1291-1292 2. McKeon A, Martinez-Hernandez E, Lancaster E, et al: Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. JAMA Neurol. 2013;70:44-50 3. Carvajal-Gonzalez A, Leite MI, Waters P, et al: Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. Brain. 2014;137:2178-2192 4. Martinez-Hernandez E, Arino H, McKeon A, et al: Clinical and immunologic investigations in patients with stiff-person spectrum disorder. JAMA Neurol. 2016;73:714-720 5. Hinson SR, Lopez-Chiriboga AS, Bower JH, et al: Glycine receptor modulating antibody predicting treatable stiff-person spectrum disorders. Neurol Neuroimmunol Neuroinflamm. 2018; 5:e438

GLYCC
606973

Glycine Receptor Alpha1 IgG, Cell Binding Assay, Spinal Fluid

Clinical Information: Inhibitory synaptic transmission is mediated by gamma-aminobutyric acid-ergic (GABA-ergic) and glycinergic spinal interneurons, which regulate motor neuron excitability in the brainstem and spinal cord. Autoimmune central nervous system disorders include classic stiff-man syndrome (also known as stiff-person syndrome), limited stiff-man forms (eg, stiff-limb syndrome) and a severe (and sometimes fatal) encephalomyelitic variant known as progressive encephalomyelitis with rigidity and myoclonus (PERM). These disorders are unified clinically by exaggerated startle, stiffness, and spasms of the axis and/or limbs. Characteristic electrophysiologic findings include continuous motor unit activity by unipolar electromyographic (EMG) recording, and exaggerated and non-habituating acoustic startle responses. Eighty percent of patients are seropositive for antibody targeting the 65 kDa isoform of glutamic acid decarboxylase (GAD65). The alpha-1-subunit of the glycine receptor (GlyRa1), which is enriched in brainstem and spinal cord, has emerged as an antigenic target with specificity for the autoimmune stiff-person spectrum, and is particularly useful for diagnostics among patients seronegative for GAD65-IgG. GlyRa1-IgG has been described among patients with PERM (33%), classic stiff-man syndrome (9%), and limited stiff-man forms (17%). Seropositivity for GlyRa1-IgG is detected in 19% of patients from the stiff-man spectrum who are GAD65-IgG seronegative. The clinical context is usually non-paraneoplastic, though thymoma and lymphomas have been occasionally described. Disease-specific antibodies may be detected in serum only, CSF only, or both. Improvements with immunotherapy (steroids, plasma exchange or intravenous immune globulin) occur more commonly in GlyRa1-IgG seropositive patients than among patients seropositive for GAD65 antibody only. In one series, improvement was noted in 6/7 GlyRa1-IgG antibody positive patients compared with only 7/25 without these antibodies.

Useful For: Evaluating patients with suspected autoimmune stiff-person spectrum disorders (stiff-person syndrome, stiff-limb, stiff trunk, or progressive encephalomyelitis with rigidity and myoclonus [PERM]) using spinal fluids specimens

Interpretation: In the appropriate clinical context, this profile is consistent with a stiff-person syndrome spectrum disorder (classical stiff-person, stiff-limb, or progressive encephalomyelitis with rigidity and myoclonus [PERM]). A paraneoplastic cause should be considered.

Reference Values:
Negative

Clinical References: 1. Hutchinson M, Waters P, McHugh J, et al: Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology. 2008;71:1291-1292 2. McKeon A, Martinez-Hernandez E, Lancaster E, et al: Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. JAMA Neurol. 2013;70:44-50 3. Carvajal-Gonzalez A, Leite MI, Waters P, et al: Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. Brain. 2014;137:2178-2192 4. Martinez-Hernandez E, Arino H, McKeon A, et al: Clinical and immunologic investigations in patients with stiff-person spectrum disorder. JAMA Neurol. 2016;73:714-720 5. Hinson SR, Lopez-Chiriboga AS, Bower JH, et al: Glycine receptor modulating antibody predicting treatable stiff-person spectrum disorders. Neurol Neuroimmunol Neuroinflamm. 2018; 5:e438

GSDGP
608012

Glycogen Storage Disease Gene Panel, Varies

Clinical Information: Glycogen storage diseases (GSD) are a group of inherited metabolic conditions caused by deficiency of enzymes responsible for glycogen metabolism, resulting in abnormal storage of glycogen in the liver and various muscles. There are over 15 different GSD that vary in symptoms and severity, dependent on the enzyme deficiency, although liver and muscle are the most frequently affected areas. Generally, GSD can be divided into 2 categories, those with hepatic involvement and those with neuromuscular involvement. Some GSD result in single tissue disease, while others affect multiple organs. Clinical features may include hepatomegaly, hypoglycemia, muscle cramps, exercise intolerance, and progressive fatigue and weakness. Preliminary biochemical testing may be helpful in making a diagnosis (ie, glucose monitoring, triglycerides, uric acid level, creatine kinase, liver function tests, and complete blood cell count). This test involves sequencing of 26 genes related to various GSD.

Useful For: Follow up of abnormal biochemical results consistent with glycogen storage disease (GSD) Establishing a molecular diagnosis for patients with GSD Identifying variants within genes known to be associated with GSD allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Chen YT, Kishani PS, Koeberl D: Glycogen storage disease. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Diseases. McGraw-Hill Education; 2019. Accessed February 8, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225080698&bookid=2709&Resultclick=2 3. Hicks J, Wartchow, E, Mierau G. Glycogen storage diseases: A brief review and update on clinical

G161
605194

Glycogen Storage Disease Panel (Bill Only)

features, genetic abnormalities, pathologic features, and treatment. Ultrastruct Pathol. 2011;35(5):183-196

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

FGLMA
91742

GlycoMark

Reference Values:

Age	Range
<18 y	Not Established
Adult Males	10.7-32.0
Adult Females	6.8-29.3

Glycemic control goal for diabetic patients: >10

GlycoMark is intended for use with managing glycemic control in diabetic patients. A low result corresponds to high glucose peaks.
1, 5-AG blood levels can be affected by clinical conditions or medications.

GLYCF
70448

Glycophorin A (CD235a) Immunostain, Technical Component Only

Clinical Information: Glycophorin A is expressed by erythroid precursors in the bone marrow and is also present on erythrocytes. Glycophorin A is useful to characterize erythroid cell development and aid in the diagnosis of erythroid leukemia.

Useful For: Aiding in the identification of erythroid precursors in bone marrow

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Reference Values:
NA

Clinical References: 1. Dong HY, Wilkes S, Yang H. CD71 is selectively and ubiquitously expressed at high levels in erythroid precursors of all maturation stages: a comparative immunochemical study with glycophorin A and hemoglobin A. Am J Surg Pathol. 2011;35(5):723-732 2. Rollins-Raval MA, Fuhrer K, Marafioti T, Roth CG. ALDH, CA I, and CD2AP: novel, diagnostically useful immunohistochemical markers to identify erythroid precursors in bone marrow biopsy specimens. Am J Clin Pathol. 2012;137(1):30-38 3. Liu W, Hasserjian RP, Hu Y, et al. Pure erythroid leukemia: a reassessment of the entity using the 2008 World Health Organization classification. Mod Pathol. 2011;24(3):375-383 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

GDOM
82847

Glycyphagus domesticus, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Glycyphagus domesticus Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GLYP3
70447

Glypican-3 Immunostain, Technical Component Only

Clinical Information: Glypican-3 (GPC3) protein is a member of the glypican family of heparin sulfate proteoglycans that are phosphatidylinositol-anchored to the cytoplasmic membrane. GPC3 acts as a coreceptor for heparin-binding growth factors, which play an important role in cell growth and

differentiation. Diagnostically, GPC3 will aid in separating hepatocellular carcinomas from other malignancies and hepatic adenomas. It is expressed in 70% to 90% of hepatocellular carcinomas.

Useful For: Differentiating hepatocellular carcinomas from other malignancies and hepatic adenomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Reference Values:
N/A

Clinical References: 1. Zhang J, Zhang M, Ma H, et al. Overexpression of glypican-3 is a predictor of poor prognosis in hepatocellular carcinoma: An updated meta-analysis. Medicine (Baltimore). 2018;97(2):e11130 2. Montalbano M, Georgiadis J, Masterson AL, et al. Biology and function of glypican-3 as a candidate for early cancerous transformation of hepatocytes in hepatocellular carcinoma. Oncol Rep. 2017;37(3):1291-1300 3. Haruyama Y, Kataoka H. Glypican-3 is a prognostic factor and an immunotherapeutic target in hepatocellular carcinoma. World J Gastroenterol. 2016;22(1):275-283 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

GOAT
82783

Goat Epithelium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to goat epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GMILK
82550

Goat's Milk, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to goat's milk Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GLDR
82717

Goldenrod, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to goldenrod Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FGAGA 75564 Golimumab and Anti-Golimumab Antibody, DoseASSURE GOL

FGNDR 75915 Gonadotropin Releasing Hormone (Gn-RH, Luteinizing Hormone-Releasing Hormone LT-RH)

Reference Values:
Male: 4.0-8.0 pg/mL
Female: 2.0-10.0 pg/mL

GOOS 82714 Goose Feathers, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to goose feathers Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon

identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GP210
620726

GP210 Antibody, IgG, Serum

Clinical Information:

Useful For: Evaluating the risk of primary biliary cholangitis in anti-mitochondrial antibody (AMA)-negative patients by identification of gp210 antibodies Estimating risk in AMA-positive patients with incomplete feature of disease

Interpretation: A positive result for anti-gp210 antibodies in the setting of chronic cholestasis after exclusion of other causes of liver disease is highly suggestive of primary biliary cholangitis.

Reference Values:

Negative: < or =20.0 Units
Equivocal: 20.1-24.9 Units
Positive: > or =25.0 Units

Clinical References: 1. Younossi ZM, Bernstein D, Shiffman ML, et al. Diagnosis and management of primary biliary cholangitis. Am J Gastroenterol. 2019;114(1):48-63 2. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance update from the American Association for the Study of Liver Diseases. Hepatology. 2019;69(1):394-419 3. International Consensus on ANA Patterns. AC-20 Cytoplasmic fine speckled. ICAP; 2015. Accessed August 18, 2023. Available at www.anapatterns.org/view_pattern.php?pattern=20 4. Zhang Q, Liu Z, Wu S, et al. Meta-analysis of

antinuclear antibodies in the diagnosis of antimitochondrial antibody-negative primary biliary cholangitis. Gastroenterol Res Pract. 2019;2019:8959103 5. Dahlqvist G, Gaouar F, Carrat F, et al. Large-scale characterization study of patients with antimitochondrial antibodies but nonestablished primary biliary cholangitis. Hepatology. 2017;65(1):152-163 6. Nakamura M, Kondo H, Mori T, et al. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. Hepatology. 2007;45(1):118-127 7. Jaskowski TD, Nandakumar V, Novis CL, Palmer M, Tebo AE. Presence of anti-gp210 or anti-sp100 antibodies in AMA-positive patients may help support a diagnosis of primary biliary cholangitis. Clin Chim Acta. 2023;540:117219 8. Munoz-Sanchez G, Perez-Isidro A, Ortiz de Landazuri I, et al. Working algorithms and detection methods of autoantibodies in autoimmune liver disease: A nationwide study. Diagnostics (Basel). 2022;12:697 9. Favoino E, Grapsi E, Barbuti G, et al. Systemic sclerosis and primary biliary cholangitis share an antibody population with identical specificity. Clin Exp Immunol. 2023;212(1):32-38 10. Wei Q, Jiang Y, Xie J, et al. Investigation and analysis of HEp 2 indirect immunofluorescence titers and patterns in various liver diseases [published correction appears in Clin Rheumatol. 2021 Apr;40(4):1667]. Clin Rheumatol. 2020;39(8):2425-2432. doi:10.1007/s10067-020-04950-7

LAGGT
8976

Granulocyte Antibodies, Serum

Clinical Information: Granulocyte antibodies are induced by pregnancy or prior transfusion and are associated with febrile, nonhemolytic transfusion reactions. Patients who have been immunized by previous transfusions, pregnancies, or allografts frequently experience febrile, nonhemolytic transfusion reactions that must be distinguished from hemolysis before further transfusions can be safely administered. Granulocyte antibodies may also be present in autoimmune neutropenia.

Useful For: Work-up of individuals having febrile, nonhemolytic transfusion reactions Detection of individuals with autoimmune neutropenia This test is not useful for the diagnosis of neutropenia caused by marrow suppression by drugs or tumors.

Interpretation: A positive result in an individual being worked up for a febrile transfusion reaction indicates the need for leukocyte-poor (filtered) red blood cells. This test cannot distinguish between allo- and autoantibodies

Reference Values:
Not applicable

Clinical References: 1. Flesch BK, Reil A. Molecular genetics of the human neutrophil antigens. Transfus Med Hemother. 2018;45(5):300-309. doi:10.1159/000491031 2. Gottschall JL, Triulzi DJ, Curtis B, et al. The frequency and specificity of human neutrophil antigen antibodies in a blood donor population. Transfusion. 2011;51(4):820-827. doi:10.1111/j.1537-2995.2010.02913.x

GMCSF
618775

Granulocyte Monocyte-Colony Stimulating Factor, Plasma

Clinical Information: Granulocyte macrophage-colony stimulating factor (GM-CSF) was initially characterized as a hematopoietic growth factor, acting on bone marrow progenitor and inducing differentiation and proliferation of myeloid cells.(1) GM-CSF gene-deficient mice, however, displayed no changes in steady state myelopoiesis. In contrast, the predominant phenotype of the GM-CSF knock-out mouse was similar to that of human pulmonary alveolar proteinosis (PAP), a condition which is characterized by an accumulation of pulmonary surfactant.(2) Subsequently, it was observed that approximately 90% of human PAP, referred to as autoimmune PAP, is associated with autoantibodies specific for GM-CSF.(3) Taken together, evidence from mice and humans point to a critical role for GM-CSF in maintenance of proper alveolar macrophage function. GM-CSF has also been shown to play an

important role in the regulation of innate and adaptive immune responses. These observations led to additional studies probing the role of this molecule in chronic inflammatory and autoimmune diseases. One of the first studies in this area demonstrated that patients with severe and moderate rheumatoid arthritis (RA) had plasma GM-CSF concentrations that were significantly elevated compared to healthy controls.(5) In addition, treatment of patients with Felty syndrome and RA with GM-CSF, which was administered in an attempt to increase neutrophil counts, led to exacerbation of the inflammatory arthritis.(6) In a recent study, elevated serum concentrations of GM-CSF were detected in patients with radiographic axial spondyloarthropathy (SpA) compared to controls, and concentrations of this cytokine correlated with disease activity score.(7) It is now well accepted that GM-CSF plays a role in the pathology of a variety of chronic inflammatory diseases and, as such, is a viable therapeutic target.(9) There are currently 4 monoclonal antibodies targeting the GM-CSF pathway.(8) One of the first, mavrilimumab, is specific for the alpha-chain of the GM-CSF receptor. Two phase IIb clinical trials in RA showed significant improvements in disease activity compared to placebo without any significant side effects or adverse events. Improvements were rapid (within 2 weeks) and dose dependent. The remaining 3 biologics, otilimab, namilumab, and lenzilumab, target GM-CSF directly. Several phase II clinical trials of namilumab in RA and plaque psoriasis have been completed, and a phase IIa trial in axial spondyloarthropathy is currently recruiting. Otilimab is being evaluated in 2 phase II clinical trials specifically targeting RA patients who have shown poor response to disease-modifying antirheumatic drugs or other treatments. Lenzilumab is currently being evaluated as a novel therapeutic in asthma.

Useful For: Measuring the concentration of granulocyte macrophage-colony stimulating factor (GM-CSF) in plasma Understanding the etiology of chronic inflammatory diseases or infections, when used in conjunction with clinical information and other laboratory testing Research studies in which an assessment of the GM-CSF response is needed

Interpretation: Elevated granulocyte macrophage-colony stimulating factor (GM-CSF) concentrations could be consistent with the presence of an inflammatory process or infection.

Reference Values:
<15.0 pg/mL

Clinical References: 1. Hamilton JA. GM-CSF in inflammation. J Exp Med. 2020;21(1):e20190945 2. Stanley E, Lieschke GJ, Grail D, et al. Granulocyte/macrophage colony-stimulating factor-deficient mice show no major perturbation of hematopoiesis but develop a characteristic pulmonary pathology. Proc Natl Acad Sci USA. 1994;91(12):5592-5596 3. Sakagami T, Uchida K, Suzuk T, et al. Human GM-CSF autoantibodies and reproduction of pulmonary alveolar proteinosis. N Eng J Med. 2009;361(27):2679-2681 4. Wicks IP, Roberts AW. Targeting GM-CSF in inflammatory diseases. Nat Rev Rheumatol. 2016;12(1);37-48 5. Fiehn C, Wermann M, Pezzutto A, Hufner M, Heilig B. Plasma GM-CSF concentrations in rheumatoid arthritis, systemic lupus erythematosus and spondyloarthropathy. Z Rheumatol. 1992;51(3);121-126 6. Hazenberg BP, Van Leeuwen MA, Van Rijswijk MH, Stern AC, Vellenga E. Correction of granulocytopenia in Felty's syndrome by granulocyte-macrophage colony-stimulating factor. Simultaneous induction of interleukin-6 and flare-up of the arthritis. Blood. 1989;74(8);2769-2770 7. Papagoras C, Tsiami S, Chrysanthopoulou A, Mitroulis I, Baraliakos X. Serum granulocyte-macrophage colony-stimulating factor (GM-CSF) is increased in patients with active radiographic axial spondyloarthritis and persists despite anti-TNF treatment. Arthritis Res Ther. 2022;24(1):195 8. Lee KMC, Achuthan AA, Hamilton JA. GM-CSF: A promising target in inflammation and autoimmunity. Immunotargets Ther. 2020;9:225-240 9. Lazarus HM, Ragsdale CE, Gale RP, Lyman GH. Sargramostim (rhu GM-CSF) as cancer therapy (systematic review) and an immunomodulator. A drug before its time? Front Immunol. 2021;12:706186

GRANB Granzyme B Immunostain, Technical Component Only
70449

Clinical Information: Granzyme B is a cytotoxic granule-associated protein, expressed constitutively in natural killer cells and in activated cytotoxic T cells. The immunostain is used to characterize T-cell lymphomas with a cytotoxic phenotype.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Reference Values:
NA

Clinical References: 1. Kadara H, Choi M, Zhang J, et al. Whole-exome sequencing and immune profiling of early-stage lung adenocarcinoma with fully annotated clinical follow-up. Ann Oncol. 2017;28(1):75-82. doi:10.1093/annonc/mdw436 2. Duan M, Goswami S, Shi JY, et al. Activated and exhausted MAIT cells foster disease progression and indicate poor outcome in hepatocellular carcinoma. Clin Cancer Res. 2019;25(11):3304-3316. doi:10.1158/1078-0432.CCR-18-3040 3. Pakish JB, Zhang Q, Chen Z, et al. Immune microenvironment in microsatellite-instable endometrial cancers: hereditary or sporadic origin matters. Clin Cancer Res. 2017;23(15):4473-4481. doi:10.1158/1078-0432.CCR-16-2655 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FGRPG
57653

Grape IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

GRAP
82800

Grape, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to grape Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GRFR
82836

Grapefruit, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to grapefruit Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of

allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GRAS1
81706

Grass Panel # 1, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to June/Kentucky blue, meadow fescue, orchard, rye, and timothy Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the

medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GRAS2
81707

Grass Panel # 2, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Bahia, Bermuda, Johnson, June/Kentucky blue, rye, and timothy Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GRAS3
81708

Grass Panel # 3, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cultivated rye, rye, sweet vernal, timothy, and velvet leaf Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with

the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GAB1
70437

GRB2-Associated Binding Protein 1 (GAB1) Immunostain, Technical Component Only

Clinical Information: GAB1 (growth factor receptor bound protein 2-associated protein) is an adapter protein that is involved in growth, transformation, and apoptosis. GAB1 can be used with a panel of immunohistochemical markers in the classification of medulloblastomas into SHH (sonic hedgehog), WNT (wingless-type murine mammary tumor), or non-SHH/WNT subgroups.

Useful For: Identification and differentiation of medulloblastomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Ellison DW, Dalton J, Kocak M, et al. Medulloblastoma clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. Acta Neuropathol. 2011;121(3):381-396 2. Northcott PA, Korshunov A, Witt H, et al. Medulloblastoma comprises four distinct molecular variants. J Clin Oncol. 2011 10;29(11):1408-1414 3. Fan Y, Yang F, Cao X, et al. Gab1 regulates SDF-1-induced progression via inhibition of apoptosis pathway induced by PI3K/AKT/Bcl-2/BAX pathway in human chondrosarcoma. Tumour Biol. 2016;37(1):1141-1149 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

GRFE
82365

Greek Fennel, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to greek fennel Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GPEA
82887

Green Pea, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to green pea Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GPEP
82623

Green Pepper, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an

allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to green pepper Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GSTB
82610

Green String Bean, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations.

In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to green string bean Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ALDR
82671

Grey Alder, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by

respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to grey alder trees Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GDF15
64637

Growth Differentiation Factor 15, Plasma

Clinical Information: Mitochondria perform many important metabolic functions, the most vital being the production of energy in the form of adenosine triphosphate (ATP) through the electron-transport chain and the oxidative phosphorylation system, which consists of 5 complexes (complex I-V). Each of these complexes consists of 4 to 46 subunits encoded by both nuclear and mitochondrial DNA. Mitochondrial diseases are caused by defects in any of the relevant metabolic pathways and have an estimated prevalence of 1:8500. Mitochondrial diseases are varied and include mitochondrial DNA deletion syndromes such as Kearns-Sayre syndrome, mitochondrial depletion syndromes such as those caused by alterations in the TK2 and SUCLA2 or POLG and C10orf2 genes, and mitochondrial point mutation syndromes such as MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), as well as others. The clinical features of mitochondrial diseases vary widely and include lactic acidosis, myopathy, ophthalmoplegia, ptosis, cardiomyopathy, sensorineural hearing loss, optic atrophy, pigmentary retinopathy, diabetes mellitus, encephalomyopathy, seizures, and stroke-like

episodes. A diagnostic workup for a mitochondrial disorder may demonstrate elevations of the lactate-to-pyruvate ratio (LAPYP / Lactate Pyruvate panel, Plasma) and an elevated growth differentiation factor 15 (GDF15) level. GDF15 is a protein of the transforming growth factor beta superfamily. GDF15 is overexpressed in muscle and serum in patients with various types of mitochondrial diseases, including those with mitochondrial deletion, depletion, and point mutation syndromes. Therefore, increased levels of GDF15 can indicate the need for further investigations, including molecular studies and muscle biopsy, to confirm the presence of a possible neuromuscular mitochondrial disease.

Useful For: A circulating biomarker in myopathy-related mitochondrial disease as well as other conditions Investigation of patients suspected of having a mitochondrial myopathy This assay is not suitable for carrier detection.

Interpretation: Abnormal results along with clinical findings may be suggestive of mitochondrial disease. Additional workup is indicated.

Reference Values:
3 months* and older: < or =750 pg/Ml

*This test is not recommended for infants younger than 3 months of age due to the high levels of growth differentiation factor 15 contributed from the placenta during pregnancy.

Clinical References:

GRH
70444

Growth Hormone Immunostain, Technical Component Only

Clinical Information: Growth hormone (GH) is a 21-kD polypeptide hormone that stimulates protein synthesis and may act primarily via the somatomedins. Somatotroph cells produce GH and constitute a high proportion of anterior pituitary cells (50%). GH shows cytoplasmic staining of normal pituitary somatotroph cells and GH adenomas. Globular juxtanuclear staining may be present in some adenomas.

Useful For: Aids in the identification of growth hormone adenomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Lea RW, Dawson T, Martinez-Moreno CG, El-Abry N, Harvey S. Growth hormone and cancer: GH production and action in glioma? Gen Comp Endocrinol. 2015;220:119-123. doi:10.1016/j.ygcen.2015.06.011 2. Mete O, Cintosun A, Pressman I, Asa SL: Epidemiology and biomarker profile of pituitary adenohypophysial tumors. Mod Pathol. 2018 Jun;31(6):900-909. doi: 10.1038/s41379-018-0016-8 3. Proudan N, Peroski M, Grignol G, Merchenthaler I, Dudas B. Juxtapositions between the somatostatinergic and growth hormone-releasing hormone (GHRH) neurons in the human hypothalamus. Neuroscience. 2015;297:205-210. doi:10.1016/j.neuroscience.2015.03.054 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FGHRH
75910

Growth Hormone Releasing Hormone (GH-RH, also known as GHRF or GRF)

Clinical Information: Growth Hormone Releasing Hormone is a 44 amino acid peptide produced primarily by the hypothalamus. It is a neurohumoral control for adenohypophyseal secretion of Growth Hormone. Other hypothalamic hormones have a stimulatory effect on pituitary hormones, but Growth Hormone Releasing Hormone has no known effect on other pituitary hormones. Somatostatin is the inhibitory counterpart of Growth Hormone Releasing Hormone. Growth Hormone Releasing Hormone has structural similarities with the Secretin-Glucagon family of gastrointestinal hormones. Growth Hormone Releasing Hormone has been isolated from pancreatic Islet Cells and various cancer tumor cells.

Reference Values:
5-18 pg/mL

Clinical References: 1. ML Vance. Growth-Hormone-Releasing Hormone. Clinical Chemistr 36: 415-420, 1990. 2. AM Sopwith, ES Penny, A Grossman, MO Savage, GM Besser, and LH Rees. Normal Circulating Growth Hormone Releasing Factor (hGRF) Concentrations in Patients with Functional Hypothalamic hGRF Deficiency. Clinical Endocrinology 24:395-400, 1986

HGH
8688

Growth Hormone, Serum

Clinical Information: The anterior pituitary secretes human growth hormone (hGH) in response to exercise, deep sleep, hypoglycemia, and protein ingestion. hGH stimulates hepatic insulin-like growth factor-1 and mobilizes fatty acids from fat deposits to the liver. Hyposecretion of hGH causes dwarfism in children. Hypersecretion causes gigantism in children or acromegaly in adults. Because hGH levels in normal and diseased populations overlap, hGH suppression and stimulation tests are needed to evaluate conditions of hGH excess and deficiency; random hGH levels are inadequate.

Useful For: Diagnosis of acromegaly and assessment of treatment efficacy when interpreted in conjunction with results from glucose suppression test Diagnosis of human growth hormone deficiency when interpreted in conjunction with results from growth hormone stimulation test This test is not intended for use as a screen for acromegaly. This test has limited value in assessing growth hormone secretion in normal children.

Interpretation: Acromegaly: For suppression testing, normal subjects have a nadir human growth hormone (hGH) concentration below 0.3 ng/mL after ingestion of a 75-gram glucose dose. Patients with acromegaly fail to show normal suppression. Using the Access ultrasensitive hGH assay, a cutoff of 0.53 ng/mL for nadir hGH was found to differentiate patients most accurately with acromegaly in remission from active disease with a sensitivity of 97% (95% CI, 83%-100%) and a specificity of 100% (95% CI, 82%-100%).(1) Deficiency: A normal response following stimulation tests is a peak hGH concentration above 5 ng/mL in children and above 4 ng/mL in adults. For children, some experts consider hGH values between 5 ng/mL and 8 ng/mL equivocal and only GH peak values greater than 8 ng/mL as truly normal. Low levels, particularly under stimulation, indicate hGH deficiency.

Reference Values:
Males:
2-<7 years:* 0.05-5.11 ng/mL
7-<12 years:* 0.02-4.76 ng/mL
12-<14 years:* 0.02-6.20 ng/mL
14-<18 years:* 0.02-3.81 ng/mL
> or =18 years: 0.02-0.97 ng/mL

Females:
2-<7 years:* 0.05-5.11 ng/mL

7-<12 years:* 0.02-4.76 ng/mL
12-<14 years:* 0.02-6.20 ng/mL
14-<18 years:* 0.03-5.22 ng/mL
> or =18 years: 0.02-3.61 ng/mL
*Source: Karbasy K, Lin DC, Stoianov A, et al. Pediatric reference value distributions and covariate-stratified reference intervals for 29 endocrine and special chemistry biomarkers on the Beckman Coulter Immunoassay Systems: a CALIPER study of healthy community children. Clin Chem Lab Med. 2016;54(4):643-657. doi:10.1515/cclm-2015-0558

Reference intervals for patients younger than 2 years have not been established.

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Bancos I, Algeciras-Schimnich A, Woodmansee WW, et al. Determination of nadir growth hormone concentration cutoff in patients with acromegaly. Endocr Pract. 2013;19(6):937-945. doi:10.4158/EP12435.OR 2. Camacho-Hubner C. Assessment of growth hormone status in acromegaly: what biochemical markers to measure and how?. Growth Horm IGF Res. 2000;10 Suppl B:S125-S199 3. Nilsson AG. Effects of growth hormone replacement therapy on bone markers and bone mineral density in growth hormone-deficient adults. Horm Res. 2000;54 Suppl 1:52-57 4. Strasburger CJ, Dattani MT. New growth hormone assays: potential benefits. Acta Paediatr Suppl. 1997;423:5-11 5. Okada S, Kopchick JJ. Biological effects of growth hormone and its antagonist. Trends Mol Med. 2001;7(3):126-132 6. Veldhuis JD, Iranmanesh A. Physiological regulation of the human growth hormone (GH)-insulin-like growth factor type I (IGF-I) axis: predominant impact of age, obesity, gonadal function, and sleep. Sleep. 1996;19(10 Suppl):S221-S224 7. Melmed S. Pathogenesis and diagnosis of growth hormone deficiency in adults. N Engl J Med. 2019;380(26):2551-2562. doi:10.1056/NEJMra1817346 8. Karbasy K, Lin DC, Stoianov A, et al. Pediatric reference value distributions and covariate-stratified reference intervals for 29 endocrine and special chemistry biomarkers on the Beckman Coulter Immunoassay Systems: a CALIPER study of healthy community children. Clin Chem Lab Med. 2016;54(4):643-657. doi:10.1515/cclm-2015-0558

GGUM
82479

Guar Gum, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to guar gum Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GUIN
82706

Guinea Pig Epithelium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to guinea pig epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with

the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GUM
82367

Gum Arabic, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to gum arabic Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FGUMX 57974 Gum Xanthan IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >=50 Very Strong Positive

Reference Values:
<0.35 kU/L

FHACK 57951 Hackberry (Celtis occidentalis) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal/Borderline 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 49.99 Very High Positive 5 50.00 – 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

FHADE 57556 Haddock (Melanogrammus aeglefinus) IgE

Interpretation: Class IgE (kU/L Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal/Borderline 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 49.99 Very High Positive 5 50.00 – 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

HIBSG
614598

Haemophilus influenzae Type B Antibody, IgG, Serum

Clinical Information: Haemophilus influenzae type B (HIB) is an encapsulated Gram-negative cocco-bacillary bacterium that can cause devastating disease in unvaccinated young children, including meningitis, bacteremia, cellulitis, epiglottitis, pneumonia, and septic arthritis. The outer surface of H influenzae is covered by a polyribosyl-ribitol-phosphate (PRP) polysaccharide that is responsible for both pathogenicity and immunity. There are currently 6 recognized PRP serotypes, referred to as a through f, among which serotype b, prior to the availability of a vaccine, accounted for up to 95% of infections. There are also unencapsulated or nontypable strains. Prior infection with H influenzae is associated with protective immunity against reinfection. One of the great advances in modern medicine has been the development of an effective vaccine against HIB, which is based on use of an unconjugated, purified PRP antigen. A patient's immunological response to HIB vaccine can be determined by measuring anti-HIB IgG antibody levels using a standardized enzyme immunoassay (EIA). Antibody levels of1 mcg/mL or more at least 3 weeks after vaccination has been correlated with long-term protective immunity.

Useful For: Assessing a patient's immunological (IgG) response to Haemophilus influenzae type B (HIB) vaccine Assessing immunity against HIB Aiding in the evaluation of immunodeficiency when the patient is tested pre- and post-vaccination

Interpretation: An anti-Haemophilus influenzae type B (HIB) IgG antibody concentration of 0.15 mcg/L is generally accepted as the minimum level for protection at a given time; however, it does not confer long-term protection. A study from Finland suggested that the optimum protective level is 1.0 mcg/L postimmunization.(1) Furthermore, studies have shown that the response to HIB vaccine is age-related.

Reference Values:
> or =0.15 mg/L
Reference values apply to all ages.

Clinical References: 1. Peltola H, Kayhty H, Virtanen M, Makela PH l. Prevention of Haemophilus influenzae type B bacteremic infections with the capsular polysaccharide vaccine. N Engl J Med. 1984;310(24):1561-1566. doi: 10.1056/NEJM198406143102404 2. Berger M. Immunoglobulin G subclass determination in diagnosis and management of antibody deficiency syndromes. J Pediatr. 1987;110(2):325-328. doi: 10.1016/s0022-3476(87)80182-8 3. Murphy TF. Haemophilus species, including H influenzae and H ducreyi (Chancroid). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2743-2752

HAKE
82348

Hake, Fish, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to hake Defining the allergen responsible for

eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FHALG
57637

Halibut IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

HALI
82633

Halibut, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from

IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to halibut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

HALO
80339

Haloperidol, Serum

Clinical Information: Haloperidol (Haldol) is a member of the butyrophenone class of neuroleptic drugs used to treat psychotic disorders (eg, schizophrenia). It is also used to control the tics and verbal utterances associated with Tourette syndrome and in the management of children who are intensely hyperexcitable and fail to respond to other treatment modalities. The daily recommended oral dose for patients with moderate symptoms is 0.5 to 2 mg; for patients with severe symptoms, 3 to 5 mg may be

used. However, some patients will respond only at significantly higher doses. Haloperidol is metabolized in the liver to reduced haloperidol, its major metabolite.(1,2) Use of haloperidol is associated with significant toxic side effects, the most serious of which include tardive dyskinesia, which can be irreversible, extrapyramidal reactions with Parkinson-like symptoms, and neuroleptic malignant syndrome. Less serious side effects can include hypotension, anticholinergic effects (blurred vision, dry mouth, constipation, urinary retention), and sedation. The risk of developing serious, irreversible side effects seems to increase with increasing cumulative doses over time.(1,3)

Useful For: Optimizing haloperidol dosage Monitoring patient compliance Assessing toxicity

Interpretation: Studies show a strong relationship between dose and serum concentration(4); however, there is a modest relationship of clinical response or risk of developing long-term side effects to either dose or serum concentration. A therapeutic window exists for haloperidol, but some patients may respond to concentrations outside of this range. Patients who respond at serum concentrations between 5 ng/mL and 17 ng/mL show no additional improvement at concentrations between 18 ng/mL and 20 ng/mL.(3,5) Some patients may respond at concentrations less than 5 ng/mL, and others may require concentrations significantly greater than 20 ng/mL before an adequate response is attained. Due to interindividual variation, the serum concentration should only be used as one factor in determining the appropriate dose and must be interpreted in conjunction with the clinical status. Although the metabolite, reduced haloperidol, has minimal pharmacologic activity, evidence has been presented suggesting that an elevated ratio of reduced haloperidol-to-haloperidol (ie, >5) is predictive of a poor clinical response.(3,6) A reduced haloperidol-to-haloperidol ratio of less than 0.5 indicates noncompliance; the metabolite does not accumulate except during steady-state conditions.

Reference Values:

Haloperidol:
5-17 ng/mL

Reduced Haloperidol:
10-80 ng/mL

Clinical References: 1. Lawson GM. Monitoring of serum haloperidol. Mayo Clin Proc. 1994;69(2):189-190 2. Ereshefsky L, Davis CM, Harrington CA, et al. Haloperidol and reduced haloperidol plasma levels in selected schizophrenic patients. J Clin Psychopharmacol. 1984;4(3):138-142 3. Volavka J, Cooper TB. Review of haloperidol blood level and clinical response: looking through the window. J Clin Psychopharmacol. 1987;7(1):25-30 4. Moulin MA, Davy JP, Debruyne D, et al. Serum level monitoring and therapeutic effect of haloperidol in schizophrenic patients. Psychopharmacology (Berl). 1982;76(4):346-350 5. Van Putten T, Marder SR, Mintz J, Poland RE. Haloperidol plasma levels and clinical response: a therapeutic window relationship. Am J Psychiatry. 1992;149 (4):500-505 6. Shostak M, Perel JM, Stiller RL, Wyman W, Curran S. Plasma haloperidol and clinical response: a role for reduced haloperidol in antipsychotic activity?. J Clin Psychopharmacol. 1987;7(6):394-400 7. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62. doi:10.1055/s-0043-116492 8. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

HEPI
82780

Hamster Epithelium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an

allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to hamster epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FHVGM
75240

Hantavirus Antibody (IgG, IgM)

Interpretation: This assay detects antibodies against recombinant Hantavirus antigens of both old world and new world Hantavirus types. The immune response to Hantavirus infection is not type-specific, and thus cross-reactivity may occur. All Hantavirus IgM-positive samples from US residents will be sent to a Public Health Laboratory for Sin Nombre Virus (SNV)-specific IgM testing. Samples that are Hantavirus IgG positive but IgM negative will not be subjected to further type-specific testing, since the lack of IgM rules out acute infection.

Reference Values:
Negative

HAPT
9168

Haptoglobin, Serum

Clinical Information: Haptoglobin is an immunoglobulin-like plasma protein that binds hemoglobin. The haptoglobin-hemoglobin complex is removed from plasma by macrophages and the hemoglobin is catabolized. When the hemoglobin-binding capacity of haptoglobin is exceeded, hemoglobin passes through the renal glomeruli, resulting in hemoglobinuria. Chronic intravascular hemolysis causes persistently low haptoglobin concentration. Regular strenuous exercise may cause sustained low haptoglobin, presumably from low-grade hemolysis. Low serum haptoglobin may also be due to severe liver disease. Neonatal plasma or serum specimens usually do not contain measurable haptoglobin; adult levels are achieved by 6 months. Increase in plasma haptoglobin concentration occurs as an acute-phase reaction. Levels may appear to be increased in conditions such as burns and nephrotic syndrome. An acute-phase response may be confirmed and monitored by assay of other acute-phase reactants such as alpha-1-antitrypsin and C-reactive protein.

Useful For: Confirmation of intravascular hemolysis

Interpretation: Absence of plasma haptoglobin may indicate intravascular hemolysis. However, congenital anhaptoglobinemia is common, particularly in African Americans. For this reason, it may be difficult or impossible to interpret a single measurement of plasma haptoglobin. If the assay value is low, the test should be repeated after 1 to 2 weeks following an acute episode of hemolysis. If all the plasma haptoglobin is removed following an episode of intravascular hemolysis and if hemolysis ceases, the haptoglobin concentration should return to normal in a week. Low levels of plasma haptoglobin may indicate intravascular hemolysis.

Reference Values:
30-200 mg/dL

Clinical References: 1. Shih AW, McFarlane A, Verhovsek M. Haptoglobin testing in hemolysis: measurement and interpretation. Am J Hematol. 2014;89(4):443-447. doi:10.1002/ajh.23623 2. di Masi A, De Simone G, Ciaccio C, D'Orso S, Coletta M, Ascenzi P. Haptoglobin: From hemoglobin scavenging to human health. Mol Aspects Med. 2020;73:100851. doi:10.1016/j.mam.2020.100851 3. Rifai N. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2022:1584

FHZCP
75565

Hazelnut Component Panel

Clinical Information: This assay is used to detect allergen specific-IgE using the ImmunoCAP FEIA method. In vitro allergy testing is the primary testing mode for allergy diagnosis.

Reference Values:

Class IgE	(kU/L)	Comment
0		Negative
0/1	0.10-0.34	Equivocal/Borderline
1	0.35-0.69	Low Positive
2	0.70-3.49	Moderate Positive

3	3.50-17.49	High Positive
4	17.50-49.99	Very High Positive
5	50.00-99.99	Very High Positive
6	>99.99	Very High Positive

FHCC1
75576

Hazelnut Component rCor a 1

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.10 kU/L

NUTHX
618848

Hazelnut-Food Components, IgE, Serum

Clinical Information:

Useful For: Evaluation of patients with suspected hazelnut-food allergy to one of 4 hazelnut-food components

Interpretation: When detectable total hazelnut-food IgE antibody is present (> or =0.10 IgE kUa/L), additional specific component IgE antibody testing will be performed. If a potential specific allergenic hazelnut-food component IgE is detectable (> or =0.10 IgE kUa/L), an interpretive report will be provided. When the sample is negative for total hazelnut-food IgE antibody (<0.10 IgE kUa/L), further testing for specific hazelnut-food component IgE antibodies will not be performed. A negative IgE result for total cashew antibody may indicate a lack of sensitization to the potential hazelnut-food allergenic components.

Reference Values:

Only orderable as a reflex. For more information see NUTHR / Hazelnut-Food, IgE with Reflex to Hazelnut-Food Components, IgE, Serum. Class	**IgE kU/L**	**Interpretation**
0		Negative
0/1	0.10-0.34	Borderline / Equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive

5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References:

NUTHR
618847

Hazelnut-Food, IgE with Reflex to Hazelnut-Food Components, IgE, Serum

Clinical Information: Allergies to tree nuts are relatively prevalent and can result in severe reactions. The main culprits in tree nut allergies include: walnut, almond, pistachio, cashew, pecan, hazelnut, macadamia, Brazil nut, and pine nuts. Tree nut allergy often appears in young children and estimates of prevalence range from 0.1% to greater than 5% of the population dependent on geographical region. In the case of nut-induced allergic reactions, as with many other foods, symptoms usually present within minutes of ingestion. Over 80% of reactions to tree nuts involve allergy related respiratory symptoms. Tree nut allergies are one of the most dangerous types of allergic reaction with 20% to 40% of cases of related anaphylaxis and 70% to 90% of fatalities attributable to nut exposure, including peanut exposure. Hazelnut allergy can occur upon ingestion as a systemic food allergy that can be associated with severe reactions or as oral allergy syndrome, often associated with pollen allergy (pollen-food allergy syndrome). It is the most common tree nut allergy in Europe. Sensitization to birch pollen is strongly associated with hazelnut sensitization, with 84% of those with birch pollen allergy being sensitized to hazelnuts. Components of hazelnut allergy can be used to stratify risk of severe systemic reactions. Hazelnut allergy can be severe or can be pollen related and less severe. The component protein Cor a 1 is heat and digestion labile and is often cross-reactive with birch pollen sensitivity due to cross-reactivity between homologous allergens of hazelnut and birch pollens (PR-10 proteins Cor a 1 and Bet v 1). Sensitization to Cor a 1 component protein is mainly associated with local reactions, posing a lower risk of severe systemic reaction. Pollen-related hazelnut allergy is often observed in adults, with symptoms limited to the oropharyngeal cavity. However, systemic symptoms and even anaphylaxis have been infrequently reported with sensitivity to Cor a 1. Cor a 8 is a heat and digestion stabile nonspecific lipid transfer protein that exhibits sensitization in 8% to 17% of hazelnut allergy cases in the United States, with high prevalence in areas that lack birch trees. Cor a 8 sensitization can be associated with clinically silent hazelnut tolerant individuals, oral allergy syndrome or in some cases severe allergy. Peach allergy may be associated with sensitivity for Cor a 8. Cor a 9 and 14 are heat and digestion stable protein components that are associated with higher risks or severe, systemic reaction. Cor a 9 and Cor a 14 sensitization serve as excellent diagnostic markers for identifying direct hazelnut allergy and for prediction of potentially severe symptoms. Sensitization to Cor a 9 (a legume like globulin) was observed in 10% of hazelnut allergic individuals and has been established to be associated with severe systemic reactions. Other studies have put the sensitization rate or Cor a 9 to be as much as 35%. Cor a 9 may show crossreactivity to 11S globulin protein components of walnut (Jug r 4), peanut (Ara h 3), Brazil nut (Ber e 2), soybean (Gly m 6), cashew (Ana o 2), almond (Pru du 6) and pistachio (Pis v 2). Sensitization to Cor a 14 (a 2S albumin allergen) has been observed in 6% of allergic individuals and is associated with moderate and severe systemic reactions. Cor a 14 is highly heat and digestion resistant and serves as an excellent predictor for clinical allergy. Cor a 14 sensitization has been reported in 15% of individuals with severe symptoms, 5.6% of individuals with moderate symptoms, and 4% of those with localized symptoms. Its cross reactivity is limited to walnut (Jug r 1) and pecan (Car i 1) protein components. Cor a 14-sIgE determination was a better predictor of oral food challenge sensitivity than other hazelnut component allergens (Cor a 1, Cor a 8, and Cor a 9).

Useful For: Evaluation of patients with suspected hazelnut-food allergy

Interpretation: When detectable total hazelnut-food IgE antibody is present (> or =0.10 IgE kUa/L), additional specific component IgE antibody testing will be performed. If at least one potential specific allergenic hazelnut-food component IgE is detectable (> or =0.10 IgE kUa/L), an interpretive report will be provided. When the sample is negative for total hazelnut-food IgE antibody (<0.10 IgE kUa/L), further testing for specific hazelnut-food component IgE antibodies will not be performed. Negative IgE results for total hazelnut-food antibody may indicate a lack of sensitization to potential hazelnut-food allergenic components.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/Equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References:

NUTH
82743

Hazelnut-Food, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to hazelnut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be

responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

HAZ
82670

Hazelnut-Tree, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to hazelnut-tree Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

HRTVS
620057

Heartland Virus, RNA, Molecular Detection, PCR, Serum

Clinical Information: Heartland virus (HRTV) disease is an emerging zoonosis, transmitted to humans through the bite of infected Amblyomma americanum (Lone Star) ticks. HRTV possesses a single-stranded negative-sense RNA genome encoded on small, medium, and large segments. HRTV is a member of the Bandavirus genus, which includes other arthropod-borne viruses (arboviruses), such as severe fever with thrombocytopenia syndrome virus (SFTSV). Reports of human HRTV disease are relatively rare, with fewer than 100 cases reported to date, most from the Central, Southern, and Northeastern United States. Symptoms generally occur within 2 weeks of a tick bite and may include non-specific symptoms such as headache, fever, fatigue, anorexia, nausea, diarrhea, and muscle or joint pain. Leukopenia, thrombocytopenia, and elevation of liver transaminases are also common laboratory findings. Rarely, multisystem organ failure and death occur. While there is no targeted antiviral therapy and treatment is entirely supportive care, diagnosis is important for several reasons, including the ability to discontinue empiric antibiotics and to provide prognostic information for patients and families. Detection of HRTV nucleic acid in serum is a marker for acute infection caused by this virus. Importantly, the period of time that the virus can be detected in serum and cerebrospinal fluid is brief. Therefore, molecular testing should be performed within the first week following onset of symptoms. After this time, serologic testing is the preferred method for diagnosis of HRTV infection. Serologic testing is currently only available through the Centers for Disease Control and Prevention.

Useful For: Aiding in the diagnosis of central nervous system infection caused by Heartland virus using serum specimens

Interpretation: Positive: The detection of Heartland virus (HRTV) nucleic acid in serum is consistent with acute-phase infection. HRTV nucleic acid may be detectable during the first week following the onset of symptoms. Negative: The absence of HRTV nucleic acid is consistent with the lack of acute-phase infection but does not rule out infection. Additional serologic testing may be indicated.

Reference Values:
Negative

Clinical References:

HRTVC 620056 Heartland Virus, RNA, Molecular Detection, PCR, Spinal Fluid

Clinical Information: Heartland virus (HRTV) disease is an emerging zoonosis, transmitted to humans through the bite of infected Amblyomma americanum (Lone Star) ticks. HRTV possesses a single-stranded negative-sense RNA genome encoded on small, medium, and large segments. HRTV is a member of the Bandavirus genus, which includes other arthropod-borne viruses (arboviruses), such as severe fever with thrombocytopenia syndrome virus (SFTSV). Reports of human HRTV disease are relatively rare with fewer than 100 cases reported to date, most from the Central, Southern, and Northeastern United States. Symptoms generally occur within 2 weeks of a tick bite and may include non-specific symptoms such as headache, fever, fatigue, anorexia, nausea, diarrhea, and muscle or joint pain. Leukopenia, thrombocytopenia, and elevation of liver transaminases are also common laboratory findings. Rarely, multisystem organ failure and death occur. While there is no targeted antiviral therapy and treatment is entirely supportive care, diagnosis is important for several reasons, including the ability to discontinue empiric antibiotics and to provide prognostic information for patients and families. Detection of HRTV nucleic acid in cerebrospinal fluid (CSF) is a marker for central nervous system infection caused by this virus. Importantly, the period of time that the virus can be detected in serum and CSF is brief. Therefore, molecular testing should be performed within the first week following onset of symptoms. After this time, serologic testing is the preferred method for diagnosis of HRTV infection. Serologic testing is currently only available through the Centers for Disease Control and Prevention.

Useful For: Aiding in the diagnosis of central nervous system infection caused by Heartland virus using spinal fluid specimens

Interpretation: Positive: The detection of Heartland virus (HRTV) nucleic acid in cerebrospinal fluid (CSF) is consistent with acute-phase infection of the central nervous system. HRTV nucleic acid may be detectable during the first week following the onset of symptoms. Negative: The absence of HRTV nucleic acid in CSF is consistent with the lack of acute-phase infection but does not rule out infection. Additional serologic testing may be indicated.

Reference Values:
Negative

Clinical References: 1. Savage HM, Godsey MS, Lambert A, et al. First detection of heartland virus (Bunyaviridae: Phlebovirus) from field collected arthropods. Am J Trop Med Hyg. 2013;89(3):445-452. doi:10.4269/ajtmh.13-0209 2. Brault AC, Savage HM, Duggal NK, Eisen RJ, Staples JE. Heartland virus epidemiology, vector association, and disease potential. Viruses. 2018;10(9):498. doi:10.3390/v10090498 3. Staples JE, Pastula DM, Panella AJ, et al. Investigation of Heartland virus disease throughout the United States, 2013-2017. Open Forum Infect Dis. 2020;7(5);ofaa125. Published 2020 Apr 11. doi:10.1093/ofid/ofaa125 4. Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) , Division of Vector-Borne Diseases (DVBD). Heartland virus disease. CDC; Updated January 26, 2023. Accessed April 25, 2024. Available at www.cdc.gov/heartland-virus/healthcare-providers/index.html

HMUOE 608889 Heavy Metal Occupational Exposure, with Reflex, Random, Urine

Clinical Information: Arsenic (As), lead, cadmium, and mercury are well-known toxins, and toxic

exposures are characterized by increased urinary excretion of these metals. Arsenic is a naturally occurring element that is usually found in the environment combined with other elements, such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As[3+]/As[III]) and arsenate (As[5+]/As[V]). Inorganic As(V) is readily reduced to inorganic As(III), which is then primarily broken down to the less toxic methylated metabolites, monomethylarsonic acid, and subsequently dimethylarsinic acid. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, from fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning, including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days. Lead toxicity primarily affects the gastrointestinal, neurologic, and hematopoietic systems. Chronic exposure to cadmium causes accumulated kidney damage. The correlation between the levels of mercury excretion in the urine and the clinical symptoms is considered poor.

Useful For: Preferred screening test for detection of arsenic, cadmium, mercury, and lead due to occupational exposure using random urine specimens

Interpretation: Arsenic: Mayo Clinic uses the American Conference of Governmental Industrial Hygienists biological exposure index (BEI) as the reference value. The BEI is the sum of all the toxic species (inorganic arsenic plus methylated arsenic metabolites). Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is a toxic form (eg, inorganic and methylated arsenic forms) or a relatively nontoxic organic form (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, As[III] and As[V]) are found in the urine shortly after ingestion, whereas the less toxic methylated forms, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) are the species that predominate longer than 24 hours after ingestion. In general, urinary As(III) and As(V) concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. This test can determine if a patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health. Cadmium: In chronic cadmium exposure, the kidneys are the primary target organ. Urine concentrations of cadmium can be useful to assess long-term exposure and determine cadmium body burden. Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. For occupational testing, the OSHA cadmium standard is below 3.0 mcg/g creatinine, and the BEI is 5 mcg/g creatinine. Mercury: The correlation between the levels of mercury excretion in the urine and the clinical symptoms is considered poor. Previous thought indicated urine as a more appropriate marker of inorganic mercury because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the

body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury levels (up to 30%),(1) which is consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood.(2) Lead: Measurements of urinary lead levels have been used to assess lead exposure. However, like blood lead, urinary lead excretion mainly reflects recent exposure and thus, shares many of the same limitations for assessing lead body burden or long-term exposure.(3,4) Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations.(5,6)

Reference Values:

ARSENIC:
Biological Exposure Indices (BEI): <35 mcg/L at end of work week

CADMIUM:
BEI: <5.0 mcg/g creatinine

MERCURY:
BEI: <35 mcg/g creatinine

LEAD:
BEI: <150 mcg/g creatinine

CREATININE:
> or =18 years: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years.

Clinical References: 1. Snoj Tratniid J, Falnoga I, Mazej D, et al. Results of the first national human biomonitoring in Slovenia: Trace elements in men and lactating women, predictors of exposure and reference values. Int J Hyg Environ Heatlh. 2019;222(3):563-582. doi:10.1016/j.ijheh.2019.02.008 2. Sherman LS, Blum JD, Franzblau A, Basu N. New insights into biomarkers of human mercury exposure using naturally occurring mercury stable isotopes. Envrn Sci Technol. 2013;47(7):3403-3409. doi:10.1021/es305250z 3. Sakai T. Biomarkers of lead exposure. Ind Health. 2000;38(2):127-142. doi:10.2486/indhealth.38.127 4. Skerfving S. Biological monitoring of exposure to inorganic lead. In: Clarkson TW, Friberg L, Nordberg GF, Sager PR, eds. Biological Monitoring of Toxic Metals. Rochester Series on Environmental Toxicity. Springer; 1988:169-197 5. Gulson BL, Jameson CW, Mahaffey KR, et al. Relationships of lead in breast milk to lead in blood, urine, and diet of the infant and mother. Environ Health Perspect. 1998;106(10):667-667. doi:10.1289/ehp.98106667 6. Skerfving S, Ahlgren L, Christoffersson JO. Metabolism of inorganic lead in man. Nutr Res. 1985;Suppl 1:601-607 7. Fillol CC, Dor F, Labat L, et al. Urinary arsenic concentrations and speciation in residents living in an area with naturally contaminated soils. Sci Total Environ. 2010;408(5):1190-1191. doi:10.1016/j.scitotenv.2009.11.046 8. Caldwell KL, Jones RL, Verdon CP, Jarrett JM, Caudill SP, Osterloh JD. Levels of urinary total and speciated arsenic in the US population: National Health and Nutrition Examination Survey 2003-2004. J Expo Sci Environ Epidemiol. 2009;19(1):59-68. doi:10.1038/jes.2008.32 9. Lee R, Middleton D, Caldwell K, et al. A review of events that expose children to elemental mercury in the United States. Environ Health Perspect. 2009;117(6):871-878. doi:10.1289/ehp.0800337 10. Kosnett MJ, Wedeen RP, Rotherberg SJ, et al. Recommendations for medical management of adult lead exposure. Environ Health Perspect. 2007;115(3):463-471. doi:10.1289/ehp.9784 11. De Burbane C, Buchet JP, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590. doi:10.1289/ehp.8202 12. Agency for Toxic Substances and Disease Registry. Toxicological profile for arsenic. US Department of Health and Human Services; 2007. Available at www.atsdr.cdc.gov/ToxProfiles/tp2.pdf 13. Bernhoft RA. Mercury toxicity and treatment: a review of the literature. J Environ Public Health. 2012;2012:460508. doi:10.1155/2012/460508 14. Strathmann FG, Blum LM. Toxic elements. In: Rifai

N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

HMUCR
608899

Heavy Metal/Creatinine Ratio, with Reflex, Random, Urine

Clinical Information: Arsenic (As), lead (Pb), cadmium (Cd), and mercury (Hg) are well-known toxins, and toxic exposures are characterized by increased urinary excretion of these metals. Arsenic is a naturally occurring element that is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As[3+]/As[III]) and arsenate (As[5+]/As[V]). Inorganic As(V) is readily reduced to inorganic As(III), which is then primarily broken down to the less toxic methylated metabolites monomethylarsonic acid and subsequently dimethylarsinic acid. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, from fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly, may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days. Arsenic toxicity affects a number of organ systems. Lead toxicity primarily affects the gastrointestinal, neurologic, and hematopoietic systems. Chronic exposure to cadmium causes accumulated kidney damage. The correlation between the levels of mercury excretion in the urine and the clinical symptoms is considered poor.

Useful For: Preferred screening test for detection of arsenic, cadmium, mercury, and lead in random urine specimens

Interpretation: Arsenic: Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is a toxic form (eg, inorganic and methylated forms) or a relatively nontoxic organic form (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, As[III] and As[V]) are found in the urine shortly after ingestion, whereas the less toxic methylated forms, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA), are the species that predominate longer than 24 hours after ingestion. In general, urinary As(III) and As(V) concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. This test can determine if a patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health. Cadmium: Urine cadmium levels primarily reflect total body burden of cadmium. Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. For occupational testing, OSHA cadmium standard is below 3.0 mcg/g creatinine, and the biological exposure index is 5 mcg/g

creatinine. Mercury: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. Previous thought indicated urine as a more appropriate marker of inorganic mercury because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury levels (up to 30%),(1) consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood.(2) Lead: Measurements of urinary lead levels have been used to assess lead exposure. However, like lead blood, urinary lead excretion mainly reflects recent exposure and thus shares many of the same limitations for assessing lead body burden or long-term exposure.(3,4) Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations.(5,6)

Reference Values:

ARSENIC/CREATININE:
0-17 years: Not established
> or =18 years: <24 mcg/g creatinine

CADMIUM/CREATININE:
0-17 years: Not established
> or =18 years: <0.6 mcg/g creatinine

MERCURY/CREATININE:
0-17 years: Not established
> or =18 years: <2 mcg/g creatinine

LEAD/CREATININE:
0-17 years: Not established
> or =18 years: <2 mcg/g creatinine

CREATININE:
> or =18 years: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years.

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HMDB
39183

Heavy Metals Screen with Demographics, Blood

Clinical Information: Arsenic: Arsenic (As) exists in many toxic and nontoxic forms. The toxic forms are the inorganic species As(5+), also denoted as As(V), the more toxic As(3+), also known as As(III), and their partially detoxified metabolites, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). Detoxification occurs in the liver as As(3+) is oxidized to As(5+) and then methylated to MMA and DMA. As a result of these detoxification steps, As(3+) and As(5+) are found in the urine shortly after ingestion, whereas MMA and DMA are the species that predominate more than 24 hours after ingestion. Blood concentrations of arsenic are elevated for a short time after exposure, after which arsenic rapidly disappears into tissues because if its affinity for tissue proteins. The body treats arsenic like phosphate, incorporating it wherever phosphate would be incorporated. Arsenic "disappears" into the normal body pool of phosphate and is excreted at the same rate as phosphate (excretion half-life of 12 days). The half-life of inorganic arsenic in blood is 4 to 6 hours, and the half-life of the methylated metabolites is 20 to 30 hours. Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure but will only be detected immediately after exposure. Arsenic is not likely to be detected in blood specimens drawn more than 2 days after exposure because it has become integrated into nonvascular tissues. Consequently, blood is not a good specimen to screen for arsenic, although periodic blood levels can be determined to follow the effectiveness of therapy. Urine is the preferred specimen for assessment of arsenic exposure. A wide range of signs and symptoms may be seen in acute arsenic poisoning, including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic (abdominal pain), diarrhea, and paresthesias of the hands and feet can occur. Lead: Lead is a heavy metal commonly found in the environment that can be an acute and chronic toxin. Lead was banned from household paints in 1978 but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids, such as vinegar and fruit juices. Lead is found in dirt from areas adjacent to homes painted with lead-based paints and highways where lead accumulates from use of leaded gasoline. Use of leaded gasoline has diminished significantly since the introduction of nonleaded gasolines, which have been required in personal automobiles since 1972. Lead is found in soil near abandoned industrial sites where lead may have been used. Water transported through lead or lead-soldered pipe will contain some lead with higher concentrations found in water that is weakly acidic. Some foods (for example: moonshine distilled in lead pipes) and some traditional home medicines contain lead. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense tissues, such as the central nervous system, being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Lead expresses its toxicity by several mechanisms. It avidly inhibits aminolevulinic acid dehydratase and ferrochelatase, 2 of the enzymes that catalyze synthesis of heme; the end result is decreased hemoglobin synthesis resulting in anemia. Lead also is an electrophile that avidly forms covalent bonds with the sulfhydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and of the kidney. Avoidance of

exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease. Oral dimercaprol may be used in the outpatient setting except in the most severe cases. Cadmium: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; kidney dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. In addition, another common source of cadmium exposure is tobacco smoke. Mercury: Mercury (Hg) is relatively nontoxic in its elemental form. If Hg(0) is chemically modified to the ionized, inorganic species, Hg(2+), it becomes toxic. Further bioconversion to an alkyl Hg, such as methyl Hg (CH3Hg[+]), yields a species of mercury that is highly selective for lipid-rich tissue such as neurons and is very toxic. The relative order of toxicity is: Least Toxic -- Hg(0) < Hg(2+) << [CH3Hg](+) -- Very Toxic Mercury can be chemically converted from the elemental state to the ionized state. In industry, this is frequently done by exposing Hg(0) to strong oxidizing agents, such as chlorine. Hg(0) can be bioconverted to both Hg(2+) and alkyl Hg by microorganisms that exist in the normal human gut as well as in the bottom sediment of lakes, rivers, and oceans. When Hg(0) enters bottom sediment, it is absorbed by bacteria, fungi, and small microorganisms; they metabolically convert it to Hg(2+), CH3Hg(+), and C2H6Hg. Should these microorganisms be consumed by larger marine animals and fish, the mercury passes up the food chain in the rather toxic form. Mercury expresses its toxicity in 3 ways: -Hg(2+) is readily absorbed and reacts with sulfhydryl groups of protein, causing a change in the tertiary structure of the protein-a stereoisomeric change-with subsequent loss of the unique activity associated with that protein. Because Hg(2+) becomes concentrated in the kidney during the regular clearance processes, this target organ experiences the greatest toxicity. -With the tertiary change noted previously, some proteins become immunogenic, eliciting a proliferation of T lymphocytes that generate immunoglobulins to bind the new antigen; collagen tissues are particularly sensitive to this. -Alkyl Hg species, such as CH3Hg(+), are lipophilic and avidly bind to lipid-rich tissues, such as neurons. Myelin is particularly susceptible to disruption by this mechanism. Members of the public will occasionally become concerned about exposure to mercury from dental amalgams. Restorative dentistry has used a mercury-silver amalgam for approximately 90 years as a filling material. A small amount of mercury (2-20 mcg/day) is released from a dental amalgam when it was mechanically manipulated, such as by chewing. The habit of gum chewing can cause release of mercury from dental amalgams greatly above normal. The normal bacterial microbiota present in the mouth converts a fraction of this to Hg(2+) and CH3Hg(+), which was shown to be incorporated into body tissues. The World Health Organization safety standard for daily exposure to mercury is 45 mcg/day. Thus, if one had no other source of exposure, the amount of mercury released from dental amalgams is not significant.(1) Many foods contain mercury. For example, commercial fish considered safe for consumption contain less than 0.3 mcg/g of mercury, but some game fish contain more than 2.0 mcg/g and, if consumed on a regular basis, contribute to significant body burdens. Therapy is usually monitored by following urine output; therapy may be terminated after urine excretion is below 50 mcg/day.

Useful For: Detecting exposure to arsenic, lead, cadmium, and mercury

Interpretation: Arsenic: Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure. Absorbed arsenic is rapidly distributed into tissue storage sites with a blood half-life of less than 6 hours. Unless a blood specimen is drawn within 2 days of exposure, arsenic is not likely to be detected in a blood specimen. Lead: For pediatric patients, there may be an association with blood lead values of 5.0 to 9.9 mcg/dL and adverse health effects. The current reference level at which the Centers of Disease Control and Prevention recommends public health actions be initiated is 3.5 mcg/dL in patients 0 to 5 years old and 5 mcg/dL for patients 6 years and older. The most recent National Health and Nutrition Examination Survey (NHANES) data shows that 97.5 percentile for blood lead levels in US adults age 16 years and older is 3.46 mcg/dL. In concurrence with the reference value concept that there is no safe level of lead in blood, the Council of State and Territorial Epidemiologists Occupational Health Subcommittee approved lowering the blood lead threshold from 5 to 3.5 mcg/dL for adults.

Follow-up testing after 3 to 6 months may be warranted. Chelation therapy is indicated when whole blood lead concentration is greater than 25.0 mcg/dL in children or greater than 45.0 mcg/dL in adults. The Occupational Safety and Health Administration has published the following standards for employees working in industry: -Employees with a single whole blood lead result greater than 60.0 mcg/dL must be removed from workplace exposure. -Employees with whole blood lead levels greater than 50.0 mcg/dL averaged over 3 blood samplings must be removed from workplace exposure. -An employee may not return to work in a lead exposure environment until their whole blood lead level is less than 40 mcg/dL. New York State has mandated inclusion of the following statement in reports for children under the age of 6 years with blood lead in the range of 5.0 to 9.9 mcg/dL: "Blood lead levels in the range of 5.0-9.9 mcg/dL have been associated with adverse health effects in children aged 6 years and younger." Cadmium: Normal blood cadmium concentration is less than 5.0 ng/mL, with most results in the range of 0.5 to 2.0 ng/mL. Acute toxicity will be observed when the blood level exceeds 50 ng/mL. Mercury: The quantity of mercury (Hg) found in blood and urine correlates with degree of toxicity. Hair analysis can be used to document the time of peak exposure if the event was in the past. Normal whole blood mercury concentration is usually less than 10 ng/mL. Individuals who have mild exposure during work, such as dentists, may routinely have whole blood mercury levels up to 15 ng/mL. Significant exposure is indicated when the whole blood mercury concentration is greater than 50 ng/mL if exposure is due to alkyl Hg, or greater than 200 ng/mL if exposure is due to Hg(2+).

Reference Values:

ARSENIC
<13 ng/mL
Reference values apply to all ages.

LEAD
<3.5 mcg/dL
Critical values
Pediatrics (< or =15 years): > or =20.0 mcg/dL
Adults (> or =16 years): > or =70.0 mcg/dL

CADMIUM
<5.0 ng/mL
Reference values apply to all ages.

MERCURY
<10 ng/mL
Reference values apply to all ages.

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HMU24
48538

Heavy Metals Screen, with Reflex, 24 Hour, Urine

Clinical Information: Arsenic: Arsenic (As) is a naturally occurring element that is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. The organic forms (eg, arsenobetaine and arsenocholine) are relatively nontoxic, while the inorganic forms are toxic. The toxic inorganic forms are arsenite (As[3+]/As[III]) and arsenate (As[5+]/As[V]). Inorganic As(V) is readily reduced to inorganic As(III), which is then primarily broken down to less toxic methylated metabolites monomethylarsonic acid and, subsequently, dimethylarsinic acid. People are exposed to arsenic by eating food, drinking water, or breathing air. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, for fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine, which is much less harmful. Some seaweed may contain arsenic in the inorganic form, which is more toxic. In the United States, some areas also contain high natural levels of arsenic in rock, which can lead to elevated levels in the soil and drinking water. Occupational (eg, copper or lead smelting, wood treating, or pesticide application) exposure is another source where people may be introduced to elevated levels of arsenic. Lastly, hazardous waste sites may contain large quantities of arsenic and, if not disposed of properly may get into the surrounding water, air, or soil. A wide range of signs and symptoms may be seen in acute arsenic poisoning, including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can also occur. Since arsenic is excreted predominantly by glomerular filtration, measurement of arsenic in urine is the most reliable means of detecting arsenic exposures within the last several days. Cadmium: The toxicity of cadmium (Cd) resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; kidney dysfunction with proteinuria and a slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid also occur over a period of years and precede overt kidney failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. For nonsmokers, the primary source of cadmium exposure is from the food supply. In general, leafy vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium. For smokers, the most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both men and women. The concentration of cadmium in the kidneys and urine is elevated in some patients exposed to cadmium. Mercury: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. Previous thought indicated urine as a more appropriate marker of inorganic mercury because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury levels (up to 30%),(1) which is consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood.(2) For additional information, see HG / Mercury, Blood Lead: Increased urine lead (Pb) excretion rate indicates significant lead exposure. Measurement of urine lead excretion rate before and

after chelation therapy has been used as an indicator of lead exposure. However, the American College of Medical Toxicology (ACMT 2010) position statement on post-chelator challenge urinary metal testing states that "post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning."(3) Blood lead measurement is the best test for clinical correlation of toxicity. For additional information, see PBDV / Lead, Venous, with Demographics, Blood.

Useful For: Detecting arsenic, cadmium, mercury, and lead exposure and toxicity using 24-hour urine specimens

Interpretation: Arsenic: Mayo Clinic uses the American Conference of Governmental Industrial Hygienists biological exposure index (BEI) as the reference value. The BEI is the sum of all the toxic species (inorganic arsenic plus methylated arsenic metabolites). Physiologically, arsenic exists in a number of toxic and nontoxic forms. The total arsenic concentration reflects all the arsenic present in the sample regardless of species (eg, inorganic vs. methylated vs. organic arsenic). The measurement of urinary total arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure. However, if the total urine arsenic concentration is elevated, arsenic speciation must be performed to identify if it is a toxic form (eg, inorganic and methylated arsenic forms) or a relatively nontoxic organic form (eg, arsenobetaine and arsenocholine). The inorganic toxic forms of arsenic (eg, As[III] and As[V]) are found in the urine shortly after ingestion, whereas the less toxic methylated forms, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA), are the species that predominate longer than 24 hours after ingestion. In general, urinary As(III) and As(V) concentrations peak in the urine at approximately 10 hours and return to normal 20 to 30 hours after ingestion. Urinary MMA and DMA concentrations normally peak at approximately 40 to 60 hours and return to baseline 6 to 20 days after ingestion. After a seafood meal (seafood generally contains the nontoxic, organic form of arsenic, eg, arsenobetaine), the urine output of arsenic may increase to over 300 mcg/24 h, after which it will decline. This test can determine if the patient has been exposed to above-average levels of arsenic. It cannot predict whether the arsenic levels in their body will affect their health. Cadmium: In chronic cadmium exposure, the kidneys are the primary target organ. Urine concentrations of cadmium can be useful to assess long-term exposure and determine cadmium body burden. Collection of urine over 24 hours minimizes fluctuations of observed cadmium concentrations in random urine samples. Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. For occupational testing, OSHA cadmium standard is less than 3.0 mcg/g creatinine, and the BEI is 5.0 mcg/g creatinine. Mercury: Daily urine excretion of mercury above 50 mcg/day indicates significant exposure (per World Health Organization standard). Lead: Measurements of urinary lead (Pb) levels have been used to assess lead exposure. However, like lead blood, urinary lead excretion mainly reflects recent exposure and, thus, shares many of the same limitations for assessing Pb body burden or long-term exposure.(4,5) Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations.(6,7)

Reference Values:

ARSENIC:
0-17 years: Not established
> or =18 years: <35 mcg/24 h

CADMIUM:
0-17 years: Not established
> or =18 years: <0.7mcg/24 h

MERCURY:
0-17 years: Not established
> or =18 years: <2 mcg/24 h
Toxic concentration: >50 mcg/24 h

The concentration at which toxicity is expressed is widely variable between patients. The lowest concentration at which toxicity is usually apparent Is 50 mcg/24 h.

LEAD:
0-17 years: Not established
> or =18 years: <2 mcg/24 h

Clinical References:

HMHA
45479

Heavy Metals, Hair

Clinical Information: Arsenic: Arsenic circulating in the blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in hair is higher than in other tissues. Arsenic binds to keratin at the time of exposure, "trapping" the arsenic in hair. Therefore, hair analysis for arsenic is not only used to document that an exposure occurred, but when it occurred. Hair collected from the nape of the neck can be used to document recent exposure. Axillary or pubic hairs are used to document long-term (6 months-1 year) exposure. Mercury: Once absorbed and circulating, mercury becomes bound to numerous proteins, including keratin. The concentration of mercury in hair correlates with the severity of clinical symptoms. If the hair can be segregated by length, such an exercise can be useful in identifying the time of exposure. Lead: Hair analysis for lead can be used to corroborate blood analysis or to document past lead exposure. If the hair is collected and segmented in a time sequence (based on length from root), the approximate time of exposure can be assessed.

Useful For: Detection of nonacute arsenic, mercury, and lead exposure using hair specimens

Interpretation: Hair grows at a rate of approximately 0.5 inch/month. Hair keratin synthesized today will protrude through the skin in approximately 1 week. Thus, a hair specimen collected at the skin level represents exposure of 1 week ago, 1 inch distally from the skin represents exposure 2 months ago, etc. Arsenic: Hair arsenic levels above 1.00 mcg/g dry weight may indicate excessive exposure. It is normal for some arsenic to be present in hair, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure, which was the cause of death. Mercury: Normally, hair contains less than 1 mcg/g of mercury; any amount more than this indicates that exposure to more than normal amounts of mercury may have occurred. Lead: Normal hair lead content is below 4.0 mcg/g. While hair lead content above 10.0 mcg/g may indicate significant lead exposure, hair is also subject to potential external contamination with environmental lead and contaminants in artificial hair treatments (eg, dyeing, bleaching, or permanents). Ultimately, the hair lead content needs to be interpreted in addition to the overall clinical scenario including symptoms, physical findings, and other diagnostic results when determining further actions.

Reference Values:

ARSENIC
0-15 years: Not established
> or =16 years: <1.0 mcg/g of hair

LEAD
<4.0 mcg/g of hair
Reference values apply to all ages.

MERCURY
0-15 years: Not established
> or =16 years:<1.0 mcg/g of hair

Clinical References: 1. Sthiannopkao S, Kim K-W, Cho KH, et al. Arsenic levels in human hair, Kandal Province, Cambodia: The influences of groundwater arsenic, consumption period, age and gender. Applied Geochemistry. 2010;25(1):81-90 2. Pearce DC, Dowling K, Gerson, AR, et al. Arsenic microdistribution and speciation in toenail clippings of children living in a historic gold mining area. Sci Total Environ. 2010;408(12):2590-2599 3. Marques RC, Dorea JG, Bastos WR, Malm O. Changes in children hair-Hg concentrations during the first 5 years: maternal, environmental and iatrogenic modifying factors. Regul Toxicol Pharmacol. 2007;49(1):17-24 4. Canuel R, de Grosbois SB, Atikesse L, et al. New evidence on variations of human body burden of methylmercury from fish consumption. Environ Health Perspect. 2006;114(2):302-306 5. Barbosa F Jr, Tanus-Santos JE, Gerlach RF, Parsons PJ. A critical review of biomarkers used for monitoring human exposure to lead: advantages, limitations, and future needs. Environ Health Perspect. 2005;113(12):1669-1674 6. DiPietro ES, Phillips DL, Paschal DC, Neese JW. Determination of trace elements in human hair. Reference intervals for 28 elements in nonoccupationally exposed adults in the US and effects of hair treatments. Biol Trace Elem Res. 1989;22(1):83-100 7. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

HMNA
31070

Heavy Metals, Nails

Clinical Information: Arsenic: Arsenic circulating in the blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in nails is higher than in other tissues. Several weeks after exposure, transverse white striae, called Mees' lines, may appear in the fingernails. Mercury: Once absorbed and circulating, mercury becomes bound to numerous proteins, including keratin. The concentration of mercury in nails correlates with the severity of clinical symptoms. Lead: Nail analysis of lead can be used to corroborate blood analysis.

Useful For: Detection of nonacute arsenic, mercury, and lead exposure

Interpretation: Nails grow at a rate of approximately 0.1 inch/month. Nail keratin synthesized today will grow to the distal end in approximately 6 months. Thus, a nail specimen collected at the distal end represents exposure of 6 months ago. Arsenic: Nail arsenic above 1.0 mcg/g dry weight may indicate excessive exposure. It is normal for some arsenic to be present in nails, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair or nail arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure, which was the cause of death. Mercury: Normally, nails contain less than 1 mcg/g of mercury; any amount above this indicates that exposure to more than normal amounts of mercury may have occurred. Lead: Normally, the nail lead content is below 4.0 mcg/g. While nail lead content above 10.0 mcg/g may indicate significant lead exposure, nails are also subject to potential external contamination with environmental lead. Ultimately, the nail lead content needs to be interpreted in addition to the overall clinical scenario including symptoms, physical findings, and other diagnostic results when determining further actions.

Reference Values:
ARSENIC
0-15 years: Not established
> or =16 years: <1.0 mcg/g of nails

LEAD

<4.0 mcg/g of nails
Reference values apply to all ages.

MERCURY
0-15 years: Not established
> or =16 years: <1.0 mcg/g of nails

Clinical References: 1. Hindmarsh JT, McCurdy RF. Clinical and environmental aspects of arsenic toxicity. Crit Rev Clin Lab Sci. 1986;23(4):315-347 2. Strumylaite L, Ryselis S, Kregzdyte R. Content of lead in human hair from people with various exposure levels in Lithuania. Int J Hyg Environ Health. 2004;207(4):345-351 3. Barbosa F Jr, Tanus-Santos JE, Gerlach RF, Parsons PJ. A critical review of biomarkers used for monitoring human exposure to lead: advantages, limitations, and future needs. Environ Health Perspect. 2005;113(12):1669-1674 4. Sanna E, Liguori A, Palmes L, Soro MR, Floris G. Blood and hair lead levels in boys and girls living in two Sardinian towns at different risks of lead pollution. Ecotoxicol Environ Saf. 2003;55(3):293-299 5. DiPietro ES, Phillips DL, Paschal DC, Neese JW. Determination of trace elements in human hair. Reference intervals for 28 elements in nonoccupationally exposed adults in the US and effects of hair treatments. Biol Trace Elem Res. 1989;22(1):83-100 6. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

HEG1
615261

HEG1 Immunostain, Technical Component Only

Clinical Information: HEG homolog 1 (HEG1) is a heavily glycosylated membrane protein that participates in endothelial cell associations that develop the vascular system. HEG1 is useful as a marker for malignant mesothelioma, particularly epithelioid mesothelioma, and as a potential marker for sarcomatoid mesothelioma.

Useful For: Diagnosis of epithelioid mesothelioma versus non-small cell carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Naso J, Tsuji S, Churg A. HEG1 is a highly specific and sensitive marker of epithelioid malignant mesothelioma. Am J Surg Pathol. 2020;44:1143-1148 2. Tsuji S, Washimi K, Kageyama T, et al. HEG1 is a novel mucin-like membrane protein that serves as a diagnostic and therapeutic target for malignant mesothelioma. Sci Rep. 2017;7:45768. doi:10.1038/srep45768 3. Matsuura R, Kaji H, Tomioka A, et al. Identification of mesothelioma-specific sialylated epitope recognized with monoclonal antibody SKM9-2 in a mucin-like membrane protein HEG1. Sci Rep. 2018;8(1):14251. doi:10.1038/s41598-018-32534-8 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HPYL
70466

Helicobacter pylori (H pylori) Immunostain, Technical Component Only

Clinical Information: Helicobacter pylori is a bacterium that frequently infects the stomach,

colonizing the gastric pits. H pylori infection is associated with the development of gastroduodenal ulcers and gastric mucosa-associated lymphoid tissue (MALT) lymphomas.

Useful For: Aiding in the identification of Helicobacter pylori infection

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Patnayak R, Reddy V, Jena A, et al. Helicobacter pylori in cholecystectomy specimens-morphological and immunohistochemical assessment. J Clin Diagn Res. 2016;10(5):EC01-3. doi:10.7860/JCDR/2016/14802.7716 2. Son JH, Lebwohl B, Sepulveda AR, Lagana SM. Utilization rate of Helicobacter pylori immunohistochemistry is not associated with the diagnostic rate of helicobacter pylori infection. Appl Immunohistochem Mol Morphol. 2019;27(9):694-698. doi:10.1097/PAI.0000000000000680 3. Lee JY, Kim N. Diagnosis of Helicobacter pylori by invasive test: histology. Ann Transl Med. 2015;3(1):10. doi:10.3978/j.issn.2305-5839.2014.11.03 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HPSAF
800272

Helicobacter pylori Antigen, Feces

Clinical Information: Helicobacter pylori is well recognized as the cause of chronic active gastritis, duodenal ulcer, and nonulcer dyspepsia. Currently accepted methods for the diagnosis of Helicobacter pylori infection include serologic tests, the urea breath test (UBT), and culture or histologic examination or direct urease testing (CLO test) of biopsy specimens obtained at the time of gastroduodenoscopy (ENDO). Each of these tests has its drawbacks, including lack of specificity (serology) or high cost, complexity, and inconvenience for the patient (UBT and ENDO). See Helicobacter pylori Diagnostic Algorithm in Special Instructions.

Useful For: As an aid in the diagnosis of Helicobacter pylori Monitoring the eradication of Helicobacter pylori after therapy (in most situations, confirmation of eradication is not mandatory) The utility of this test in asymptomatic individuals is not known, but testing for Helicobacter pylori in such individuals is not generally recommended

Interpretation: Positive results indicate the presence of Helicobacter pylori antigen in the stool. Negative results indicate the absence of detectable antigen but does not eliminate the possibility of infection due to Helicobacter pylori.

Reference Values:
Negative

Clinical References: 1. NIH Consensus Development Panel. Helicobacter pylori in peptic ulcer disease. JAMA 1994;272:65-69 2. Report of the Digestive Health Initiative. International Update Conference on H. pylori. Tysons Corner, McLean, VA, Feb 13-16, 1997

UBT
81590

Helicobacter pylori Breath Test

Clinical Information: Helicobacter pylori is recognized as an important pathogen and a causal

relationship between H pylori and chronic active gastritis, duodenal ulcer, and gastric ulcer is well documented. Currently there are numerous H pylori detection technologies for upper gastrointestinal disease including biopsy and serum analysis. These technologies depend on 2 general approaches for obtaining a sample for testing: invasive and noninvasive. The most common invasive test method requires an endoscopic gastric biopsy. The tissue collected from the biopsy is then examined in a laboratory by microbiologic culture of the organism, direct detection of urease activity in the tissue, by molecular testing, or by histological examination of stained tissue. Biopsy-based methods present an element of patient risk and discomfort and may provide false-negative results due to sampling errors. The (13)C-urea breath test provides a noninvasive and nonhazardous analysis of the exhaled breath. The BreathID test measures the (12)CO2 (carbon dioxide) and (13)CO2 (labelled carbon dioxide) components of the exhaled breath before and after the oral ingestion of (13)C-enriched urea. This establishes the baseline ratio of (13)CO2/(12)CO2 and the post ingestion ratio of (13)CO2/(12)CO2 in order to determine the delta over baseline (change in the (13)CO2/(12)CO2 ratio). The BreathID Hp Lab System, using molecular correlation spectroscopy (MCS), is intended for use to noninvasively measure changes in the (13)CO2/(12)CO2 ratio of exhaled breath, which may be indicative of increased urease production associated with active H pylori infection in the stomach. MCS uses infrared light to precisely match the CO2 molecule wavelength allowing for a smaller sample and minimal cross-sensitivity and low power consumption. For more information see Helicobacter pylori Diagnostic Algorithm.

Useful For: Diagnostic testing for Helicobacter pylori infection in patients suspected to have active H pylori infection Monitoring response to therapy This test is not appropriate for asymptomatic people.

Interpretation: The Helicobacter pylori urea breath test can detect very low levels of H pylori and, by assessing the entire gastric mucosa, avoids the risk of sampling errors inherent in biopsy-based methods. In the absence of gastric H pylori, the (13)C-urea does not produce (13)CO2 (carbon dioxide) in the stomach. A negative result does not rule out the possibility of H pylori infection. If clinical signs are suggestive of H pylori infection, retest with a new specimen or by using an alternative method. A false-positive test may occur due to urease associated with other gastric spiral organisms observed in humans such as Helicobacter heilmannii. A false-positive test could occur in patients who have achlorhydria.

Reference Values:

Negative

Reference values apply to all ages.

Clinical References: 1. Talley NJ, Vakil NB, Moayyedi P. American gastroenterological association technical review on the evaluation of dyspepsia. Gastroenterology. 2005;129(5):1756-1780 2. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori infection. Am J Gastroenterol. 2017;112(2):212-239. doi:10.1038/ajg.2016.563 3. Talley NJ, Ford AC. Functional dyspepsia. N Engl J Med. 2015;373(19):1853-1863. doi:10.1056/NEJMra1501505

HELIS 62769 Helicobacter pylori Culture with Antimicrobial Susceptibilities, Varies

Clinical Information: Helicobacter pylori is a spiral-shaped gram-negative bacterium that may cause chronic gastritis, peptic ulcer disease, or gastric neoplasia. In adults of industrialized countries, an estimated 0.5% of the susceptible population becomes infected each year, although the incidence has been decreasing over time. The organism may asymptomatically colonize humans. In suspected H pylori-associated disease, the H pylori with clarithromycin resistance prediction polymerase chain reaction (PCR) test or urea breath test is recommended for patients younger than 60 years old without

alarming signs and symptoms (see Helicobacter pylori Diagnostic Algorithm). If clarithromycin resistance is predicted by the PCR test, endoscopy with biopsy should be considered for H pylori culture with antimicrobial susceptibility testing. For those 60 years old or older who have alarming signs and symptoms, endoscopy with biopsy is recommended, with consideration for H pylori culture with antimicrobial susceptibility testing on the gastric biopsy. If patients fail to respond to treatment, endoscopy with biopsy should be considered for H pylori culture with antimicrobial susceptibility testing. The Clinical and Laboratory Standards Institute (CLSI) recommends agar dilution for H pylori antimicrobial susceptibility testing. Amoxicillin, clarithromycin, levofloxacin, metronidazole, rifampin, and tetracycline are routinely tested. CLSI has defined interpretive categories for clarithromycin. The antimicrobials for which the European Committee on Antimicrobial Susceptibility Testing defines interpretive categories include amoxicillin, clarithromycin, levofloxacin, metronidazole, rifampin, and tetracycline.

Useful For: Recovery of Helicobacter pylori from gastric specimens for antimicrobial susceptibility testing of the organism (amoxicillin, clarithromycin, levofloxacin, metronidazole, rifampin, and tetracycline are routinely tested)

Interpretation: A positive result provides definitive evidence of the presence of Helicobacter pylori. Organisms may be detected in asymptomatic (colonized) individuals. False-negative culture results may occur since the organism may die between biopsy collection and laboratory culture.

Reference Values:
No growth of Helicobacter pylori

Susceptibility results are reported as minimal inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as clinical breakpoints) are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, or nonsusceptible according to breakpoint setting organizations, either the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST), as applicable.

In some instances, an interpretive category cannot be provided based on available data; therefore, the following comment will be included on the report: There are no established interpretive guidelines for agents reported without interpretations.

For information regarding CLSI and EUCAST susceptibility interpretations, see Susceptibility Interpretative Category Definitions.

Clinical References: Chen D, Cunningham SA, Cole NC, Kohner PC, Mandrekar JN, Patel R: Phenotypic and molecular antimicrobial susceptibility of Helicobacter pylori. Antimicrob Agents Chemother. 2017;61(4):e02530-16

HPCR1 607597 Helicobacter pylori with Clarithromycin Resistance Prediction, Molecular Detection, PCR (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

HPFRP 607594 Helicobacter pylori with Clarithromycin Resistance Prediction, Molecular Detection, PCR, Feces

Clinical Information: Helicobacter pylori is the main cause of peptic ulcer disease and, when left untreated, a risk factor for gastric cancer. Traditionally, H pylori diagnosis has included noninvasive tests (eg, urea breath test, fecal antigen test) or invasive tests (eg, gastric biopsy). Antimicrobial resistance in H pylori is poorly studied but is rising, challenging its treatment; in 2012, an international clinical consortium study group recommended monitoring of clarithromycin resistance rates and ceasing its use at a threshold range of 15% to 20%.(1) Local monitoring has been practically impossible as not all patients undergo invasive testing, which yields a culture isolate that can be subjected to susceptibility testing. Even if invasive testing is performed, the organism can be difficult to isolate in culture and is highly fastidious once isolated, oftentimes not being amenable to phenotypic susceptibility testing. Further, there are only a handful of specialized microbiology laboratories that perform H pylori susceptibility testing. In an internal study of local and referred isolates published in 2016, clarithromycin resistance was observed to be most commonly due to A2143G (70/88 isolates, 79.6%), followed by A2142G (12/88 isolates, 13.6%) and A2142C (3/88 isolates, 3.4%) alterations in the 23S ribosomal RNA gene.(2) Overall, one of these alterations was found in 97% of clarithromycin resistant H pylori isolates studied.

Useful For: Aiding in the diagnosis of Helicobacter pylori infection and prediction of clarithromycin resistance or susceptibility directly from stool

Interpretation: A detected result indicates the presence of Helicobacter pylori 23S ribosomal RNA gene; also indicated is whether or not one the 3 most common 23S ribosomal RNA gene single nucleotide variations (A2143G, A2142G, and A2142C) associated with clarithromycin resistance is detected. A not detected result for H pylori indicates the absence of detectable H pylori DNA but does not negate the presence of the organism and may occur due to inhibition of the polymerase chain reaction (PCR), sequence variability underlying primers or probes, or the presence of H pylori DNA in quantities less than the limit of detection of the assay.

Reference Values:
Not detected

Clinical References: 1. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection--the Maastricht IV/Florence Consensus Report. Gut. 2012;61(5):646-664. doi:10.1136/gutjnl-2012-302084 2. Chen D, Cunningham SA, Cole N, Kohner PC, Mandrekar JN, Patel R. Phenotypic and molecular antimicrobial susceptibility of Helicobacter pylori. Antimicrob Agents Chemother. 2017;61(4):e02530-16. doi:10.1128/AAC.02530-16 3. Beckman E, Saracino I, Fiorini G, et al. A novel stool PCR test for Helicobacter pylori may predict Clarithromycin resistance and eradication of infection at a high rate. J Clin Microbiol. 2017;55(8):2400-2405 4. Marrero Rolon R, Cunningham SA, Mandrekar JN, Polo ET, Patel R. Clinical evaluation of a real-time PCR assay for simultaneous detection of helicobacter pylori and genotypic markers of clarithromycin resistance directly from stool. J Clin Microbiol. 2021;59(5):e03040-20. doi:10.1128/JCM.03040-20 5. Savarino V, Tracci D, Dulbecco P, et al. Negative effect of ranitidine on the results of urea breath test for the diagnosis of Helicobacter pylori. AM J Gastroenterol. 2001;96(2):348-52. doi:10.1111/j.1572-0241.2001.03517.x 6. Chey WD, Grigorios L, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori infection. Am J Gastroenterol. 2017;112(2):p 212-239. doi:10.1038/ajg.2016.563 7. Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents. J Pediatr Gastroenterol Nutr. 2017:64(6):p 991-1003. doi:10.1097/MPG.0000000000001594 8. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut. 2017;66(1):6-30. doi:10.1136/gutjnl-2016-312288

HPRP 607595 Helicobacter pylori with Clarithromycin Resistance Prediction, Molecular Detection, PCR, Tissue

Clinical Information: Helicobacter pylori is a cause of peptic ulcer disease and, when left untreated, a risk factor for gastric cancer. H pylori diagnosis includes noninvasive tests (eg, stool polymerase chain reaction [PCR], urea breath test, stool antigen test) and tests requiring endoscopy to collect specimens for analysis. Several tests can be performed on gastric specimens, including H pylori PCR. Antimicrobial resistance in H pylori is poorly studied but is rising, challenging its treatment. Assessment of antimicrobial resistance can guide treatment. Endoscopically collected gastric specimens can be cultured for H pylori and the recovered organism tested for phenotypic antimicrobial susceptibility. However, the organism can be difficult to isolate in culture, and even when isolated, may not amenable to phenotypic susceptibility testing due to its fastidious nature. Clarithromycin resistance is most often associated with 23S ribosomal RNA (rRNA) gene mutations (particularly A2143G, A2142G/C). A systematic review and meta-analysis showed the sensitivity and specificity of detection of the H pylori A2142G/C and/or A2143G combination for prediction of clarithromycin resistance in H pylori in biopsy samples to be 96% each. This test detects H pylori in gastric and duodenal biopsy specimens and, when detected, assesses for H pylori 23S rRNA gene mutations associated with clarithromycin resistance.

Useful For: Aiding in the diagnosis of Helicobacter pylori infection and prediction of clarithromycin resistance or susceptibility directly from gastric biopsies

Interpretation:

Reference Values:
Not detected

Clinical References: 1. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection--the Maastricht IV/Florence consensus report. Gut. 2012;61(5):646-664. doi:10.1136/gutjnl-2012-302084 2. Chen D, Cunningham SA, Cole N, Kohner PC, Mandrekar JN, Patel R. Phenotypic and molecular antimicrobial susceptibility of Helicobacter pylori. Antimicrob Agents Chemother. 2017;61(4):e02530-16. doi:10.1128/AAC.02530-16 3. Beckman E, Saracino I, Fiorini G, et al. A novel stool PCR test for Helicobacter pylori may predict Clarithromycin resistance and eradication of infection at a high rate. J Clin Microbiol. 2017;55(8):2400-2405 4. Marrero Rolon R, Cunningham SA, Mandrekar JN, Polo ET, Patel R: Clinical evaluation of a real-time PCR assay for simultaneous detection of Helicobacter pylori and genotypic markers of clarithromycin resistance directly from stool. J Clin Microbiol. 2021;59(5):e03040-20. doi:10.1128/JCM.03040-20 5. Savarino V, Tracci D, Dulbecco P, et al. Negative effect of ranitidine on the results of urea breath test for the diagnosis of Helicobacter pylori. AM J Gastroenterol. 2001;96(2):348-52. doi:10.1111/j.1572-0241.2001.03517.x 6. Chey WD, Grigorios L, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori infection. Am J Gastroenterol. 2017;112(2):p 212-239. doi:10.1038/ajg.2016.563 7. Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents. J Pediatr Gastroenterol Nutr. 2017:64(6):991-1003. doi:10.1097/MPG.0000000000001594 8. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut. 2017;66(1):6-30. doi:10.1136/gutjnl-2016-312288

HPCRP 607596 Helicobacter pylori with Clarithromycin Resistance Prediction, Molecular Detection, PCR, Varies

Clinical Information: Helicobacter pylori is the main cause of peptic ulcer disease and a risk factor for gastric cancer when left untreated. Traditionally, H pylori diagnosis has included noninvasive tests (eg, urea breath test, fecal antigen test) or invasive tests (eg, gastric biopsy). Antimicrobial resistance in H pylori is poorly studied but is rising, challenging its treatment. In 2012, an international clinical consortium study group recommended monitoring of clarithromycin resistance rates and ceasing its use at a threshold range of 15% to 20%.(1) Local monitoring has been practically impossible as not all patients

undergo invasive testing, which yields a culture isolate that can be subjected to susceptibility testing. Even if invasive testing is performed, the organism can be difficult to isolate in culture and is highly fastidious once isolated, oftentimes not being amenable to phenotypic susceptibility testing. Further, there are only a handful of specialized clinical microbiology laboratories that perform H pylori susceptibility testing. In an internal study of local and referred isolates, clarithromycin resistance was observed to be most commonly due to A2143G (70/88 isolates, 79.6%), followed by A2142G (12/88 isolates, 13.6%) and A2142C (3/88 isolates, 3.4%) alterations in the 23S ribosomal RNA gene.(2) Overall, one of these alterations was found in 97% of clarithromycin-resistant H pylori isolates studied.

Useful For: Assessing pure isolates of Helicobacter pylori to predict clarithromycin resistance or susceptibility

Interpretation: A detected result indicates the presence of Helicobacter pylori 23S ribosomal RNA gene; the presence or absence of the 3 most common 23S ribosomal RNA gene single nucleotide variations (A2143G, A2142G, and A2142C) is reported. A not detected result indicates the absence of detectable H pylori DNA.

Reference Values:
Not applicable

Clinical References: 1. Malfertheiner P, Megraud F, O'Morain CA, et al: Management of Helicobacter pylori infection--the Maastricht IV/Florence Consensus Report. Gut. 2012 May;61(5):646-664. doi: 10.1136/gutjnl-2012-302084 2. Chen D, Cunningham SA, Cole NC, Kohner PC, Mandrekar JN, Patel R: Phenotypic and molecular antimicrobial susceptibility of Helicobacter pylori. Antimicrob Agents Chemother. 2017 Mar 24;61(4):e02530-16 3. Beckman E, Saracino I, Fiorini G, et al: A novel stool PCR test for Helicobacter pylori may predict clarithromycin resistance and eradication of infection at a high rate. J Clin Microbiol. 2017 Aug;55(8):2400-2405 4. Monteiro L, Gras N, Vidal R, Megraud F: Detection of Helicobacter pylori DNA in human feces by PCR: DNA stability and removal of inhibitors. J Microbiol Methods. 2001 Jun;45(2):89-94

HELM
82749

Helminthosporium halodes, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Helminthosporium halodes Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FHSSE
57532

Helminthosporium sativum/Drechslera IgE

Clinical Information: This assay is used to detect allergen specific-IgE using an enzyme immunoassay (EIA). In vitro allergy testing is the primary testing mode for allergy diagnosis.

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >=50 Very Strong Positive

Reference Values:
<0.35 kU/L

HOLDC
35848

Hematologic Disorders, Chromosome Hold, Varies

Clinical Information: Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities for most hematologic malignancies. Based on morphologic review of the bone marrow or peripheral blood specimen by a hematopathologist, a determination of additional appropriate testing can be made. If the specimen does not show evidence of malignancy, chromosome analysis may not be necessary. Depending on the diagnosis, fluorescence in situ hybridization assays may also be more informative.

Useful For: Holding the bone marrow or peripheral blood specimen in the laboratory but delaying chromosome analysis while preliminary morphologic assessment is in process

Interpretation: If notified by the client, this test may be canceled, and a processing fee assessed. If no notification to cancel testing is received, this test will be reported as "reflexed for chromosome analysis" and depending on the specimen received, CHRBM / Chromosome Analysis, Hematologic Disorders, Bone Marrow or CHRHB / Chromosome Analysis, Hematologic Disorders, Blood will be performed, and an interpretive report provided.

Reference Values:
Not applicable

Clinical References: 1. Mellors PW, Binder M, Ketterling RH, et al. Metaphase cytogenetics and plasma cell proliferation index for risk stratification in newly diagnosed multiple myeloma. Blood Adv. 2020;4(10):2236-2244

EXHR 65114 Hematologic Disorders, DNA and RNA Extract and Hold, Varies

Clinical Information: It is frequently useful to obtain nucleic acids from clinical samples containing a hematopoietic neoplasm at the time of diagnosis so appropriate material is available for molecular analysis should subsequent testing be required. For example, when a diagnosis of acute myelogenous leukemia is made, there is a delay before karyotype information, which determines whether testing for molecular prognostic markers is necessary, is available. After this delay, the diagnostic sample is usually no longer available or the nucleic acid has degraded to such an extent that it is no longer adequate for testing. Thus, it is useful to obtain nucleic acids on such specimens promptly at diagnosis and retain it until it is known whether additional testing is necessary.

Useful For: Reserving nucleic acids on any specimen for which molecular analysis requiring DNA or RNA may be necessary at a future date, ensuring that adequate material for testing is available

Interpretation: A report of "Performed" will be sent and a $75 processing fee will be assessed. No interpretation will be given. Should the sample be used in future testing, interpretation would be incorporated with the final testing.

Reference Values:
Not applicable

EXHD 64779 Hematologic Disorders, DNA Extract and Hold, Varies

Clinical Information: It is frequently useful to obtain DNA from clinical samples containing a hematopoietic neoplasm at the time of diagnosis so appropriate material is available for molecular analysis should subsequent testing be required. For example, when a diagnosis of acute myelogenous leukemia is made, there is a delay before karyotype information, which determines whether testing for molecular prognostic markers is necessary, is available. After this delay, the diagnostic sample is usually no longer available, or the DNA has degraded to such an extent that it is no longer adequate for testing. Thus, it is useful to obtain DNA on such specimens promptly at diagnosis and retain it until it is known whether additional testing is necessary.

Useful For: Reserving DNA on any specimen for which molecular analysis requiring DNA may be necessary at a future date, ensuring that adequate material for testing is available

Interpretation: A report of "Performed" will be sent and a $50 processing fee will be assessed. No

interpretation will be given. Should the sample be used in future testing, interpretation would be incorporated with the final testing.

Reference Values:
Not applicable

HOLDF 35847 Hematologic Disorders, Fluorescence In Situ Hybridization (FISH) Hold, Varies

Clinical Information: Fluorescence in situ hybridization (FISH) analysis using gene-specific probes is a useful methodology to detect common, recurrent chromosome abnormalities for most hematologic malignancies. Based on morphologic review of the bone marrow or peripheral blood specimen by a hematopathologist, a determination of additional appropriate testing can be made. If the specimen does not show evidence of malignancy, FISH analysis may not be necessary. Depending on the diagnosis, conventional chromosome analysis may also be more informative.

Useful For: Processing the bone marrow or peripheral blood specimen but delaying fluorescence in situ hybridization analysis while preliminary morphologic assessment is in process

Interpretation: If notified by the client, this test may be canceled, and a processing fee will be assessed. If no notification to proceed with testing is received, this test will be reported as "cancelled."

Reference Values:
Not applicable

HLLFH 34854 Hematologic Disorders, Leukemia/Lymphoma; Flow Hold, Varies

Clinical Information: Diagnostic hematopathology has become an increasingly complex subspecialty, particularly with neoplastic disorders of blood and bone marrow. While morphologic assessment of blood smears, bone marrow smears, and tissue sections remains the cornerstone of lymphoma and leukemia diagnosis and classification, immunophenotyping is a very valuable and important complementary tool. Immunophenotyping hematopoietic specimens can help resolve many differential diagnostic problems posed by the clinical or morphologic features.

Useful For: Evaluating lymphocytoses of undetermined etiology Identifying B- and T-cell lymphoproliferative disorders involving blood and bone marrow Distinguishing acute lymphoblastic leukemia (ALL) from acute myeloid leukemia (AML) Immunologic subtyping of acute leukemias Distinguishing reactive lymphocytes and lymphoid hyperplasia from malignant lymphoma Distinguishing between malignant lymphoma and acute leukemia Phenotypic subclassification of B- and T-cell chronic lymphoproliferative disorders, including chronic lymphocytic leukemia, mantle cell lymphoma, and hairy cell leukemia Recognizing AML with minimal morphologic or cytochemical evidence of differentiation Recognizing monoclonal plasma cells This test is not intended for detection of minimal residual disease below 5% blasts.

Interpretation: This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist. Report will include a morphologic description, a summary of the procedure, the percent positivity of selected antigens, and an interpretive conclusion based on the correlation of the clinical history with the morphologic features and immunophenotypic results.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Jevremovic D, Dronca RS, Morice WG, et al. CD5+ B-cell lymphoproliferative disorders: Beyond chronic lymphocytic leukemia and mantle cell lymphoma. Leuk Res. 2010;34(9):1235-1238 2. Hanson CA. Acute leukemias and myelodysplastic syndromes. In: McClatchey KD, ed. Clinical Laboratory Medicine. Williams and Wilkins; 1994:939-969 3. Jevremovic D, Olteanu H. Flow cytometry applications in the diagnosis of T/NK-Cell lymphoproliferative disorders. Cytometry B Clin Cytom. 2019;96(2):99-115 4. Rosado FG, Morice WG, He R, Howard MT, Timm M, McPhail ED. Immunophenotypic features by multiparameter flow cytometry can help distinguish low grade B-cell lymphomas with plasmacytic differentiation from plasma cell proliferative disorders with an unrelated clonal B-cell process. Br J Haematol. 2015;169(3):368-376 5. Shi M, Ternus JA, Ketterling RP, et al. Immunophenotypic and laboratory features of t(11;14)(q13;q32)-positive plasma cell neoplasms. Leuk Lymphoma. 2018;59(8):1913-1919 6. Morice WG, Kimlinger T, Katzmann JA, et al. Flow cytometric assessment of TCR-V-beta expression in the evaluation of peripheral blood involvement by T-cell lymphoproliferative disorders: a comparison with conventional T-cell immunophenotyping and molecular genetic techniques. Am J Clin Pathol. 2004;121(3):373-383 7. Shi M, Jevremovic D, Otteson GE, Timm MM, Olteanu H, Horna P. Single antibody detection of T-Cell receptor alpha beta clonality by flow cytometry rapidly identifies mature T-Cell neoplasms and monotypic small CD8-positive subsets of uncertain significance. Cytometry B Clin Cytom. 2020;98(1):99-107 8. Jevremovic D, Olteanu H. Flow cytometry applications in the diagnosis of T/NK-cell lymphoproliferative disorders. Cytometry B Clin Cytom. 2019;96(2):99-115

P53CA
62402

Hematologic Neoplasms, TP53 Somatic Mutation, DNA Sequencing Exons 4-9, Varies

Clinical Information: Patients with chronic lymphocytic leukemia (CLL) have variable disease course influenced by a series of tumor biologic factors. The presence of chromosomal 17p- or a TP53 gene variant confers a very poor prognosis to a subset of CLL patients, both at time of initial diagnosis, as well as at disease progression, or in the setting of therapeutic resistance. TP53 gene variant status in CLL has emerged as the single most predictive tumor genetic abnormality associated with adverse outcome and poor response to standard immunochemotherapy; however, patients can be managed with alternative therapeutic options. Although the prognostic relevance of an acquired TP53 gene variant is best studied for CLL, similar findings are also reported for other hematologic malignancies including low-grade B-cell lymphoma, diffuse large B-cell lymphoma, and some types of myelodysplastic syndromes and acute myeloid leukemia. Therefore, while this test has been developed to be primarily focused on high-risk CLL patients, TP53 gene sequencing analysis can also be performed in additional neoplasms, as clinically indicated.

Useful For: Evaluating chronic lymphocytic leukemia patients at diagnosis or during disease course for the presence of TP53 gene variants indicating high risk of disease progression and adverse outcomes This test is not intended for the evaluation of patients suspected of having an inherited or germline TP53 cancer syndrome (eg, Li Fraumeni syndrome)

Interpretation: Results are reported in standard nomenclature according to the most recent Human Genome Variation Society recommendations and an interpretive comment regarding the nature of the sequence variant (eg, known deleterious, suspected deleterious, synonymous change) will be included to complete the clinical report.

Reference Values:
Genetic variants present or absent as compared to a reference sequence of the normal TP53 gene

Clinical References: 1. Zenz T, Krober A, Scherer K, et al: Monoallelic TP53 inactivation is associated with poor prognosis in chronic lymphocytic leukemia: results from a detailed genetic characterization with long-term follow-up. Blood. 2008;112:3322-3329 2. Lehmann S, Oqawa S, Raynaud SD, et al: Molecular allelokaryotyping of early-stage, untreated chronic lymphocytic leukemia. Cancer. 2008;112:1296-1305 3. Rossi D, Cerri M, Deambrogi C, et al: The prognostic value of TP53 mutations in chronic lymphocytic leukemia is independent of Del17p13: implications for overall survival and chemorefractoriness. Clin Cancer Res. 2009;15(3):995-1004 4. Zent CS, Call TG, Hogan WJ, et al: Update on risk-stratified management for chronic lymphocytic leukemia. Leuk Lymphoma. 2006;47(9):1738-1746 5. Trbusek M, Smardova J, Malcikova J, et al: Missense mutations located in structural p53 DNA-binding motifs are associated with extremely poor survival in chronic lymphocytic leukemia. J Clin Oncol. 2011;29:2703-2708 6. Halldorsdottir AM, Lundin A, Murray F, et al: Impact of TP53 mutation and 17p deletion in mantle cell lymphoma. Leukemia. 2011;25:1904-1908 7. Young KH, Leroy K, Moller MB, et al: Structural profiles of TP53 gene mutations predict clinical outcome in diffuse large B-cell lymphoma: an international collaborative study. Blood. 2008;112:3088-3098 8. Malcikova J, Tausch E, Rossi D, et al: ERIC recommendations for TP53 mutation analysis in chronic lymphocytic leukemia - update on methodological approaches and results interpretation. Leukemia. 2018;32:1070-1080

HEMMF
614265

Hematologic Specified FISH, Varies

Clinical Information: Fluorescence in situ hybridization using gene-specific probes and various probe strategies can help characterize chromosome abnormalities in hematologic malignancies for diagnostic, prognostic, and therapeutic purposes.

Useful For: The detection of specific chromosomal abnormalities in hematologic malignancies

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: Swerdlow SH, Campo E, Harris NL, et al, eds.: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press; 2017

HFWET
616820

Hematopathology Consult, MCL

Clinical Information: Diagnosis of a hematologic disease requires thorough and accurate morphologic examination of peripheral blood and bone marrow as well as interpretation of ancillary testing results (eg, cytochemistry, immunohistochemistry, flow cytometric immunophenotyping, chromosome analysis, fluorescence in situ hybridization, and molecular testing) by a highly qualified hematopathologist. With recent advent of new understanding and treatment options, more ancillary tests are available. Efficient utilization and accurate interpretation of these tests are crucial for patient care. These tests can assist in rendering an accurate diagnosis and could provide prognostic prediction and potential indication or guidance of therapy.

Useful For: Obtaining a rapid, expert opinion for diagnosis of hematologic and non-hematologic diseases using unprocessed bone marrow biopsy specimens referred by the primary pathologist Obtaining special studies that are not available locally

Interpretation: Results of the consultation are reported in a formal pathology report that includes a description of ancillary test results (if applicable) and an interpretive comment. This consultative practice strives to bring the physician and patient the highest quality of diagnostic pathology in all areas of expertise, aiming to utilize only those ancillary tests that support the diagnosis in a cost-effective manner, and to provide a rapid turnaround time for diagnostic results.

Reference Values:
An interpretive report will be provided.

Clinical References: Sundaram S, Jizzini M, Lamonica D, et al: Utility of bone marrow aspirate and biopsy in staging of patients with T-cell lymphoma in the PET-Era-tissue remains the issue. Leuk Lymphoma. 2020 Dec;61(13)3226-3233. doi: 10.1080/10428194.2020.1798950

HPCUT 71743 Hematopathology Consultation, Client Embed

Clinical Information: Diagnosis of a hematologic disease requires thorough and accurate morphologic examination of peripheral blood and bone marrow as well as interpretation of ancillary testing results (eg, cytochemistry, immunohistochemistry, flow-cytometric immunophenotyping, chromosome analysis, fluorescence in situ hybridization testing, and molecular genetics) by a highly qualified hematopathologist. With recent advent of new understanding and treatment options, more ancillary tests are available. Efficient utilization and accurate interpretation of these tests are crucial for patient care. These tests can assist in rendering an accurate diagnosis and could provide prognostic prediction and potential indication or guidance of therapy.

Useful For: Obtaining a rapid, expert opinion for diagnosis of hematologic and nonhematologic diseases using bone marrow biopsy specimens referred by the primary pathologist Obtaining special studies that are not available locally

Interpretation: Results of the consultation are reported in a formal pathology report that includes a description of ancillary test results (if applicable) and an interpretive comment. When the case is completed, results may be communicated by a phone call.

Reference Values:
An interpretive report will be provided.

Clinical References: Sundaram S, Jizzini M, Lamonica D, et al. Utility of bone marrow aspirate and biopsy in staging of patients with T-cell lymphoma in the PET-Era - tissue remains the issue, Leuk Lymphoma. 2020;61(13):3226-3233. doi:10.1080/10428194.2020.1798950

HPWET 70343 Hematopathology Consultation, MCL Embed

Clinical Information: Diagnosis of a hematologic disease requires thorough and accurate morphologic examination of peripheral blood and bone marrow as well as interpretation of ancillary testing results (eg, cytochemistry, immunohistochemistry, flow cytometric immunophenotyping, chromosome analysis, and fluorescence in situ hybridization and molecular testing) by a highly qualified hematopathologist. With recent advent of new understanding and treatment options, more ancillary tests are available. Efficient utilization and accurate interpretation of these tests are crucial for patient care. These tests can assist in rendering an accurate diagnosis and could provide prognostic prediction and potential indication or guidance of therapy.

Useful For: Obtaining a rapid, expert opinion for diagnosis of hematologic and non-hematologic diseases using unprocessed bone marrow biopsy specimens referred by the primary pathologist Obtaining special studies that are not available locally

Interpretation: Results of the consultation are reported in a formal pathology report that includes a description of ancillary test results (if applicable) and an interpretive comment. When the case is completed, results may be communicated by a phone call.

Reference Values:
An interpretive report will be provided.

Clinical References: Sundaram S, Jizzini M, Lamonica D, et al. Utility of bone marrow aspirate and biopsy in staging of patients with T-cell lymphoma in the PET-Era-tissue remains the issue. Leuk Lymphoma. 2020;61(13)3226-3233. doi:10.1080/10428194.2020.1798950

HMEP 616524 Hemiplegic Migraine With or Without Epilepsy Gene Panel, Varies

Clinical Information: Familial hemiplegic migraine (FHM) is a rare form of migraine with aura. The associated motor aura typically presents as unilateral weakness (hemiparesis) or unilateral paralysis (hemiplegia); however, other forms of aura may occur including visual, speech, and/or sensory disturbances. Headache may occur during or after aura. The neurological manifestations are almost always fully reversible but are highly variable in terms of frequency and duration. Seizures have also been reported to occur both during severe attacks and independent of attacks, and cerebellar ataxia may occur with disease-causing variants in the CACNA1A gene. Onset is typically in the first or second decade of life, and attacks often decrease with age. The genetics aspects of FHM are complex. The primary genes associated with FHM include ATP1A2, CACNA1A, and SCN1A. FHM follows an autosomal dominant inheritance pattern with reduced penetrance. Some individuals with FHM may not have an overt family history of FHM if the condition occurred due to a de novo disease-causing variant or if inherited from an asymptomatic parent. Each of the primary genes causative of FHM may also cause different allelic genetic conditions (eg, CACNA1A disease-causing variants may also cause developmental and epileptic encephalopathy) and disease-causing variants in genes causing conditions with overlapping phenotypes may mimic FHM (eg, disease-causing NOTCH3 variants).

Useful For: Establishing a molecular diagnosis in individuals with hemiplegic migraine Identifying disease-causing variants within genes known to be associated with hemiplegic migraine, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 2. Stefano V, Rispoli M, Pellegrino N, et al: Diagnostic and therapeutic aspects of hemiplegic migraine. J Neurol Neurosurg Psychiatry. 2020 Jul; 91(7):764-771 3. Huang Y, Xiao H, Qin

X, et al: The genetic relationship between epilepsy and hemiplegic migraine. Neuropsychiatr Dis Treat. 2017 Apr;13: 1175-1179

HEMB
70454

Hemoglobin (Hb) Immunostain, Technical Component Only

Clinical Information: This immunostain uses antibodies to hemoglobin that stain red blood cells and their precursors in bone marrow and in other sites in a diffuse cytoplasmic staining pattern. This stain may be useful in the diagnosis of erythroleukemia or myelodysplastic neoplasms.

Useful For: Identification of red blood cells and red blood cell precursors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chuang SS, Li CY. Useful panel of antibodies for the classification of acute leukemia by immunohistochemical methods in bone marrow trephine biopsy specimens. Am J Clin Pathol. 1997;107(4):410-418 2. Dong HY, Wilkes S, Yang H. CD71 is selectively and ubiquitously expressed at high levels in erythroid precursors of all maturation stages: A comparative immunochemical study with glycophorin A and hemoglobin A. Am J Surg Pathol. 2011;35(5):723-732 3. O'Malley DP, Young SK, Perkins SL, Baldridge L, Juliar BE, Orazi A. Morphologic and immunohistochemical evaluation of splenic hematopoietic proliferations in neoplastic and benign disorders. Mod Pathol. 2005;18:1550-1561 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

A1CJ
800277

Hemoglobin A1c, Blood

Clinical Information: Diabetes mellitus is a chronic disorder associated with disturbances in carbohydrate, fat, and protein metabolism characterized by hyperglycemia. It is one of the most prevalent diseases, affecting approximately 24 million individuals in the United States. Long-term treatment of the disease emphasizes control of blood glucose levels to prevent the acute complications of ketosis and hyperglycemia. In addition, long-term complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease can be minimized if blood glucose levels are effectively controlled. Hemoglobin A1c (HbA1c) is a result of the nonenzymatic attachment of a hexose molecule to the N-terminal amino acid of the hemoglobin molecule. The attachment of the hexose molecule occurs continually over the entire life span of the erythrocyte and is dependent on blood glucose concentration and the duration of exposure of the erythrocyte to blood glucose. Therefore, the HbA1c level reflects the mean glucose concentration over the previous period (approximately 8-12 weeks, depending on the individual) and provides a much better indication of long-term glycemic control than blood and urinary glucose determinations. Diabetic patients with very high blood concentrations of glucose have from 2 to 3 times more HbA1c than normal individuals. Diagnosis of diabetes includes 1 of the following: -Fasting plasma glucose of 126 mg/dL or greater -Symptoms of hyperglycemia and random plasma glucose of 200 mg/dL or greater -Two-hour glucose of 200 mg/dL or greater during oral glucose tolerance test unless there is unequivocal hyperglycemia, confirmatory testing should be repeated on a different day In addition, recommendations from the American Diabetes Association (ADA) include the use of HbA1c to diagnose diabetes, using a threshold of 6.5%. The threshold is based upon sensitivity and specificity data from several studies. Advantages to using HbA1c for diagnosis include: -Provides an assessment of chronic hyperglycemia -Assay standardization efforts

from the National Glycohemoglobin Standardization Program have been largely successful and the accuracy of HbA1c is closely monitored by manufacturers and laboratories -No fasting is necessary -Intraindividual variability is very low (critical value of <2%) -A single test could be used for both diagnosing and monitoring diabetes When using HbA1c to diagnose diabetes, an elevated HbA1c should be confirmed with a repeat measurement, except in those individuals who are symptomatic with a plasma glucose concentration above 200 mg/dL. Patients who have an HbA1c between 5.7 and 6.4 are considered at increased risk for developing diabetes in the future. (The terms prediabetes, impaired fasting glucose, and impaired glucose tolerance will eventually be phased out by the ADA to eliminate confusion.) The ADA recommends measurement of HbA1c (typically 3-4 times per year for type 1 and poorly controlled type 2 diabetic patients, and 2 times per year for well-controlled type 2 diabetic patients) to determine whether a patient's metabolic control has remained continuously within the target range.

Useful For: Diagnosis of diabetes Evaluating the long-term control of blood glucose concentrations in patients with diabetes Identifying patients at an increased risk for developing diabetes This assay is not useful in determining day-to-day glucose control and should not be used to replace daily home testing of blood glucose.

Interpretation:

Reference Values:
4.0-5.6%
<18 years: Hemoglobin A1c criteria for diagnosing diabetes have not been established for patients who are <18 years of age.
> or =18 years: Increased risk for diabetes (prediabetes): 5.7-6.4%
Diabetes: > or =6.5%

Interpretive information based on Diagnosis and Classification of Diabetes Mellitus, American Diabetes Association.

Estimated Average Glucose (eAG)
The range of eAG concentrations that correspond to hemoglobin A1c values of 4.0-5.6% is 68-114 mg/dL (> or =18 years).

Clinical References: 1. Goldstein DE, Little RR, Lorenz RA, et al: Tests of glycemia in diabetes. Diabetes Care. 2003 Jan;26:S106-S108 2. Nathan DM, Kuenen J, Borg R, et al: Translating the A1c assay into estimated average glucose values. Diabetes Care. 2008 Aug;31:1473-1478 3. American Diabetes Association, Position Statement, Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2014 Jan;37:S14-S80 4. Little RR, Wiedmeyer HM, England JD, et al: Interlaboratory standardization of measurements of glycohemoglobins. Clin Chem. 1992;38:2472-2478 5. Hoelzel W, Weykamp C, Jeppsson JO, et al: IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem. 2004;50(1):166-174

HBA1C
82080

Hemoglobin A1c, Blood

Clinical Information:

Useful For: Evaluating the long-term control of blood glucose concentrations in patients with diabetes Diagnosing diabetes Identifying patients at increased risk for diabetes (prediabetes) This assay is not useful in determining day-to-day glucose control and should not be used to replace daily home testing of blood glucose.

Interpretation:

Reference Values:
4.0-5.6%
<18 years: Hemoglobin A1c criteria for diagnosing diabetes have not been established for patients who are <18 years of age.
> or =18 years: Increased risk for diabetes (prediabetes): 5.7-6.4%
Diabetes: > or =6.5%

Interpretive information based on Diagnosis and Classification of Diabetes Mellitus, American Diabetes Association.

Clinical References:

HBEL1 Hemoglobin Electrophoresis Evaluation, Blood
608083

Clinical Information: A large number of variants of hemoglobin (Hb) have been recognized. Although many do not result in clinical or hematologic effects, clinical symptoms that can be associated with Hb disorders include microcytosis, sickling disorders, hemolysis, erythrocytosis/polycythemia, cyanosis/hypoxia, anemia (chronic, compensated, or episodic), and increased methemoglobin or sulfhemoglobin results (M-hemoglobins). For many common Hb variants (eg, HbS, HbC, HbD and HbE, among many others), protein studies will be sufficient for definitive identification. However, some Hb conditions may be difficult to identify by protein methods alone and may require molecular methods for confirmation. Hb disorders commonly occur as compound disorders (2 or more genetic variants) that can have complex interactions and variable phenotypes. In these situations, molecular testing may be necessary for accurate classification. It is important to note that although powerful as an adjunct for a complete and accurate diagnosis, molecular methods without protein data can give incomplete and possibly misleading information due to limitations of the methods. Accurate classification of hemoglobin disorders and interpretation of genetic data requires the incorporation of protein analysis results. This profile is well-suited for the classification of hemoglobin disorders. Mayo Clinic Laboratories receives specimens from a wide geographic area and nearly one-half of all specimens tested exhibit abnormalities. The most common abnormality is an increase in HbA2 to about 4% to 8%, which indicates beta-thalassemia minor when present in the correct clinical context. A wide variety of other hemoglobinopathies are also frequently encountered. Ranked in order of relative frequency, these are: Hb S (sickle cell disease and trait), C, E, Lepore, G-Philadelphia, HbH disease, D-Los Angeles, Koln, Constant Spring, O-Arab. Other variants associated with hemolysis, erythrocytosis/polycythemia, microcytosis, cyanosis/hypoxia are routinely identified; however, some will not be detected by routine screening methods and require communication of clinical findings to prompt indicated reflex testing options. Alpha-thalassemia genetic variants are very common in the United States, occurring in approximately 30% of African Americans and accounting for the frequent occurrence of microcytosis in persons of this ethnic group. Some alpha-thalassemia conditions (eg, HbH, Barts) can be identified in the hemoglobin electrophoresis protocol, although Hb Constant Spring may or may not be evident by protein methods alone dependent upon the percentage present. It is important to note, alpha thalassemias that are from only 1 or 2 alpha-globin gene deletions are not recognized by protein studies alone and alpha-gene deletion and duplication testing is required.

Useful For: Diagnosis and classification of hemoglobin disorders, including thalassemias and hemoglobin variants

Interpretation: The hemoglobin fractions, including hemoglobin variants are identified and quantitated. An interpretive report that summarizes all testing, including the significance of the findings, is issued.

Reference Values:

Hemoglobin Electrophoresis Interpretation
Definitive results and an interpretative report will be provided.

Hemoglobin Variant, A2 and F Quantitation
HEMOGLOBIN A
0-30 days: 5.9-77.2%
1-2 months: 7.9-92.4%
3-5 months: 54.7-97.1%
6-8 months: 80.0-98.0%
9-12 months: 86.2-98.0%
13-17 months: 88.8-98.0%
18-23 months: 90.4-98.0%
> or =24 months: 95.8-98.0%

HEMOGLOBIN A2
0-30 days: 0.0-2.1%
1-2 months: 0.0-2.6%
3-5 months: 1.3-3.1%
> or =6 months: 2.0-3.3%

HEMOGLOBIN F
0-30 days: 22.8-92.0%
1-2 months: 7.6-89.8%
3-5 months: 1.6-42.2%
6-8 months: 0.0-16.7%
9-12 months: 0.0-10.5%
13-17 months: 0.0-7.9%
18-23 months: 0.0-6.3%
> or =24 months: 0.0-0.9%

VARIANT 1
0.0

VARIANT 2
0.0

VARIANT 3
0.0

Clinical References: 1. Hoyer JD, Hoffman DR. The thalassemia and hemoglobinopathy syndromes. In: McClatchey KD, Amin HM, Curry JL, eds. Clinical Laboratory Medicine. 2nd ed. Lippincott Williams and Wilkins; 2002:866-895 2. Oliveira JL. Diagnostic strategies in hemoglobinopathy testing, the role of a reference laboratory in the USA. Thalassemia Reports. 2018;8(1):7476. doi:10.4081/thal.2018.7476 3. Brancaleonai V, Di Pierro E, Motta I, Cappellini MD. Laboratory diagnosis of thalassemia. Int J Lab Hematol. 2016;38 Suppl 1:32-40. doi:10.1111/ijlh.12527 4. Hartveld CI. State of the art and new developments in molecular diagnostics for hemoglobinopathies in multiethnic societies. Int J Lab Haematol. 2014;36(1):1-12. doi:10.1111/ijlh.12108 5. Riou J, Szuberski J, Godart C, et al. Precision of CAPILLARYS 2 for the detection of hemoglobin variants based on their migration positions. Am J Clin Pathol. 2018;149(2):172-180. doi:10.1093/ajcp/aqx148

HBELI
608088

Hemoglobin Electrophoresis Interpretation

Clinical Information: A large number of variants of hemoglobin (Hb) have been recognized. Although many do not result in clinical or hematologic effects, clinical symptoms that can be associated with Hb disorders include microcytosis, sickling disorders, hemolysis, erythrocytosis/polycythemia, cyanosis/hypoxia, anemia (chronic, compensated, or episodic), and increased methemoglobin or sulfhemoglobin results (M-Hb). For many common Hb variants (eg, Hb S, Hb C, Hb D, and Hb E, among many others), protein studies will be sufficient for definitive identification. However, some Hb conditions may be difficult to identify by protein methods alone and may require molecular methods for confirmation. Hb disorders commonly occur as compound disorders (2 or more genetic variants) that can have complex interactions and variable phenotypes. In these situations, molecular testing may be necessary for accurate classification. It is important to note that although powerful as an adjunct for a complete and accurate diagnosis, molecular methods without protein data can give incomplete and possibly misleading information due to limitations of the methods. Accurate classification of Hb disorders and interpretation of genetic data requires the incorporation of protein analysis results. This profile is well-suited for the classification of Hb disorders. Mayo Clinic Laboratories receives specimens from a wide geographic area and nearly one-half of all specimens tested exhibit abnormalities. The most common abnormality is an increase in Hb A2 to about 4% to 8%, which indicates beta-thalassemia minor when present in the correct clinical context. A wide variety of other hemoglobinopathies are also frequently encountered. Ranked in order of relative frequency, these are: Hb S (sickle cell disease and trait), C, E, Lepore, G-Philadelphia, Hb H disease, D-Los Angeles, Koln, Constant Spring, O-Arab. Other variants associated with hemolysis, erythrocytosis/polycythemia, microcytosis, cyanosis/hypoxia are routinely identified; however, some will not be detected by routine screening methods and require communication of clinical findings to prompt indicated reflex testing options. Alpha-thalassemia genetic variants are very common in the United States, occurring in approximately 30% of African Americans and accounting for the frequent occurrence of microcytosis in persons of this ethnic group. Some alpha-thalassemia conditions (eg, Hb H, Barts) can be identified in the Hb electrophoresis protocol, although Hb Constant Spring may or may not be evident by protein methods alone dependent upon the percentage present. It is important to note, alpha-thalassemias that are from only 1 or 2 alpha-globin gene deletions are not recognized by protein studies alone and alpha gene deletion and duplication testing is required.

Useful For: Interpretation for the results of hemoglobin electrophoresis Diagnosis and classification of hemoglobin disorders, including thalassemias and hemoglobin variants

Interpretation: Abnormal hemoglobin variants are identified. An interpretive report will be provided.

Reference Values:
Only orderable as part of a profile. For more information see HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood.

Definitive results and an interpretative report will be provided.

Clinical References: 1. Hoyer JD, Hoffman DR. The Thalassemia and hemoglobinopathy syndromes. In: McClatchey KD, Amin HM, Curry JL, eds. Clinical Laboratory Medicine. 2nd ed. Lippincott Williams and Wilkins; 2002:866-895 2. Oliveira JL. Diagnostic strategies in hemoglobinopathy testing, the role of a reference laboratory in the USA. Thalassemia Reports. 2018;8(1). doi:10.4081/thal.2018.7476 3. Brancaleoni V, Di Pierro E, Motta I, Cappellini MD. Laboratory diagnosis of thalassemia. Int J Lab Haematol. 2016;38(suppl 1):32-40 4. Hartveld CI. State of the art and new developments in molecular diagnostics for hemoglobinopathies in multiethnic societies. Int J Lab Hematol. 2014;36(1):1-12 5. Szuberski J, Oliveira JL, Hoyer JD. A comprehensive analysis of hemoglobin variants by high-performance liquid chromatography (HPLC). Int J Lab Hematol. 2012;34(6):594-604 6. Riou J, Szuberski J, Godart C, et al. Precision of CAPILLARYS 2 for the detection of hemoglobin variants based on their migration positions. Am J Clin Pathol. 2018;149(2):172-180

HBEL0
608091

Hemoglobin Electrophoresis Summary Interpretation

Clinical Information: The evaluation of hemoglobin disorders can be very complex. This can involve abnormalities in the alpha, beta, delta, or gamma chains. Molecular testing is performed to fully evaluate complex situations. A summary interpretation that incorporates all of the testing performed is beneficial to the ordering physician.

Useful For: Incorporating and summarizing results into an overall evaluation for the HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood

Interpretation: An interpretive report will be provided that summarizes all testing as well as any pertinent clinical information.

Reference Values:
Only orderable as a reflex. For more information see HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood.

An interpretive report will be provided.

Clinical References: 1. Hoyer JD, Hoffman DR. The thalassemia and hemoglobinopathy syndromes. In: McClatchey KD, ed. Clinical Laboratory Medicine. 2nd ed. Lippincott Williams and Wilkins; 2002:866-895 2. Harteveld CL, Higgs DR. Alpha-thalassemia. Orphanet J Rare Dis. 2010;5:13 3. Thein SL. The molecular basis of beta-thalassemia. Cold Spring Harb Perspect Med. 2013;3(5):a011700 4. Crowley MA, Mollan TL, Abdulmalik OY, et al. A hemoglobin variant associated with neonatal cyanosis and anemia. N Engl J Med. 2011;364(19):1837-1843 5. Kipp BR, Roellinger SE, Lundquist PA, Highsmith WE, Dawson DB. Development and clinical implementation of a combination deletion PCR and multiplex ligation-dependent probe amplification assay for detecting deletions involving the human alpha-globin gene cluster. J Mol Diagn. 2011;13(5):549-557. doi:10.1016/j.jmoldx.2011.04.001 6. Hein MS, Oliveira JL, Swanson KC, Lundquist PA. Large deletions involving the beta globin gene complex: genotype-phenotype correlation of 119 cases. Blood. 2015;126(23):3374. doi:10.1182/blood.V126.23.3374.3374

HPFH
8270

Hemoglobin F Distribution, Blood

Clinical Information: More than 75% of the hemoglobin of the newborn is hemoglobin (Hb) F; it diminishes over a period of several months to adult levels, reducing to less than 2% by 1 year of age and less than 1% by 2 years of age. Hb F may constitute 90% of the total Hb in patients with beta-thalassemia major or other combinations of beta thalassemia and fetal Hb (hereditary persistence of fetal hemoglobin [HPFH]) variants. Hb F is often mildly to moderately elevated in sickle cell disease, aplastic anemia, acute leukemia, and myeloproliferative disorders such as juvenile myelomonocytic leukemia, hereditary spherocytosis, and alpha-thalassemia minor. It is commonly increased in hemoglobinopathies associated with hemolysis. Hb F increases to as high as 10% during normal pregnancy. Hb F is also increased due to medications such as hydroxyurea, decitabine, and lenalidomide. Elevation in Hb F has a been cited as a discriminator between Diamond-Blackfan congenital pure red cell aplasia (elevated) and transient erythroblastopenia of childhood (normal), but whether this simply reflects the chronicity of anemia inherent to the former condition rather than a specific finding is unclear. In the common (large deletional) form of the genetic trait HPFH, all of the erythrocytes contain Hb F. When tested by flow cytometry using specificity for Hb F, these HPFH cases display a homocellular distribution pattern of Hb F within the red blood cell population. Other causes of increased Hb F, including delta beta thalassemia, hydroxyurea, and some nondeletional HPFH variants, typically display a heterocellular distribution of Hb F within the erythrocytes, reflecting disparate populations of F cells and cells lacking Hb F. Quantification of Hb F percentage should be determined prior to flow cytometry of Hb F red blood cell distribution to establish

the appropriateness of this test. The flow cytometry analysis of elevated Hb F levels is useful when Hb F percentage is 15% to 35% and the clinical differential diagnosis includes large deletional HPFH. Hb F percentages below 15% are likely not due to large deletional HPFH, and the causes of Hb F percentages above 35% are better confirmed by molecular and family studies.

Useful For: Distinguishing large deletional hereditary persistence of fetal hemoglobin from other conditions with increased percentage of fetal hemoglobin (Hb F) Determining the distribution of Hb F within red blood cells

Interpretation: Homocellular distribution of fetal hemoglobin (Hb) is found in large deletional hereditary persistence of fetal Hb. Heterocellular distribution is found in delta beta thalassemia, medication induced, and other causes of increased Hb F. An equivocal result indicates the pattern is not typical for either a homocellular or heterocellular distribution.

Reference Values:
Only orderable as a reflex. For more information see:
-HAEV1 / Hemolytic Anemia Evaluation, Blood
-HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood
-MEV1 / Methemoglobinemia Evaluation, Blood
-REVE2 / Erythrocytosis Evaluation, Blood
-THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood

Reported as: Heterocellular, Homocellular, or Equivocal

Clinical References: 1. Kleihauer E, Braun H, Betke K. Demonstration von fetalem Hamoglobin in den Erythrocyten eines Blutaustrichs. Klin Wschr. 1957;35(12):637-638 2. Shepard MK, Weatherall DJ, Conley CC. Semi-quantitative estimation of the distribution of fetal hemoglobin in red cell populations. Bull Johns Hopkins Hospital. 1962;110:293-310 3. Davis BH, Olsen S, Bigelow NC, Chen JC. Detection of fetal red cells in fetomaternal hemorrhage using a fetal hemoglobin monoclonal antibody by flow cytometry. Transfusion. 1998;38(8):749-756 4. Hoyer JD, Penz CS, Fairbanks VF, et al. Flow cytometric measurement of hemoglobin F in RBCs: diagnostic usefulness in the distinction of hereditary persistence of fetal hemoglobin (HPFH) and hemoglobin S-hPFH from other conditions with elevated levels of hemoglobin F. Am J Clin Pathol. 2002;117(6):857-863 5. Stephens AD, Angastiniotis M, Baysal E, et al. International Council for The Standardisation of Haematology (ICSH). ICSH recommendations for the measurement of haemoglobin F. Int J Lab Hematol. 2012;34(1):14-20

UNHB
9095

Hemoglobin Stability, Blood

Clinical Information: Unstable hemoglobin disease is rare and may be caused by any one of a large number of hemoglobin variants. They are inherited as autosomal dominant traits. The severity of the disease varies according to the hemoglobin variant; there may be no clinical symptoms, or the disease may produce a mild, moderate, or severe hemolytic anemia. The stained peripheral blood smear shows anisocytosis, poikilocytosis, basophilic stippling, polychromasia and, sometimes, hypochromia. The reticulocyte count may be increased. Splenomegaly and Heinz bodies may also be present.

Useful For: Work-up of congenital hemolytic anemias

Interpretation: An abnormal or unstable result is indicative of a hemoglobin variant present. Other confirmatory tests should be performed to identify the hemoglobinopathy (HBEL1 / Hemoglobin Electrophoresis Cascade, Blood).

Reference Values:

Only orderable as part of a profile or as a reflex. For more information see:
-HAEV1 / Hemolytic Anemia Evaluation, Blood
-HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood
-THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum
-REVE2 / Erythrocytosis Evaluation, Blood
-MEV1 / Methemoglobinemia Evaluation, Blood

Normal (reported as normal [stable] or abnormal [unstable])

Clinical References: 1. Hoyer JD, Hoffman DR. The thalassemia and hemoglobinopathy syndromes. In: McClatchey KD, Amin HM, Curry JL, eds. Clinical Laboratory Medicine. 2nd ed. Lippincott Williams and Wilkins; 2002:866-895 2. Benz EJ, Ebert BL. Hemoglobin variants associated with hemolytic anemia, altered oxygen affinity, and methemoglobinemias. In: Hoffman R, Benz EJ, Silberstein LE, et al. eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018:608-615

HGBCE
65039

Hemoglobin Variant, A2 and F Quantitation, Blood

Clinical Information: The treatment of red blood cell sickling disorders may involve many therapeutic modalities. Two of the most important and beneficial are treatment with hydroxyurea and chronic transfusion therapy. Hydroxyurea causes elevation of fetal hemoglobin (HbF) levels, and transfusion serves to lower the percentage of hemoglobin S (HbS). Both of these therapeutic modalities act to lessen the number and severity of sickling crises. Thus, periodic monitoring of HbF and HbS levels are needed to guide further therapy.

Useful For: Monitoring patients with sickling disorders who have received hydroxyurea or transfusion therapy This test is not intended for diagnostic purposes. This test is not useful for screening purposes.

Interpretation: Clinically, optimal levels of hemoglobin (Hb) S and fetal hemoglobin (HbF) are patient specific and depend on a number of factors including response to therapy. This test will be performed by capillary electrophoresis and any detected variant present will be reported as their zone only, including HbS. No confirmatory functional study, such as sickle solubility, will be performed as this test is designed for quantitative monitoring of previously confirmed hemoglobin fractions. Information reported: Percentages of HbA, HbA2, HbF and any detected hemoglobin variant present. Variants will be reported as zones and are not specific, even if present in Z5 (Zone S). If the identity of the variant has not been previously confirmed, diagnostic hemoglobin electrophoresis testing is necessary; see HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood.

Reference Values:
HEMOGLOBIN A
0-30 days: 5.9-77.2%
1-2 months: 7.9-92.4%
3-5 months: 54.7-97.1%
6-8 months: 80.0-98.0%
9-12 months: 86.2-98.0%
13-17 months: 88.8-98.0%
18-23 months: 90.4-98.0%
> or =24 months: 95.8-98.0%

HEMOGLOBIN A2
0-30 days: 0.0-2.1%
1-2 months: 0.0-2.6%
3-5 months: 1.3-3.1%

> or =6 months: 2.0-3.3%

HEMOGLOBIN F
0-30 days: 22.8-92.0%
1-2 months: 7.6-89.8%
3-5 months: 1.6-42.2%
6-8 months: 0.0-16.7%
9-12 months: 0.0-10.5%
13-17 months: 0.0-7.9%
18-23 months: 0.0-6.3%
> or =24 months: 0.0-0.9%

VARIANT 1
0.0

VARIANT 2
0.0

VARIANT 3
0.0

Clinical References: 1. Riou J, Szuberski J, Godart C, et al. Precision of CAPILLARYS 2 for the detection of hemoglobin variants based on their migration positions. Am J Clin Pathol. 2018;149(2):172-180 2. National Heart, Lung, and Body Institute Expert Panel: Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014. NIH Publication No. 02-2117 US Department of Health and Human Services: National Institutes of Health; 2014:1-142 3. Rosse WF, Telen M, Ware R: Transfusion Support for Patients with Sickle Cell Disease. American Association of Blood Banks; 1998 4. Ferster A, Tahriri P, Vermylen C, et al. Five years of experience with hydroxyurea in children and young adults with sickle cell disease. Blood. 2001;97:3268-3632 5. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med. 1995;332(20):1317-1322 6. Keren DF, Shalhoub R, Gulbranson R, Hedstrom D. Expression of hemoglobin variant migration by capillary electrophoresis relative to hemoglobin A2 improves precision. Am J Clin Pathol. 2012;137(4):660-664

HGB
801417

Hemoglobin, Blood

Clinical Information: Hemoglobin transports oxygen and CO2. This activity is decreased in anemia and increased in polycythemia, erythrocytosis, and dehydration. Hemoglobin measurements are used as clinical guides in the diagnosis or monitoring of many diseases.

Useful For: Screening tool to confirm a hematologic disorder Establishing or ruling out a diagnosis Detecting an unsuspected hematologic disorder Monitoring the effects of radiation or chemotherapy

Interpretation: Results outside of normal value ranges may reflect a primary disorder of the cell-producing organs or an underlying disease. Results should be interpreted in conjunction with the patient's clinical picture and appropriate additional testing performed.

Reference Values:
HEMOGLOBIN
Males:
0-14 days: 13.9-19.1 g/dL

15 days-4 weeks: 10.0-15.3 g/dL
5 weeks-7 weeks: 8.9-12.7 g/dL
8 weeks-5 months: 9.6-12.4 g/dL
6 months-23 months: 10.1-12.5 g/dL
24 months-35 months: 10.2-12.7 g/dL
3-5 years: 11.4-14.3 g/dL
6-8 years: 11.5-14.3 g/dL
9-10 years: 11.8-14.7 g/dL
11-14 years: 12.4-15.7 g/dL
15-17 years: 13.3-16.9 g/dL
Adults: 13.2-16.6 g/dL
Females:
0-14 days: 13.4-20.0 g/dL
15 days-4 weeks: 10.8-14.6 g/dL
5 weeks-7 weeks: 9.2-11.4 g/dL
8 weeks-5 months: 9.9-12.4 g/dL
6 months-35 months: 10.2-12.7 g/dL
3-5 years: 11.4-14.3 g/dL
6-8 years: 11.5-14.3 g/dL
9-10 years: 11.8-14.7 g/dL
11-17 years: 11.9-14.8 g/dL
Adults: 11.6-15.0 g/dL

Clinical References: 1. CLSI. Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory. Approved Guideline-Third Edition. CLSI document EP28-A3c. Wayne, PA. Clinical and Laboratory Standards Institute, 2008 2. Klee G: Decision rules for accelerated hematology laboratory investigation. University of Minnesota 1974; PhD thesis 3. McKenzie SB: Textbook of Hematology. Lea and Febiger, Philadelphia 1988 4. Orkin SH, Fisher DE, Ginsburg D, et al: Nathan and Oski's Hematology and Oncology of Infancy and Childhood. Edited by ST Orkin, DE Fisher, AT Look, et al. WB Saunders Co, Philadelphia, 1981 5. Adeli, K, Raizman, J, Chen, Y, et al: Complex Biological Profile of Hematologic Markers Across Pediatric, Adult, and Geriatric Ages: Establishment of Robust Pediatric and Adult Reference Intervals on the Basis of the Canadian Health Measures Survey. Clin Chem 61:8 2015 6. Soldin, J, Brugnara, C, Wong, EC: Pediatric Reference Intervals. In Pediatric References Intervals. Fifth Edition. Edited by SJ Soldin, C Brugnara, EC Wong. AACC Press. Washington DC, 2005. ISBN 1-594250-32-4

THEVI
608425

Hemoglobinopathy Interpretation

Clinical Information: This consultative study is primarily designed for the evaluation of microcytosis but also can test for the detection of almost all known hemoglobin disorders in an economical manner. Because this can include multiple tests for alpha thalassemias, beta thalassemias, delta-beta thalassemia, hereditary persistence of fetal hemoglobin (HPFH), and for all known hemoglobin (Hb) variants, an expert in these disorders can guide testing to explain the clinical question or reported complete blood count values. This evaluation is particularly useful for complete classification of compound combinations of Hb S with alpha or beta thalassemia, Hb E/beta-0 thalassemia, and many other complex alpha and beta thalassemia disorders. Since iron deficiency can mimic thalassemias, if a serum sample is received, ferritin levels are measured to evaluate this possibility. Hb disorders include those associated with thalassemias (decreased protein quantity) and Hb variants (abnormal protein production). Many are clinically harmless, while others cause symptoms including microcytosis, sickling disorders, hemolysis, erythrocytosis, cyanosis/hypoxia, long-standing or familial anemia, compensated or episodic anemia, and increased methemoglobin or sulfhemoglobin results. Hb disorders can show patterns of either autosomal recessive or autosomal dominant inheritance. The thalassemias are a group of disorders of Hb synthesis. Normal adult Hb consists of 2 alpha globin chains (encoded by 2 pairs of alpha globin genes,

each pair located on chromosome 16), and 2 beta globin chains (encoded by 2 beta globin genes, each located on chromosome 11). Thalassemia syndromes result from an underproduction of 1 or 2 types of globin chains and are characterized by the type (alpha, beta, delta, gamma), magnitude of underproduction (number of defective genes), and the severity of clinical symptoms (minor, intermedia, major). The severity of the clinical and hematologic effects is directly related to the imbalance of alpha-like to beta-like chains. The most common form of thalassemia is alpha thalassemia. Alpha thalassemia usually involves deletion of entire alpha genes and varies in severity depending on the number of alpha chains deleted (or rendered nonfunctional). Alpha thalassemia trait usually results from the deletion of 2 alpha genes. The most common form of Hb H disease results from dysfunction of 3 alpha chains and shows a variable phenotype, with most cases showing moderate anemia. The deletion of all 4 alpha genes (Barts hydrops fetalis) is incompatible with life without significant medical intervention. Non-deletion alpha thalassemia genetic variants can also result in either thalassemia trait or Hb H disease and are less common than deletion forms. Conversely most beta thalassemia genetic variants are due to single nucleotide substitutions that can occur anywhere in the beta globin gene. Large deletions of the beta globin gene complex can result in elevations in Hb F, such as HPFH or delta-beta thalassemia. While the presence of a single beta gene variant (beta thalassemia trait) results primarily in red blood cell microcytosis, cases with two beta gene abnormalities show a wide range in clinical severity, and many cases require molecular testing to understand the phenotype.

Useful For: Interpretation of results for the evaluation of thalassemias and hemoglobinopathies Evaluation of microcytosis Extensive and economical diagnosis and classification of hemoglobinopathies or thalassemia including complex disorders Diagnosis of hereditary persistence of hemoglobin

Interpretation: A hematopathologist expert in these disorders evaluates the case and an interpretive report is issued.

Reference Values:
Only orderable as part of a profile. For more information see THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum.

Definitive results and an interpretive report will be provided.

Clinical References: 1. Hoyer JD, Hoffman DR. The thalassemia and hemoglobinopathy syndromes. In: McClatchey KD, Amin HM, Curry JL, eds. Clinical Laboratory Medicine. 2nd ed. Lippencott Williams and Wilkins; 2002:866-892 2. Brancaleoni V, Di Pierro E, Motta I, Cappellini MD. Laboratory diagnosis of thalassemia. Int J Lab Hematol. 2016;38 (Suppl 1):32-40 3. Hartveld C. State of the art and new developments in molecular diagnostics for hemoglobinopathies in multiethnic societies. Int J Lab Hematol. 2013;36:1-12

HAEV1
607494

Hemolytic Anemia Evaluation, Blood

Clinical Information: Hemolytic anemia (HA) is characterized by increased red blood cell (RBC) destruction and a decreased RBC life span. Patients usually have decreased hemoglobin concentration, hematocrit, and RBC count, but some can have compensated disorders, and symptoms such as reticulocytosis, pigmented gallstones, and decreased haptoglobin are factors that raise clinical suspicion. Blood smear abnormalities may include variable amounts of poikilocytosis including spherocytes, elliptocytes, schistocytes, stomatocytes, echinocytes, polychromasia, basophilic stippling, and target cells. Osmotic fragility can be increased due to the presence of spherocytes. These are all nonspecific features that can be present in both hereditary and acquired hemolytic disorders. Inherited hemolytic disorders may include RBC membrane disorders, RBC enzyme defects, or abnormalities in the hemoglobin molecule in the RBC. This panel assesses for possible causes of congenital/hereditary

causes of HA and does not evaluate for acquired causes. Therefore, the anemia should be lifelong or familial in nature. Examples of acquired HA include autoimmune HA (Coombs-positive HA, Coombs-negative autoimmune HA), cold agglutinin disease, paroxysmal nocturnal hemoglobinuria, paroxysmal cold hemoglobinuria, mechanical hemolysis (aortic stenosis or prosthetic heart valves), disseminated intravascular coagulation/thrombotic microangiopathy, and drug-induced HA. This consultation evaluates for a hereditary cause of increased RBC destruction and includes testing for RBC membrane disorders, such as hereditary spherocytosis and hereditary pyropoikilocytosis, hemoglobinopathies, and red blood cell enzyme abnormalities. This panel is of limited use in patients with a history of recent transfusion and should be ordered as remote a date from transfusion as possible in those patients who are chronically transfused.

Useful For: Evaluation of lifelong or inherited hemolytic anemias, including red blood cell membrane disorders, unstable or abnormal hemoglobin variants, and red blood cell enzyme disorders This evaluation is not suitable for acquired causes of hemolysis.

Interpretation: A hematopathologist expert in these disorders evaluates the case, appropriate tests are performed, and an interpretive report is issued.

Reference Values:

Hemoglobin Variant, A2 and F Quantitation

HEMOGLOBIN A
0-30 days: 5.9-77.2%
1-2 months: 7.9-92.4%
3-5 months: 54.7-97.1%
6-8 months: 80.0-98.0%
9-12 months: 86.2-98.0%
13-17 months: 88.8-98.0%
18-23 months: 90.4-98.0%
> or =24 months: 95.8-98.0%

HEMOGLOBIN A2
0-30 days: 0.0-2.1%
1-2 months: 0.0-2.6%
3-5 months: 1.3-3.1%
> or =6 months: 2.0-3.3%

HEMOGLOBIN F
0-30 days: 22.8-92.0%
1-2 months: 7.6-89.8%
3-5 months: 1.6-42.2%
6-8 months: 0.0-16.7%
9-12 months: 0.0-10.5%
13-17 months: 0.0-7.9%
18-23 months: 0.0-6.3%
> or =24 months: 0.0-0.9%

VARIANT 1
0.0

VARIANT 2
0.0

VARIANT 3
0.0

Hemoglobin Stability
Normal (reported as normal [stable] or abnormal [unstable])

OSMOTIC FRAGILITY
> or =12 months:
0.50 g/dL NaCl (unincubated): 3-53% hemolysis
0.60 g/dL NaCl (incubated): 14-74% hemolysis
0.65 g/dL NaCl (incubated): 4-40% hemolysis
0.75 g/dL NaCl (incubated): 1-11% hemolysis
NaCl = sodium chloride

Reference values have not been established for patients who are younger than 12 months of age.

BAND 3 FLUORESCENCE STAINING RED BLOOD CELLS(RBC)
> or =12 months: Normal (reported as normal, decreased, or equivocal)

Reference values have not been established for patients who are younger than 12 months of age.

Glucose 6 Phosphate Dehydrogenase Enzyme Activity
> or =12 months of age: 8.0-11.9 U/g Hb
Reference values have not been established for patients who are younger than 12 months of age.

Pyruvate Kinase Enzyme Activity
> or =12 months of age: 5.5-12.4 U/g Hb
Reference values have not been established for patients who are younger than 12 months of age.

Glucose Phosphate Isomerase Enzyme Activity
> or =12 months of age: 40.0-58.0 U/g Hb
Reference values have not been established for patients who are younger than 12 months of age.

Hexokinase Enzyme Activity
> or =12 months: 0.7-1.7 U/g Hb
Reference values have not been established for patients who are younger than 12 months of age.

Adenylate Kinase Enzyme Activity
> or =12 months: 195-276 U/g Hb
Reference values have not been established for patients who are younger than 12 months of age.

Phosphofructokinase Enzyme Activity
> or =12 months of age: 5.8-10.9 U/g Hb
Reference values have not been established for patients who are younger than 12 months of age.

Phosphoglycerate Kinase Enzyme Activity
> or =12 months: 142-232 U/g Hb
Reference values have not been established for patients who are younger than 12 months of age.

Triosephosphate Isomerase Enzyme Activity
> or =12 months of age: 1033-1363 U/g Hb
Reference values have not been established for patients who are younger than 12 months of age.

Glutathione
> or =12 months: 46.9-90.1 mg/dL RBC
Reference values have not been established for patients who are younger than 12 months of age.

Pyrimidine 5' Nucleotidase
Normal

Clinical References: 1. Steiner LA, Gallagher PG. Erythrocyte disorders in the perinatal period. Semin Perinatol. 2007;31(4):254-261 2. Beutler E: Glucose-6-phosphate dehydrogenase deficiency and other enzyme abnormalities. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, eds. Hematology. 5th ed. McGraw-Hill Book Company; 1995:564-581 3. Hoyer JD, Hoffman DR: The thalassemia and hemoglobinopathy syndromes. In: McClatchey KD, Amin HM, Curry JL, eds. Clinical Laboratory Medicine. 2nd ed. Lippincott, Williams and Wilkins; 2002:866-895 4. King MJ, Garcon L, Hoyer JD, et al. International Council for Standardization in Haematology. ICSH guidelines for the laboratory diagnosis of nonimmune hereditary red cell membrane disorders. Int J Lab Hematol. 2015;37(3):304-325 5. Lux SE: Anatomy of the red cell membrane skeleton: unanswered questions. Blood. 2016;127(2):187-199. doi:10.1182/blood-2014-12-512772 6. Gallagher PG. Abnormalities of the erythrocyte membrane. Pediatr Clin North Am. 2013;60(6):1349-1362 7. Bianchi P, Fermo E, Vercellati C, et al. Diagnostic power of laboratory tests for hereditary spherocytosis: a comparison study in 150 patients grouped according to molecular and clinical characteristics. Haematologica. 201297(4):516-523 8. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008;371:64-74 9. Glader B: Hereditary hemolytic anemias due to red blood cell enzyme disorders. In: Greer JP, Arber DA, Glader B, et al, eds. Wintrobe's Clinical Hematology. 13th ed. Wolters Kluwer/Lippincott, Williams and Wilkins; 2014:728 10. Gallagher PG. Diagnosis and management of rare congenital nonimmune hemolytic disease. Hematology Am Soc Hematol Educ Program. 2015;2015:392-399 11. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia - pathophysiology, clinical aspects, and laboratory diagnosis. Int J Lab Hematol. 2014;36(3):388-397

HAEVI
608427

Hemolytic Anemia Interpretation

Clinical Information: Hemolytic anemia (HA) is characterized by increased red cell destruction and a decreased red cell life span. Patients usually have decreased hemoglobin concentration, hematocrit, and red blood cell count, but some can have compensated disorders, and symptoms such as reticulocytosis, pigmented gallstones, and decreased haptoglobin are factors that raise clinical suspicion. Blood smear abnormalities may include variable amounts of poikilocytosis including spherocytes, elliptocytes, schistocytes, stomatocytes, echinocytes, polychromasia, basophilic stippling, and target cells. Osmotic fragility can be increased due to the presence of spherocytes. These are all nonspecific features that can be present in both hereditary and acquired hemolytic disorders. Inherited hemolytic disorders may include red cell membrane disorders, red cell enzyme defects, or abnormalities in the hemoglobin molecule in the red cell. This panel assesses for possible causes of congenital/hereditary causes of hemolytic anemia and does not evaluate for acquired causes. Therefore, the anemia should be lifelong or familial in nature. Examples of acquired HA (which should be excluded prior to ordering this panel) include: autoimmune HA (Coombs-positive HA, Coombs-negative autoimmune HA), cold agglutinin disease, paroxysmal nocturnal hemoglobinuria, paroxysmal cold hemoglobinuria, mechanical hemolysis (aortic stenosis or prosthetic heart valves), disseminated intravascular coagulation/thrombotic microangiopathy, and drug-induced HA. This consultation evaluates for a hereditary cause of increased red cell destruction and includes testing for red cell membrane disorders, such as hereditary spherocytosis and hereditary pyropoikilocytosis, hemoglobinopathies, and red cell enzyme abnormalities. This panel is of limited use in patients with a history of recent transfusion and should be ordered as remote a date from transfusion as possible in those patients who are chronically transfused.

Useful For: Interpretation of the results for the evaluation of hemolytic anemia Evaluation of lifelong or inherited hemolytic anemias, including red cell membrane disorders, unstable or abnormal hemoglobin variants, and red cell enzyme disorders

Interpretation: A hematopathologist expert in these disorders evaluates the case, appropriate tests are performed, and an interpretive report is issued.

Reference Values:
Only orderable as part of a profile. For more information see HAEV1 / Hemolytic Anemia Evaluation, Blood.

Definitive results and an interpretive report will be provided.

Clinical References: 1. Steiner LA, Gallagher PG. Erythrocyte disorders in the perinatal period. Semin Perinatol. 2007;31(4):254-261. doi:10.1053/j.semperi.2007.05.003 2. Beutler E. Glucose-6-phosphate dehydrogenase deficiency and other enzyme abnormalities. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, eds. Hematology. 5th ed. McGraw-Hill Book Company; 1995: 564-581 3. Hoyer JD, Hoffman DR. The thalassemia and hemoglobinopathy syndromes. In: McClatchey KD, Amin HM, Curry JL, eds. Clinical Laboratory Medicine. 2nd ed. Lippincott, Williams and Wilkins; 2002: 866-895 4. King MJ, Garcon L, Hoyer JD, et al. International Council for Standardization in Haematology. ICSH guidelines for the laboratory diagnosis of nonimmune hereditary red cell membrane disorders. Int J Lab Hematol. 2015;37(3):304-325. doi:10.1111/ijlh.12335 5. Lux SE. Anatomy of the red cell membrane skeleton: unanswered questions. Blood. 2016;127(2):187-199 doi:10.1182/blood-2014-12-512772 6. Gallagher PG. Abnormalities of the erythrocyte membrane. Pediatr Clin North Am. 2013;60(6):1349-1362. doi:10.1016/j.pcl.2013.09.001 7. Bianchi P, Fermo E, Vercellati C, et al. Diagnostic power of laboratory tests for hereditary spherocytosis: a comparison study in 150 patients grouped according to molecular and clinical characteristics. Haematologica. 2012;97(4):516-523. doi:10.3324/haematol.2011.052845 8. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008;371(9606):64-74 9. Glader B. Hereditary hemolytic anemias due to red blood cell enzyme disorders. In: Greer JP, Arber DA, Glader B, et al, eds. Wintrobe's Clinical Hematology. 13th ed. Wolters Kluwer/Lippincott, Williams and Wilkins; 2014:728 10. Gallagher PG. Diagnosis and management of rare congenital nonimmune hemolytic disease. Hematology Am Soc Hematol Educ Program. 2015; 392-399. doi:10.1182/asheducation-2015.1.39211 11. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia- pathophysiology, clinical aspects, and laboratory diagnosis. Int J Lab Hematol. 2014;36(3):388-397. doi:10.1111/ijlh.12223

HAEV0 608090 Hemolytic Anemia Summary Interpretation

Clinical Information: The evaluation of patients with hemolytic anemia can be very complex and involves incorporation of not only testing, but integration of clinical and peripheral blood findings. Nonimmune hemolytic anemia can be due to many causes, including abnormalities in the hemoglobin molecule, red blood cell (RBC) membrane/cytoskeleton, or RBC enzyme cascade. If the evaluation of nonimmune hemolytic anemia utilizes the reflex molecular tests, a summary interpretation will be added to summarize the genetic, protein, peripheral blood, and clinical findings (if provided) will be added. This is beneficial to the ordering provider.

Useful For: Incorporating and summarizing subsequent results into an overall interpretation for the HAEV1 / Hemolytic Anemia Evaluation, Blood

Interpretation: An interpretive report will be provided that summarizes all testing as well as any pertinent clinical information.

Reference Values:
Only orderable as a reflex. For more information see HAEV1 / Hemolytic Anemia Evaluation, Blood.

An interpretation report will be provided.

Clinical References: 1. Steiner LA, Gallagher PG. Erythrocyte disorders in the perinatal period. Semin Perinatol. 2007;31(4):254-261 2. Beutler E. Glucose-6-phosphate dehydrogenase deficiency and other enzyme abnormalities. In: Beutler E, Lichtman MA, Collar BS, Kipps TJ, eds. Hematology. 5th ed. McGraw-Hill Book Company; 1995:564-581 3. Hoyer JD, Hoffman DR. The thalassemia and hemoglobinopathy syndromes. In: McClatchey KD, ed. Clinical Laboratory Medicine. 2nd ed. Lippincott, Williams and Wilkin; 2002:866-895 4. King MJ, Garcon L, Hoyer JD, et al. International Council for Standardization in Haematology: ICSH guidelines for the laboratory diagnosis of nonimmune hereditary red cell membrane disorders. Int J Lab Hematol. 2015;37(3):304-325 5. Lux SE. Anatomy of the red cell membrane skeleton: unanswered questions. Blood. 2016;127(2):187-199 doi:10.1182/blood-2014-12-512772 6. Gallagher PG. Abnormalities of the erythrocyte membrane. Pediatr Clin North Am. 2013;60(6):1349-1362 7. Bianchi P, Fermo E, Vercellati C, et al. Diagnostic power of laboratory tests for hereditary spherocytosis: a comparison study in 150 patients grouped according to molecular and clinical characteristics. Haematologica. 2012;97(4):516-523 8. Glader B. Hereditary hemolytic anemias due to red blood cell enzyme disorders. In: Greer JP, Arber DA, Glader B, et al, eds. Wintrobe's Clinical Hematology. 13th ed. Wolters Kluwer/Lippincott, Williams and Wilkins; 2014:728 9. Kipp BR, Roellinger SE, Lundquist PA, Highsmith WE, Dawson DB. Development and clinical implementation of a combination deletion PCR and multiplex ligation-dependent probe amplification assay for detecting deletions involving the human alpha-globin gene cluster. J Mol Diagn. 2011;13(5):549-557 doi:10.1016/j.jmoldx.2011.04.001 10. Harteveld CL, Higgs DR. Alpha-thalassemia. Orphanet J Rare Dis. 2010;5:13 11. Thein SL. The molecular basis of beta-thalassemia. Cold Spring Harb Persepct Med. 2013;1;3(5):a011700 12. Hein MS, Oliveira JL, Swanson KC, et al. Large deletions involving the beta globin gene complex: genotype-phenotype correlation of 119 cases. Blood. 2015;126:3374 13. Gallagher PG. Diagnosis and management of rare congenital nonimmune hemolytic disease. Hematology Am Soc Hematol Educ Program. 2015;2015:392-399 14. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia - pathophysiology, clinical aspects, and laboratory diagnosis. Int J Lab Hematol. 2014;36(3):388-397

F8INP 66206 Hemophilia A F8 Gene, Intron 1 and 22 Inversion Mutation Analysis, Prenatal

Clinical Information: Hemophilia A (HA) is due to a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5000 male individuals. Male patients are typically affected with bleeding symptoms, whereas female carriers generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of female carriers have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels of below 1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In male patients with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a variant in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 and 22 inversion variants account for approximately 50% of variants associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. It is recommended that the F8 variant be confirmed in the affected male patient or obligate female carrier prior to testing at-risk individuals. Affected male patients are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate female carriers are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial variant. Of note, not all women with an affected son are germline carriers of a F8 variant, as de novo variants in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 variant. Importantly, there is a small risk for recurrence

even when the familial F8 variant is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

Useful For: Prenatal testing for hemophilia A when a variant has not been identified in the family

Interpretation: The interpretive report will include assay information, background information, and conclusions based on the test results.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Antonarakis SE, Rossiter JP, Young M, et al: Factor VIII gene inversions in severe hemophilia A: results of an international consortium study. Blood. 1995 Sep 15;86(6):2206-2212 2. Rossiter JP, Young M, Kimberland ML, et al: Factor VIII gene inversions causing severe hemophilia A originate almost exclusively in male germ cells. Hum Mol Genet. 1994 Jul;3(7):1035-1039 3. Castaldo G, D'Argenio V, Nardiello P, et al: Haemophilia A: molecular insights. Clin Chem Lab Med. 2007;45(4):450-461 4. Oldenburg J, Rost S, El-Maarri O, et al: De novo factor VIII gene intron 22 inversion in a female carrier presents as a somatic mosaicism. Blood. 2000 Oct 15;96(8):2905-2906 5. Johnsen JM, Fletcher SN, Huston H, et al: Novel approach to genetic analysis and results in 3000 hemophilia patients enrolled in the My Life, Our Future initiative. Blood Adv. 2017 May 18;1(13):824-834 doi:10.1182/bloodadvances.2016002923 6. Pruthi RK: Hemophilia: a practical approach to genetic testing. Mayo Clin Proc. 2005 Nov;80(11):1485-1499

F8INV
66205

Hemophilia A F8 Gene, Intron 1 and 22 Inversion Mutation Analysis, Whole Blood

Clinical Information: Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5000 male individuals. Male patients are typically affected with bleeding symptoms, whereas female carriers generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of female carriers have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels below 1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In male patients with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a variant in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 and 22 inversion variants account for approximately 50% of variants associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. It is recommended that the F8 variant be confirmed in the affected male patient or obligate female carrier prior to testing at-risk individuals. Affected male patients are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate female carriers are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial variant. Of note, not all women with an affected son are germline carriers of a F8 variant, as de novo variants in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 variant. Importantly, there is a small risk for recurrence even when the familial F8 variant is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

Useful For: First-tier molecular testing for male patients affected with severe hemophilia A when a variant has not been identified in the family Determining hemophilia A carrier status for at-risk female patients, ie, individuals with a family history of severe hemophilia A

Interpretation: The interpretive report will include assay information, background information, and conclusions based on the test results.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Antonarakis SE, Rossiter JP, Young M, et al: Factor VIII gene inversions in severe hemophilia A: results of an international consortium study. Blood 1995 Sep;86(6):2206-2212 2. Rossiter JP, Young M, Kimberland ML, et al: Factor VIII gene inversions causing severe hemophilia A originate almost exclusively in male germ cells. Hum Mol Genet 1994 Jul;3(7):1035-1039 3. Castaldo G, D'Argenio V, Nardiello P, et al: Haemophilia A: molecular insights. Clin Chem Lab Med 2007;45(4):450-461 4. Johnsen JM, Fletcher SN, Huston H, et al: Novel approach to genetic analysis and results in 3000 hemophilia patients enrolled in the My Life, Our Future initiative. Blood Adv 2017 May;1(13):824-834. doi: 10.1182/bloodadvances.2016002923 5. Pruthi RK: Hemophilia: A practical approach to genetic testing. Mayo Clin Proc 2005 Nov;80(11):1485-1499

F81P
88806

Hemophilia A F8 Gene, Intron 1 Inversion Known Mutation Analysis, Prenatal

Clinical Information: Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5000 male individuals. Male patients are typically affected with bleeding symptoms, whereas female carriers generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of female carriers have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels below 1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In male patients with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a variant in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 inversion variant accounts for approximately 5% of variants associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. Intron 1 inversion known variant analysis on a prenatal specimen can only be performed when there is a known intron 1 inversion in the family. It is recommended that the F8 variant be confirmed in the affected male patient or obligate female carrier prior to testing at-risk individuals. Affected male patients are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate female carriers are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial variant. Of note, not all women with an affected son are germline carriers of a F8 variant, as de novo variants in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 variant. Importantly, there is a small risk for recurrence even when the familial F8 variant is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

Useful For: Prenatal testing for hemophilia A when a F8 intron 1 inversion has been identified in a family member

Interpretation: The interpretive report will include assay information, background information, and conclusions based on the test results.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Antonarakis SE, Rossiter JP, Young M, et al: Factor VIII gene inversions in severe hemophilia A: results of an international consortium study. Blood. 1995 Sep;86(6):2206-2212 2. Rossiter JP, Young M, Kimberland ML, et al: Factor VIII gene inversions causing severe hemophilia A originate almost exclusively in male germ cells. Hum Mol Genet. 1994 Jul;3(7):1035-1039 3. Castaldo G, D'Argenio V, Nardiello P, et al: Haemophilia A: molecular insights. Clin Chem Lab Med 2007;45(4):450-461 4. Johnsen JM, Fletcher SN, Huston H, et al: Novel approach to genetic analysis and results in 3000 hemophilia patients enrolled in the My Life, Our Future initiative. Blood Adv. 2017 May;1(13):824-834. doi: 10.1182/bloodadvances.2016002923 5. Pruthi RK: Hemophilia: a practical approach to genetic testing. Mayo Clin Proc. 2005 Nov;80(11):1485-1499

F81B 60555 Hemophilia A F8 Gene, Intron 1 Inversion Known Mutation, Whole Blood

Clinical Information: Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5000 male individuals. Male patients are typically affected with bleeding symptoms, whereas female carriers generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of female carriers have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels below 1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In male patients with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a variant in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 inversion variant accounts for approximately 5% of variants associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. Intron 1 inversion known variant analysis is only recommended for individuals when an intron 1 inversion has already been identified in the family. If a familial mutation has not been identified in a severely affected HA patient, the F8 gene intron 1 and 22 inversion analysis (F8INV / Hemophilia A F8 Gene, Intron 1 and 22 Inversion Mutation Analysis, Whole Blood) should be ordered. If the intron 1 inversion analysis is negative, the tested individual has not inherited the familial variant. It is recommended that the F8 variant be confirmed in the affected male patient or obligate female carrier prior to testing at-risk individuals. Affected male patients are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate female carriers are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial variant. Of note, not all women with an affected son are germline carriers of a F8 variant, as de novo variants in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 variant. Importantly, there is a small risk for recurrence even when the familial F8 variant is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

Useful For: First-tier molecular testing for male patients affected with severe hemophilia A, when a familial intron 1 inversion has been previously identified Determining hemophilia A carrier status for at-risk female patients, ie, individuals with a family history of severe hemophilia A due to F8 intron 1 inversion

Interpretation: The interpretive report will include assay information, background information, and conclusions based on the test results.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Antonarakis SE, Rossiter JP, Young M, et al: Factor VIII gene inversions in severe hemophilia A: results of an international consortium study. Blood. 1995 Sep;86(6):2206-2212 2. Rossiter JP, Young M, Kimberland ML, et al: Factor VIII gene inversions causing severe hemophilia A originate almost exclusively in male germ cells. Hum Mol Genet. 1994 Jul;3(7):1035-1039 3. Castaldo G, D'Argenio V, Nardiello P, et al: Haemophilia A: molecular insights. Clin Chem Lab Med. 2007;45(4):450-461 4. Johnsen JM, Fletcher SN, Huston H, et al: Novel approach to genetic analysis and results in 3000 hemophilia patients enrolled in the My Life, Our Future initiative. Blood Adv. 2017 May;1(13):824-834. doi: 10.1182/bloodadvances.2016002923 5. Pruthi RK: Hemophilia: a practical approach to genetic testing. Mayo Clin Proc. 2005 Nov;80(11):1485-1499

F822B
60554

Hemophilia A F8 Gene, Intron 22 Inversion Known Mutation, Whole Blood

Clinical Information: Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5000 male individuals. Male patients are typically affected with bleeding symptoms, whereas female carriers generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of female carriers have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels below 1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In male patients with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a variant in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 22 inversion variants account for approximately 45% of variants associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. Intron 22 inversion known variant analysis is only recommended for individuals when an intron 22 inversion has already been identified in the family. If a familial mutation has not been identified in a severely affected HA patient, the F8 gene intron 1 and 22 inversion analysis (F8INV / Hemophilia A F8 Gene, Intron 1 and 22 Inversion Mutation Analysis, Whole Blood) should be ordered. If the intron 22 inversion analysis is negative, the tested individual has not inherited the familial mutation. It is recommended that the F8 variant be confirmed in the affected male patient or obligate female carrier prior to testing at-risk individuals. Affected male patients are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate female carriers are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial variant. Of note, not all women with an affected son are germline carriers of a F8 variant, as de novo variants in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 variant. Importantly, there is a small risk for recurrence even when the familial F8 variant is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

Useful For: First-tier molecular testing for male patients affected with severe hemophilia A, when a familial intron 22 inversion has been previously identified Determining hemophilia A carrier status for at-risk female patients, ie, individuals with a family history of severe hemophilia A due to F8 intron 22 inversion

Interpretation: The interpretive report will include assay information, background information, and conclusions based on the test results.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Antonarakis SE, Rossiter JP, Young M, et al: Factor VIII gene inversions in

severe hemophilia A: results of an international consortium study. Blood. 1995 Sep;86(6):2206-2212 2. Rossiter JP, Young M, Kimberland ML, et al: Factor VIII gene inversions causing severe hemophilia A originate almost exclusively in male germ cells. Hum Mol Genet. 1994 Jul;3(7):1035-1039 3. Castaldo G, D'Argenio V, Nardiello P, et al: Haemophilia A: molecular insights. Clin Chem Lab Med. 2007;45(4):450-461 4. Johnsen JM, Fletcher SN, Huston H, et al: Novel approach to genetic analysis and results in 3000 hemophilia patients enrolled in the My Life, Our Future initiative. Blood Adv. 2017 May;1(13):824-834. doi:10.1182/bloodadvances.2016002923 5. Pruthi RK: Hemophilia: A practical approach to genetic testing. Mayo Clin Proc. 2005 Nov;80(11):1485-1499

F822P 89454 Hemophilia A F8 Gene, Intron 22 Inversion Mutation Analysis, Prenatal

Clinical Information: Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5000 male individuals. Male patients are typically affected with bleeding symptoms, whereas female carriers generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of female carriers have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels below 1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In male patients with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a variant in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 inversion variant accounts for approximately 5% of variants associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. Intron 22 inversion known variant analysis on a prenatal specimen can only be performed when there is a known intron 22 inversion in the family. It is recommended that the F8 variant be confirmed in the affected male patient or obligate female carrier prior to testing at-risk individuals. Affected male patients are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate female carriers are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial variant. Of note, not all women with an affected son are germline carriers of a F8 variant, as de novo variants in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 variant. Importantly, there is a small risk for recurrence even when the familial F8 variant is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

Useful For: Prenatal testing for hemophilia A when a F8 intron 22 inversion has been identified in a family member

Interpretation: The interpretive report will include assay information, background information, and conclusions based on the test results.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Antonarakis SE, Rossiter JP, Young M, et al: Factor VIII gene inversions in severe hemophilia A: results of an international consortium study. Blood. 1995 Sep 15;86(6):2206-2212 2. Rossiter JP, Young M, Kimberland ML, et al: Factor VIII gene inversions causing severe hemophilia A originate almost exclusively in male germ cells. Hum Mol Genet. 1994 Jul;3(7):1035-1039 3. Castaldo G, D'Argenio V, Nardiello P, et al: Haemophilia A: molecular insights. Clin Chem Lab Med. 2007;45(4):450-461 4. Oldenburg J, Rost S, El-Maarri O, et al: De novo factor

VIII gene intron 22 inversion in a female carrier presents as a somatic mosaicism. Blood. 2000 Oct 15;96(8):2905-2906 5. Pruthi RK: Hemophilia: a practical approach to genetic testing. Mayo Clin Proc. 2005 Nov;80(11):1485-1499 6. Johnsen JM, Fletcher SN, Huston H, et al: Novel approach to genetic analysis and results in 3000 hemophilia patients enrolled in the My Life, Our Future initiative. Blood Adv. 2017 May 18;1(13):824-834. doi: 10.1182/bloodadvances.2016002923

GNHMA
619103

Hemophilia A, F8 Gene, Next-Generation Sequencing, Varies

Clinical Information: Hemophilia A is a hereditary bleeding disorder associated with germline variants in the F8 gene. It is inherited in an X-linked recessive manner with variable expressivity and is estimated to affect 1 in 4000-5000 live male births.(2) Hemophilia A is characterized by a deficiency in clotting factor VIII (FVIII), an essential blood coagulation protein. Symptomatic male patients may experience mild to severe bleeding problems, including excessive bruising, prolonged epistaxis, post-operative bleeding, hemarthrosis, deep-muscle hematomas, and/or intracranial or gastrointestinal tract bleeding.(2,3) Female carriers are not typically affected but some may experience increased bleeding tendencies especially after medical procedures and surgery. Note that FVIII activity may not correlate with the severity of symptoms in females.(4-6) Several causes of acquired (nongenetic) hemophilia A should be excluded prior to genetic testing, including heparin use, disorders associated with antibodies to clotting factors such as systemic lupus erythematosus or antiphospholipid syndrome, pregnancy and the postpartum period, rheumatic disease, solid and hematologic malignancies, and use of certain drugs (eg, penicillin, sulfamides, phenytoin, interferon, fludarabine).(7) The World Federation of Hemophilia provides guidelines regarding diagnosis, management, and laboratory testing for individuals with hemophilia A.(8)

Useful For: Confirming a clinical diagnosis of hemophilia A in affected male patients with the identification of a disease-causing variant in the F8 gene Determining the disease-causing alteration within the F8 gene to delineate the underlying molecular defect in a male patient with a laboratory diagnosis of hemophilia A Identifying the causative alteration for prognostic and genetic counseling purposes Assessing hemophilia A carrier status for female patients with a family history of hemophilia A Prenatal testing for hemophilia A when a familial F8 variant has been previously identified in a family member

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(9) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Pruthi RK: Hemophilia: a practical approach to genetic testing. Mayo Clin Proc. 2005 Nov;80(11):1485-1499 2. Berntorp E, Fischer K, Hart DP, et al: Haemophilia. Nat Rev Dis Primers. 2021 Jun 24;7(1):45 3. Konkle BA, Fletcher SN: Hemophilia A. In: Adam MP, Everman DB, Mirzaa GM, et al. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated October 27, 2022. Accessed November 28, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1404/ 4. Plug I, Mauser-Bunschoten EP, Brocker-Vriends AHJT, et al: Bleeding in carriers of hemophilia. Blood. 2006 Jul 1;108(1):52-56 5. Miesbach W, Alesci S, Geisen C, Oldenburg J: Association between phenotype and genotype in carriers of haemophilia A. Haemophilia. 2011 Mar;17(2):246-251 6. Paroskie A, Gailani D, DeBaun MR, Sidonio RF Jr: A cross-sectional study of bleeding phenotype in haemophilia A carriers. Br J Haematol. 2015 Jul;170(2):223-228 7. Haider MZ: Acquired hemophilia. In: Anwer F, ed. StatPearls [Internet]. StatPearls Publishing; 2021. Updated September 26, 2022. Accessed November 28, 2022. Available at www.statpearls.com/articlelibrary/viewarticle/114240 8. Srivastava A, Santagostino E,

Dougall A, et al: WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020 Aug;26 Suppl 6:1-158 9. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

GNHMB 619117 Hemophilia B, F9 Gene, Next-Generation Sequencing, Varies

Clinical Information:

Useful For: Confirming a clinical diagnosis of hemophilia B in affected male patients with the identification of a disease-causing variant in the F9 gene Determining the disease-causing alteration within the F9 gene to delineate the underlying molecular defect in a male patient with a laboratory diagnosis of hemophilia B Identifying the causative alteration for prognostic and genetic counseling purposes Assessing hemophilia B carrier status for female patients with a family history of hemophilia B Prenatal testing for hemophilia B when a familial F9 variant has been previously identified in a family member

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(10) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Pruthi RK: Hemophilia: a practical approach to genetic testing. Mayo Clin Proc. 2005 Nov;80(11):1485-1499 2. Berntorp E, Fischer K, Hart DP: Haemophilia. Nat Rev Dis Primers. 2021 Jun 24;7(1):45 3. Konkle BA, Huston H, Fletcher SN: Hemophilia B. In: Adam MP, Everman DB, Mirzaa GM, et al. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated June 15, 2017. Accessed December 1, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1495/ 4. Sidonio RF Jr, Malec L: Hemophilia B (factor IX deficiency). Hematol Oncol Clin North Am. 2021 Dec;35(6):1143-1155 5. Dolan G, Benson G, Duffy A, et al: Haemophilia B: Where are we now and what does the future hold? Blood Rev. 2018 Jan;32(1):52-60 6. Plug I, Mauser-Bunschoten EP, Brocker-Vriends AHJT, et al: Bleeding in carriers of hemophilia. Blood. 2006 Jul 1;108(1):52-56 7. Goodeve AC: Hemophilia B: molecular pathogenesis and mutation analysis. J Thromb Haemost. 2015 Jul;13(7):1184-1195 8. Alshaikhli A. Hemophilia B: In: Rokkam VR, ed. StatPearls [Internet]. StatPearls Publishing; 2021. Updated February 8, 2022. Accessed December 1, 2022. Available at https://www.statpearls.com/ArticleLibrary/viewarticle/22744/ 9. Srivastava A, Santagostino E, Dougall A, et al: WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020 Aug;26 Suppl 6:1-158 10. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

GNF11 619131 Hemophilia C (Factor XI Deficiency), F11 Gene, Next-Generation Sequencing, Varies

Clinical Information: Factor XI deficiency (FXID) is a rare hereditary bleeding diathesis (also known as hemophilia C) caused by reduced levels of clotting factor XI. It is characterized by a bleeding

disorder that is relatively mild, rarely spontaneous, and predominantly occurs in the oral cavity, nasopharynx, and urinary tract. Bleeding frequency and severity are highest when trauma or certain surgical procedures involve tissues in these areas. Menorrhagia and nose bleeds are common.(1-3) Hereditary FXID is associated with germline variants in the F11 gene. It is typically inherited in an autosomal recessive manner, although some rare variants in F11 cause an autosomal dominant form. Both male and female individuals may be affected. The estimated prevalence of severe FXID is 1 per million. However, it is more common in certain ethnic groups. In the Ashkenazi and Iraqi Jewish populations, severe deficiency may be found in 1 in 450 individuals.(1-5) Plasma FXI activity levels correlate poorly with bleeding severity. This discordance indicates there may be other contributing factors to FXID severity, including differences in clinical criteria for bleeding, variation in genetic backgrounds, the qualities of specific genetic alterations, and coinheritance of other bleeding disorders.(1-3,5) Acquired (nongenetic) FXID appears to be a rare complication of liver transplantation and should be excluded prior to genetic testing.(6) The United Kingdom Haemophilia Centre Doctors' Organization provides guidelines regarding diagnosis and management for individuals with inherited bleeding disorders, including FXID.(7)

Useful For: Evaluating factor XI deficiency (FXID) in patients with a personal or family history suggestive of FXID Confirming an FXID diagnosis with the identification of known or suspected disease-causing alterations in the F11 gene Determining the disease-causing alterations within the F11 gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of FXID Identifying the causative alterations for genetic counseling purposes Prognosis and risk assessment based on the genotype-phenotype correlations Carrier testing for close family members of an individual with a diagnosis of FXID

HQ
607706

HemoQuant, Feces

Clinical Information: Several noninvasive tests are available to detect gastrointestinal (GI) bleeding. However, guaiac type and immunochemical tests for occult bleeding are affected by the presence of reducing or oxidizing substances and are insensitive for the detection of upper GI tract (esophagogastric) bleeding, where most clinically significant occult GI bleeding occurs. The HemoQuant test is the most reliable, noninvasive test currently available for detecting bleeding of the esophago-GI tract. Unlike other tests for blood in feces, this test detects both intact heme and porphyrins from partly degraded heme. Additionally, test results are not complicated by either the water content of the specimen or the presence of reducing or oxidizing substances. Furthermore, HemoQuant testing is sensitive to both proximal and distal sources of occult GI bleeding. Normally, one gram of feces may contain 0.0 to 2.0 mg hemoglobin; this corresponds to a daily loss of up to 2 mL blood. A demonstration of increased Hb in feces indicates bleeding in the alimentary tract (or ingestion of anticoagulants, aspirin, or red meat).

Useful For: Detection of blood in feces Evaluation of iron deficiency Detection of bleeding as a complication of anticoagulant therapy and other medication regimens This test is not specific for bowel cancer.

Interpretation: Elevated levels are an indicator of the presence of blood in the feces, either from benign or malignant causes.

Reference Values:

Normal:
< or =2.0 mg total hemoglobin/g feces

Marginal:
2.1-4.0 mg total hemoglobin/g feces*
*2.1-4.0 mg Hb/g is considered marginally elevated, but not clinically significant, if red meat, warfarin, or aspirin was ingested 72 hours prior to collection.

Elevated:
>4.0 mg total hemoglobin/g feces

Clinical References: 1. Ahlquist DA, McGill DB, Schwartz S, Taylor WF, Ellefson M, Owen RA. HemoQuant, a new quantitative assay for fecal hemoglobin. Comparison with Hemoccult. Ann Intern Med. 1984;101(3):297-302 2. Ahlquist DA, Wieand HS, Moertel CG, et al. Accuracy of fecal occult blood screening for colorectal neoplasia. A prospective study using Hemoccult and HemoQuant tests. JAMA. 1993;269(10):1262-1267 3. Harewood GC, McConnell JP, Harrington JJ, Mahoney DW, Ahlquist DA. Detection of occult upper gastrointestinal bleeding: performance differences in fecal blood tests. Mayo Clin Proc. 2002;77(1):23-28 4. Ahlquist DA, McGill DB, Schwartz S, Taylor WF, Owens RA. Fecal blood levels in health and disease. A study using HemoQuant. N Engl J Med. 1985;312(22):1422-1428 5. Barber MD, Abraham A, Brydon WG, Waldron BM, Williams AJ. Assessment of faecal occult blood loss by qualitative and quantitative methods. J R Coll Surg Edinb. 2002;47(2):491-494 6. Rockey DC, Altayar O, Falck-Ytter Y, Kalmaz D. AGA Technical review on gastrointestinal evaluation of iron deficiency anemia. Gastroenterology. 2020;159(3):1097-1119. doi:10.1053/j.gastro.2020.06.045

UHSD2 Hemosiderin, Random, Urine

620554

Clinical Information: When the plasma hemoglobin level is 50 to 200 mg/dL after hemolysis, the capacity of haptoglobin to bind hemoglobin is exceeded, and hemoglobin readily passes through the glomeruli of the kidney. Part of the hemoglobin is absorbed by the proximal tubular cells where the hemoglobin iron is converted to hemosiderin. When these tubular cells are later shed into the urine, hemosiderinuria results. If the hemoglobin cannot be absorbed into the tubular cells, hemoglobinuria results. Hemosiderin is found as yellow-brown granules that are free or in epithelial cells and occasionally in casts in an acidic or neutral urine.

Useful For: Detecting hemosiderinuria, secondary to excess hemolysis, as in incompatible blood transfusions, severe acute hemolytic anemia, or hemochromatosis for external patients.

Interpretation: A positive hemosiderin indicates excess red cell destruction.

Reference Values:
Negative

Clinical References: 1. Brunzel N. Chemical examination of urine. Fundamentals of Urine and Body Fluid Analysis. 4th ed. Saunders; 2018:98-99 2. Henry JB. Clinical Diagnosis and Management by Laboratory Methods. 18th ed. WB Saunders Company; 1991:412-413 3. Cappellini MD, Lo SF, Swinkles DW. Hemoglobin, iron, bilirubin. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:747

FWWE Hemp Western Water (Acnida tamariscina) IgE

57956

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

HEPTP Heparin Anti-Xa, Plasma

40938

Clinical Information: Heparins are sulphated glycosaminoglycans that inactivate thrombin, factor Xa, and several other coagulation factors; act by enhancing activity of the plasma coagulation inhibitor, antithrombin III; and prolong the activated partial thromboplastin time (APTT). The anti-Xa assay is the preferred method for monitoring low-molecular-weight heparin (LMWH) therapy because of reduced sensitivity of APTT. Heparin is absent in normal plasma. The heparin level obtained must be analyzed in the context of the treatment given to the patient (type of heparin, dosage, administration mode, time of sampling, etc) and the desired therapeutic effect. It is clinically recommended that platelet counts be monitored frequently in patients receiving unfractionated heparin or LMWH in order to detect heparin-induced thrombocytopenia.

Useful For: Measuring heparin concentration: -In patients treated with low-molecular-weight heparin preparations -In the presence of prolonged baseline activated partial thromboplastin time (APTT) (eg, lupus anticoagulant, "contact factor" deficiency, etc) -When unfractionated heparin dose needed to achieve desired APTT prolongation is unexpectedly higher (>50%) than expected This test is not useful for monitoring therapy with the heparinoid "danaparoid."

Interpretation: Results above the therapeutic range may be supratherapeutic suggesting that the heparin dose may need to be decreased. Results below the therapeutic range may be subtherapeutic suggesting that the heparin dose may need to be increased.

Reference Values:

Adult Therapeutic Range
UFH therapeutic range: 0.30-0.70 IU/mL
(6 hours following initiation or dose adjustment)
LMWH therapeutic range: 0.50-1.00 IU/mL for twice daily dosing*
LMWH therapeutic range: 1.00-2.00 IU/mL for once daily dosing*
LMWH prophylactic range: 0.10-0.30 IU/mL

*Sample obtained 4 to 6 hours following subcutaneous injection

Clinical References: 1. Marci CD, Prager D. A review of the clinical indications for the plasma heparin assay. Am J Clin Pathol. 1993;99(5):546-550 2. Houbouyan L, Boutiere B, Contant G, et al. Validation of analytical hemostasis systems: measurement of anti-Xa activity of low-molecular-weight-heparins. Clin Chem. 1996;42(8 Pt 1):1223-1230 3. Jeske W, Messmore HL Jr, Fareed J. Pharmacology of heparin and oral anticoagulants. In: Loscalzo J, Schafer AI. Thrombosis and Hemorrhage. 2nd ed. Williams and Wilkins; 1998:1193-1204 4. Monagle P, Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. Chest. 2001;119(1 Suppl):344S-370S 5. Fraser G, McKenna J. Monitoring low molecular weight heparins with antiXa activity: house of cards or firm foundation? Hospital Pharmacy. 2003;38(3):202-211. doi:10.1177/001857870303800302 6. Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother. 2009;43(6):1064-1083 7. Hoffman R, Benz Jr EJ, Silberstein LE, et al. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018

FHEP2 Heparin Cofactor II

75683

Clinical Information: Heparin cofactor II is a glycoprotein that belongs to the serine protease inhibitor family. Heparin cofactor II, also known as heparin cofactor A or dermatan sulfate cofactor, has a molecular weight of approximately 65 kilodaltons and has a plasma concentration of 9 mg/dL. Heparin cofactor II is synthesized by the liver and has a plasma half-life of 60 hours. Heparin cofactor II specifically inhibits thrombin, in contrast to antithrombin, which inhibits thrombin, factor Xa, and other serine proteases. The inhibition of thrombin by heparin cofactor II is approximately 10 times slower than

antithrombin-mediated inhibition and occurs through the formation of equimolar complexes between the reactive site of the inhibitor and the active site of thrombin. The antithrombotic activity of heparin cofactor II is greatly enhanced (over 1000-fold) in the presence of heparin and dermatan sulfate. The physiologic function of the molecule is unclear, but its role may be to serve as an antithrombotic agent in the presence of dermatan sulfate. Acquired deficiencies of heparin cofactor II are reported in patients with liver disease and disseminated intravascular coagulation. Conversely, increased levels of heparin cofactor II may be observed in individuals with renal disorders with proteinuria, during pregnancy, and with oral contraceptive usage. Inherited deficiency of heparin cofactor II has been reported in rare instances and is inherited as an autosomal dominant trait. A clear relationship between increased risk of thrombosis and heparin cofactor II deficiency has not been established since deficiency of heparin cofactor II is observed in both healthy individuals and those with thrombotic episodes. Limited studies have shown that heterozygosity for heparin cofactor II is not a likely risk for thrombosis without other concomitant risk factors. Other studies have reported thrombotic episodes in 36% of individuals with the deficiency.

Useful For: Assessment of thrombotic risk associated with heparin cofactor II levels.

Reference Values:

65-145%

In healthy adults, heparin cofactor II reference range in plasma is 65% to 145%. Plasma levels of heparin cofactor II are approximately 50% of adult levels at birth and reach adult levels at six months of age.

HITIG
86533

Heparin-PF4 IgG Antibody, Serum

Clinical Information: There are established and emerging disorders that are collectively termed thrombocytopenia and thrombosis syndromes; the most commonly recognized is heparin-induced thrombocytopenia (HIT). Newer associations have also been recognized including adenovirus vector-based SARS-CoV-2 vaccine-induced thrombocytopenia and HIT-like syndromes that occur in the absence of exposure to heparin (currently termed spontaneous or autoimmune HIT). In this situation, the heparin platelet-factor 4 (PF4) IgG antibody typically develops after surgery or infection. HIT is a serious immune-mediated syndrome (ie, type II HIT or immune HIT) that occurs in 1% to 5% of patients treated with unfractionated heparin and at a lower frequency in patients treated with low-molecular weight heparin. The 4Ts score is a validated scoring system to estimate the pretest clinical probability of HIT. Scores are assigned to the degree and timing of onset of thrombocytopenia, and the presence or absence of thrombosis (arterial or venous) in the absence of other potential explanations for the thrombocytopenia. In HIT, typical onset of thrombocytopenia is between days 5 and 10 of heparin therapy, but thrombocytopenia can arise earlier (<5 days after heparin exposure, ie, rapid onset of HIT) or later (>4 weeks after heparin exposure, ie, delayed onset of HIT). The platelet count typically decreases by 40% to 50% from baseline or the postoperative peak (in surgical patients), even though the absolute count may remain normal and the thrombocytopenia resolves within 7 to 14 days of cessation of heparin therapy (unless there is another coexisting cause of thrombocytopenia). Development or progression of (venous or arterial) thrombosis is termed heparin-induced thrombocytopenia with thrombosis syndrome and can occur in 30% to 50% of patients, rarely even following discontinuation of heparin therapy. Other Syndromes of Thrombocytopenia and Thrombosis: There are an increasing number of reports of patients who develop thrombocytopenia and thrombosis after surgery, particularly after orthopedic surgery and after selected infections. The clinical course and laboratory characteristics of this group of patients are similar to the classical HIT occurring with heparin exposure except perhaps development of high titer antibodies against heparin/PF4 complexes. An emerging recognition is the development of thrombocytopenia and thrombosis occurring 3 to 4 weeks after adenovirus vector SARS-CoV-2 exposure. The clinical course is also similar to immune HIT. Laboratory Characteristics of HIT: HIT is caused, in at least 90% of cases, by antibodies to antigen complexes of heparinoid (heparin or similar glycosaminoglycans) and PF4. PF4 is a platelet-specific heparin-binding protein that is abundant

in platelet alpha granules from which it is secreted following platelet stimulation. A reservoir of PF4 normally accumulates on vascular endothelium. Following heparin administration, immunogenic complexes of PF4 and heparin can provide an antigenic stimulus for antibody development in some patients. Antibodies bound to platelets that display complexes of PF4/heparin antigen can activate platelets via interaction of the Fc immunoglobulin tail of the IgG antibody with platelet Fc gamma IIa receptors, leading to perpetuation of the pathologic process that can cause platelet-rich thrombi in some cases. Functional assays for HIT antibody detection rely on antibody-mediated heparin-dependent platelet activation. The endpoint of platelet activation may be platelet aggregation or platelet secretion of serotonin or adenosine triphosphate (ATP) using patient serum or plasma supplemented with heparin and platelets from carefully normal selected donors. The sensitivity of functional assays for HIT ranges from 50% to 60% for heparin-dependent platelet aggregation assays to 70% to 80% for serotonin release assays. The specificity of positive functional tests for HIT diagnosis is believed to be high (> or =90%). However, because of their complexity, functional tests for detecting HIT antibodies are not widely available. Enzyme-linked immunosorbent assays (ELISA) are available to detect HIT type 2 (HIT-II) antibodies and are based on the detection of human IgG antibodies that react with solid phase antigen complexes of heparinoid and human PF4 (H/PF4) complexes. The ELISA for H/PF4 antibodies is very sensitive for antibody detection but relatively nonspecific for clinical HIT diagnosis. Routine screening of all patients prior to, during, or following heparin use is currently not recommended. A positive H/PF4 ELISA result has relatively low and uncertain predictive value for the development of clinical HIT-II. Clinical Picture of Immune HIT or HIT-like Syndromes: HIT in patients not previously exposed to heparin: 1. Decrease in platelet count (thrombocytopenia) of 50% from baseline or postoperative peak. 2. Onset of thrombocytopenia beginning approximately 5 to 10 days after initiation of heparin. This may or may not be associated with new or progressive thrombosis in patients treated with heparin. Patients previously exposed to heparin (especially within the preceding 100 days): in addition to the above findings, the onset of thrombocytopenia could occur within 24 to 48 hours after reexposure to heparin. Spontaneous or Autoimmune HIT: Patients typically present a week to 10 days after surgery or viral infections with symptoms of thrombosis (venous thromboembolism) or abdominal pain (suggesting adrenal infarction) and thrombocytopenia. Vaccine Induced Thrombocytopenia and Thrombosis: Patients typically present 4 days to 4 weeks after receiving the vaccine. Symptoms may include new onset of severe headache (suggesting cerebral venous sinus thrombosis), abdominal pain (suggesting mesenteric/portal vein thrombosis), or venous/arterial thromboembolism.

Useful For: Detection of IgG antibodies directed against heparin/platelet factor 4 complexes that are implicated in the pathogenesis of immune-mediated type II heparin-induced thrombocytopenia, spontaneous heparin platelet-factor 4 IgG antibody, and thrombocytopenia and thrombosis occurring after SARS-CoV2 adenovirus vector vaccine

Interpretation: Results are reported as: 1. Heparin-induced thrombocytopenia (HIT) enzyme-linked immunosorbent assay (ELISA) optical density (OD) 2. Heparin inhibition (%) 3. Interpretation. Typical patterns of results and interpretations are depicted in the following table. Interpretive comments will also accompany test reports, when indicated. Table. Results and Interpretation HIT ELISA OD Heparin inhibition Interpretation Normal range <0.400 Not done Negative Positive > or =0.400 > or =50% Positive Equivocal > or =0.400 <50% Equivocal A negative result of testing for human platelet factor 4 (H/PF4) antibodies has about a 90% negative predictive value for exclusion of clinical type II HIT (HIT-II). As up to 10% of patients with clinical HIT may have a negative H/PF4 antibody ELISA result, a negative H/PF4 antibody ELISA result does not exclude the diagnosis of HIT when clinical suspicion remains high. A functional assay for HIT antibodies (eg, heparin-dependent platelet aggregation or serotonin release assay) may be helpful in these circumstances. Call 800-533-1710 for ordering information. A positive result is indicative of the presence of H/PF4 complex antibodies. However, this test's specificity is as low as 20% to 50% for clinical diagnosis of HIT, depending on the patient population studied. For example, up to 50% of surgical patients and up to 20% of medical patients treated with heparin may develop H/PF4 antibodies as measured by ELISA, and only a small proportion (1%-5%) develop clinical HIT. Accordingly, this test does not confirm the diagnosis of HIT-II. The diagnosis must be made in conjunction with clinical findings, including evaluation for other potential causes of

thrombocytopenia. The presence of H/PF4 antibodies likely increases the risk of clinical HIT, with risk probably partly dependent on associated medical and surgical conditions, but currently there is little data about relative risk of HIT in various populations with positive tests for H/PF4 antibodies.

Reference Values:
HIT ELISA:
<0.400

HIT Interpretation:
Negative

Clinical References: 1. Husseinzadeh HD, Gimotty PA, Pishko AM, Buckley M, Warkentin TE, Cuker A. Diagnostic accuracy of IgG-specific versus polyspecific enzyme-linked immunoassays in heparin-induced thrombocytopenia: a systematic review and meta-analysis. J Thromb Haemost. 2017;15(6):1203-1212. doi:10.1111/jth.13692 2. Warkentin TE, Greinacher A, eds. Heparin Induced Thrombocytopenia. Marcel Dekker; 2000:400 3. Warkentin TE, Sheppard JI, Moore JC, Sigouin CS, Kelton JG. Quantitative interpretation of optical density measurements using PF4-dependent enzyme-immunoassays. J Thromb Haemost. 2008;6(8):1304-1312. doi:10.1111/j.1538-7836.2008.03025.x 4. Trossaert M, Gaillard A, Commin PL, Amiral J, Vissac AM, Fressinaud E. High incidence of anti-heparin/platelet factor 4 antibodies after cardiopulmonary bypass surgery. Br J Haematol. 1998;101(4):653-655. doi:10.1046/j.1365-2141.1998.00750.x

HAIGM
48064

Hepatitis A Virus IgM Antibody, Serum

Clinical Information: Hepatitis A virus (HAV) is endemic throughout the world, occurring most commonly in areas of poor hygiene and low socioeconomic conditions. The virus is transmitted primarily by the fecal-oral route and spread by close person-to-person contact and by food and waterborne epidemics. Outbreaks frequently occur in overcrowded situations and high-density institutions and centers, such as prisons and healthcare or daycare centers. Viral spread by parenteral routes (eg, exposure to blood) is possible, but rare, because infected individuals are viremic for a short period of time (usually <3 weeks). There is little or no evidence of transplacental transmission from mother to fetus or transmission to newborn during delivery. Serological diagnosis of acute viral hepatitis A depends on the detection of specific anti-HAV IgM. Its presence in the patient's serum indicates a recent exposure to HAV. HAV-specific IgM antibody level becomes detectable in the blood by 4 weeks after infection, persisting at elevated levels for about 2 months before declining to undetectable levels by 6 months. They rarely persist beyond 12 months after infection.

Useful For: Diagnosis of acute or recent hepatitis A infection

Interpretation: This assay detects the presence of hepatitis A virus (HAV)-specific IgM antibody in serum. Negative results indicate either inadequate or delayed anti-HAV IgM response after known exposure to HAV or absence of acute or recent hepatitis A. Equivocal results may be seen in early acute hepatitis A associated with rising anti-HAV IgM levels or recent hepatitis A infection associated with declining anti-HAV IgM levels. Retesting for both anti-HAV IgM (HAIGM / Hepatitis A Virus IgM Antibody, Serum) and anti-HAV Total (HAVTA / Hepatitis A Virus Total Antibodies, Serum) in 2 to 4 weeks is recommended to determine the definitive HAV infection status. Positive results indicate acute or recent (<6 months) hepatitis A infection. As required by laws in almost all states, positive anti-HAV IgM test results must be urgently reported to state health departments for epidemiologic investigations of possible outbreak transmission.

Reference Values:
Negative

See Viral Hepatitis Serologic Profiles.

Clinical References: 1. de Paula VS. Laboratory diagnosis of hepatitis A. Future Virology. 2012;7(5):461-472 2. Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(5):1-38. Erratum in MMWR Morb Mortal Wkly Rep. 2021;70(8):294 3. Webb GW, Kelly S, Dalton HR. Hepatitis A and hepatitis E: clinical and epidemiological features, diagnosis, treatment, and prevention. Clin Microbiol Newslett. 2020;42(21):171-179

HAVTA
620407

Hepatitis A Virus Total Antibodies, Serum

Clinical Information: Hepatitis A virus (HAV) is endemic throughout the world, occurring most commonly, however, in areas of poor hygiene and low socioeconomic conditions. The virus is transmitted primarily by the fecal-oral route, and it is spread by close person-to-person contact and by food- and water-borne epidemics. Outbreaks frequently occur in overcrowded situations and in high-density institutions and centers, such as prisons and health care or day care centers. Viral spread by parenteral routes (eg, exposure to blood) is possible but rare, because infected individuals are viremic for a short period of time (usually <3 weeks). There is little or no evidence of transplacental transmission from mother to fetus or transmission to newborn during delivery. In most cases, HAV-specific antibodies (anti-HAV) are detectable by the time that symptoms occur, usually 15 to 45 days after exposure. Initial antibodies consist almost entirely of the IgM subclass. Anti-HAV IgM usually falls to an undetectable level by 6 months after HAV infection. Anti-HAV IgG levels rise quickly once the virus is cleared and may persist for many years. Currently, commercial diagnostic assays are available for detecting anti-HAV IgM alone (HAIGM / Hepatitis A IgM Antibody, Serum) or anti-HAV total (IgM and IgG) but not anti-HAV IgG alone.

Useful For: Detection of recent or previous exposure or immunity to hepatitis A. This test should not be used as a screening or confirmatory test for blood or solid or soft tissue donor specimens.

Interpretation: This assay detects the presence of hepatitis A virus (HAV)-specific total antibodies (both anti-HAV IgG and anti-HAV IgM combined). A positive result indicates that the patient had hepatitis A either recently or in the past or immunity to hepatitis A from vaccination. A reactive (positive) result by the Elecsys Anti-HAV II assay does not differentiate between acute or past HAV infection or immunity from vaccination, and it does not necessarily rule out other hepatitis infections. If clinically indicated, specific testing for anti-HAV IgM is necessary to confirm the presence of acute or recent hepatitis A. A positive result for anti-HAV total with a negative anti-HAV IgM result indicates immunity to hepatitis A from either past HAV infection or vaccination against HAV. A negative result indicates the absence of recent or past hepatitis A or a lack of immunity to HAV infection. A non-reactive (negative) test result does not exclude the possibility of early acute infection with HAV.

Reference Values:
Unvaccinated: Negative
Vaccinated: Positive

Clinical References: 1. De Paula VS. Laboratory diagnosis of hepatitis A. Future Virology. 2012;7(5):461-472 2. Prasidthrathsint K, Stapleton JT. Laboratory Diagnosis and Monitoring of Viral Hepatitis. Gastroenterol Clin North Am. 2019;48(2):259-279. doi:10.1016/j.gtc.2019.02.007 3. Centers for Disease Control and Prevention. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. Mort Morbid Wkly Rpt. 2020;69(5):1-38. doi:10.15585/mmwr.rr6905a1 4. Van Damme P, Pinto RM, Feng Z, Cui F, Gentile A, Shouval D. Hepatitis A virus infection. Nature Rev Dis Primers. 2023;9(1):51. doi:10.1038/s41572-023-00461-2

HEPBC
70451

Hepatitis B Core (HBc) Immunostain, Technical Component Only

Clinical Information: The hepatitis B nucleocapsid contains 2 serologically distinct antigens, the core and envelope antigens, surrounded by an outer envelope-hepatitis B virus surface antigen. The core antigen is most often present in chronic active hepatitis, compared to the surface antigen, which is present in the carrier state.

Useful For: Aiding in the identification of hepatitis B infection (chronic active state)

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Bonino F, Pratvisuth T, Brunetto MR, Liaw YF. Diagnostic markers of chronic hepatitis B infection and disease. Antivi Ther. 2010;15(Suppl 3):35-44 2. Yang H, Fu Q, Liu C, et al. Hepatitis B virus promotes autophagic degradation but not replication in autophagosome. Biosci Trends. 2015;9(2):111-116. doi:10.5582/bst.2015.01049 3. Liu D, Ni B, Wang L, Zhang M, Liu W, Wu Y. Hepatitis B virus core protein interacts with CD59 to promote complement-mediated liver inflammation during chronic hepatitis B virus infection. FEBS Lett. 2013;587(20):3314-3320. doi:10.1016/j.febslet.2013.08.044 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HEPBS
70453

Hepatitis B Surface (HBs) Antigen Immunostain, Technical Component Only

Clinical Information: Hepatitis B surface antigen stains the cytoplasm of hepatitis B-infected hepatocytes in a granular pattern. The complete infective virion consists of a core of double-stranded DNA, a specific DNA polymerase, and structural proteins. The nucleocapsid contains 2 serologically distinct antigens, the core antigen and envelope antigen. These are surrounded by an outer envelope of surface protein that is recognized serologically as hepatitis B virus surface antigen. Core antigen is most often demonstrated in chronic active hepatitis, compared to surface antigen in the carrier state.

Useful For: Aiding in the identification of hepatitis B infection (carrier state)

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

HBGCD
83626

Hepatitis B Surface Antigen for Cadaveric or Hemolyzed Specimens, Serum

Clinical Information: Hepatitis B virus (HBV) is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles by intravenous drug users). The virus is found in various human body fluids, and it is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 16 weeks following HBV infection. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for greater than 6 months indicates development of either a chronic carrier or chronic HBV infection.

Useful For: Testing cadaveric and hemolyzed blood specimens for hepatitis B surface antigen (HBsAg); US Food and Drug Administration-licensed for use with hemolyzed specimens Diagnosis of acute, recent (<6-month duration), or chronic hepatitis B infection; determination of chronic hepatitis B carrier status This test is not useful during the "window period" of acute hepatitis B virus (HBV) infection, (ie, after disappearance of HBsAg and prior to appearance of anti-HBs antibody).

Interpretation: A positive result (reactive screening and confirmed positive by neutralization test) is indicative of acute or chronic hepatitis B virus (HBV) infection or chronic HBV carrier state. A positive confirmatory test result is considered the definitive test result for hepatitis B surface antigen (HBsAg). Specimens that are reactive by the screening test but negative (not confirmed) by the confirmatory test are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. These unconfirmed HBsAg screening test results should be interpreted in conjunction with test results of other HBV serological markers (eg, anti-hepatitis B surface antibody, anti-hepatitis B core total antibody). The presence of HBsAg is frequently associated with HBV infectivity, especially when accompanied by the presence of HBeAg or HBV DNA.

Reference Values:
Negative

Clinical References: 1. Servoss JC, Friedman LS. Serologic and molecular diagnosis of hepatitis B virus. Clin Liver Dis. 2004;8(2):267-281 2. Badur S, Akgun A. Diagnosis of hepatitis B infections and monitoring of treatment. J Clin Virol. 2001;21(3):229-237 3. Bonino F, Piratvisuth T, Brunetto MR, Liaw YF. Diagnostic markers of chronic hepatitis B infection and disease. Antivir Ther. 2010;15 Suppl 3:35-44 4. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63(1):261-283

HBVQN
65555

Hepatitis B Virus (HBV) DNA Detection and Quantification by Real-Time PCR, Serum

Clinical Information: Diagnosis of acute or chronic hepatitis B virus (HBV) infection is based on the presence of HBV serologic markers such as hepatitis B surface antigen (HBsAg) and hepatitis B core IgM antibody (anti-HBc IgM), or the presence of HBV DNA detected by molecular assays. Although the diagnosis of acute and chronic HBV infection is usually made by serologic methods, the detection and quantification of HBV DNA in serum are useful to: -Diagnose some cases of early acute HBV infection (before the appearance of HBsAg) -Distinguish active from inactive HBV infection -Monitor a patient's response to anti-HBV therapy The presence of HBV DNA in serum is a reliable marker of active HBV replication. HBV DNA levels are detectable by 30 days following infection, generally reach a peak at the time of acute hepatitis, and gradually decrease and disappear when the infection resolves spontaneously. In cases of acute viral hepatitis with equivocal HBsAg test results, testing for HBV DNA in serum may be a useful adjunct in the diagnosis of acute HBV infection, since HBV DNA can be detected approximately 21 days before HBsAg typically appears in the serum. Patients with chronic HBV infection fail to clear the virus and remain HBsAg-positive. Such cases may be further classified as chronic active (replicative)

HBV (high HBV levels, hepatitis Be antigen [HBeAg]-positive) or chronic inactive (nonreplicative) HBV (low or undetectable HBV DNA levels, HBeAg-negative). HBV DNA levels in serum are useful in determining the status of chronic HBV infection, by differentiating between active and inactive disease states. Patients with chronic active HBV are at greater risk for more serious liver disease and are more infectious than patients with inactive HBV infection. Reactivation of inactive chronic HBV infection (HBeAg-negative state) may occur with or without reappearance of HBeAg in serum. In patients with HBeAg-negative disease, detection of HBV DNA is the only reliable marker of active HBV replication. The therapeutic goal of anti-HBV therapy in patients who are HBeAg-positive is to achieve long-term suppression of viral replication with undetectable HBV DNA, HBe seroconversion and loss of HBeAg. The therapeutic goal in patients with HBeAg-negative disease is typically long-term viral suppression. The emergence of drug-resistant HBV strains in response to treatment with nucleoside/nucleotide analogs (eg, lamivudine, adefovir, entecavir, tenofovir), is characterized by either the reappearance of HBV DNA in serum (after it had become undetectable) or an increase in HBV DNA levels (following an initial decline). The following algorithms are available: -Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management -HBV Infection-Monitoring Before and After Liver Transplantation

Useful For: Detection and quantification of hepatitis B virus (HBV) DNA in serum of patients with chronic HBV infection (ie, hepatitis B surface antigen-positive) Monitoring disease progression in chronic HBV infection Monitoring response to anti-HBV therapy

Interpretation:

Reference Values:
Undetected

Clinical References: 1. Bonino F, Piratvisuth T, Brunetto MR, Liaw YF. Diagnostic markers of chronic hepatitis B infection and disease. Antivir Ther. 2010;15 Supply 15:35-44 2. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. World Health Organization; March 2015. Accessed January 29, 2025. Available at www.who.int/publications/i/item/9789241549059 3. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63(1):261-283 4. World Health Organization: Guidelines on hepatitis B and C testing. World Health Organization; February 2017. Accessed January 29, 2025. Available at www.who.int/publications/i/item/9789241549981

HBIM
9015

Hepatitis B Virus Core IgM Antibody, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. In the initial (acute) phase of infection, HBV core antibodies (anti-HBc) consist almost entirely of the IgM antibody class and appear shortly after the onset of symptoms. Anti-HBc IgM can be detected in serum and is usually present for up to 6 months after acute HBV infection. Anti-HBc IgM may be the only serologic marker of a recent hepatitis B infection detectable following the disappearance of hepatitis B surface antigen and prior to the appearance of hepatitis B virus surface antibody (ie, serologic window period).

Useful For: Diagnosis of acute hepatitis B virus (HBV) infection Identifying acute HBV infection in the serologic window period when HBV surface antigen and HBV surface antibody results are negative Differentiation between acute, chronic, or past HBV infections in the presence of positive hepatitis B virus core total antibodies

Interpretation: A positive result indicates recent acute hepatitis B infection. Positive results should

be correlated with hepatitis B virus core total antibody test result and the patient's epidemiologic exposure history. A negative result suggests a lack of recent exposure to the virus in the preceding 6 months.

Reference Values:
Negative

See Viral Hepatitis Serologic Profiles

Clinical References: 1. LeFevre ML; U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 2. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis (Hoboken). 2018;12(1):5-11. doi:10.1002/cld.729 3. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019;156(2):355-368.e3. doi:10.1053/j.gastro.2018.11.037 4. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization. Updated February 16, 2017. Accessed May 5, 2025. Available at www.who.int/publications/i/item/9789241549981 5. Division of Viral Hepatitis, National Center for HIV, Viral Hepatitis, STD, and TB Prevention: Testing and public health management of persons with chronic hepatitis B virus infection. Centers for Disease Control and Prevention. Updated January 31, 2025. Accessed May 6, 2025. Available at www.cdc.gov/hepatitis-b/hcp/diagnosis-testing/ 6. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

HBCPR
610462

Hepatitis B Virus Core Total Antibodies Prenatal, Serum

Clinical Information: Hepatitis B virus core antibodies (anti-HBc) appear shortly after the onset of symptoms of hepatitis B infection and soon after the appearance of hepatitis B virus surface antigen (HBsAg). Initially, anti-HBc consist almost entirely of the IgM antibody class, followed by appearance of anti-HBc IgG for which there is no commercial diagnostic assay. The HBc total antibody test, which detects both IgM and IgG antibodies, and the test for anti-HBc IgM may be the only markers of recent hepatitis B detectable in the "window period." The window period begins with the clearance of HBsAg and ends with the appearance of anti-HBs. Anti-HBc total may be the only serologic marker remaining years after exposure to hepatitis B virus. This assay is US Food and Drug Administration-approved for in vitro diagnostic use and not for screening cell, tissue, and blood donors.

Useful For: Diagnosis of recent or past hepatitis B in pregnant individuals Determination of occult hepatitis B in otherwise healthy hepatitis B virus carriers with negative test results for hepatitis B surface (HBs) antigen, anti-HBs, anti-hepatitis B core IgM, hepatitis Be (HBe) antigen, and anti-HBe This assay is not useful for differentiating among acute, chronic, and past or resolved hepatitis B. This test should not be used as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative hepatitis B virus core total antibody (anti-HBc total) test results indicate the absence of exposure to hepatitis B virus and no evidence of recent, past/resolved, or chronic hepatitis B. A positive result indicates acute, chronic, or past or resolved hepatitis B. Positive anti-HBc total test results should be correlated with the presence of other hepatitis B virus serologic markers, elevated liver enzymes, clinical signs and symptoms, and a history of risk factors. If clinically indicated, testing for anti-HBc IgM (HBIM / Hepatitis B Virus Core IgM Antibody, Serum) is necessary to confirm an acute or recent infection. Neonatal patients (<1 month old) with positive anti-HBc total results from this assay should be tested for anti-HBc IgM (HBIM / Hepatitis B Virus Core IgM Antibody, Serum) to rule out possible maternal anti-HBc causing false-positive results. Repeat testing using this assay for anti-HBc total within 1 month is also recommended for these neonatal patients.

Reference Values:
Negative
Interpretation depends on clinical setting.

For more information, see Viral Hepatitis Serologic Profiles.

Clinical References: 1. LeFevre ML, U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014; 161(1):58-66. doi:10.7326/M14-1018 2. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; February 2017. Accessed December 19, 2023. Available at www.who.int/publications/i/item/9789241549981 3. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis. 2018; 12(1):5-11. doi:10.1002/cld.729 4. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019; 156(2):355-368. doi:10.1053/j.gastro.2018.11.037 5. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

HBCSN
610471

Hepatitis B Virus Core Total Antibodies Screen, Serum

Clinical Information: Hepatitis B virus core antibodies (anti-HBc) appear shortly after the onset of symptoms of hepatitis B infection and soon after the appearance of hepatitis B virus surface antigen (HBsAg). Initially, anti-HBc consist almost entirely of the IgM antibody class, followed by the appearance of anti-HBc IgG for which there is no commercial diagnostic assay. The HBc total antibody test, which detects both IgM and IgG antibodies, and the test for anti-HBc IgM may be the only markers of recent hepatitis B detectable in the "window period." The window period begins with the clearance of HBsAg and ends with the appearance of anti-HBs. Anti-HBc may be the only serologic marker remaining years after exposure to hepatitis B virus (HBV). This assay is US Food and Drug Administration approved for in vitro diagnostic use and not for screening cell, tissue, and blood donors.

Useful For: Diagnosis of recent or past hepatitis B Determination of occult hepatitis B in otherwise healthy hepatitis B virus carriers with negative test results for hepatitis B surface (HBs) antigen, anti-HBs, anti-hepatitis B core IgM, hepatitis Be (HBe) antigen, and HBe antibody This assay is not useful for differentiating between acute, chronic, past, or resolved hepatitis B. This test should not be used as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative hepatitis B virus core total antibody (anti-HBc total) test results indicate the absence of exposure to hepatitis B virus and no evidence of recent, past/resolved, or chronic hepatitis B. A positive result indicates acute, chronic, or past or resolved hepatitis B. Positive anti-HBc total test results should be correlated with the presence of other hepatitis B virus serologic markers, elevated liver enzymes, clinical signs and symptoms, and a history of risk factors. If clinically indicated, testing for anti-HBc IgM (HBIM / Hepatitis B Virus Core Antibody, IgM, Serum) is necessary to confirm an acute or recent infection. Neonatal patients (<1 month old) with positive anti-HBc total results from this assay should be tested for anti-HBc IgM (HBIM / Hepatitis B Virus Core Antibody, IgM, Serum) to rule out possible maternal anti-HBc causing false-positive results. Repeat testing using this assay for anti-HBc total within 1 month is also recommended for these neonatal patients.

Reference Values:
Negative
Interpretation depends on clinical setting.
See Viral Hepatitis Serologic Profiles

Clinical References: 1. LeFevre ML; U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 2. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; February 2017. Accessed December 20, 2023. Available at www.who.int/publications/i/item/9789241549981 3. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis. 2018;12(1):5-11. doi:10.1002/cld.729 4. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019;156(2):355-368. doi:10.1053/j.gastro.2018.11.037 5. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

HBC
8347

Hepatitis B Virus Core Total Antibodies, Serum

Clinical Information: Hepatitis B virus core antibodies (anti-HBc) appear shortly after the onset of symptoms of hepatitis B infection and soon after the appearance of hepatitis B virus surface antigen (HBsAg). Initially, anti-HBc consist almost entirely of the IgM antibody class, followed by appearance of anti-HBc IgG for which there is no commercial diagnostic assay. The anti-HBc total antibody test, which detects both IgM and IgG antibodies, and the test for anti-HBc IgM may be the only markers of recent hepatitis B detectable in the "window period." The window period begins with the clearance of HBsAg and ends with the appearance of anti-HBs. Anti-HBc total may be the only serologic marker remaining years after exposure to hepatitis B virus. This assay is US Food and Drug Administration-approved for in vitro diagnostic use and not for screening cell, tissue, and blood donors.

Useful For: Diagnosis of recent or past hepatitis B Determination of occult hepatitis B in otherwise healthy hepatitis B virus carriers with negative test results for hepatitis B surface (HBs) antigen, anti-HBs, anti-HB core IgM, hepatitis Be (HBe) antigen, and anti-HBe This assay is not useful for differentiating among acute, chronic, and past or resolved hepatitis B. This test should not be used as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative hepatitis B virus core total antibody (anti-HBc total) test results indicate the absence of exposure to hepatitis B virus and no evidence of recent, past/resolved, or chronic hepatitis B. A positive result indicates acute, chronic, or past or resolved hepatitis B. Positive anti-HBc total test results should be correlated with the presence of other hepatitis B virus serologic markers, elevated liver enzymes, clinical signs and symptoms, and a history of risk factors. If clinically indicated, testing for anti-HBc IgM (HBIM / Hepatitis B Virus Core Antibody, IgM, Serum) is necessary to confirm an acute or recent infection. Neonatal patients (<1 month old) with positive anti-HBc total results from this assay should be tested for anti-HBc IgM (HBIM / Hepatitis B Virus Core Antibody, IgM, Serum) to rule out possible maternal anti-HBc causing false-positive results. Repeat testing using this assay for anti-HBc total within 1 month is also recommended for these neonatal patients.

Reference Values:

Negative
Interpretation depends on clinical setting.
See Viral Hepatitis Serologic Profiles

Clinical References: 1. LeFevre ML; U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 2. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; February 2017. Accessed September 9, 2023. Available at www.who.int/publications/i/item/9789241549981 3. Jackson K, Locarnini S, Gish R: Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis.

2018;12(1):5-11. doi:10.1002/cld.729 4. Coffin CS, Zhou K, Terrault NA: New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019;156(2):355-368. doi:10.1053/j.gastro.2018.11.037 5. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

CORAB 32111 Hepatitis B Virus Core Total Antibodies, with Reflex to Hepatitis B Virus Core IgM Antibody, Serum

Clinical Information: During the course of a typical case of acute hepatitis B, hepatitis B virus (HBV) core IgM antibodies (anti-HBc IgM) to HBc antigen are present in the serum shortly before clinical symptoms appear. Anti-HBc total is detectable during the prodromal, acute, and early convalescent phases when it exists as anti-HBc IgM. Anti-HBc IgM increase in level and are present during the core window period (ie, after HBV surface (HBs) antigen disappears and before anti-HBs appear). Anti-HBc total may be the only serologic marker remaining years after exposure to HBV.

Useful For: Detection and differentiation between recent, past/resolved, or chronic hepatitis B Diagnosis of recent hepatitis B virus (HBV) infection during the "window period" when both hepatitis B surface (HBs) antigen and anti-HBs are negative This test is not useful for determining immunity to or recovery from HBV infection.

Interpretation: Negative hepatitis B virus core total antibody (anti-HBc total) results indicate the absence of recent, past/resolved, or chronic hepatitis B. Positive anti-HBc total result may indicate recent, past/resolved, or chronic hepatitis B. Testing for anti-HBc IgM is necessary to confirm the presence of acute or recent hepatitis B. A positive anti-HBc total result with a negative anti-HBc IgM result indicates past or chronic hepatitis B virus (HBV) infection. Differentiation between past/resolved and chronic hepatitis B can be based on the presence of hepatitis B virus surface antigen (HBsAg) in the latter condition. Positive anti-HBc total results with negative anti-HBc IgM results in infants younger than 18 months may be due to passively acquired maternal IgG antibodies. Additional testing, such as HBsAg, anti-HBc IgM, and hepatitis Be antigen, are necessary to confirm a diagnosis of acute or recent hepatitis B in these infants.

Reference Values:

Negative

Interpretation depends on clinical setting.

See Viral Hepatitis Serologic Profiles

Clinical References: 1. LeFevre ML. U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 2. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; February 2017. Accessed May 5, 2025. Available at www.who.int/publications/i/item/9789241549981 3. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis. 2018;12(1):5-11. doi:10.1002/cld.729 4. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019;156(2):355-368. doi:10.1053/j.gastro.2018.11.037 5. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

HBCRQ
621765

Hepatitis B Virus Core-Related Antigen, Quantitative, Serum

Clinical Information: During antiviral treatment of chronic hepatitis B (CHB), measurement of hepatitis B virus (HBV) DNA in serum or plasma is used as a marker of treatment efficacy, providing an estimate of the viral replicative activity in the treated individual. However, with nucleoside/nucleotide analogues (NA) acting on limited steps of the viral replication cycle, the production of HBV intermediate proteins (such as hepatitis B core antigen [HBcAg], hepatitis B surface antigen [HBsAg], and hepatitis B e antigen [HBeAg]) may not be affected significantly during such treatment. Therefore, measurement of such HBV proteins in serum or plasma can be useful in monitoring treatment efficacy, especially in patients receiving NA therapy when serum or plasma HBV DNA levels are undetectable. Another recently discovered group of HBV intermediate proteins, hepatitis B core-related antigens (HBcrAgs), comprises 3 related proteins sharing an identical 149 amino acid sequence: HBcAg, HBeAg, and a truncated 22-kDa precore protein. HBcrAg levels in serum or plasma of individuals with CHB showed good correlation with intrahepatic covalently closed circular DNA (cccDNA) and total HBV DNA, serum HBV DNA, and HBsAg to a lesser extent. In situations where serum HBV DNA levels become undetectable or HBsAg loss is achieved, HBcrAg can still be detectable. Serum HBcrAg concentration correlates strongly with the serum HBV DNA concentration in a positive and linear manner, regardless of the HBeAg status. Intrahepatic total HBV DNA also correlates well with serum HBcrAg in treatment-naive or -experienced individuals. For these reasons, HBcrAg levels in serum or plasma can estimate the intrahepatic cccDNA quantity and serve as a useful marker for disease monitoring, predicting treatment response and disease outcome of CHB. HBcrAg levels in serum or plasma are also helpful in differentiating HBeAg-negative CHB from HBeAg-positive CHB, predicting spontaneous or treatment-induced HBeAg seroconversion, sustained response to NA therapy, risk of HBV reactivation in occult HBV infection under immunosuppressive therapies, and risk of hepatocellular carcinoma (HCC) development as well as post-operative HCC recurrence.

Useful For: Monitoring of response to antiviral therapy in individuals with chronic hepatitis B who are negative for hepatitis B e antigen (HBeAg), positive for hepatitis B e antibody, and undetectable or low hepatitis B virus DNA levels (eg, <500 IU/mL) in serum

Interpretation: This assay has a limit of detection of 158 U/mL and quantifies hepatitis B core-related antigen (HBcrAg) in serum within the range of 1000 to 7,500,000 U/mL (or 3.00 log to 6.88 log U/mL). Result of <1000 U/mL indicates that the HBcrAg level present in the serum specimen tested is less than 1000 U/mL (the lower limit of quantification of this assay).

Reference Values:
<1,000 U/mL

Clinical References: 1.Chen EQ, Feng S, Wang ML, et al. Serum hepatitis B core-related antigen is a satisfactory surrogate marker of intrahepatic covalently closed circular DNA in chronic hepatitis B. Sci Rep. 2017;7(1):173. doi:10.1038/s41598-017-00111-0 2. Zhang ZQ, Zhang XN, Lu W, et al. Distinct patterns of serum hepatitis B core-related antigen during the natural history of chronic hepatitis B. BMC Gastroenterol. 2017;17:140. doi:10.1186/s12876-017-0703-9 3. Mak, LY,Wong DK, Cheung KS, et al. Hepatitis B core-related antigen (HbcrAg): an emerging marker for chronic hepatitis B virus infection. Aliment Pharmacol Ther. 2018;47(1):43-54. doi:10.1111/apt.14376 4. Van Halewijn GJ, Geurtsvankessel CH, Klaasse J, et al. Diagnostic and analytical performance of the hepatitis B core related antigen immunoassay in hepatitis B patients. J Clin Virol. 2019;114:1-5. doi:10.1016/j.jcv.2019.03.003

HEAB
80973

Hepatitis B Virus e Antibody, Serum

Clinical Information: During recovery from acute hepatitis B, the hepatitis B e virus antigen (HBeAg) level declines and becomes undetectable and HBe antibody (anti-HBe) appears in the serum.

Anti-HBe usually remains detectable for many years after recovery from acute hepatitis B. In hepatitis B virus (HBV) carriers and in patients with chronic hepatitis B, positive anti-HBe results usually indicate inactivity of the virus and low infectivity of the patients. Positive anti-HBe results in the presence of detectable HBV DNA in serum indicate active viral replication. For more information, see the following: -Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management -Viral Hepatitis Serologic Profiles

Useful For: Determining the presence or absence of detectable hepatitis B virus e antibody in monitoring infection status of individuals with chronic hepatitis B Determining infectivity of hepatitis B virus (HBV) carriers Monitoring serologic response of chronically HBV-infected patients receiving antiviral therapy

Interpretation: Absence of hepatitis B e antigen (HBeAg) with appearance of HBe antibody (anti-HBe) is consistent with inactivity of the virus and loss of hepatitis B virus (HBV) infectivity. Although resolution of chronic HBV infection generally follows the appearance of anti-HBe, the HBV carrier state may persist.

Reference Values:
Negative

See Viral Hepatitis Serologic Profiles.

Clinical References: 1. LeFevre ML, U.S. Preventive Services Task Force: Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014; 161(1):58-66. doi:10.7326/M14-1018 2. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016; 63(1):261-283 3. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; February 2017. Accessed December21, 2023. Available at www.who.int/publications/i/item/9789241549981 4. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis. 2018; 12(1):5-11. doi:10.1002/cld.729 5. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019; 156(2):355-368. doi:10.1053/j.gastro.2018.11.037 6. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC Recommendations-United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25

HEAG
8311

Hepatitis B Virus e Antigen and Hepatitis B Virus e Antibody, Serum

Clinical Information: Hepatitis B virus (HBV) e antigen (HBeAg) is a small polypeptide, which exists in a free form in the serum of individuals during the early phase of hepatitis B infection, soon after hepatitis B virus surface antigen (HBsAg) becomes detectable. Serum levels of both HBeAg and HBsAg rise rapidly during the period of viral replication. The presence of HBeAg in serum correlates with viral infectivity, the number of infectious virions, and the presence of HBV core antigen in the infected hepatocytes. During recovery from acute hepatitis B, HBeAg level declines and becomes undetectable in the serum, while HBe antibody (anti-HBe) appears and becomes detectable in the serum. Anti-HBe usually remains detectable for many years after recovery from acute HBV infection. In HBV carriers and patients with chronic hepatitis B, positive HBeAg results usually indicate presence of active HBV replication and high infectivity. A negative HBeAg result indicates very minimal or no HBV replication. Positive anti-HBe test results usually indicate inactivity of the virus and low infectivity, and such positive results in the presence of detectable HBV DNA in serum also indicate active viral replication in these patients.

Useful For: Determining the presence or absence of detectable hepatitis B virus e antigen and antibody in monitoring infection status of individuals with chronic hepatitis B Determining infectivity of hepatitis B virus (HBV) carriers Monitoring serologic response of chronically HBV-infected patients receiving antiviral therapy

Interpretation: Presence of hepatitis B virus e antigen (HBeAg) and absence of HBe antibody (anti-HBe) usually indicate active hepatitis B virus (HBV) replication and high infectivity. Absence of HBeAg with appearance of anti-HBe is consistent with loss of HBV infectivity. Although resolution of chronic HBV infection generally follows the appearance of anti-HBe, the HBV carrier state may persist.

Reference Values:
HEPATITIS Be ANTIGEN:
Negative

HEPATITIS Be ANTIBODY:
Negative

For more information see Viral Hepatitis Serologic Profiles.

Clinical References: 1. LeFevre ML, U.S. Preventive Services Task Force: Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 2. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016; 63(1):261-283 3. WHO guidelines on hepatitis B and C testing. World Health Organization; 2017. Accessed December 21, 2023. Available at www.who.int/publications/i/item/9789241549981 4. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis. 2018; 12(1):5-11. doi:10.1002/cld.729 5. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019; 156(2):355-368. doi:10.1053/j.gastro.2018.11.037 6. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25

EAG
80510

Hepatitis B Virus e Antigen, Serum

Clinical Information: Hepatitis B virus e antigen (HBeAg) is found in the early phase of hepatitis B infection soon after hepatitis B virus surface antigen becomes detectable. Serum levels of both antigens rise rapidly during the period of viral replication. The presence of HBeAg correlates with hepatitis B virus (HBV) infectivity, the number of infectious virions, and the presence of HBV core antigen in the infected hepatocytes. In HBV carriers and patients with chronic hepatitis B, positive HBeAg results usually indicate presence of active HBV replication and high infectivity. A negative HBeAg result indicates very minimal or no HBV replication. For more information, see the following: -Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management -Viral Hepatitis Serologic Profiles

Useful For: Determining the presence or absence of detectable hepatitis B virus e antigen in monitoring infection status of individuals with chronic hepatitis B Determining infectivity of hepatitis B virus (HBV) carriers Monitoring serologic response of chronically HBV-infected patients receiving antiviral therapy

Interpretation: Presence of hepatitis B virus e antigen (HBeAg) and absence of HBe antibody (anti-HBe) usually indicate active hepatitis B virus (HBV) replication and high infectivity. Absence of HBeAg with appearance of anti-HBe is consistent with loss of HBV infectivity.

Reference Values:
Negative

Clinical References:

FHBG
57618

Hepatitis B Virus Genotyping

Reference Values:
Interpretive Information: Hepatitis B Virus Genotype

HBV genotype and resistance interpretation is provided by SeqHepB software from Evivar Medical. The following mutations are reported: reverse transcriptase L80I/V, Il69T, V173L, L180M, A181S/T/V, T184A/C/F/I/G/S/M/L, S202C/G/I, M204I/V, N236T, M250I/L/V; surface antigen P120T, D144A, G145R.

Both the HBV RT polymerase and the HBsAg encoding regions are sequenced. Resistance and surface antigen mutations are reported. In addition, the major HBV genotypes are identified. Mutations in viral sub-populations below 20% of total may not be detected.

This test is performed pursuant to a license agreement with Roche Molecular Systems, Inc.

HBPES
615271

Hepatitis B Virus Past Exposure Panel, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. HBV is transmitted parenterally or percutaneously from exposure to contaminated blood, blood products, or injection needles, sexually from exposure to body fluids from infected individuals, or perinatally from mother to child during birth delivery by contact with infected mother's blood and vaginal secretions. Transplacental transmission from mother to fetus is uncommon. HBV persists and causes chronic infection (defined as being positive for hepatitis B virus surface antigen [HBsAg] in serum or plasma for minimum 6 months) in about 10% of individuals who had acute infection during childhood. These individuals may become asymptomatic HBV carriers (ie, inactive chronic hepatitis B), while others may develop chronic liver diseases including cirrhosis and hepatocellular carcinoma. Asymptomatic HBV carriers are at risk (up to 50%) for decompensation of liver function with acute HBV replication (ie, HBV reactivation) during immunosuppression from chemotherapy, immunosuppressive therapy, or organ transplantation. Individuals who recovered from acute hepatitis B (defined as being negative for HBsAg, positive for HBc total antibodies, negative or positive for HBs antibody) are at lower risk (up to 20%) of HBV reactivation than those with inactive chronic hepatitis B during immunosuppressive therapy or organ transplantation. For individuals born in regions of the world where HBV prevalence is moderate to high, universal HBV serologic screening before initiation of immunosuppressive therapy is recommended. In the absence of systematic, risk-based testing, universal HBV serologic screening is an option to reduce the risk of missing persons with HBV infection prior to initiation of immunosuppressive treatment.

Useful For: Screening for past exposure to hepatitis B virus (HBV) Determining HBV infection and immunity status prior to initiating chemotherapy or other immunosuppressive agents

Interpretation:

Reference Values:
Negative
See Viral Hepatitis Serologic Profiles.

Clinical References:

HBABY 63137 Hepatitis B Virus Perinatal Exposure Follow-up Panel, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles among injection drug users). The virus is found in virtually every type of human body fluid and is also spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. Infection of the infant can occur if the mother is a chronic hepatitis B surface antigen (HBsAg) carrier or has an acute HBV infection at the time of delivery. Transmission is rare if an acute infection occurs in either the first or second trimester of pregnancy. After a course of acute illness, HBV persists in about 10% of patients who were infected during adulthood. Some chronic carriers are asymptomatic while others may develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. Without postexposure prophylaxis (a combination of HBV vaccination and hepatitis B immune globulin), the risk of an infant acquiring HBV from an infected mother as a result of perinatal exposure is 70% to 90% for infants born to mothers who are positive for HBsAg and HBeAg. The risk is 5% to 20% for infants born to HBsAg-positive but HBeAg-negative mothers.

Useful For: Determining hepatitis B virus infection and immunity status (with or without perinatal prophylaxis) in infants born to mothers with chronic hepatitis B

Interpretation: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in blood 6 to 8 weeks after exposure to hepatitis B virus (HBV). A confirmed positive HBsAg result is indicative of acute or chronic hepatitis B. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6-months duration indicates development of either a chronic carrier state or chronic hepatitis B. Hepatitis B surface antibody (anti-HBs) appears with the resolution of HBV infection and disappearance of HBsAg. A positive result indicates recovery from acute or chronic hepatitis B or acquired immunity from HBV vaccination. This assay does not differentiate between a vaccine-induced immune response and recovery from HBV infection. Per assay manufacturer's instructions for use, positive results are defined as anti-HBs levels of 11.5 mIU/mL or greater, with adequate immunity to hepatitis B after recovery from past infection or HBV vaccination. Per current Centers for Disease Control and Prevention guidance, individuals with anti-HBs levels of 10 mIU/mL or greater after completing an HBV vaccination series are considered protected from hepatitis B infection.(1) Negative ant-HBs results, defined as anti-HBs levels of less than 8.5 mIU/mL, indicate a lack of recovery from acute or chronic hepatitis B or inadequate immune response to HBV vaccination. Indeterminate anti-HBs results, defined as anti-HBs levels in the range from 8.5 to less than 11.5 mIU/mL, indicate inability to determine if anti-HBs is present at levels consistent with recovery or immunity. Repeat testing in 1 to 3 months is recommended to determine definitive anti-HBs status. Hepatitis B virus core (HBc) total and IgM antibodies appear shortly after the onset of symptoms of HBV infection and may be the only serologic marker remaining years after exposure to HBV. A positive result indicates exposure to HBV infection. A positive anti-HBs result along with a positive HBc total antibody result is indicative of recovery from HBV infection. A positive anti-HBs result with a negative HBc total antibody result is consistent with immunity to hepatitis B from HBV vaccination. For more information see: -Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management -Viral Hepatitis Serologic Profiles

Reference Values:

Negative

See Viral Hepatitis Serologic Profiles.

Clinical References: 1. LeFevre ML; U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force

recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 2. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560-1599. Available at https://journals.lww.com/hep/fulltext/2018/04000/update_on_prevention,_diagnosis,_and_treatment_of.34.aspx 3. Centers for Disease Control and Prevention: Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep. 2018;67(1):1-31. Available at www.cdc.gov/mmwr/volumes/67/rr/pdfs/rr6701-H.PDF 4. Centers for Disease Control and Prevention (CDC), Division of Viral Hepatitis: Interpretation of hepatitis B serologic test results. CDC; Accessed December 21, 2023. Available at www.cdc.gov/hepatitis/hbv/interpretationOfHepBSerologicResults.htm 5. Centers for Disease Control and Prevention: Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations-United States, 2023. CDC; Updated August 10, 2023. Accessed December 21, 2023. Available at www.cdc.gov/mmwr/volumes/72/rr/rr7201a1.htm?s_cid=rr7201a1_w

HBABT
87893

Hepatitis B Virus Surface Antibody Monitor, Post-Transplant, Serum

Clinical Information: For patients with chronic hepatitis B, outcomes following liver transplantation for end-stage liver disease are poor. Recurrent hepatitis B is common and associated with decreased liver graft and patient survival (approximately 50% at 5 years). Studies have shown administration of hepatitis B immune globulin (HBIG) in the perioperative and early posttransplant periods could delay or prevent recurrent hepatitis B virus (HBV) infection in these transplant recipients. Since mid-1990, intravenous or intramuscular administration of HBIG has become the standard of care for these liver transplant recipients in most liver transplant programs in the United States. Most therapy protocols administer HBIG in high doses (10,000 IU) during the perioperative period and first week after transplantation with the goal of achieving serum hepatitis B virus surface antibody (anti-HBs) levels of above 500 mIU/mL. Serial levels of anti-HBs are obtained to determine the pharmacokinetics of HBIG in each patient to guide frequency of HBIG dosing. During the first few weeks to months after transplantation, there is a high degree of variability in HBIG dosage required to achieve desirable serum anti-HBs levels among transplant recipients. Patients who were hepatitis B e antigen positive before transplantation usually require more HBIG to achieve the target anti-HBs levels, especially in the first week after transplantation. Duration of HBIG therapy varies from 6 months to indefinite among different US liver transplant programs. Protocols providing less than 12 months of therapy usually combine HBIG with another effective anti-HBV agent, such as lamivudine.

Useful For: Monitoring serum hepatitis B virus surface antibody levels during intravenous or intramuscular hepatitis B immune globulin therapy to prevent hepatitis B virus reinfection in liver transplant recipients with known previous chronic hepatitis B

Interpretation: Refer to the healthcare provider's institutional hepatitis B immune globulin (HBIG) therapy protocol for desirable hepatitis B virus surface antibody (anti-HBs) levels. Studies indicated that serum anti-HBs levels needed to prevent hepatitis B virus reinfection were greater than 500 mIU/mL during the first week after transplantation, greater than 250 mIU/mL during weeks 2 to 12, and greater than 100 mIU/mL after week 12. For more information see HBV Infection-Monitoring Before and After Liver Transplantation

Reference Values:
Not applicable

Clinical References:

HBABP
610465

Hepatitis B Virus Surface Antibody Prenatal, Qualitative/Quantitative, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through blood transfusion or percutaneous contact with infected blood products, such as sharing of needles among injection drug users. The virus is found in virtually every type of human body fluid and has been known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted via the transplacental route. The incubation period for HBV infection averages 60 to 90 days (range of 45-180 days). Common symptoms include malaise, fever, gastroenteritis, and jaundice (icterus). After acute infection, HBV infection becomes chronic in 30% to 90% of infected children younger than 5 years and in 5% to 10% of infected individuals 5 years or older. Some of these chronic carriers are asymptomatic, while others progress to chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis B surface antigen (HBsAg) is the first serologic marker, appearing in the serum 6 to 8 weeks following HBV infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms with the appearance of hepatitis B surface antibody (anti-HBs). Anti-HBs also appears as the immune response following hepatitis B vaccination.

Useful For: Identifying previous exposure to hepatitis B virus in pregnant individuals Determining adequate immunity from hepatitis B vaccination during pregnancy

Interpretation: A positive result indicates recovery from acute or chronic hepatitis B or acquired immunity from hepatitis B virus (HBV) vaccination. This assay does not differentiate between a vaccine-induced immune response and an immune response induced by HBV. A positive total hepatitis B core antibody result would indicate that the hepatitis B surface antibody (anti-HBs) response is due to past HBV infection. Per assay manufacturer's instructions for use, positive results, defined as anti-HBs levels of 11.5 mIU/mL or greater, indicate adequate immunity to hepatitis B from past hepatitis B or HBV vaccination. However, per current Centers for Disease Control and Prevention guidance,(1) individuals with anti-HBs levels greater than 10 mIU/mL after completing an HBV vaccination series are considered protected from hepatitis B. Negative results, defined as anti-HBs levels of less than 8.5 mIU/mL, indicate a lack of recovery from acute or chronic hepatitis B or inadequate immune response to HBV vaccination. The US Advisory Committee on Immunization Practices does not recommend more than 2 HBV vaccine series in vaccine nonresponders. Indeterminate results, defined as anti-HBs levels in the range from 8.5 to less than 11.5 mIU/mL, indicate inability to determine if anti-HBs is present at levels consistent with recovery or immunity. Repeat testing in 1 to 2 months is recommended to determine definitive anti-HBs status. For more information see Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management

Reference Values:

Hepatitis B Surface Antibody
Unvaccinated: Negative
Vaccinated: Positive

Hepatitis B Surface Antibody, Quantitative
Unvaccinated: <8.5 mIU/mL
Vaccinated: > or =11.5 mIU/mL

See Viral Hepatitis Serologic Profiles.

Clinical References: 1. Advisory Committee on Immunization Practices; Centers for Disease Control and Prevention: Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011 Nov 25;60(RR-7):1-45 2. LeFevre ML; U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in

nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014; 161(1):58-66. doi:10.7326/M14-1018 3. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis. 2018;12(1):5-11. doi:10.1002/cld.729 4. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019;156(2):355-368. doi:10.1053/j.gastro.2018.11.037 5. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; February 2017. Accessed December 19, 2023. Available at www.who.int/publications/i/item/9789241549981 6. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

HBBSN
610474

Hepatitis B Virus Surface Antibody Screen, Qualitative/Quantitative, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through blood transfusion or percutaneous contact with infected blood products, such as sharing needles among injection drug users. The virus is found in virtually every type of human body fluid and has been known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted via the transplacental route. The incubation period for HBV infection averages 60 to 90 days (range of 45-180 days). Common symptoms include malaise, fever, gastroenteritis, and jaundice (icterus). After acute infection, HBV infection becomes chronic in 30% to 90% of infected children younger than 5 years and in 5% to 10% of infected individuals 5 years or older. Some chronic carriers are asymptomatic, while others progress to chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis B surface antigen (HBsAg) is the first serologic marker, appearing in the serum 6 to 8 weeks following HBV infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms with the appearance of hepatitis B surface antibody (anti-HBs). Anti-HBs also appears as the immune response following hepatitis B vaccination.

Useful For: Identifying previous exposure to hepatitis B virus

Interpretation: A positive result indicates recovery from acute or chronic hepatitis B virus (HBV) infection or acquired immunity from HBV vaccination. This assay does not differentiate between a vaccine-induced immune response and an immune response induced by HBV. A positive total hepatitis B core antibody result would indicate that the hepatitis B surface antibody (anti-HBs) response is due to past HBV infection. Per assay manufacturer's instructions for use, positive results, defined as anti-HBs levels of 11.5 mIU/mL or greater, indicate adequate immunity to HBV from past hepatitis B or HBV vaccination. However, per current Centers for Disease Control and Prevention guidance,(1) individuals with anti-HBs levels greater than 10 mIU/mL after completing an HBV vaccination series are considered protected from hepatitis B infection. Negative results, defined as anti-HBs levels of less than 8.5 mIU/mL, indicate a lack of recovery from acute or chronic hepatitis B or inadequate immune response to HBV vaccination. The US Advisory Committee on Immunization Practices does not recommend more than 2 HBV vaccine series in vaccine nonresponders. Indeterminate results, defined as anti-HBs levels in the range from 8.5 to less than 11.5 mIU/mL, indicate inability to determine if anti-HBs is present at levels consistent with recovery or immunity. Repeat testing is recommended in 1 to 2 months to determine definitive anti-HBs status. For more information see Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management.

Reference Values:
Hepatitis B Surface Antibody
Unvaccinated: Negative
Vaccinated: Positive

Hepatitis B Surface Antibody, Quantitative
Unvaccinated: <8.5 mIU/mL
Vaccinated: > or =11.5 mIU/mL

See Viral Hepatitis Serologic Profiles

Clinical References: 1. Advisory Committee on Immunization Practices; Centers for Disease Control and Prevention: Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011 Nov 25;60(RR-7):1-45 2. LeFevre ML: U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 3. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis. 2018;12(1):5-11. doi:10.1002/cld.729 4. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019;156(2):355-368. doi:10.1053/j.gastro.2018.11.037 5. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; February 2017. Accessed December 19, 2023. Available at www.who.int/publications/i/item/9789241549981 6. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

HBAB
8254

Hepatitis B Virus Surface Antibody, Qualitative/Quantitative, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through blood transfusion or percutaneous contact with infected blood products, such as sharing of needles among injection drug users. The virus is found in virtually every type of human body fluid and has been known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted via the transplacental route. The incubation period for HBV infection averages 60 to 90 days (range of 45-180 days). Common symptoms include malaise, fever, gastroenteritis, and jaundice (icterus). After acute infection, HBV infection becomes chronic in 30% to 90% of infected children younger than 5 years and in 5% to 10% of infected individuals 5 years or older. Some of these chronic carriers are asymptomatic, while others progress to chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis B surface antigen (HBsAg) is the first serologic marker, appearing in the serum 6 to 8 weeks following HBV infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms with the appearance of HBs antibody (anti-HBs). Anti-HBs also appears as the immune response following hepatitis B vaccination.

Useful For: Identifying previous exposure to hepatitis B virus Determining adequate immunity from hepatitis B vaccination

Interpretation: A positive result indicates recovery from acute or chronic hepatitis B virus (HBV) infection or acquired immunity from HBV vaccination. This assay does not differentiate between a vaccine-induced immune response and an immune response induced by HBV. A positive hepatitis B core (anti-HBc) total antibody result would indicate that the hepatitis B surface antibody (anti-HBs) response is due to past HBV infection. Per assay manufacturer's instructions for use, positive results, defined as anti-HBs levels of 11.5 mIU/mL or greater, indicate adequate immunity to HBV from past hepatitis B or HBV vaccination. However, per current Centers for Disease Control and Prevention guidance,(1) individuals with anti-HBs levels greater than 10 mIU/mL after completing an HBV vaccination series are considered protected from hepatitis B infection. Negative results, defined as anti-HBs levels of less than 8.5 mIU/mL,

indicate a lack of recovery from acute or chronic hepatitis B or inadequate immune response to HBV vaccination. The US Advisory Committee on Immunization Practices does not recommend more than 2 HBV vaccine series in vaccine nonresponders. Indeterminate results, defined as anti-HBs levels in the range from 8.5 to less than 11.5 mIU/mL, indicate inability to determine if anti-HBs is present at levels consistent with recovery or immunity. Repeat testing is recommended in 1 to 2 months to determine definitive anti-HBs status. For more information see Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management.

Reference Values:

Hepatitis B Surface Antibody
Unvaccinated: Negative
Vaccinated: Positive

Hepatitis B Surface Antibody, Quantitative
Unvaccinated: <8.5 mIU/mL
Vaccinated: > or =11.5 mIU/mL

See Viral Hepatitis Serologic Profiles.

Clinical References: 1. Advisory Committee on Immunization Practices; Centers for Disease Control and Prevention: Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011 Nov 25;60(RR-7):1-45 2. LeFevre ML. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 3. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis. 2018; 12(1):5-11. doi:10.1002/cld.729 4. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019;156(2):355-368. doi:10.1053/j.gastro.2018.11.037 5. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; February 2017. Accessed December 21, 2023. Available at www.who.int/publications/i/item/9789241549981 6. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

HBNTP
35936

Hepatitis B Virus Surface Antigen Confirmation, Prenatal, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles among injection drug users). The virus is found in various human body fluids, and it is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 8 weeks following exposure to HBV. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months in duration indicates development of either a chronic carrier state or chronic HBV infection. For more information see: -Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profiles

Useful For: Diagnosis of acute, recent, or chronic hepatitis B in prenatal patients This test is not useful during the "window period" of acute hepatitis B (ie, after disappearance of hepatitis B virus surface antigen [HBsAg] and prior to appearance of HBs antibody). This test is not suitable as stand-

alone prenatal screening test of HBsAg status in pregnant women. This test is not offered as a HBsAg screening or confirmatory test for blood donor specimens.

Interpretation: A reactive screen result (cutoff index values > or =1.00) confirmed as positive by a hepatitis B surface antigen (HBsAg) confirmatory test is indicative of acute or chronic hepatitis B or chronic hepatitis B virus (HBV) carrier state. Specimens with reactive screen results but negative (ie, not confirmed) HBsAg confirmatory test results are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. If clinically indicated, repeat testing, at a later date, is recommended. Confirmed presence of HBsAg is frequently associated with HBV replication and infectivity, especially when accompanied by presence of hepatitis B e (HBe) antigen or detectable HBV DNA.

Clinical References: 1. LeFevre ML, U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 2. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis. 2018;12(1):5-11. doi:10.1002/cld.729 3. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019;156(2):355-368. doi:10.1053/j.gastro.2018.11.037 4. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; February 2017. Accessed December 19, 2023. Available at www.who.int/publications/i/item/9789241549981 5. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

HBAGP
86185

Hepatitis B Virus Surface Antigen Prenatal, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles among injection drug users). The virus is found in various human body fluids, and it is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Infection of the infant can occur if the mother is a chronic hepatitis B surface antigen carrier or has an acute HBV infection at the time of delivery. Transmission is rare if an acute infection occurs in either the first or second trimester of pregnancy.

Useful For: Diagnosis of acute, recent, or chronic hepatitis B Determination of chronic hepatitis B status Screening pregnant women for evidence of chronic hepatitis B (or hepatitis B carrier state) to identify neonates who are at high risk of acquiring hepatitis B at birth This test should not be used as a screening or confirmatory test for blood donor specimens. This test is not useful for diagnosis of hepatitis B during the "window period" of acute HBV infection (ie, after disappearance of hepatitis B surface antigen and prior to appearance of hepatitis B surface antibody).

Interpretation: A reactive screen result (cutoff index value >1.00) confirmed as positive by hepatitis B surface antigen (HBsAg) confirmatory test is indicative of acute or chronic hepatitis B or chronic hepatitis B virus (HBV) carrier state. Specimens with initially reactive test results but negative (not confirmed) by HBsAg confirmatory testing are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. These unconfirmed HBsAg-reactive screening test results should be interpreted in conjunction with test results of other HBV serologic markers (eg, HBs antibody; hepatitis B core [HBc] total antibody, and HBc IgM antibody). If clinically indicated, repeat testing at a later date is recommended. Confirmed presence of HBsAg is frequently associated with HBV replication and infectivity, especially when accompanied by the presence of HBe antigen or detectable HBV DNA.

Reference Values:

Negative
See Viral Hepatitis Serologic Profiles.

Clinical References: 1. LeFevre ML; U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 2. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis. 2018;12(1):5-11. doi:10.1002/cld.729 3. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019;156(2):355-368. doi:10.1053/j.gastro.2018.11.037 4. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; February 2017. Accessed December 21, 2023. Available at www.who.int/publications/i/item/9789241549981 5. Centers for Disease Control and Prevention: Testing and public health management of persons with chronic hepatitis B virus infection. CDC; Updated March 28, 2022. Accessed December 21, 2023. Available at www.cdc.gov/hepatitis/hbv/testingchronic.htm 6. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

HBGSN
610468

Hepatitis B Virus Surface Antigen Screen, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles among injection drug users). The virus is also found in various human body fluids, and it is known to be spread through oral and genital contacts. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Hepatitis B virus surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 8 weeks following exposure to HBV. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months in duration indicates development of either a chronic carrier state or chronic HBV infection.

Useful For:

Interpretation: A reactive screen result (cutoff index value >1.00) confirmed as positive by hepatitis B virus surface antigen (HBsAg) confirmatory test is indicative of acute or chronic hepatitis B or chronic hepatitis B virus (HBV) carrier state. Specimens with initially reactive screen results, but negative (not confirmed) by HBsAg confirmatory test results, are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. These unconfirmed HBsAg-reactive screening test results should be interpreted in conjunction with test results of other HBV serologic markers (eg, HBs antibody; hepatitis B core [HBc] total antibody, and HBc IgM antibody). If clinically indicated, repeat testing at a later date is recommended. Confirmed presence of HBsAg is frequently associated with HBV replication and infectivity, especially when accompanied by presence of hepatitis B e antigen or detectable HBV DNA. See the following: -Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profiles

Reference Values:
Negative

See Viral Hepatitis Serologic Profiles

Clinical References: 1. LeFevre ML. U.S. Preventive Services Task Force. Screening for hepatitis

B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 2. Jackson K, Locarnini S, Gish R. Diagnostics of Hepatitis B Virus: Standard of Care and Investigational. Clin Liver Dis (Hoboken). 2018;12(1):5-11. doi:10.1002/cld.729 3. Coffin CS, Zhou K, Terrault NA. New and Old Biomarkers for Diagnosis and Management of Chronic Hepatitis B Virus Infection. Gastroenterology. 2019;156(2):355-368.e3. doi:10.1053/j.gastro.2018.11.037 4. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; February 2017. Accessed December 21, 2023. Available at www.who.int/publications/i/item/9789241549981 5. Centers for Disease Control and Prevention. Testing and public health management of persons with chronic hepatitis B virus infection. CDC; Updated March 28, 2022. Accessed December 21, 2023. Available at www.cdc.gov/hepatitis/hbv/testingchronic.htm 6. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

HBAGQ
621764

Hepatitis B Virus Surface Antigen, Quantitative, Serum

Clinical Information: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum or plasma at 6 to 16 weeks following exposure to hepatitis B virus (HBV). In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months in duration indicates development of either a chronic carrier state or chronic HBV infection. Production of HBsAg is modulated by the interplay between the virus and host immune response, and the HBsAg level in serum inversely correlates with the immune control of HBV: the higher the immune control, the lower the HbsAg level in the infected individual. Quantitative HbsAg levels in serum or plasma reflect the amount and transcriptional activity of covalently closed circular DNA (cccDNA) inside the hepatocytes of individuals with chronic hepatitis B (CHB). Therefore, quantitative HBsAg provides information concerning disease activity over and above an estimation of viral replication. In general, together with HBV DNA in serum or plasma, quantification of HBsAg in the same specimen is useful in the diagnosis of the true inactive HBV carrier state and in monitoring the clinical response to pegylated-interferon (PegIFN) and/or nucleoside/nucleotide analog (NA) therapy for CHB. The inactive HBV carrier state is often defined by persistently normal alanine aminotransferase levels and low HBV DNA levels in serum or plasma (<2000 IU/mL) in an individual negative for hepatitis B e antigen (HBeAg) with no or minimal liver injury. These individuals can have very good prognosis without the need of antiviral therapy, despite having fluctuating levels of HBV DNA over time. Some patients have low HBV DNA levels at one time but viral and biochemical reactivation later. The HBsAg levels in serum or plasma of inactive HBV carriers tend to change very slowly with time and remain at low levels (ie, <1000 IU/mL), serving as a useful adjunct to HBV DNA level to aid in the identification of these individuals. Clinical studies have shown that the change of HBsAg level in serum or plasma during PegIFN therapy mimics the change of both intrahepatic cccDNA and intrahepatic HBsAg, suggesting that a decline of HBsAg level in serum or plasma is associated with the induction of an effective anti-HBV immune response for monitoring CHB patients treated with PegIFN. Since decline of HBsAg level in serum or plasma during PegIFN therapy is confined mainly to patients who achieve therapeutic response, monitoring of HBsAg levels help distinguish patients likely to achieve a response from those who will not. On treatment, HBsAg levels at weeks 12 and 24 of PegIFN therapy have high negative predictive values for therapeutic response and are useful to serve as stopping rules for the non-responders. Although HBV DNA remains the key molecular marker to monitor the response and adherence of NA treatment in CHB patients, monitoring of the HBsAg level every 6 months can give an estimate on the duration of NA treatment needed to achieve HBsAg seroclearance. HBsAg levels may be useful to predict HBV reactivation or sustained response after cessation of NA therapy. Currently, HBsAg seroclearance is still the acceptable endpoint to stop NA in patients who are HBeAg negative.

Useful For: Monitoring of progression of chronic hepatitis B in individuals who are confirmed to be positive for hepatitis B surface antigen Monitoring of response to antiviral therapy in individuals who have chronic hepatitis B but are negative for hepatitis B e antigen and positive for hepatitis B e antibody

Interpretation: This assay quantifies hepatitis B surface antigen (HBsAg) in serum within the range of 0.005 to 150 IU/mL. A result of less than 0.005 IU/mL indicates that HBsAg is present in the serum specimen at a level below the lower limit of quantification of this assay. A result of greater than 150 IU/mL indicates that HBsAg is present in the serum specimen at a level above the upper limit of quantification of this assay. In untreated hepatitis B e antigen (HBeAg)-positive patients, HBsAg levels of greater than 100,000 IU/ml are associated with high replicative HBsAg carrier (immune tolerance). In untreated, HBeAg-negative patients, HBsAg levels of less than 1000 IU/ml and hepatitis B virus DNA less than 2000 IU/ml in serum or plasma are associated with lower risk for hepatocellular carcinoma, while HBsAg levels of less than 100 IU/ml are associated with high rates of spontaneous HBsAg clearance.

Reference Values:
<0.005 IU/mL

Clinical References: 1. Wong GLH, Chan HL. Use of quantitative hepatitis B surface antigen with hepatitis B virus DNA in clinical practice. Clin Liver Dis. 2013;2(1):8-10. doi:10.1002/cld.165 2. Tseng TC, Kao JH: Clinical utility of quantitative HBsAg in natural history and nucleos(t)ide analogue treatment of chronic hepatitis B: new trick of old dog. J Gastroenterol. 2013;48(1):13-21. doi:10.1007/s00535-012-0668-y 3. Choi SJ, Park Y, Lee EY, et al. Performance evaluation of LUMIPULSE G 1200 autoimmunoanalyzer for the detection of serum hepatitis B virus markers. J Clin Lab Anal. 2013;27(3):204-206. doi:10.1002/jcla.21584 4. Yang R, Song G, Guan W, Wang Q, Liu Y, Wei L. The lumipulse g HBsAg-quant assay for screening and quantification of the hepatitis B surface antigen. J Virol Methods. 2016;228:39-47 5. Cornberg M, Wong VWS, Locarnini S, Brunetto M, Janssen HLA, Chan HL. The role of quantitative hepatitis B surface antigen revisited. J Hepatol. 2017;66(2):398-411. doi:10.1016/j.jhep.2016.08.009

HBAG
9013

Hepatitis B Virus Surface Antigen, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles among injection drug users). The virus is also found in various human body fluids, and it is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. HBV surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 8 weeks following exposure to HBV. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months in duration indicates development of either a chronic carrier state or chronic HBV infection.

Useful For: Diagnosis of acute, recent, or chronic hepatitis B Determination of chronic hepatitis B status This test should not be used as a screening or confirmatory test for blood donor specimens.

Interpretation: A reactive screen result (cutoff index value >1.00) confirmed as positive by hepatitis B surface antigen (HBsAg) confirmatory test is indicative of acute or chronic hepatitis B, or chronic hepatitis B virus (HBV) carrier state. Specimens with initially reactive screen results, but negative (not confirmed) by HBsAg confirmatory test results, are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. These unconfirmed HBsAg-reactive screening test results should be interpreted in conjunction with test results of other HBV serologic markers (eg, HBs antibody; hepatitis B core [HBc] total antibody, and HBc IgM antibody). If clinically indicated, repeat testing at a later date is recommended. Confirmed presence of HBsAg is frequently associated with HBV replication and infectivity, especially when accompanied by presence of hepatitis B e antigen or detectable HBV DNA. For more information see: -Hepatitis B: Testing Algorithm for Screening, Diagnosis, and Management -HBV Infection-Monitoring Before and After Liver Transplantation -Viral

Hepatitis Serologic Profiles

Reference Values:
Negative

See Viral Hepatitis Serologic Profiles

Clinical References: 1. LeFevre ML, U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(1):58-66. doi:10.7326/M14-1018 2. Jackson K, Locarnini S, Gish R. Diagnostics of hepatitis B virus: Standard of care and investigational. Clin Liver Dis. 2018;12(1):5-11. doi:10.1002/cld.729 3. Coffin CS, Zhou K, Terrault NA. New and old biomarkers for diagnosis and management of chronic hepatitis B virus infection. Gastroenterology. 2019;156(2):355-368. doi:10.1053/j.gastro.2018.11.037 4. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; February 2017. Accessed December 23, 2024. Available at www.who.int/publications/i/item/9789241549981 5. Centers for Disease Control and Prevention: Testing and public health management of persons with chronic hepatitis B virus infection. CDC; Updated March 6, 2024. Accessed December 23, 2024. Available at www.cdc.gov/hepatitis-b/hcp/diagnosis-testing/ 6. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC recommendations - United States, 2023. MMWR Recomm Rep. 2023;72(1):1-25. doi:10.15585/mmwr.rr7201a1

HCVSP
609748

Hepatitis C Virus (HCV) Antibody Screen Prenatal, Serum

Clinical Information: Hepatitis C virus (HCV) is recognized as the cause of most cases of posttransfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 2.4 million chronically HCV-infected individuals. Laboratory testing for HCV infection usually begins by screening for the presence of HCV-specific antibodies in serum, using an US Food and Drug Administration-approved screening test. Specimens that are repeatedly reactive by screening tests should be confirmed with HCV tests with higher specificity, such as direct detection of HCV RNA by reverse transcription-polymerase chain reaction or HCV-specific antibody confirmatory tests. Hepatitis C virus antibodies are usually not detectable during the first 2 months following infection, but they are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies do not neutralize the virus and they do not provide immunity against this viral infection. Current screening serologic tests to detect antibodies to HCV include enzyme and chemiluminescence immunoassays. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing exist: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable HCV-specific antibodies in immunocompromised individuals -False-reactive screening test result can occur -A reactive screening test result does not distinguish between past (resolved) and present HCV infection -Serologic tests cannot provide information on clinical response to anti-HCV therapy Reactive screening test results should be followed by a supplemental or confirmatory test, such as a nucleic acid test for HCV RNA or HCV antibody confirmatory test. Nucleic acid tests provide a very sensitive and specific approach for the direct detection of HCV RNA. For more information see Hepatitis C: Testing Algorithm for Screening and Diagnosis.

Useful For: Screening of pregnant women for hepatitis C virus (HCV) infection in primary care settings, with or without risk factors for hepatitis C This test should not be used as a screening test for hepatitis C in blood or human cells/tissue donors. This test profile is not useful for detection or diagnosis of acute hepatitis C since HCV antibodies may not be detectable until after 2 months following exposure and HCV RNA testing is not performed on specimens with negative HCV antibody screening test results.

Interpretation: Reactive hepatitis C virus (HCV) antibody screening results with cutoff index (COI) values less than or equal to 20.0 with this assay are not predictive of the true HCV antibody status. Additional testing is recommended to confirm HCV antibody status. Reactive results with COI values greater than 20.0 with this assay are highly predictive (95% or greater probability) of the true HCV antibody status, but additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. Based on Centers for Disease Control and Prevention recommendations, reactive HCV antibody screen results should be followed by HCV RNA testing (HCVQN). Detection of HCV RNA indicates current HCV infection. If HCV RNA is not detected, that indicates either past, resolved HCV infection, or false HCV antibody positivity. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to low antibody levels that are below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with acute or recent HCV infections (<2 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks). Testing for HCV RNA using HCVRP / Hepatitis C Virus (HCV) RNA Detection and Quantification, Real-Time Reverse Transcription-PCR Prenatal, Serum is recommended for detection of HCV infection in such patients.

Reference Values:
Negative

For more information see Viral Hepatitis Serologic Profiles.

Clinical References: 1. Centers for Disease Control and Prevention (CDC). Testing for HCV infection: an update of guidance for clinicians and laboratorians. Morb Mortal Wkly Rep. 2013;62(18):362-365 2. Society for Maternal-Fetal Medicine (SMFM). Hughes BL, Page CM, Kuller JA: Hepatitis C in pregnancy: screening, treatment, and management. Am J Obstet Gynecol. 2017; 217(5):B2-B12 3. Centers for Disease Control and Prevention (CDC). Pregnancy and HIV, viral hepatitis STD and TB prevention: HCV challenges. CDC; Reviewed October 31, 2023. Accessed. December 19, 2023. Available at www.cdc.gov/nchhstp/pregnancy/challenges/hcv.html 4. Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC Recommendations for hepatitis C screening among adults - United States, 2020. MMWR Recomm Rep. 2020;69(2):1-17 5. American Association for the Study of Liver Diseases and Infectious Diseases Society of America: HCV guidance: Recommendations for testing, managing, and treating hepatitis C. Updated October 24, 2022. Accessed December 19, 2023. Available at www.hcvguidelines.org/evaluate/testing-and-linkage

HCSRN 113122 Hepatitis C Virus (HCV) Antibody Screen with Reflex to HCV RNA, PCR, Asymptomatic, Serum

Clinical Information: Hepatitis C virus (HCV) is recognized as the cause of most cases of posttransfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 2.4 million chronically HCV-infected individuals. Laboratory testing for HCV infection usually begins by screening for the presence of HCV-specific antibodies in serum, using an U.S. Food and Drug Administration-approved screening test. Specimens that are repeatedly reactive by screening tests should be confirmed with HCV tests with higher specificity, such as direct detection of HCV RNA by reverse transcription polymerase chain reaction or HCV-specific antibody confirmatory tests. HCV antibodies are usually not detectable during the first 2 months following infection, but they are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies do not neutralize the virus and they do not provide immunity against this viral infection. Current screening serologic tests to detect antibodies to HCV include enzyme immunoassay and chemiluminescence immunoassays. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing exist: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable HCV-specific

antibodies in immunocompromised individuals -False-reactive screening test result can occur -A reactive screening test result does not distinguish between past (resolved) and present HCV infection -Serologic tests cannot provide information on clinical response to anti-HCV therapy Reactive screening test results should be followed by a supplemental or confirmatory test, such as a nucleic acid test for HCV RNA or HCV antibody confirmatory test. Nucleic acid tests provide a very sensitive and specific approach for the direct detection of HCV RNA. For more information, see Hepatitis C: Testing Algorithm for Screening and Diagnosis.

Useful For: Screening for hepatitis C virus (HCV) infection in primary care settings in high-risk persons with a current or previous history of illicit injection drug use or a history of receiving a blood transfusion prior to 1992 Screening for hepatitis C in primary care settings in non-high-risk persons born from 1945 through 1965 Screening at least once in a lifetime for all adults greater or equal to 18 years, except in settings where the prevalence of HCV infection is less than 0.1% This test is not offered as a screening or confirmatory test for hepatitis C in blood or human cells/tissue donors. This test profile is not useful for detection or diagnosis of acute hepatitis C, since HCV antibodies may not be detectable until after 2 months following exposure and HCV RNA testing is not performed on specimens with negative HCV antibody screening test results.

Interpretation:

Reference Values:
Negative

See Viral Hepatitis Serologic Profiles

Clinical References: 1. Centers for Disease Control and Prevention (CDC). Testing for HCV infection: an update of guidance for clinicians and laboratorians. Morb Mortal Wkly Rep. 2013;62(18):362-365 2. Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC Recommendations for hepatitis C screening among adults - United States, 2020. MMWR Recomm Rep. 2020;69(2):1-17 3. Chou R, Dana T, Fu R, et al. Screening for hepatitis C virus infection in adolescents and adults: updated evidence report and systematic review for the U.S. Preventive Services Task Force. JAMA; 2020; 323(10):976-991. Accessed December 21, 2023. Available at https://jamanetwork.com/journals/jama/fullarticle/2762185 4. American Association for the Study of Liver Diseases and Infectious Diseases Society of America: HCV guidance: Recommendations for testing, managing, and treating hepatitis C. Accessed December 21, 2023. Available at www.hcvguidelines.org/evaluate/testing-and-linkage

HCVDX
113121

Hepatitis C Virus (HCV) Antibody with Reflex to HCV RNA, PCR, Symptomatic, Serum

Clinical Information: Hepatitis C virus (HCV) is recognized as the cause of most cases of posttransfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 2.4 million chronically HCV-infected individuals. Laboratory testing for HCV infection usually begins by screening for the presence of HCV-specific antibodies in serum, using an US Food and Drug Administration-approved screening test. Specimens that are repeatedly reactive by screening tests should be confirmed with HCV tests with higher specificity, such as direct detection of HCV RNA by reverse transcription polymerase chain reaction or HCV-specific antibody confirmatory tests. Hepatitis C virus antibodies are usually not detectable during the first 2 months following infection, but they are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies do not neutralize the virus and they do not provide immunity against this viral infection. Current screening serologic tests to detect antibodies to HCV include enzyme immunoassay and chemiluminescence immunoassay. Despite the value of serologic tests

to screen for HCV infection, several limitations of serologic testing exist: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable HCV-specific antibodies in immunocompromised individuals -False-reactive screening test result can occur -A reactive screening test result does not distinguish between past (resolved) and present HCV infection -Serologic tests cannot provide information on clinical response to anti-HCV therapy Reactive screening test results should be followed by a supplemental or confirmatory test, such as nucleic acid test for HCV RNA or HCV antibody confirmatory test. Nucleic acid tests provide a very sensitive and specific approach for the direct detection of HCV RNA. For more information see Hepatitis C: Testing Algorithm for Screening and Diagnosis.

Useful For: Diagnosis of recent or chronic hepatitis C virus (HCV) infection in symptomatic patients This test should not be used as a screening or confirmatory test for hepatitis C in blood or human cells/tissue donors. This test profile is not useful for detection or diagnosis of acute hepatitis C, since HCV antibodies may not be detectable until after 2 months following exposure and HCV RNA testing is not performed on specimens with negative HCV antibody screening test results.

Interpretation: Reactive hepatitis C virus (HCV) antibody screening results with cutoff index (COI) values less than or equal to 20.0 with this assay are not predictive of the true HCV antibody status. Additional testing is available to confirm HCV antibody status. Reactive results with COI values of greater than 20.0 with this assay are highly predictive (95% or greater probability) of the true HCV antibody status, but additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. Based on Centers for Disease Control and Prevention recommendations, reactive HCV antibody screen results should be followed by HCV RNA testing (HCVQN / Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR, Serum). Detection of HCV RNA indicates current HCV infection. If HCV RNA is not detected, that indicates either past, resolved HCV infection, or false HCV antibody positivity. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to low antibody levels that are below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with acute or recent HCV infections (<2 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks). Testing for HCV RNA using HCVQN / Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR, Serum is necessary for detection of HCV infection in such patients.

Reference Values:

Negative

For more information see Viral Hepatitis Serologic Profiles

Clinical References: 1. Centers for Disease Control and Prevention (CDC). Testing for HCV infection: an update of guidance for clinicians and laboratorians. Morb Mortal Wkly Rep. 2013;62(18):362-365 2. Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC Recommendations for hepatitis C screening among adults - United States, 2020. MMWR Recomm Rep. 2020;69(2):1-17 3. Chou R, Dana T, Fu R, et al. Screening for hepatitis C virus infection in adolescents and adults: updated evidence report and systematic review for the U.S. Preventive Services Task Force. JAMA. 2020;323(10):976-991 4. American Association for the Study of Liver Diseases and Infectious Diseases Society of America: HCV guidance: Recommendations for testing, managing, and treating hepatitis C. Updated October 24, 2022. Accessed August 12, 2024. Available at www.hcvguidelines.org/evaluate/testing-and-linkage

HCVQN
97291

Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR, Serum

Clinical Information: About 75% of all individuals infected with hepatitis C virus (HCV) will develop chronic hepatitis C with ongoing viral replication in the liver and detectable HCV RNA in serum or plasma, eventually resulting in cirrhosis. The remaining 25% of the infected individuals recover from the infection without evidence of viral replication or presence of detectable HCV RNA in serum or plasma. Chronic HCV infection can be cured at variable success rates with either combined interferon-alpha and ribavirin therapy or interferon-free combination of direct-acting antiviral (DAA) agents. The antiviral response rates correlate with pretreatment serum or plasma HCV RNA levels (viral load) and the HCV genotype found in the infected individuals. The optimal duration of combined interferon and ribavirin therapy can be determined from the patient's pretreatment viral load and HCV genotype. Clinical trial studies indicated that a decrease in HCV RNA levels of more than 2 log IU/mL at 4 weeks or 12 weeks of therapy is predictive of an increased chance of achieving a sustained virologic response (defined as undetectable HCV RNA levels in serum 6 months after completing antiviral therapy). Despite receiving longer duration of antiviral therapy (48 weeks versus 24 weeks), patients with chronic infection due to HCV genotypes 1 and 4 generally have less favorable sustained virologic response rates (40%-50%) than those infected with genotypes 2 and 3 (>80%). Due to the necessary prolonged duration (typically 24- to 48-week duration) and low cure rates of such antiviral therapy, interferon-based therapy has been supplanted with potent interferon-free DAA combination therapy. Cure rates, as defined by sustained virologic response, of over 90% are observed among patients infected with HCV and treated with interferon-free DAA combinations that are of shorter treatment duration (eg, 8 or 12 weeks) than those of interferon-based therapy. Current guidelines for antiviral therapy of chronic hepatitis C recommend quantitative testing for HCV RNA in serum or plasma before initiating antiviral therapy, at 4 weeks of therapy, and 12 weeks after completion of therapy. A HCV RNA level below 25 IU/mL in serum or plasma 12 weeks after ending therapy is the therapeutic goal and indicates an SVR is achieved. Quantitative HCV RNA testing can be considered at the end of therapy and at 24 weeks or later after completion of antiviral therapy. For more information, see the following: -Chronic Hepatitis C Treatment and Monitoring Algorithm: Direct Antiviral Antigen (DAA) Combination -Hepatitis C: Testing Algorithm for Screening and Diagnosis

Useful For: Detection of acute hepatitis C virus (HCV) infection before the appearance of HCV antibodies in serum (ie, <2 months from exposure) Detection and confirmation of chronic HCV infection Quantification of HCV RNA in serum of patients with chronic HCV infection (HCV antibody-positive) Monitoring disease progression in chronic HCV infection and response to antiviral therapy Determining cure and detection of relapse after completion of antiviral therapy

Interpretation: This assay has a result range of 15 to 100,000,000 IU/mL (1.18 log to 8.00 log IU/mL) for quantification of hepatitis C virus (HCV) RNA in serum. An "Undetected" result indicates that the HCV is absent in the patient's serum specimen. A result of "<15 IU/mL (<1.18 log IU/mL)" indicates that HCV RNA is detected, but the HCV RNA level present cannot be quantified accurately below this lower limit of quantification of this assay. When clinically indicated, follow-up testing with this assay is recommended in 1 to 2 months. To assess response-guided therapy eligibility, an "Undetected" result is required, and a result of "<15 IU/mL mL (<1.18 log IU/mL)" should not be considered equivalent to an "Undetected" result. A quantitative result expressed in IU/mL and log IU/mL indicates the degree of active HCV viral replication in the patient. Monitoring HCV RNA levels over time is important to assess disease progression and/or monitoring a patient's response to anti-HCV therapy. A result of ">100,000,000 IU/mL (>8.00 log IU/mL)" indicates the presence of active HCV viral replication, and the HCV RNA level present cannot be quantified accurately above this upper limit of quantification of this assay. An "Inconclusive" result reported with a comment indicates that testing failed, likely due to presence of inhibitory substances in the submitted serum specimen. A new specimen should be collected for retesting.

Reference Values:
Undetected

Clinical References: 1. de Leuw P, Sarrazin C, Zeuzem S. How to use virological tools for the

optimal management of chronic hepatitis C. Liver Int. 2011;31 Suppl 1:3-12 2. Centers for Disease Control and Prevention: Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep. 2013;62(18):362-365 3. American Association for the Study of Liver Diseases, Infectious Diseases Society of America: HCV guidance: Recommendations for testing, managing, and treating hepatitis C. AASLD, IDSA; Accessed May 9, 2024. Available at www.hcvguidelines.org/contents

HCVRP 609749 Hepatitis C Virus (HCV) RNA Detection and Quantification, Real-Time Reverse Transcription-PCR, Prenatal, Serum

Clinical Information: About 75% of all individuals infected with hepatitis C virus (HCV) will develop chronic hepatitis C with ongoing viral replication in the liver and detectable HCV RNA in serum or plasma, eventually resulting in cirrhosis. The remaining 25% of the individuals infected recover from the infection without evidence of viral replication or presence of detectable HCV RNA in serum or plasma. Chronic HCV infection can be cured at variable success rates with either combined interferon-alpha and ribavirin therapy or interferon-free combination of direct-acting antiviral (DAA) agents. The antiviral response rates correlate with pretreatment serum or plasma HCV RNA levels (viral load) and the HCV genotype found in the individuals infected. The optimal duration of combined interferon and ribavirin therapy can be determined from the patient's pretreatment viral load and HCV genotype. Clinical trial studies indicated that a decrease in HCV RNA levels of more than 2 log IU/mL at 4 weeks or 12 weeks of therapy is predictive of an increased chance of achieving a sustained virologic response (defined as undetectable HCV RNA levels in serum 6 months after completing antiviral therapy). Despite receiving longer duration of antiviral therapy (48 weeks versus 24 weeks), patients with chronic infection due to HCV genotypes 1 and 4 generally have less favorable sustained virologic response rates (40%-50%) than those infected with genotypes 2 and 3 (>80%). Due to the necessary prolonged duration (typically 24- to 48-weeks duration) and low cure rates of such antiviral therapy, interferon-based therapy has been supplanted with potent interferon-free DAA combination therapy. Cure rates, as defined by sustained virologic response, of over 90% are observed among patients who are HCV-infected and treated with interferon-free DAA combinations that are of shorter treatment duration (eg, 8 or 12 weeks) than those of interferon-based therapy. Current guidelines for antiviral therapy of chronic hepatitis C recommend quantitative testing for HCV RNA in serum or plasma before initiating antiviral therapy, at 4 weeks of therapy, and 12 weeks after completion of therapy. A HCV RNA level below 25 IU/mL in serum or plasma 12 weeks after ending therapy is the therapeutic goal and indicates an SVR is achieved. Quantitative HCV RNA testing can be considered at the end of therapy and at 24 weeks or later after completion of antiviral therapy. For more information, see the following: -Chronic Hepatitis C Treatment and Monitoring Algorithm: Direct Antiviral Antigen (DAA) Combination -Hepatitis C: Testing Algorithm for Screening and Diagnosis

Useful For: Detection of acute hepatitis C virus (HCV) infection before the appearance of HCV antibodies in serum (ie, <2 months from exposure) in women who are pregnant Detection and confirmation of chronic HCV infection in women who are pregnant Quantification of HCV RNA in serum of women who are pregnant for monitoring disease progression of chronic HCV infection (HCV antibody-positive)

Interpretation: This assay has a result range of 15 to 100,000,000 IU/mL (1.18 log to 8.00 log IU/mL) for quantification of hepatitis C virus (HCV) RNA in serum. An "Undetected" result indicates that the HCV is absent in the patient's serum specimen. A result of "<15 IU/mL (<1.18 log IU/mL)" indicates that HCV RNA is detected, but the HCV RNA level present cannot be quantified accurately below this lower limit of quantification of this assay. When clinically indicated, follow-up testing with this assay is recommended in 1 to 2 months. To assess response-guided therapy eligibility, an "Undetected" result is required, and a result of "<15 IU/mL mL (<1.18 log IU/mL)" should not be considered equivalent to an "Undetected" result. A quantitative result expressed in IU/mL and log

IU/mL indicates the degree of active HCV viral replication in the patient. Monitoring HCV RNA levels over time is important to assess disease progression and/or monitoring a patient's response to anti-HCV therapy. A result of ">100,000,000 IU/mL (>8.00 log IU/mL)" indicates the presence of active HCV viral replication, and the HCV RNA level present cannot be quantified accurately above this upper limit of quantification of this assay. An "Inconclusive" result reported with a comment indicates that testing failed, likely due to presence of inhibitory substances in the submitted serum specimen. A new specimen should be collected for retesting.

Reference Values:
Undetected

Clinical References: 1. Centers for Disease Control and Prevention (CDC). Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep. 2013;62(18):362-365 2. American Association for the Study of Liver Diseases (AASLD), Infectious Diseases Society of America (IDSA): HCV guidance: Recommendations for testing, managing, and treating hepatitis C. AASLD, IDSA; Accessed May 9, 2024. Available at www.hcvguidelines.org/contents 3. Society for Maternal-Fetal Medicine (SMFM), Hughes BL, Page CM, Kuller JA. Hepatitis C in pregnancy: screening, treatment, and management. Am J Obstet Gynecol. 2017;217(5):B2-B12 4. National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention: Pregnancy and HIV, viral hepatitis STD and TB prevention: HCV challenges. CDC; Reviewed October 31, 2023. Accessed May 9, 2024. Available at www.cdc.gov/nchhstp/pregnancy/challenges/hcv.html 5. Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC recommendations for hepatitis C screening among adults-United States, 2020. MMWR Recomm Rep. 2020;69(2):1-17

HCVQG 603602 Hepatitis C Virus (HCV) RNA Quantification with Reflex to HCV Genotype, Serum

Clinical Information: About 75% of all individuals infected with hepatitis C virus (HCV) will develop chronic hepatitis C with ongoing viral replication in the liver and detectable HCV RNA in serum or plasma, eventually resulting in cirrhosis. The remaining 25% of the infected individuals recover from the infection without evidence of viral replication or the presence of detectable HCV RNA in serum or plasma. Chronic HCV infection can be cured at variable success rates with either combined interferon-alpha and ribavirin therapy or interferon-free combination of direct-acting antiviral (DAA) agents. The antiviral response rates correlate with pretreatment serum or plasma HCV RNA levels (viral load) and the HCV genotype found in the infected individuals. The optimal duration of combined interferon and ribavirin therapy can be determined from the patient's pretreatment viral load and HCV genotype. Clinical trial studies indicated that a decrease in HCV RNA levels of more than 2 log IU/mL at 4 weeks or 12 weeks of therapy is predictive of an increased chance of achieving a sustained virologic response (defined as undetectable HCV RNA levels in serum 6 months after completing antiviral therapy). Despite receiving longer duration of antiviral therapy (48 weeks versus 24 weeks), patients with chronic infection due to HCV genotypes 1 and 4 generally have less favorable sustained virologic response rates (40%-50%) than those infected with genotypes 2 and 3 (>80%). Due to the necessary prolonged duration (typically 24- to 48-week duration) and low cure rates of such antiviral therapy, interferon-based therapy has been supplanted with potent interferon-free DAA combination therapy now. Unique nucleotide sequences of certain regions (eg, 5'-noncoding, core, NS5b) of the HCV genome allow classification of HCV into 6 major genotypes or clades (1-6), based on the most recently proposed HCV genotype nomenclature. In the United States, the most commonly encountered HCV genotypes are 1a and 1b, followed by genotypes 2 and 3. Worldwide geographic distribution, disease outcome, and response to antiviral therapy differ among the genotypes. HCV genotype determination is important for proper selection of antiviral therapy and optimal patient management. Therapeutic response rates for chronic HCV infection have improved significantly (cure rates of >90%) over the past 5 years when oral DAA agents are used in lieu of interferon-based combination therapy. However, antiviral resistance can emerge during such combination

therapy, and occurrence of such resistance is more frequent with HCV subtype 1a than 1b for simeprevir-treated patients. The American Association for the Study of Liver Diseases and Infectious Disease Society of America recommendations for testing, managing, and treating hepatitis C are available at www.hcvguidelines.org/contents.

Useful For: Detection of acute hepatitis C virus (HCV) infection before the appearance of HCV antibodies in serum (ie, <2 months from exposure) Detection and confirmation of chronic HCV infection and determining HCV genotype (1 to 5) to guide antiviral therapy in patients with chronic hepatitis C Quantification of HCV RNA in serum of patients with chronic HCV infection (HCV antibody-positive) before initiating antiviral therapy Determining cure and detection of relapse of HCV infection after completion of antiviral therapy

Interpretation: This assay has a result range of 15 to 100,000,000 IU/mL (1.18 log to 8.00 log IU/mL) for quantification of hepatitis C virus (HCV) RNA in serum. Only those specimens with HCV RNA levels greater than or equal to 500 IU/mL will be tested for HCV genotype (HCVG / Hepatitis C Virus Genotype, Serum or HCVGR / Hepatitis C Virus Genotype Resolution, Serum). An "Undetected" result indicates that the HCV is absent in the patient's serum specimen. Such specimens will not be tested for HCV genotype. A result of "<15 IU/mL (<1.18 log IU/mL)" indicates that HCV RNA is detected, but the HCV RNA level present cannot be quantified accurately below this lower limit of quantification of this assay. Such specimens will not be tested for HCV genotype. A result of ">100,000,000 IU/mL (>8.00 log IU/mL)" indicates the presence of active HCV viral replication, and the HCV RNA level present cannot be quantified accurately above this upper limit of quantification of this assay. An "Inconclusive" result reported with a comment indicates that testing failed, likely due to the presence of inhibitory substances in the submitted serum specimen. A new specimen should be collected for retesting. Such specimens will not be tested for HCV genotype.

Reference Values:
Undetected

Clinical References: 1. de Leuw P, Sarrazin C, Zeuzem S. How to use virological tools for the optimal management of chronic hepatitis C. Liver Int. 2011;31 Suppl 1:3-12 2. Centers for Disease Control and Prevention: Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep. 2013;62(18):362-365 3. American Association for the Study of Liver Diseases and Infectious Diseases Society of America: HCV guidance: Recommendations for testing, managing, and treating hepatitis C. Accessed May 10, 2024. Available at www.hcvguidelines.org/contents

HCVL
63063

Hepatitis C Virus Antibody Confirmation, Serum

Clinical Information: Laboratory testing for hepatitis C virus (HCV) infection in patients and donors of organ, blood, cells, tissue, and tissue products usually begins by screening for the presence of HCV antibodies (anti-HCV) in serum, using an US Food and Drug Administration or Food and Drug Administration approved anti-HCV screening test. Specimens that are repeatedly reactive by screening tests should be confirmed by more HCV-specific tests, such as direct detection of HCV RNA by the reverse transcriptase-polymerase chain reaction assay or confirmatory detection of HCV antibodies by serologic assays using recombinant HCV-specific antigens. In patients with reactive HCV antibody screening test results but negative or undetectable HCV RNA test results, HCV antibody confirmatory tests would be useful to distinguish between true- and false-reactive HCV antibody screening test results. HCV antibodies are usually not detectable during the first 2 months following infection, and they are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies do not neutralize the virus, and they do not provide immunity against this viral infection. Loss of HCV antibodies may occur in the years following resolution of infection. Despite the value of

serologic confirmation of HCV infection, several limitations of this test exist: -There may be a long delay (up to 6 months) between exposure to the virus and development of detectable HCV antibodies, especially in immunocompromised patients -A positive test result does not distinguish between past (resolved) and chronic HCV infection -Serologic tests cannot predict or monitor response to antiviral therapy For more information see Hepatitis C: Testing Algorithm for Screening and Diagnosis.

Useful For: Confirming the presence of hepatitis C virus (HCV)-specific IgG antibodies in serum specimens that are reactive by HCV antibody screening tests Distinguishing between true- and false-reactive HCV antibody screening test results This test is not intended for use as an HCV antibody screening test for blood or human cells/tissue donors. This assay is not useful for detection of early or acute hepatitis C (<2 months from exposure) as immunocompromised patients may not develop detectable HCV antibodies in blood until 6 months after infection. This assay is not useful for differentiating between past (resolved) and chronic hepatitis C.

Interpretation: A positive result indicates the presence of hepatitis C virus (HCV)-specific IgG antibodies due to past (resolved) or chronic hepatitis C. Past (resolved) HCV infection (accounting for about 25% of all HCV-infected patients) can be distinguished from chronic HCV infection (about 75% of all cases) only by direct detection of HCV RNA using molecular test methods; eg, HCVQN / Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR (RT-PCR), Serum. HCV RNA is present in acute or chronic hepatitis C but not in past (resolved) HCV infection. A negative result indicates the absence of HCV-specific IgG antibodies. A reactive HCV antibody screening test result with a negative HCV antibody confirmatory result indicates a probable false-reactive screening test result. An indeterminate result indicates that HCV-specific IgG antibodies may or may not be present. Indeterminate results should be interpreted along with patient's risk factors for HCV infection and clinical findings. Individuals at risk for HCV infection with indeterminate results should be retested with an HCV antibody confirmatory test in 1 to 2 months to determine the definitive HCV antibody status. Molecular tests to detect HCV RNA may be necessary to determine HCV infection status in those at-risk immunocompromised patients with indeterminate HCV antibody confirmatory test results due to delayed appearance of fully complement of HCV-specific antibodies. An unreadable result indicates nonspecific cross reactivity was present and HCV-specific antibody bands could not be visualized reliably. Repeat confirmatory serologic testing in 1 to 2 months or HCV RNA (HCVQN / Hepatitis C Virus [HCV] RNA Detection and Quantification by Real-Time Reverse Transcription-PCR [RT-PCR], Serum) is recommended for at-risk patients.

Reference Values:
Negative

Clinical References: 1. American Association for the Study of Liver Diseases/Infectious Diseases Society of America/International Antiviral Society-USA. Recommendations for Testing, Managing, and Treating Hepatitis C. Updated October 24, 2022. Accessed July 26, 2023. Available at www.hcvguidelines.org 2. Carithers RL, Marquardt A, Gretch DR. Diagnostic testing for hepatitis C. Semin Liver Dis. 2000;20(2):159-171 3. Pawlotsky JM: Use and interpretation of hepatitis C virus diagnostic assays. Clin Liver Dis. 2003;7:127-137 4. Centers for Disease Control and Prevention: Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. MMWR Morb Mortal Wkly Rep. 2003;52(No. RR-3):1-14. Accessed July 26, 2023. Available at www.cdc.gov/mmwr/preview/mmwrhtml/rr5203a1.htm 5. Centers for Disease Control and Prevention: Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep. 2013;62(18):362-365

HCCAD 87858 Hepatitis C Virus Antibody Screen, Cadaveric or Hemolyzed Specimens, Asymptomatic, Serum

Clinical Information: Hepatitis C virus (HCV) is recognized as the cause of most cases of post-transfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 2.4 million chronic HCV carriers. HCV antibodies are usually not detectable during the early months following infection, but they are almost always detectable by the late convalescent stage (>6 months after onset of acute infection). These antibodies do not neutralize the virus, and they do not provide immunity against this viral infection. Loss of HCV antibodies may occur many years following resolution of infection. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing are known: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable antibodies. -False-reactive screening test results can occur. -A reactive screening test result does not distinguish between past (resolved) and present HCV infection. -Serologic tests cannot provide information on clinical response to antiviral therapy. Positive screening serologic test results should be followed by a confirmatory or supplemental test, such as line immunoassay (HCVL / Hepatitis C Virus Antibody Confirmation, Serum) for HCV antibodies or a nucleic acid test for HCV RNA. Although nucleic acid tests provide a very sensitive and specific approach to directly detect HCV RNA in a patient's blood, they are not suitable for use in testing cadaveric blood specimens due to interference of heme with the nucleic acid amplification processes.

Useful For: Screening cadaveric or hemolyzed serum specimens for hepatitis C virus (HCV) infection in asymptomatic individuals with or without risk factors for HCV infection Note: In accordance with National Coverage Determination guidance, this test is indicated for asymptomatic patients born from 1945 through 1965, those with history of injection drug use, or history of receiving blood transfusion prior to 1992. This test is not intended for screening blood, cell, or tissue donors. This test is not intended for testing symptomatic individuals (ie, diagnostic purposes). This test is not useful for ruling out acute HCV infection. This test is not useful for differentiation between resolved and acute or chronic HCV infection.

Interpretation: All specimens with signal-to-cutoff ratios of 1.0 or greater will be considered reactive and reflex to the hepatitis C virus (HCV) antibody confirmatory test by line immunoassay (HCVL / Hepatitis C Virus Antibody Confirmation, Serum) at an additional charge. Additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to antibody levels below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks).

Reference Values:
Negative

Clinical References: 1. Carithers RL, Marquardt A, Gretch DR. Diagnostic testing for hepatitis C. Semin Liver Dis. 2000;20(2):159-171 2. Pawlotsky JM. Use and interpretation of virological tests for hepatitis C. Hepatology. 2002;36(5 Suppl 1):S65-S73 3. Panagiotakopoulos L, Sandul AL; DHSc, et al. CDC Recommendations for Hepatitis C Testing Among Perinatally Exposed Infants and Children - United States, 2023. MMWR Recomm Rep. 2023;72(4):1-21. Published 2023 Nov 3. doi:10.15585/mmwr.rr7204a1 4. Moorman AC, de Perio MA, Goldschmidt R, et al. Testing and Clinical Management of Health Care Personnel Potentially Exposed to Hepatitis C Virus - CDC Guidance, United States, 2020. MMWR Recomm Rep. 2020;69(6):1-8. Published 2020 Jul 24. doi:10.15585/mmwr.rr6906a1 5. Panagiotakopoulos L, Sandul AL; DHSc, et al. CDC Recommendations for Hepatitis C Testing Among Perinatally Exposed Infants and Children - United States, 2023. MMWR Recomm Rep. 2023;72(4):1-21. Published 2023 Nov 3. doi:10.15585/mmwr.rr7204a1

HCCDD
58127

Hepatitis C Virus Antibody, Cadaveric or Hemolyzed Specimens, Symptomatic, Serum

Clinical Information: Hepatitis C virus (HCV) is recognized as the cause of most cases of post-transfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 2.4 million chronic HCV carriers. HCV antibodies are usually not detectable during the early months following infection, but they are almost always detectable by the late convalescent stage (>6 months after onset of acute infection). These antibodies do not neutralize the virus, and they do not provide immunity against this viral infection. Loss of HCV antibodies may occur many years following resolution of infection. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing are known: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable antibodies. -False-reactive screening test results can occur. -A reactive screening test result does not distinguish between past (resolved) and present HCV infection. -Serologic tests cannot provide information on clinical response to antiviral therapy. Positive screening serologic test results should be followed by a confirmatory or supplemental test, such as line immunoassay (HCVL / Hepatitis C Virus Antibody Confirmation, Serum) for HCV antibodies or a nucleic acid test for HCV RNA. Although nucleic acid tests provide a very sensitive and specific approach to directly detect HCV RNA in a patient's blood, they are not suitable for use in testing cadaveric blood specimens due to interference of heme with the nucleic acid amplification processes.

Useful For: Diagnosis of hepatitis C virus (HCV) infection in cadaveric or hemolyzed serum specimens from symptomatic patients with or without risk factors for HCV infection This test is not intended for screening blood, cell, or tissue donors. This test is not useful for ruling out acute HCV infections. This test is not useful for differentiation between resolved and acute or chronic hepatitis C infections. This test is not intended for testing asymptomatic individuals (ie, screening purposes).

Interpretation: All specimens with signal-to-cutoff ratios of 1.0 or greater will be considered reactive and reflex to the hepatitis C virus (HCV) antibody confirmatory test by line immunoassay (HCVL / Hepatitis C Virus Antibody Confirmation, Serum) at an additional charge. Additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to antibody levels below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks).

Reference Values:
Negative

Clinical References: 1. Carithers RL, Marquardt A, Gretch DR. Diagnostic testing for hepatitis C. Semin Liver Dis. 2000;20(2):159-171 2. Pawlotsky JM. Use and interpretation of virological tests for hepatitis C. Hepatology. 2002;36(5 Suppl 1):S65-S73 3. Panagiotakopoulos L, Sandul AL; DHSc, et al. CDC Recommendations for Hepatitis C Testing Among Perinatally Exposed Infants and Children - United States, 2023. MMWR Recomm Rep. 2023;72(4):1-21. Published 2023 Nov 3. doi:10.15585/mmwr.rr7204a1 4. Moorman AC, de Perio MA, Goldschmidt R, et al. Testing and Clinical Management of Health Care Personnel Potentially Exposed to Hepatitis C Virus - CDC Guidance, United States, 2020. MMWR Recomm Rep. 2020;69(6):1-8. Published 2020 Jul 24. doi:10.15585/mmwr.rr6906a1 5. Panagiotakopoulos L, Sandul AL; DHSc, et al. CDC Recommendations for Hepatitis C Testing Among Perinatally Exposed Infants and Children - United States, 2023. MMWR Recomm Rep. 2023;72(4):1-21. Published 2023 Nov 3. doi:10.15585/mmwr.rr7204a1

HCVG
81618

Hepatitis C Virus Genotype, Serum

Clinical Information: Unique nucleotide sequences of certain regions (eg, 5'-noncoding, core, NS5b) of the hepatitis C virus (HCV) genome allow classification of HCV into 6 major genotypes or clades (1-6), based on the most recently proposed HCV genotype nomenclature. In the United States, the most frequently encountered HCV genotypes are 1a and 1b, followed by genotypes 2 and 3. Worldwide geographic distribution, disease outcome, and response to antiviral therapy differ among the genotypes. Therefore, reliable methods for genotype determination are important for proper selection of antiviral therapy and optimal patient management. Infections with HCV genotypes 2 and 3 have better therapeutic response rates (80%-90%) than genotypes 1 and 4 (40%-50%) to previous standard combination therapy (ribavirin plus pegylated interferon alpha-2a or alpha-2b). Duration of such combination therapy is 24 weeks for chronic HCV genotype 2 and 3 infections in patients who show early virologic response (>2 log or 100-fold decrease in HCV RNA or no detectable HCV RNA at week 12 of therapy), while patients with chronic HCV genotype 1 and 4 infections receive a minimum of 48 weeks of such combination therapy if early virologic response is achieved (undetectable HCV RNA at week 4 of therapy). Therapeutic response rates for HCV genotype 1 infection are improved significantly (80%-90%) when oral direct acting antiviral agents (eg, daclatasvir, sofosbuvir, ledipasvir + sofosbuvir, velpatasvir + sofosbuvir, glecaprevir + pibrentasvir, elbasvir + grazoprevir, velpatasvir + voxilaprevir + sofosbuvir) are added or used in lieu of interferon-based combination therapy. The American Association for the Study of Liver Diseases and Infectious Disease Society of America recommendations for testing, managing, and treating hepatitis C are available at www.hcvguidelines.org/contents. The following algorithms are available: -Chronic Hepatitis C Treatment and Monitoring Algorithm: Direct Antiviral Antigen (DAA) Combination -Hepatitis C: Testing Algorithm for Screening and Diagnosis

Useful For: Determining hepatitis C virus (HCV) genotype (1 to 5) to guide antiviral therapy in patients with chronic hepatitis C Differentiating between HCV subtypes 1a and 1b This assay should not be used as a screening test for HCV infection. It should be performed only on specimens obtained from patients confirmed to have HCV RNA levels in serum of 500 IU/mL or higher.

Interpretation: Hepatitis C virus (HCV) genotyping result Interpretation Resolution test (reflex test) ordered? 1a 1a is the definitive subtype/genotype No 1b 1b is the definitive subtype/genotype No 2 2 is the definitive genotype No 3 3 is the definitive genotype No 4 4 is the definitive genotype No 5 5 is the definitive genotype No 1 A definitive genotype/subtype (1a, 1b, 6) could not be assigned. Resolution testing ordered. Yes 1a, 2 (any 2 genotypes) Result may be due to mixed genotype infection, recombination of HCV genotypes, or assay probe cross-reactivity. No 1, 3 (2 genotypes with a 1, no subtype) Result may be due to mixed genotype infection, recombination of HCV genotypes, or assay probe cross-reactivity. Resolution testing ordered. Yes HCV not detected Assay failed to detect HCV RNA. No Indeterminate (undetermined genotype) HCV RNA detected, but genotype could not be determined. Resolution testing ordered. Yes Indeterminate (mix) Result may be due to mixed genotype infection, recombination of HCV genotypes, or assay probe cross-reactivity. No An "Undetected" result indicates the absence of detectable hepatitis C virus (HCV) RNA in the specimen. An "Indeterminate" result may be due to one or more of the following causes: 1. Low HCV RNA level (ie, <500 IU/mL) 2. HCV genotype 6 3. Probe reactivity with multiple HCV genotypes 4. Variation in patient's HCV target sequences with mismatches to polymerase chain reaction primers and/or probes. Specimens generating indeterminate results with this assay will be automatically evaluated with the subsequent test HCVGR / Hepatitis C Virus Genotype Resolution, Serum. An HCV genotype result of "1" without a subtype result may be due to one or more of the following causes: 1. Low HCV RNA level (ie, <500 IU/mL) 2. Probe reactivity with multiple genotype 1 subtypes 3. Variation in HCV genotype 1 target sequence 4. Misclassification of some true genotype 6 strains This assay can differentiate between HCV subtypes 1a and 1b. However, subtypes are not reported for HCV genotypes 2 to 5 due to limitations of the current genotyping assay in accurately differentiating the various subtypes of these genotypes. Results with multiple or mixed HCV genotypes (eg, 1, 5; 1a, 2; or 3, 5) may be due to mixed genotype infection or assay probe cross-reactivity. Only those specimens with multiple or mixed genotype results containing

genotype 1 but no subtype will be automatically evaluated with the subsequent test HCVGR / Hepatitis C Virus Genotype Resolution, Serum.

Reference Values:
Undetected

Clinical References: 1. Germer JJ, Mandrekar JN, Bendel JL, et al. Hepatitis C virus genotypes in clinical specimens tested at a national reference testing laboratory in the United States. J Clin Microbiol. 2011;49(8):3040-3043 2. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Updated October 24, 2022. Accessed March 27, 2025. Available at www.hcvguidelines.org

HCVDR
604410

Hepatitis C Virus Genotypic Antiviral Drug Resistance, Serum

Clinical Information: Interferon-free, direct antiviral agent (DAA) drug combination therapy is now a standard of care for patients with chronic hepatitis C virus (HCV) infection. However, poor compliance with therapy and the existence of pretreatment antiviral drug resistance may compromise efficacy of such drug therapy. Naturally occurring (preexisting) or treatment-induced mutations in the viral genomic sequences that are targets of such antiviral agents can lead to antiviral resistance and therapeutic failure. Clinical trials and postmarketing studies of DAA therapy indicated that preexisting, resistance-associated substitutions (RAS) in the relevant HCV genomic regions of certain genotypes or emergence of certain RAS during DAA therapy can lead to treatment failure. Per current recommendations from the US Food and Drug Administration (FDA) and professional society practice guidelines (see Table and Clinical Reference section), use of certain FDA-approved DAA drugs for treating chronic HCV due to genotypes 1a, 1b, and 3 (any subtype) requires pretreatment testing for RAS in the relevant HCV genomic regions to guide selection of optimal DAA combination therapy. Table. HCV genomic target of DAA drug HCV genotype 1a 1b 3 (any subtype) NS3/4 Glecaprevir(a) Grazoprevir(b) Voxilaprevir(c) Glecaprevir(a) Grazoprevir(b) Voxilaprevir(c) Glecaprevir(a) Voxilaprevir(c) NS5A Daclatasvir(d) Elbasvir(b) Ledipasvir(e) Pibrentasvir(a) Velpatasvir(c,f) Daclatasvir(d) Elbasvir(b) Ledipasvir(e) Pibrentasvir(a) Velpatasvir(c,e) Daclatasvir(d) Pibrentasvir(a) Velpatasvir(c,e) NS5B Sofosbuvir(c,e,f,g) Sofosbuvir(c,e,f,g) Sofosbuvir(c,f,g) Trade names of DAA: (a) Mavyret = Glecaprevir + Pibrentasvir (b) Zepatier = Elbasvir + Grazoprevir (c) Vosevi = Sofosbuvir + Velpatasvir + Voxilaprevir (d) Daklinza = Daclatasvir (e) Harvoni = Ledipasvir + Sofosbuvir (f) Epclusa = Sofosbuvir + Velpatasvir (g) Sovaldi = Sofosbuvir Antiviral drug RAS in the relevant HCV genomic regions can be detected and identified genotypically using either Sanger sequencing or next-generation sequencing (NGS) methods. Amino acid changes deemed as RAS are predicted by the NS3, NS5A, and NS5B sequences of the patient's HCV strain by comparing them to the expected amino acid at relevant codon positions within a wild-type HCV reference sequence. DAA drug resistance may be predicted for each drug based on the relevant RAS present in the HCV sequences found in the patient's serum. Prediction of HCV antiviral drug resistance in this NGS assay is based on a combination of FDA-approved prescribing information for the drug and professional society practice guidelines (see Table and www.hcvguidelines.org/evaluate/resistance).

Useful For: Detecting and identifying codon substitutions in the hepatitis C virus (HCV) NS3, NS5A, and NS5B genomic regions that confer resistance to current direct-acting antiviral drugs used for treatment of chronic hepatitis C infection due to HCV genotype 1a, 1b, or 3 (any subtype) Guiding initiation or change of antiviral drug combinations for the treatment of chronic HCV infection This assay should not be used as a screening test for HCV infection. This test should not be ordered for HCV infection due to genotypes 2, 4, 5, or 6.

Interpretation: Interpretation of antiviral drug resistance in this assay is based on a detection threshold of 10% of resistance-associated hepatitis C virus (HCV) variants present in the patient's serum specimen (ie, minimum 10% frequency of such variants). This assay will confirm the patient's HCV genotype, with

possible genotype results generated as 1a; 1b; 1, no subtype; 2a; 2b; 2, no subtype; 3a; 3, no subtype; 4a; 4, no subtype; 5a; 6a; 6, no subtype. However, analysis of resistance-associated substitutions (RAS) and prediction of antiviral drug resistance are restricted only to HCV genotype test results of 1a, 1b, 3a, or 3 no subtype. Inconclusive result indicates that testing failed, likely due to presence of inhibitory substances in the submitted serum specimen. A new serum specimen should be collected and submitted for retesting if clinically indicated. Indeterminate result is due to presence of atypical HCV genomic sequences, such as a recombinant HCV strain comprised of genomic sequences from multiple genotypes, preventing definitive determination of the HCV genotype. Unable to genotype indicates that the assay is unable to reliably determine antiviral resistance because of either low HCV viral load (ie, <5000 IU/mL) or ambiguous or incomplete HCV target sequences generated with the assay. Predicted resistance means that the RAS detected have been reported to be associated with reduction in susceptibility to the specific direct-acting antiviral (DAA) drug. Possible resistance means that the RAS detected may be associated with a reduction in susceptibility to the specific DAA drug due to possible cross-resistance within the same drug class. Current peer-reviewed, published reports do not have sufficient data to definitively rule out antiviral resistance to the drug. Not predicted means that no RAS were detected and no resistance to the specific DAA drug is predicted for patient's HCV strain.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Pawlotsky JM. Hepatitis C virus resistance to direct-acting antiviral drugs in interferon-free regimens. Gastroenterology. 2016;151(1):70-86. doi:10.1053/j.gastro.2016.04.003 2. Wyles DL, Luetkemeyer AF. Understanding hepatitis C virus drug resistance: clinical implications for current and future regimens. Top Antivir Med. 2017;25(3):103-109 3. Sorbo MC, Cento V, Di Maio VC, et al. Hepatitis C virus drug resistance associated substitutions and their clinical relevance: Update 2018. Drug Resist Updat. 2018;37:17-39. doi:10.1016/j.drup.2018.01.004 4. Wyles DL. Resistance to DAAs: When to look and when it matters. Curr HIV/AIDS Rep. 2017;14(6):229-237. doi:10.1007/s11904-017-0369-5 5. European Association for the Study of the Liver: EASL recommendations on treatment of hepatitis C 2018. J Hepatol. 2018;69(2):461-511. doi:10.1016/j.jhep.2018.03.026 6. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America: HCV guidance: recommendations for testing, managing, and treating hepatitis C. HCV resistance primer. Updated October 24, 2022. Accessed January 4, 2024. Available at www.hcvguidelines.org/evaluate/resistance

AHDV
9209

Hepatitis D Virus Total Antibodies, Serum

Clinical Information: Hepatitis D virus (HDV), also known as delta hepatitis virus, is a defective RNA virus comprised of a delta antigen and a hepatitis B surface antigen as the core and protein coat of the virus, respectively. This virus cannot replicate effectively by itself as it requires the presence of hepatitis B virus (HBV) to initiate and maintain its replication in the infected liver cells. Infection with HDV occurs either as an acute coinfection with HBV or an acute superinfection of chronic HBV. Acute HBV-HDV coinfection usually follows a self-limited clinical course with spontaneous resolution but may have a fulminant clinical presentation. HDV superinfection in chronic HBV, or HBV carrier state, typically manifests as an acute exacerbation of chronic hepatitis B, with tendency to result in chronic HBV-HDV coinfection and early cirrhosis or liver failure. In the United States, chronic HDV infection is found in 1% of all individuals with a chronic HBV-infection. Diagnosis of HDV can be established by detecting HDV antigen, HDV-specific IgM, or HDV-specific total antibodies (combined IgM and IgG) in the sera of infected patients with clinically evident acute or chronic hepatitis B. Anti-HDV IgM typically appears in serum at 2 to 3 weeks after onset of symptoms and disappears by 2 months after acute HDV infection, but it may persist up to 9 months in HDV superinfection. HDV IgG and HDV total antibodies persist in serum after resolution of acute HDV infection and in chronic coinfection.

Useful For: Detection of hepatitis D virus (HDV)-specific total antibodies (combined IgG and IgM) in human serum Diagnosis of concurrent HDV infection in patients with fulminant acute hepatitis B virus (HBV) infection (acute coinfection), chronic HBV infection (chronic coinfection), or acute exacerbation of known chronic HBV infection (HDV superinfection)

Interpretation: This assay detects the presence of hepatitis D virus (HDV)-specific total (combined IgG and IgM) antibodies in serum. Negative results indicate the absence of HDV infection and no past exposure to HDV. Equivocal results indicate borderline level of anti-HDV total antibodies. Repeat testing in 1 to 2 weeks is recommended to determine the definitive HDV infection status. Positive results usually indicate simultaneous acute or chronic coinfection with hepatitis B virus (HBV) and HDV; acute HDV infection in patients with known chronic HBV infection (ie, HDV superinfection); or resolved HDV infection. Results should be correlated with medical history and clinical findings. For more information see Viral Hepatitis Serologic Profiles.

Reference Values:
Negative

Clinical References: 1. Olivero A, Smedile A. Hepatitis delta virus diagnosis. Semin Liver Dis. 2012;32(3):220-227 2. Shah PA, Choudhry S, Reyes KJC, Lau DTY. An update on the management of chronic hepatitis D. Gastroenterol Rpt (Oxf). 2019;7(6):396-402. doi:10.1093/gastro/goz052 3. Chen LY, Pang XY, Goyal H, et al. Hepatitis D: challenges in the estimation of true prevalence and laboratory diagnosis. Gut Pathog. 2021;13(1):66. doi.10.1186/s13099-021-00462-0

HEVG
86211

Hepatitis E Virus IgG Antibody, Serum

Clinical Information: Hepatitis E virus (HEV) causes an acute, usually self-limited, infection. This small, nonenveloped RNA virus is transferred from an animal reservoir (eg, hogs) to humans via the fecal-oral route. HEV is endemic in Southeast and Central Asia, with several outbreaks observed in the Middle East, northern and western parts of Africa, and Mexico. In developed countries, HEV infection occurs mainly in persons who have traveled to disease-endemic areas. Transmission of HEV may also occur parenterally, and direct person-to-person transmission is rare. Clinically severe cases occur in young to middle-aged adults. Unusually high mortality (approximately 20%) occurs in patients infected during the third trimester of pregnancy. Although there is no carrier state associated with HEV, immunocompromised patients may have prolonged periods (eg, months) of viremia and virus shedding in the feces. In immunocompetent patients, viremia and virus shedding in the feces occur in the pre-icteric phase, lasting up to 10 days into the clinical phase. After an incubation period ranging from 15 to 60 days, HEV-infected patients develop symptoms of hepatitis with appearance of anti-HEV IgM antibody in serum, followed by detectable anti-HEV IgG within a few days. Anti-HEV IgM may remain detectable up to 6 months after onset of symptoms, while anti-HEV IgG usually persists for many years after infection. Anti-HEV IgG is the serologic test of choice to determine past exposure to HEV.

Useful For: Diagnosis of past exposure to hepatitis E virus

Interpretation: Positive results indicate past or resolved hepatitis E infection. Negative results indicate absence of previous exposure to hepatitis E virus (HEV). Borderline results may be seen in acute or recent hepatitis E infection with rising level of anti-HEV IgG or cross-reactivity with nonspecific antibodies (ie, false-positive results). Repeat testing of serum for anti-HEV IgG in 4 to 6 weeks is recommended to determine the definitive HEV infection status.

Reference Values:
Negative

Clinical References: 1. Aggarwal R: Diagnosis of hepatitis E. Nat Rev Gastroenterol Hepatol. 2013;10(1):24-33 2. Schemmerer M, Rauh C, Jilg W, Wenzel JJ. Time course of hepatitis E-specific antibodies in adults. J Viral Hepat. 2017;24(1):75-79. doi:10.1111/jvh.12621 3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on hepatitis E virus infection. J Hepatol. 2018;68(6):1256-1271. doi:10.1016/j.jhep.2018.03.005 4. Kar P, Karna R. A Review of the Diagnosis and Management of Hepatitis E. Curr Treat Options Infect Dis. 2020;12(3):310-320. doi:10.1007/s40506-020-00235-4

HEVML
61903

Hepatitis E Virus IgM Antibody Confirmation, Serum

Clinical Information: Hepatitis E virus (HEV) causes an acute, usually self-limited, infection. This small, non-enveloped RNA virus is from animal reservoirs (eg, hogs) and is transmitted to humans via the fecal-oral route. HEV is endemic in Southeast and Central Asia, with several outbreaks observed in the Middle East, northern and western parts of Africa, and Mexico. In developed countries, HEV infection occurs mainly in individuals who have traveled to disease-endemic areas. Transmission of HEV may also occur rarely from direct person-to-person contact or transfusion of blood or blood products. Clinically severe cases occur in young to middle-aged adults. Unusually high mortality (approximately 20%) occurs in women infected during the third trimester of pregnancy. Although there is no carrier state associated with HEV, patients who are immunocompromised may have prolonged periods (eg, months) of viremia and virus shedding in the stool. In immunocompetent individuals, viremia and virus shedding in the stool occur in the pre-icteric phase, lasting up to 10 days into the clinical phase. After an incubation period ranging from 15 to 60 days, patients infected withHEV develop symptoms of hepatitis with appearance of anti-HEV IgM antibody in serum, followed by detectable anti-HEV IgG within a few days. Anti-HEV IgM may remain detectable up to 6 months after onset of symptoms, while anti-HEV IgG usually persists for many years after infection. Anti-HEV IgM is the serologic marker of choice for diagnosis of acute HEV infection. The positive predictive value of a given diagnostic laboratory test is dependent on the prevalence rate of the disease for which the test is being used. Screening tests for detection of diseases with low prevalence rates, such as acute hepatitis E, will have low positive predictive values (ie, relatively high rates of false-positive test results), despite having high specificity rates for such tests. Therefore, an HEV IgM antibody confirmatory test is helpful and necessary to determine the true infection status of patients with reactive HEV IgM antibody screening test results.

Useful For: Confirmation of reactive hepatitis E virus IgM antibody screening test results for the diagnosis of acute or recent (<6 months) hepatitis E infection

Interpretation: Positive results confirm the presence of acute or recent (in the preceding 6 months) hepatitis E infection. Negative results indicate absence of acute or recent hepatitis E infection. Indeterminate results may be seen in: 1. Acute hepatitis E infection with rising level of anti-hepatitis E virus (HEV) IgM 2. Recent hepatitis E infection with declining level of anti-HEV IgM 3. Acute hepatitis E infection due to HEV genotype 2 strains 4. Cross-reactivity with nonspecific antibodies (ie, false-positive results). Repeat testing of serum for anti-HEV IgM and anti-HEV IgG in 4 to 6 weeks is recommended to determine the definitive HEV infection status. Unreadable results indicate the presence of unusually strong, nonspecific reactivity of the assay strip background that obscures proper reading of the bands. Such findings are usually due to nonspecific binding of non-hepatitis E IgM antibodies in patient's serum to the HEVM antigens present on the assay strip. Repeat testing with anti-HEV IgM screen and anti-HEV IgG in 4 to 6 weeks is recommended.

Reference Values:
Negative

Clinical References: 1. Aggarwal R. Diagnosis of hepatitis E. Nat Rev Gastroenterol Hepatol.

2013;10(1):24-33 2. Pas SD, Streefkerk RH, Pronk M, et al. Diagnostic performance of selected commercial HEV IgM and IgG ELISAs for immunocompromised and immunocompetent patients. J Clin Virol. 2013;58(4):629-634. doi:10.1016/j.jcv.2013.10.010 3. Webb GW, Dalton HR. Hepatitis E: an underestimated emerging threat. Ther Adv Infect Dis. 2019;6:2049936119837162. doi:10.1177/2049936119837162

HEVM
86212

Hepatitis E Virus IgM Antibody Screen with Reflex to Confirmation, Serum

Clinical Information: Hepatitis E virus (HEV) causes an acute, usually self-limited infection. This small, nonenveloped RNA virus is transmitted from animal reservoir (eg, hogs) to humans via the fecal-oral route. HEV is endemic in Southeast and Central Asia, with several outbreaks observed in the Middle East, northern and western parts of Africa, and Mexico. In developed countries, HEV infection occurs mainly in persons who have traveled to disease-endemic areas. Transmission of HEV may also occur parenterally, and direct person-to-person transmission is rare. Clinically severe cases occur in young to middle-aged adults. Unusually high mortality (approximately 20%) occurs in patients infected during the third trimester of pregnancy. Although there is no carrier state associated with HEV, immunocompromised patients may have prolonged periods (eg, months) of viremia and virus shedding in the feces. In immunocompetent patients, viremia and virus shedding in the feces occur in the pre-icteric phase, lasting up to 10 days into the clinical phase. After an incubation period ranging from 15 to 60 days, HEV-infected patients develop symptoms of hepatitis with appearance of anti-HEV IgM antibody in serum, followed by detectable anti-HEV IgG within a few days. Anti-HEV IgM may remain detectable up to 6 months after onset of symptoms, while anti-HEV IgG usually persists for many years after infection. Anti-HEV IgM is the serologic marker of choice for diagnosis of acute HEV infection.

Useful For: Diagnosis of acute or recent (<6 months) hepatitis E infection

Interpretation:

Reference Values:
Negative

Clinical References: 1. Aggarwal R, Jameel S. Hepatitis E. Hepatology. 2011;54(6):2218-2226 2. Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. New Engl J Med. 2012;367(13):1237-1244 3. Aggarwal R. Diagnosis of hepatitis E. Nat Rev Gastroenterol Hepatol. 2013;10(1):24-33

HEVQU
62929

Hepatitis E Virus RNA Detection and Quantification, Real-Time RT-PCR, Serum

Clinical Information: Hepatitis E virus (HEV) is a causative agent of acute self-limited or fulminant hepatitis. HEV has been responsible for large outbreaks of disease in developing countries, primarily through waterborne transmission. Hepatitis E also can occur in industrialized countries, usually as sporadic cases due to zoonotic infection transmitted by the fecal-oral route. A major natural reservoir of HEV is pigs. In immunocompetent individuals, hepatitis E is mainly a self-limited infection, frequently nonsymptomatic, and does not result in chronic infection. However, in otherwise healthy pregnant patients, hepatitis E can be severe, resulting in significant morbidity and mortality. In individuals who are immunocompromised, such as organ transplant recipients, hepatitis E can be chronic with detectable HEV RNA levels in serum and plasma beyond 3 months after infection. HEV-specific IgM antibody is detectable by serologic testing by 4 weeks after infection in immunocompetent individuals, but it may not be detectable until 6 months after infection in patients who are immunosuppressed. Hepatitis E virus RNA

levels in serum or plasma are usually detectable in all infected individuals by 3 weeks after infection and become undetectable by 7 weeks in immunocompetent individuals. Due to the limitations of HEV serologic testing in patients who are immunosuppressed, molecular testing (eg, real-time reverse-transcriptase polymerase chain reaction assay) for HEV RNA in serum or plasma is an increasingly important tool in the diagnosis of acute or chronic HEV infection in these patients. Currently, ribavirin is used as the antiviral agent of choice for organ transplant recipients with chronic HEV, and monitoring of HEV RNA levels in serum or plasma is used to assess response to such antiviral therapy. Significant decreases in HEV viral load or clearance of HEV RNA may be important predictors of virologic response during antiviral therapy.

Useful For: Virologic detection and confirmation of hepatitis E virus (HEV) infection in individuals who are immunocompromised and are at risk for or suspected to have acute or chronic hepatitis E
Monitoring HEV RNA levels and determining eradication of chronic HEV infection in individuals who are immunocompromised

Interpretation: The quantification range of this assay is 50 to 5,000,000 IU/mL (1.70 log to 6.70 log IU/mL), with a limit of detection (based on a 95% detection rate) of 20 IU/mL (1.40 log IU/mL). An "Undetected" result indicates that hepatitis E virus (HEV) RNA is not detected in the serum specimen (see Cautions). Repeat testing in 1 to 2 months is recommended for those at risk of HEV infection. The limit of detection (based on a 95% detection rate) for this assay is 20 IU/mL. A result of "<50 IU/mL" indicates that the HEV RNA level present in the serum specimen is below 50 IU/mL (1.70 log IU/mL), and the assay cannot accurately quantify the HEV RNA present below this level. A quantitative value (reported in IU/mL and log IU/mL) indicates the HEV RNA level (ie, viral load) present in the serum specimen. A result of ">5,000,000 IU/mL" indicates that the HEV RNA level present in the serum specimen is above 5,000,000 IU/mL (6.70 log IU/mL), and this assay cannot accurately quantify the HEV RNA present above this level. An "Indeterminate" result suggests the presence of an atypical HEV target sequence. Since the HEV RNA sequence is atypical, repeat testing is unlikely to change this result and therefore is not recommended. An "Equivocal" result indicates that the presence or absence of HEV RNA in the serum specimen could not be determined with certainty due to atypical real-time reverse transcriptase-polymerase chain reaction (RT-PCR) probe reactivity. Submission of a new specimen for testing is recommended. An "Inconclusive" result indicates that the presence or absence of HEV RNA in the serum specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to RT-PCR inhibition. Submission of a new specimen for testing is recommended.

Reference Values:
Undetected

Clinical References: 1. Aggarwal R. Diagnosis of hepatitis E. Nat Rev Gastroenterol Hepatol. 2013;10(1):24-33. doi:10.1038/nrgastro.2012.187 2. Kamar N, Rostaing L, Izopet J. Hepatitis E virus infection in immunosuppressed patients: natural history and therapy. Semin Liver Dis. 2013;33(1):62-70. doi:10.1055/s-0033-1338115 3. Kamar N, Lhome S, Abravanel F, et al. An early viral response predicts the virological response to ribavirin in hepatitis E virus organ transplant patients. Transplantation. 2015;99(10):2124-2131. doi:10.1097/TP.0000000000000850

HCCGS 606585 Hepatocellular Carcinoma Risk Panel with GALAD Score, Serum

Clinical Information: Worldwide, hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death.(1) While HCC can be treated effectively in its early stages, most patients are not diagnosed until they are symptomatic and at higher grades and stages, which are less responsive to therapies. Alpha-fetoprotein (AFP) is the standard serum tumor marker utilized in the evaluation of

suspected HCC. However, increased serum concentrations of AFP might be found in chronic hepatitis and liver cirrhosis, as well as in other tumor types (eg, germ cell tumors),(2) decreasing the specificity of AFP testing for HCC. Furthermore, AFP is not expressed at high levels in all HCC patients, resulting in decreased sensitivity, especially in potentially curable small tumors. AFP-L3: AFP is differentially glycosylated in several hepatic diseases. For example, alpha-(1,6)-fucosyltransferase is differentially expressed in hepatocytes following malignant transformation.(3) This enzyme incorporates fucose residues on the carbohydrate chains of AFP. Different glycosylated forms of AFP can be recognized following electrophoresis by reaction with different carbohydrate-binding plant lectins. The fucosylated form of serum AFP that is most closely associated with HCC is recognized by a lectin from the common lentil (Lens culinaris). This is designated as AFP-L3 (third electrophoretic form of lentil lectin-reactive AFP). AFP-L3 is most useful in the differential diagnosis of individuals with total serum AFP of 200 ng/mL or less, which may result from a variety of benign pathologies, such as chronic liver diseases. Des-gamma-carboxy prothrombin: Des-gamma-carboxy prothrombin (DCP), also known as the protein induced by vitamin K absence or antagonist II (PIVKA-II), is an abnormal form of the coagulation protein, prothrombin. DCP is a nonfunctional prothrombin resulting from a lack of carboxylation of 10 glutamic acid residues in the N-terminal portion of the molecule. In normal liver, prothrombin undergoes post-translational carboxylation before release into the peripheral blood. The carboxylation converts specific amino-terminal glutamic acid residues to gamma-carboxyglutamic acid. The vitamin K-dependent carboxylase responsible for the carboxylation is absent in many HCC cells, and an abnormal prothrombin with all or some unconverted glutamic acid is secreted. Therefore, this non-carboxylated form (DCP) has been used as an HCC biomarker. DCP is considered a complementary biomarker to AFP and AFP-L3 for assessing the risk of developing HCC. Elevations of both AFP-L3 and DCP indicate progression of HCC, albeit they reflect different features of the progression. In a prospective study of patients in the United States with an established diagnosis of HCC, sensitivities for AFP, AFP-L3, and DCP were 68%, 62%, and 73%, respectively. When the 3 markers were combined, the sensitivity was 86%. In another study, DCP levels were shown to correlate with tumor size and metastatic HCC. In this study, compared to AFP and AFP-L3, DCP had the highest sensitivity (87%) and the highest positive predictive value (87%) in patients with HCC due to chronic hepatitis B and C infections. A number of studies have shown that elevated serum DCP is significantly related to portal vein invasion or intrahepatic metastasis, which significantly affect prognosis for patients with HCC. DCP can be elevated in other conditions besides HCC. Conditions such as obstructive jaundice, intrahepatic cholestasis causing chronic decrease in vitamin K, and ingestion of drugs such as warfarin or wide-spectrum antibiotics can result in high concentrations of DCP. In addition, 25% to 50% of patients with HCC will have a DCP value within the reference range. Because of this, a normal DCP value does not rule out HCC. Gender, Age, AFP-L3, AFP, DCP (GALAD) Score: Biomarkers of HCC include AFP, AFP-L3, and DCP. The GALAD model combines these three biomarkers with the patient's gender and age to estimate the risk of HCC in patients with chronic liver disease based on the following equation Z = -10.08 + 0.09 x age + 1.67 x sex + 2.34 log(10) (AFP) + 0.04 x AFP - L3 + 1.33 x log(10) (DCP), where sex = 1 for males, 0 for females. The GALAD score is calculated using the lower limit of quantitation (LLOQ) when one or more of the following values are below the lower limit of quantitation: %L3, Total AFP, or DCP. In the event this occurs, the GALAD score is resulted as (<)GALAD score. The GALAD model has been demonstrated to have higher diagnostic accuracy for the detection of HCC when compared to the use AFP, AFP-L3, and DCP markers alone or in combination. The performance of the GALAD score has also been reported to be superior to ultrasound for HCC detection.

Useful For: Risk assessment for development of hepatocellular carcinoma in patients with chronic liver disease

Interpretation: Alpha-fetoprotein (AFP)-L3 results of 10% or more are associated with a 7-fold increased risk of developing hepatocellular carcinoma (HCC). Patients with AFP-L3 levels of 10% or more should be monitored more intensely for evidence of hepatocellular carcinoma according to current practice guidelines. Total serum AFP results above 200 ng/mL are highly suggestive of a diagnosis of HCC. In patients with liver disease, a total serum AFP level above 200 ng/mL is near 100% predictive of HCC. With lower total AFP levels, there is an increased likelihood that chronic liver disease, rather than

HCC, is responsible for the AFP elevation. Based on a retrospective study at Mayo Clinic, for patients with total AFP levels 200 ng/mL or less, AFP-L3 specificity approaches 100% for HCC when its percentage exceeds 35% of the total AFP.(4) AFP concentrations over 100,000 ng/mL have been reported in normal newborns, and the values rapidly decline in the first 6 years of life. Des-gamma-carboxy prothrombin: In patients with an elevated des-gamma-carboxy prothrombin (DCP) result (> or =7.5 ng/mL), the risk of developing HCC is 36.5% (95% CI 23.5%-49.6%). The risk of developing HCC with a negative DCP result (<7.5 ng/mL) is 7.6% (95% CI 4.4%-10.8%). Gender, Age, AFP-L3, AFP, DCP (GALAD) Score: Higher GALAD model scores correlate with increased risk of HCC. The area under the curve (AUC) of a receiver operating characteristic curve of the GALAD score was 0.95 for all HCC detection, and 0.92 for the detection of early-stage HCC. Additionally, the AUC of the GALAD score (0.95) was higher than that of ultrasound alone for all HCC detection (AUC of 0.82, P <0.01). The sensitivity and specificity performance characteristics of the GALAD score for HCC will be influenced by the selected GALAD score cut-off. For example, at an optimal AUC cutoff of -0.76, the GALAD score had 91% sensitivity and 85% specificity for HCC detection. At a more specific GALAD score cutoff of 0.88, the observed sensitivity was 80% for HCC detection with an observed specificity of 97%. The GALAD model was developed and validated in patient cohorts with a prevalence of HCC ranging from 35% to 49%. The performance of the model may be altered in populations with different HCC prevalence. In addition, the clinical performance of the GALAD score varies by etiology of HCC and therefore may be different in different regions of the world.

Reference Values:

TOTAL ALPHA-FETOPROTEIN (AFP):
<4.7 ng/mL

AFP L3-PERCENT:
<10%

DES-GAMMA-CARBOXY PROTHROMBIN:
<7.5 ng/mL

GAL1:
Not applicable

Clinical References: 1. Okuda K: Hepatocellular carcinoma. J Hepatol. 2000;32(Suppl 1):225-237 2. Kawai K, Kojima T, Miyanaga N, et al. Lectin-reactive alpha-fetoprotein as a marker for testicular tumor activity. Int J Urol. 2005;12(3):284-289 3. Noda K, Miyoshi E, Kitada T, et al. The enzymatic basis for the conversion of nonfucosylated to fucosylated alpha-fetoprotein by acyclic retinoid treatment in human hepatoma cells: activation of alpha 1-6 fucosyltransferase. Tumor Biol. 2002;23(4):202-211 4. Leerapun A, Suravarapu SV, Bida JP, et al. The utility of Lens culinaris agglutinin-reactive alpha-fetoprotein in the diagnosis of hepatocellular carcinoma: evaluation in a United States referral population. Clin Gastroenterol Hepatol. 2007;5(3):394-402 5. Carr BI, Kanke F, Wise M, Satomura S: Clinical evaluation of Lens culinaris agglutinin-reactive alpha-fetoprotein and des-gamma-carboxy prothrombin in histologically proven hepatocellular carcinoma in the United States. Dig Dis Sci. 2007;52(3):776-782 6. Durazo FA, Blatt LM, Corey WG, et al. Des-gamma-carboxy prothrombin, alpha-fetoprotein and AFP-L3 in patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma. J Gastroenterol Hepatol. 2008;23(10):1541-1548 7. Marrero JA, Feng Z, Wang Y, et al. Alpha-fetoprotein, des-gamma carboxyprothrombin, and lectin-bound alpha-fetoprotein in early hepatocellular carcinoma. Gastroenterology. 2009;137(1):110-118 8. Bertino G, Ardiri AM, Calvagno GS, Bertino N, Boemi PM. Prognostic and diagnostic value of des-y-carboxy prothrombin in liver cancer. Drug News Perspect. 2010;23(8):498-508 9. Johnson PJ, Pirrie SJ, Cox TF, et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev. 2014;23(1):144-153 10. Berhane S, Toyoda H, Tada T, et al. Role of the GALAD and BALAD-2 serologic models in diagnosis of hepatocellular carcinoma and prediction of survival in patients. Clin Gastroenterol Hepatol. 2016;14(6):875-886 11. Yang JD, Addissie BD,

Mara KC, et al. GALAD Score for Hepatocellular Carcinoma Detection in Comparison with Liver Ultrasound and Proposal of GALADUS Score. Cancer Epidemiol Biomarkers Prev. 2019;28(3):531-538. doi:10.1158/1055-9965 12. Chaiteerakij R, Addissie BD, Roberts LR. Update on biomarkers of hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2015;13(2):227-245 doi:10.1016/j.cgh.2013.10.038

HEPAT 70456 Hepatocyte Immunostain, Technical Component Only

Clinical Information: Normal liver tissue is positive with a distinct granular cytoplasmic staining of hepatocytes. Bile ducts and nonparenchymal liver cells are negative.

Useful For: Distinguishing hepatocellular carcinoma from other types of cancer

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Nguyen T, Phillips D, Jain D, et al. Comparison of 5 Immunohistochemical Markers of Hepatocellular Differentiation for the Diagnosis of Hepatocellular Carcinoma. Arch Pathol Lab Med. 2015;139(8):1028-1034. doi:10.5858/arpa.2014-0479-OA 2. Krings G, Ramachandran R, Jain D, et al. Immunohistochemical pitfalls and the importance of glypican 3 and arginase in the diagnosis of scirrhous hepatocellular carcinoma. Mod Pathol. 2013;26(6):782-791. doi:10.1038/modpathol.2012.243 3. Shibuya M, Kondo F, Sano K, Takada T, Asano T. Immunohistochemical study of hepatocyte, cholangiocyte and stem cell markers of hepatocellular carcinoma. J Hepatobiliary Pancreat Sci. 2011;18(4):537-543. doi:10.1007/s00534-010-0365-2 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HNF1B 70461 Hepatocyte Nuclear Factor 1Beta Immunostain, Technical Component Only

Clinical Information: Hepatocyte nuclear factor-1beta (HNF-1beta) is a transcription factor that regulates the transcription of the TCF2 gene into proteins. HNF-1beta has been shown to be upregulated in ovarian clear cell carcinoma.

Useful For: Diagnosis of ovarian clear cell carcinoma and endometrial clear cell carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. DeLair D, Han G, Irving JA, et al. HNF-1beta in ovarian carcinomas with serous and clear cell change. Int J Gynecol Pathol. 2013;32(6):541-546. doi:10.1097/PGP.0b013e318273fd07 2. Fadare O, Zhao C, Khabele D, et al. Comparative analysis of napsin A, alpha-methylacyl-coenzyme A racemase (AMACR, P504S), and hepatocyte nuclear factor 1 beta as diagnostic markers of ovarian clear cell carcinoma: an immunohistochemical study of 279 ovarian tumours. Pathology. 2015;47(2):105-111. doi:10.1097/PAT.0000000000000223 3. Li Q, Zeng X, Cheng X, et al. Diagnostic value of dual detection of hepatocyte nuclear factor 1 beta (HNF-1beta) and napsin A for diagnosing ovarian clear cell carcinoma. Int J Clin Exp Pathol. 2015;8(7):8305-8310 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry.

Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HSMWB 65695 Hepatosplenomegaly Panel, Blood

Clinical Information: Hepatosplenomegaly is a presenting or accompanying feature for many different inborn errors of metabolism. It typically is a consequence of chronic hepatic dysfunction or abnormal storage of lipids, sugars, or other improperly metabolized analytes due to a particular enzymatic deficiency. The diagnosis can occasionally be narrowed down by consideration of clinical symptoms; however, clinical diagnosis can be difficult due to similarity of clinical features across disorders as well as phenotypic variability. Therefore, screening tests can play an important role in the workup of a patient presenting with hepatosplenomegaly who may have a lysosomal or lipid storage disorder. The conditions detected in this assay are cerebrotendinous xanthomatosis, Gaucher disease, and Niemann-Pick (NP) disease types A, B (also known as acid sphingomyelinase deficiency), and, with a lower sensitivity and specificity, NPC. Patients with abnormal results should have follow-up enzymatic or molecular testing for confirmation of diagnosis. Table. Conditions Identifiable by Method Disorder Onset Analyte detected Gene Incidence Cerebrotendinous xanthomatosis (CTX) Infancy - adulthood 7-Alpha-hydroxy-4-cholesten-3-one (7aC4) 7-Alpha,12-aplha-dihydroxycholest-4-en-3-one (12aC4) CYP27A1 1 in 50,000 As high as 1 in 400 in Druze population. Phenotype: Early onset diarrhea, cataracts, tendon/cerebral xanthomas, osteoporosis, neuropsychological manifestations, liver disease/hepatosplenomegaly. Gaucher disease Type I: childhood/adult Types II/III: neonatal-early childhood Glucopsychosine (GPSY) GBA Type I: 1 in 30,000 to 1 in 100,000 Types II/III: 1 in 100,000 Phenotype: All types exhibit hepatosplenomegaly and hematological abnormalities. Type I: Organomegaly, thrombocytopenia, and bone pain. Absence of neurologic symptoms. Types II/III: Primary neurologic disease, developmental delay/regression, hepatosplenomegaly, lung disease. Patients with type II typically die by 2 to 4 years of age. Patients with type III may have a less progressive phenotype and may survive into adulthood. Niemann-Pick type A/B (NPA, NPB) NPA: neonatal NPB: birth-adulthood Lyso-sphingomyelin (LSM) LSM 509 SMPD1 Combined incidence 1 in 250,000 Phenotype: NPA: Feeding difficulties, jaundice, hepatosplenomegaly, neurologic deterioration, lung disease, hearing and vision impairment, cherry red macula, death usually by 3 years of age. NPB: Mainly limited to visceral symptoms; hepatosplenomegaly, stable liver dysfunction, pulmonary compromise, osteopenia. Niemann-Pick type C (NPC) Variable (perinatal-adulthood) Cholestane-3 beta, 5 alpha, 6 beta-triol (COT) LSM 509 NPC1 or NPC2 1 in 120,000 to 1 in 150,000 Phenotype: Variable clinical presentation; ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, seizures, +/- hepatosplenomegaly.

Useful For: As a component of the initial evaluation of a patient presenting with hepatosplenomegaly This test is not useful for the identification of carriers. This test should not be used as a monitoring for patients with confirmed diagnoses.

Interpretation: An elevation of 7-alpha-hydroxy-4-cholesten-3-one (7aC4) and 7-alpha,12-alpha-dihydroxycholest-4-en-3-one (12aC4) is strongly suggestive of cerebrotendinous xanthomatosis. An elevation particulary of lyso-sphingomyelin (LSM) is highly suggestive of Niemann-Pick type A or B (NPA or NPB) disease. An elevation of cholestane-3 beta, 5 alpha, 6 beta-triol is highly suggestive of Niemann-Pick disease type C. An elevation of glucopsychosine is indicative of Gaucher disease.

Reference Values:

Cholestane-3 beta, 5 alpha, 6 beta-triol
Cutoff: < or =0.800 nmol/mL

Lyso-sphingomyelin
Cutoff: < or =0.100 nmol/mL

Glucopsychosine
Cutoff: < or =0.040 nmol/mL

7-Alpha-hydroxy-4-cholesten-3-one (7aC4)
Cutoff: < or =0.750 nmol/mL

7-Alpha,12-aplha-dihydroxycholest-4-en-3-one (12aC4)
Cutoff: < or =0.250 nmol/mL

Clinical References:

HSMBS 601519 Hepatosplenomegaly Panel, Blood Spot

Clinical Information:

Useful For: As a component of the initial evaluation of a patient presenting with hepatosplenomegaly, using dried blood spot specimens This test is not useful for the identification of carriers. This test should not be used as a monitoring tool for patients with confirmed diagnoses.

Interpretation: An elevation of 7-alpha-hydroxy-4-cholesten-3-one (7aC4) and 7-alpha,12-alpha-dihydroxycholest-4-en-3-one (12aC4) is strongly suggestive of cerebrotendinous xanthomatosis. An elevation particularly of lyso-sphingomyelin (LSM) is highly suggestive of Niemann-Pick type A or B (NPA or NPB) disease. An elevation of cholestane-3-beta, 5-alpha, 6-beta-triol is highly suggestive of Niemann-Pick disease type C. An elevation of glucopsychosine is indicative of Gaucher disease.

Reference Values:
Cholestane-3-beta, 5-alpha, 6-beta-triol
Cutoff: < or =0.800 nmol/mL

Lyso-Sphingomyelin
Cutoff: < or =0.100 nmol/mL

Glucopsychosine
Cutoff: < or =0.040 nmol/mL

7-Alpha-hydroxy-4-cholesten-3-one (7a-C4)
Cutoff: < or =0.750 nmol/mL

7-Alpha,12-alpha-dihydroxycholest-4-en-3-one (7a12aC4)
Cutoff: < or =0.250 nmol/mL

Clinical References: 1. DeBarber AE, Luo J, Star-Weinstock M, et al. A blood test for cerebrotendinous xanthomatosis with potential for disease detection in newborns. J. Lipid Res. 2014;55(1):146-154 2. Federico A, Dotti MT, Gallus GN. Cerebrotendinous xanthomatosis. In: Adam MP, Feldman J, Mirzaa GM,, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated March 17, 2022. Accessed November 5, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1409/ 3. Grabowski GA, Petsko GA, Phil D, Kolodny EH. Gaucher disease. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed November 5, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225546056&bookid=2709 4. Murugeasan V, Chuan WL, Liu J, et al. Glucosylsphingosine is a key biomarker of Gaucher disease. Am J Hematol. 2016;91(11):1082-1089 5. Wasserstein MP, Schuchman EH. Acid sphingomyelinase deficiency. In:

Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated April 27, 2023. Accessed November 5, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1370/. 6. Wasserstein M, Dionisi-Vici C, Giugliani R, et al. Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD). Mol Genet Metab. 2019;126(2):98-105 7. Patterson M. Niemann-Pick disease type C. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated December 10, 2020. Accessed November 5, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1296/ 8. Geberhiwot T, Moro A, Dardis A, et al. International Niemann-Pick Disease Registry (INPDR): Consensus clinical management guidelines for Niemann-Pick disease type C. Orphanet J Rare Dis. 2018;13(1):50. doi:10.1186/s13023-018-0785-7

HSMP
65694

Hepatosplenomegaly Panel, Plasma

Clinical Information:

Useful For: As a component to the initial evaluation of a patient presenting with hepatosplenomegaly, using plasma specimens This test is not useful for the identification of carriers. This test should not be used as a monitoring tool for patients with confirmed diagnoses.

Interpretation: An elevation of 7-alpha-hydroxy-4-cholesten-3-one (7a-C4) or 7-alpha,12-alpha-dihydroxycholest-4-en-3-one (7a12aC4) or both is strongly suggestive of cerebrotendinous xanthomatosis. An elevation of glucopsychosine is indicative of Gaucher disease. An elevation particularly of lyso-sphingomyelin (LSM) is highly suggestive of Niemann-Pick type A or B disease. An elevation of cholestane-3-beta, 5-alpha, 6-beta-triol is highly suggestive of Niemann-Pick disease type C.

Reference Values:
Cholestane -3-beta, 5-alpha, 6-beta-troil
Cutoff: < or =0.070 nmol/mL

7-Ketocholesterol
Cutoff: < or =0.100 nmol/mL

Lyso-sphingomyelin Cutoff: < or =0.100 nmol/mL

Glucopsychosine Cutoff: < or =0.003 nmol/mL

7-Alpha-hydroxy-4-cholesten-3-one Cutoff: < or =0.300 nmol/mL

7-Alpha,12-alpha-dihydroxycholest-4-en-3-one
Cutoff: < or =0.100 nmol/mL

Clinical References:

JHERF
615003

HER2 Amplification Associated with Breast Cancer, FISH, Breast Primary, Tissue

Clinical Information: HER2 (ERBB2: c-erb-b2) is an oncogene on the long arm of chromosome 17 that is amplified in approximately 15% to 20% of breast cancers. Amplification or overexpression of HER2 has been shown to be associated with shorter disease-free survival and poorer overall survival in

breast cancer. Patients with HER2 gene amplification or overexpression are candidates for treatment with the drugs that target the human epidermal growth factor receptor 2 (HER2) protein or its downstream pathways (eg, trastuzumab [Herceptin], pertuzumab). Fluorescence in situ hybridization (FISH) with labeled DNA probes to the pericentromeric region of chromosome 17 and to the HER2 locus can be used to determine if a patient's breast cancer has HER2 gene amplification. Immunohistochemical analysis is used to determine if a tumor exhibits HER2 overexpression.

Useful For:

Interpretation:

Reference Values:
An interpretive report will be provided.

Clinical References: 1. American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol. 2018;36(20):2105-2122. doi:10.1200/JCO.2018.77.8738) 2. American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. J Clin Oncol. 2023;41(22):3867-3872 3. CAP Accreditation Program. CYG.48932 Fixation - HER2 (ERBB2) Breast Predictive Marker Testing. Cytogenetics Checklist. College of American Pathologists. 08/20233. 4. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society for Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31(31):3997-4013. doi:10.1200/JCO.2013.50.9984 5. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673-1684. doi:10.1056/NEJMoa052122 6. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol. 2011;29(25):3366-3373. doi:10.1200/JCO.2011.35.0868 7. Blumenthal GM, Scher NS, Cortazar P, et al. First FDA approval of dual anti-HER2 regimen: pertuzumab in combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer. Clin Cancer Res. 2013;19(18):4911-4916. doi:10.1158/1078-0432.CCR-13-1212

H2BR
65879

HER2 Amplification Associated with Breast Cancer, FISH, Tissue

Clinical Information: HER2 (ERBB2: c-erb-b2) is an oncogene on the long arm of chromosome 17 that is amplified in approximately 15% to 20% of breast cancers. Amplification or overexpression of HER2 has been shown to be associated with shorter disease-free survival and poorer overall survival in breast cancers. Patients with HER2 gene amplification or overexpression are candidates for treatment with the drugs that target the human epidermal growth factor receptor 2 (HER2) protein or its downstream pathways (eg, trastuzumab [Herceptin], pertuzumab). Fluorescence in situ hybridization with labeled DNA probes to the pericentromeric region of chromosome 17 and to the HER2 locus can be used to determine if a patient's breast cancer has HER2 gene amplification. Immunohistochemical analysis is used to determine if a tumor exhibits HER2 overexpression.

Useful For: A predictive marker for patients with both node-positive or node-negative primary and metastatic breast cancer Patients with HER2 amplification that may be candidates for therapies targeting the human epidermal growth factor receptor 2 (HER2) protein (eg, trastuzumab [Herceptin], pertuzumab, lapatinib) Confirming the presence of HER2 amplification in cases with 2+ (low level) or 3+ (high level) HER2 overexpression by immunohistochemistry, and for certain histologic subtypes with aberrant patterns of HER2 expression seen by immunohistochemistry (eg, micropapillary carcinoma)

Interpretation: An interpretive report will be provided. Results are interpreted utilizing the current American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines.(1) Under the 2018 Focused Update to the ASCO/CAP Guidelines, reflex immunohistochemistry (IHC) is performed for certain categories of results, known as Groups 2, 3, and 4. These categories are shown in the table below (Group 4 is the category formerly referred to as fluorescence in situ hybridization [FISH] "equivocal"). If reflex IHC is performed and is either negative (0, 1+) or positive (3+), the result of the FISH assay is considered resolved by IHC as either negative or positive. If the IHC assay shows an equivocal (2+) result, then the FISH slide is reanalyzed within the areas showing the most intense membranous (2+) staining, and the final FISH result is used to determine whether the result is negative or positive. Table. ASCO/CAP result category HER2:D17Z1 ratio; Average HER2 copies per cell Reporting approach per 2018 ASCO/CAP guidelines Group 1 HER2:D17Z1 =2.0; HER2/cell > or =4.0 Positive Group 2 HER2:D17Z1 =2.0; HER2/cell <4.0 Reflex IHC; FISH reanalysis if 2+ Group 3 HER2:D17Z1 <2.0; HER2/cell > or =6.0 Reflex IHC; FISH reanalysis if 2+ Group 4 HER2:D17Z1 <2.0; HER2/cel > or =4.0 and <6.0 Reflex IHC; FISH reanalysis if 2+ Group 5 HER2:D17Z1 <2.0; HER2/cell <4.0 Negative The degree of HER2 amplification varies in tumors. Some exhibit high levels of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have the same prognosis and response to therapy. Rare cases may not show HER2 amplification but still have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and be candidates for treatments that target the HER2 protein or its downstream pathways.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol. 2018;36(20):2105-2122 doi:10.1200/JCO.2018.77.8738 2. CAP Accreditation Program. CYG.48932 Fixation - HER2 (ERBB2) Breast Predictive Marker Testing. Cytogenetics Checklist. College of American Pathologists. 08/2023 3. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society for Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Onc. 2013;31(31):3997-4013 4. Perez EA, Roche PC, Jenkins RB, et al. HER2 testing in patients with breast cancer: poor correlation between weak positively by immunohistochemistry and gene amplification by fluorescence in situ hybridization. Mayo Clin Proc. 2002;77(2):148-154 5. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673-1684 6. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol. 2011;29(25):3366-3373 7. Blumenthal GM, Scher NS, Cortazar P, et al. First FDA approval of dual anti-HER2 regimen: pertuzumab in combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer. Clin Cancer Res. 2013;19(18):4911-4916 8. Robidoux A, Tang G, Rastogi P. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomized phase 3 trial. Lancet Oncol. 2013;14(12):1183-1192

H2GE 65880 HER2 Amplification Associated with Gastroesophageal Cancer, FISH, Tissue

Clinical Information: Gastroesophageal cancer is one of the most diagnosed cancers. To date,

chemotherapy for gastroesophageal cancer is often ineffective, and its prognosis remains poor. Recent studies suggest that the HER2 oncogene can be used as a marker to identify aggressive disease. In much the same way as was demonstrated for HER2-positive breast cancer, the HER2 gene status in gastroesophageal cancers can be used to determine treatment approaches. Amplification of the HER2 gene and overexpression of the human epidermal growth factor receptor 2 (HER2) protein have been associated with a shorter disease-free survival and shorter overall survival in gastric and gastroesophageal junction cancers. Patients whose tumors demonstrate HER2 amplification or overexpression may be candidates for treatment with the drugs that target the HER2 protein or its downstream pathways (eg, trastuzumab [Herceptin], pertuzumab).

Useful For: A predictive marker for patients with both node-positive or node-negative primary and metastatic gastroesophageal cancer Guiding therapy for patients with primary or metastatic gastroesophageal tumors, as patients with HER2 amplification may be candidates for therapies that target the human epidermal growth factor receptor 2 (HER2) protein (eg, trastuzumab [Herceptin], pertuzumab) Confirming the presence or absence of HER2 amplification in cases with 2+ (equivocal) HER2 overexpression by immunohistochemistry

Interpretation: An interpretive report will be provided. Results are interpreted utilizing the 2016 College of American Pathologists/American Society for Clinical Pathology/American Society of Clinical Oncology guidelines for gastric tumors (2) and the guidelines used by the Traztuzumab for Gastric Cancer (ToGA) trial.(3) Specimens with equivocal results as defined by 2016 CAP/ASCP/ASCO guidelines will not have additional testing performed using an alternative fluorescence in situ hybridization probe set. The report will include a complete interpretation, including the HER2:D17Z1 results. The degree of HER2 amplification varies in tumors. Some exhibit high levels of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have the same prognosis or response to therapy. Rare cases may not show HER2 amplification but still have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and be candidates for treatments that target the HER2 protein or its downstream pathways.

Reference Values:
An interpretative report will be provided.

Clinical References: 1. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society for Clinical Oncology/College of American Pathologists Clinical Practice Guideline update. J Clin Oncol. 2013;31(31):3997-4013 2. Bartley AN, Washington MK, Ventura CB, et al. HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. Am J Clin Pathol. 2016;146(6):647-669 3. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. Lancet. 2010;376(9742):687-697 4. Hofmann M, Stoss O, Shi D, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology. 2008;52:797-805 5. Reichelt U, Duesedau P, Tsourlakis MCh, et al. Frequent homogeneous HER-2 amplification in primary and metastatic adenocarcinoma of the esophagus. Mod Pathol. 2007;20:120-129

H2MT
65881

HER2 Amplification, Miscellaneous Tumor, FISH, Tissue

Clinical Information: In much the same way as was demonstrated for HER2-positive breast cancer,

the HER2 gene status in some cancers can be used to determine treatment approaches. Amplification of the HER2 gene and overexpression of the human epidermal growth factor receptor 2 (HER2) protein have been associated with a shorter disease-free survival and shorter overall survival in some cancers. Patients whose tumors demonstrate HER2 amplification or overexpression may be candidates for treatment with the drugs that target the HER2 protein or its downstream pathways (eg, trastuzumab [Herceptin], pertuzumab).

Useful For: Guiding cancer therapy, as patients with HER2 amplification may be candidates for therapies that target the human epidermal growth factor receptor 2 (HER2) protein (eg, trastuzumab [Herceptin], pertuzumab) Confirming the presence of HER2 amplification in cases with 2+ (low level) or 3+ (high level) HER2 protein overexpression by immunohistochemistry

Interpretation: An interpretive report will be provided. Results for tumors of colorectal origin are interpreted with reference to the definition of HER2 amplification in colorectal cancer in the HERACLES trial, a HER2 / centromere ratio 2.0 or above is considered positive(2) as well as with reference to the MyPathway trial, a HER2 / centromere ratio above 2.0 or average HER2 copy number above 6.0 is considered positive.(3) Results for primary or metastatic endometrial serous carcinomas are interpreted according to expert recommendations(4) and according to updated American Society of Clinical Oncology/College of American Pathologists (ASCP/CAP) (2018) guidelines for breast cancer.(5) All other tumors are interpreted as amplified if HER2 / centromere ratio is greater than or equal to 2.0 or average HER2 copy number greater than or equal to 6.0 and according to according to updated ASCO/CAP (2013) guidelines for breast cancer.(1) The degree of HER2 amplification varies in tumors. Some exhibit a high level of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have a similar prognosis or response to therapy. Rare cases may not show HER2 amplification but have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and may be candidates for treatments that target the HER2 protein or its downstream pathways.

Reference Values:
An interpretative report will be provided.

Clinical References:

HER2I
70457

HER2 Immunostain, Technical Component Only

Clinical Information: The human HER2 gene (also known as ERBB2 or NEU) encodes a protein often referred to as HER2 protein or P185(HER2). The HER2 protein is a membrane receptor tyrosine kinase with homology to the epidermal growth factor receptor (EGFR or HER1). The HER2 protein is a normal component expressed by a variety of epithelial cell types.

Useful For: Qualitative detection of HER2 protein overexpression in a diagnostic setting in formalin-fixed paraffin-embedded tissue sections

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Calhoun BC, Collins LC. Predictive markers in breast cancer: an update

on ER and HER2 testing and reporting. Semin Diagn Pathol. 2015;32(5):362-369. doi:10.1053/j.semdp.2015.02.011 2. Bahreini F, Soltanian AR, Mehdipour P. A meta-analysis on concordance between immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) to detect HER2 gene overexpression in breast cancer. Breast Cancer. 2015;22(6):615-625. doi:10.1007/s12282-014-0528-0 3. Wolff AC, Hammond EH, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31(31):3997-4013. doi:10.1200/JCO.2013.50.9984

HERDN 71498 HER2, Breast, DCIS, Quantitative Immunohistochemistry, Manual No Reflex

Clinical Information: The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene in human breast, endometrial, ovarian, and other epithelial cancers have been associated with a shorter disease-free interval and shorter overall survival. Overexpression of HER2 protein is an indication for Herceptin therapy in patients with breast cancer.

Useful For: Determining overexpression of HER2 protein on formalin-fixed, paraffin-embedded tissue sections in ductal carcinoma in situ or solid/intracystic papillary carcinoma breast tissue This FDA-approved test is most frequently used to evaluate HER2 overexpression in breast cancer

Interpretation: Results are reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.

Reference Values:
Reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.

Clinical References: 1. Riber-Hansen R, Vainer B, Steiniche T: Digital image analysis: a review of reproducibility, stability and basic requirements for optimal results. Apmis 2012 April;120(4):276-289 2. Gavrielides MA, Gallas BD, Lenz P, et al: Observer variability in the interpretation of HER2/neu immunohistochemical expression with unaided and computer-aided digital microscopy. Arch Pathol Lab Med Feb;135(2):233-242 3. Cuadros M, Villegas R: Systematic review of HER2 breast cancer testing. Appl Immunohistochem Mol Morphol Jan 2009;17(1):1-7 4. Nassar A, Cohen C, Agersborg SS, et al: Trainable immunohistochemical HER2/neu image analysis: a multisite performance study using 260 breast tissue specimens. Arch Pathol Lab Med 2011 July;135(7):896-902

HERDM 70915 HER2, Breast, DCIS, Quantitative Immunohistochemistry, Manual with HER2 FISH Reflex

Clinical Information: The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene in human breast, endometrial, ovarian, and other epithelial cancers have been associated with a shorter disease-free interval and shorter overall survival. Overexpression of HER2 protein is an indication for Herceptin therapy in patients with breast cancer.

Useful For: Determining overexpression of HER2 protein on formalin-fixed, paraffin-embedded tissue sections in ductal carcinoma in situ or solid/intracystic papillary carcinoma breast tissue with a reflex to FISH testing if the specimen is equivocal (2+)

Interpretation: Results are reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.

Reference Values:
Reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.

Clinical References: 1. Riber-Hansen R, Vainer B, Steiniche T: Digital image analysis: a review of reproducibility, stability and basic requirements for optimal results. Apmis 2012 April;120(4):276-289 2. Gavrielides MA, Gallas BD, Lenz P, et al: Observer variability in the interpretation of HER2/neu immunohistochemical expression with unaided and computer-aided digital microscopy. Arch Pathol Lab Med Feb;135(2):233-242 3. Cuadros M, Villegas R: Systematic review of HER2 breast cancer testing. Appl Immunohistochem Mol Morphol Jan 2009;17(1):1-7 4. Nassar A, Cohen C, Agersborg SS, et al: Trainable immunohistochemical HER2/neu image analysis: a multisite performance study using 260 breast tissue specimens. Arch Pathol Lab Med 2011 July;135(7):896-902

HERBN
70913

HER2, Breast, Quantitative Immunohistochemistry, Automated, No Reflex

Clinical Information: The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene in human breast, endometrial, ovarian, and other epithelial cancers have been associated with a shorter disease-free interval and shorter overall survival. Overexpression of HER2 protein is an indication for Herceptin therapy in patients with breast cancer.

Useful For: Determining overexpression of HER2 protein on formalin-fixed, paraffin-embedded tissue sections without a reflex to FISH testing This FDA-approved test is most frequently used to evaluate HER2 overexpression in breast cancer

Interpretation: Results are reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody. The scoring method using the Aperio digital pathology system was developed and validated in the Molecular Anatomic Pathology Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic (see Method Description).

Reference Values:
Reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.

Clinical References: 1. Riber-Hansen R, Vainer B, Steiniche T: Digital image analysis: a review of reproducibility, stability and basic requirements for optimal results. Apmis 2012 April;120(4):276-289 2. Gavrielides MA, Gallas BD, Lenz P, et al: Observer variability in the interpretation of HER2/neu immunohistochemical expression with unaided and computer-aided digital microscopy. Arch Pathol Lab Med Feb;135(2):233-242 3. Cuadros M, Villegas R: Systematic review of HER2 breast cancer testing. Appl Immunohistochem Mol Morphol Jan 2009;17(1):1-7 4. Nassar A, Cohen C, Agersborg SS, et al: Trainable immunohistochemical HER2/neu image analysis: a multisite performance study using 260 breast tissue specimens. Arch Pathol Lab Med 2011 July;135(7):896-902

HERMB
620800

HER2, Breast, Semi-Quantitative Immunohistochemistry,

Manual with HER2 FISH Reflex

Clinical Information: The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene in human breast, endometrial, ovarian, and other epithelial cancers have been associated with a shorter disease-free interval and shorter overall survival. Overexpression of HER2 protein is an indication for Herceptin (trastuzumab) therapy in patients with breast cancer. This test is most frequently used to evaluate HER2 overexpression in breast cancer.

Useful For: Determining overexpression of HER2 protein on formalin-fixed, paraffin-embedded tissue sections

Interpretation: Results are reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the published American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) interpretation guidelines.(1)

Reference Values:
Reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the US Food and Drug Administration-approved Ventana Pathway HER2 (4B5) antibody.

Clinical References: 1. Wolff AC, Hammond ME, Hicks DG, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol. 2018;36(20):2105-2122 doi:10.1200/JCO.2018.77.8738 2. Riber-Hansen R, Vainer B, Steiniche T. Digital image analysis: a review of reproducibility, stability and basic requirements for optimal results. Apmis. 2012;120(4):276-289 3. Gavrielides MA, Gallas BD, Lenz P, Badano A, Hewitt SM.: Observer variability in the interpretation of HER2/neu immunohistochemical expression with unaided and computer-aided digital microscopy. Arch Pathol Lab Med. 2011;135(2):233-242 4. Cuadros M, Villegas R. Systematic review of HER2 breast cancer testing. Appl Immunohistochem Mol Morphol. 2009;17(1):1-7 5. Nassar A, Cohen C, Agersborg SS, et al. Trainable immunohistochemical HER2/neu image analysis: a multisite performance study using 260 breast tissue specimens. Arch Pathol Lab Med. 2011;135(7):896-902

HERGM
70911

HER2, Gastric/Esophageal, Semi-Quantitative Immunohistochemistry, Manual

Clinical Information: The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene have been associated with a shorter disease-free survival and shorter overall survival in gastric and gastroesophageal junction cancers, as well as breast, endometrial, and ovarian cancer.(1,2)

Useful For: Determining overexpression of HER2 protein of gastric and esophageal adenocarcinoma in formalin-fixed, paraffin-embedded tissue sections (with reflex to FISH testing)

Interpretation: Results are reported as positive (3+ HER2 protein expression), equivocal (2+), or negative (0 or 1+). Equivocal (2+) cases will automatically reflex to FISH testing at an additional charge.

Reference Values:
Reported as negative (0, 1+), equivocal (2+), and positive (3+)

Clinical References: 1. Pergam M, Slamon D: Biological rationale for HER2/neu (c-erbB2) as a

target for monoclonal therapy. Semin Oncol 2000;27(5):13-19 2. Gravalos C, Jimeno A: HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol 2008 Sep;19(9):1523-1529 3. Meza-Junco J, Au HJ, Sawyer MB: Transtuzumab for gastric cancer. Expert Opin Biol Ther 1009;9(12):1543-1551

HERGN 70914 HER2, Gastric/Esophageal, Semi-Quantitative Immunohistochemistry, Manual, No Reflex

Clinical Information: The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene have been associated with a shorter disease-free survival and shorter overall survival in gastric and gastroesophageal junction cancers, as well as breast, endometrial, and ovarian cancer.(1,2)

Useful For: Determining overexpression of HER2 protein of gastric and esophageal adenocarcinoma in formalin-fixed, paraffin-embedded tissue sections (no reflex to FISH testing)

Interpretation: Results are reported as positive (3+ HER2 protein expression), equivocal (2+), or negative (0 or 1+)

Reference Values:
Reported as negative (0, 1+), equivocal (2+), and positive (3+)

Clinical References: 1. Pergam M, Slamon D: Biological rationale for HER2/neu (c-erbB2) as a target for monoclonal therapy. Semin Oncol 2000;27(5):13-19 2. Gravalos C, Jimeno A: HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol 2008 Sep;19(9):1523-1529 3. Meza-Junco J, Au HJ, Sawyer MB: Transtuzumab for gastric cancer. Expert Opin Biol Ther 1009;9(12):1543-1551

GNANG 619215 Hereditary Angioedema Focused Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Hereditary angioedema with normal C1 inhibitor (HAE with normal C1INH) is a rare blood and immunologic disorder associated with germline variants in the F12 gene (F12-HAE), PLG gene (PLG-HAE), and KNG1 gene (KNG1-HAE). It is inherited in an autosomal dominant manner with incomplete penetrance.(3,4) HAE with normal C1INH is characterized by recurrent episodes of severe skin and submucosal swelling, abdominal pain attacks, and upper airway obstruction that does not respond to high-dose antihistamine therapy. Facial and tongue swelling are common. Affected individuals have normal complement studies, normal C1INH antigen and function, and no exposure to medications that could cause angioedema, such as angiotensin-converting-enzyme inhibitors or non-steroidal anti-inflammatory drugs. Estrogen exposure exacerbates disease severity in many patients.(2-6) Acquired angioedema is associated with B-cell lymphoproliferative disorders in some patients, the presence of autoantibodies to C1-INH, and the use of renin-angiotensin-aldosterone system-blockers.(4) In addition to HAE with normal C1INH, germline variants in the F12 gene are associated with autosomal recessive factor XII deficiency. While this rare blood disorder is characterized by prolonged activated partial thromboplastin time and reduced factor XII activity, it is rarely associated with an excessive bleeding tendency or abnormal bleeding during trauma or surgery. Individuals with factor XII deficiency are generally asymptomatic.(7) Causes of acquired (nongenetic) factor XII deficiency should be excluded prior to genetic testing, including liver disease, nephrotic syndrome, and chronic granulocytic leukemia.

Useful For: Evaluating hereditary angioedema (HAE) with normal C1 inhibitor (C1INH) in patients with a suggestive personal or family history Confirming a diagnosis of HAE with normal C1INH with the identification of a known or suspected disease-causing alteration in the F12, PLG or KNG1 gene Determining the disease-causing alteration within the F12, PLG or KNG1 gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of HAE with normal C1INH Evaluating factor XII deficiency in patients with a suggestive personal or family history Confirming a factor XII deficiency diagnosis with the identification of known or suspected disease-causing alteration(s) in the F12 gene Determining the disease-causing alteration(s) within the F12 gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of factor XII deficiency Identifying the causative alteration(s) for genetic counseling purposes Prognosis and risk assessment based on the genotype-phenotype correlations Carrier testing for close family members of an individual with a diagnosis of factor XII deficiency This test is not intended for prenatal diagnosis.

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

BRGYP
614320

Hereditary Breast/Gynecologic Cancer Panel, Varies

Clinical Information: Breast and gynecologic cancers including ovarian and endometrial carcinoma occur in about 12% and 1% to 3% of the general population, respectively.(1) In some cases, breast and gynecologic cancers may be attributed to a hereditary cancer syndrome.(2-5) Evaluation of the genes on this panel may be useful for families with a history of breast, ovarian, or endometrial cancers to determine cancer risk, surveillance recommendations, and targeted treatments. Hereditary breast and ovarian cancer syndrome (HBOC), caused by disease-causing variants in the BRCA1 and BRCA2 genes, account for the majority of hereditary breast and ovarian cancer.(2,4) HBOC is predominantly characterized by early-onset breast and ovarian cancer. Individuals with HBOC are also at increased risks for prostate, pancreatic, and male breast cancers.(2,4) Lynch syndrome is one of the most common endometrial and ovarian cancer syndromes, caused by variants in the MLH1, MSH2, MSH6, PMS2, mismatch-repair genes, or deletions of the EPCAM gene.(3,5) Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer.(3,5) The lifetime risk for cancer is highly variable and dependent on the gene involved. Other malignancies within the tumor spectrum include gastric, ovarian, prostate, hepatobiliary, upper urinary tract, and small bowel cancers.(3,5) Other genes known to increase risk for breast, ovarian, or uterine cancer are also included on this panel.(2) The risk for developing cancer associated with these syndromes varies.(2) Some individuals with a disease-causing variant in one of these genes develop multiple primary or bilateral cancers.(2) The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with hereditary breast and gynecologic cancer syndromes.(2,3,6,7)

Useful For: Evaluating patients with a personal or family history suggestive of a hereditary breast or gynecological cancer syndrome Establishing a diagnosis of a hereditary breast or gynecological cancer syndrome allowing for targeted cancer surveillance based on associated risks Identifying genetic variants associated with increased risk for breast or gynecological cancers, allowing for predictive testing and appropriate screening of at-risk family members Therapeutic eligibility with poly adenosine diphosphate-ribose polymerase (PARP) inhibitors based on certain gene alterations (eg, BRCA1, BRCA2) in selected

tumor types

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Howlader N, Noone AM, Krapcho M, et al: SEER Cancer Statistics Review. 1975-2018. National Cancer Institute; Updated April 15, 2021. Accessed September 12, 2024. Available at: https://seer.cancer.gov/csr/1975_2018/ 2. Daly MB, Pal T, Berry M, et al. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021 6;19(1):77-102 3. Gupta S, Provenzale D, Llor X, et al. NCCN Guidelines Insights: Genetic/familial high-risk assessment: colorectal, version 2.2019. J Natl Compr Canc Netw. 2019;17(9):1032-1041 4. Petrucelli N, Daley MB, Pal T: BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. In: Adams MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998 Updated September 21, 2023. Accessed September 12, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1247/ 5. Idos G, Valle L. Lynch syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated February 4, 2021. Accessed September 12, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1211/ 6. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007;57(2):75-89 7. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2019;69(3):184-210 8. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

COMCP
614319

Hereditary Common Cancer Panel, Varies

Clinical Information: Hereditary cancer syndromes account for approximately 5% to 10% of cancer cases.(1,2) Determining if there is a genetic risk factor contributing to cancer in an individual or family can be useful for tailoring surveillance plans, consideration of prophylactic risk reducing interventions, consideration of targeted treatments, and determining risk for family members.(3-9) This panel evaluates 36 genes known to be associated with an increased risk of polyposis and several common cancers, including breast, colon, gastric, ovarian, pancreatic, prostate, skin, thyroid, and endometrial cancers. The risk for developing cancer, as well as other features associated with these syndromes, varies. Many of the genes on this panel have established cancer risk and National Comprehensive Cancer Network or expert group guidelines and recommendations for management.(3-8) Indications for testing include but are not limited to: -Individuals with multiple primary cancers -Individuals with cancer diagnosed at young ages -Individuals with a family history of multiple relatives with cancer -Individuals whose family history of cancer may seem to overlap with more than one hereditary cancer syndrome

Useful For: Evaluating hereditary cancer for patients with a personal or family history suggestive of a hereditary cancer syndrome using a panel of 36 genes Establishing a diagnosis of a hereditary cancer syndrome allowing for targeted cancer surveillance based on associated risks Identifying genetic variants associated with increased risk for cancer, allowing for predictive testing, and appropriate screening of at-risk family members Therapeutic eligibility with poly adenosine diphosphate-ribose

polymerase (PARP) inhibitors based on certain gene alterations (eg, BRCA1, BRCA2) in selected tumor types

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review. 1975-2018. National Cancer Institute. Updated April 15, 2021. Accessed March 18, 2025. Available at: https://seer.cancer.gov/csr/1975_2018/ 3. Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. Oncogene. 2004;23(38):6445-6470 4. Daly MB, Pal T, Berry MP, et al. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(1):77-102 5. Gupta S, Provenzale D, Llor X, et al. NCCN Guidelines Insights: Genetic/familial high-risk assessment: colorectal, Version 2.2019. J Natl Compr Canc Netw. 2019;17(9):1032-1041 6. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007;57(2):75-89 7. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2019;69(3):184-210 8. Coit DG, Thompson JA, Albertini MR, et al. Cutaneous Melanoma, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(4):367-402 9. Haddad RI, Nasr C, Bischoff L, et al. NCCN Guidelines Insights: thyroid carcinoma, Version 2.2018. J Natl Compr Canc Netw. 2018;16(12):1429-1440 10. Samadder NJ, Riegert-Johnson D, Boardman L, et al. Comparison of universal genetic testing vs guideline-directed targeted testing for patients with hereditary cancer syndrome. JAMA Oncol. 2021;7(2):230-237

CDHZ
614582

Hereditary Diffuse Gastric Cancer Syndrome, CDH1, Full Gene Analysis, Varies

Clinical Information: Germline variants in the CDH1 gene are associated with hereditary diffuse gastric cancer (HDGC) syndrome, a rare autosomal dominant hereditary cancer syndrome representing 30% to 50% of all diffuse gastric cancer cases. HDGC syndrome is characterized by increased risk to develop diffuse (signet ring cell) gastric cancer and lobular breast cancer, with overall penetrance of this condition approaching 80%.(1-5) Colorectal cancer has been reported in individuals with germline CDH1 variants, however, the specific lifetime risk for colorectal cancer is unknown.(1,5) The National Comprehensive Cancer Network and the International Gastric Cancer Linkage Consortium provide recommendations regarding the medical management of individuals with hereditary diffuse gastric cancer syndrome.(1,4-5)

Useful For: Evaluating patients with a personal or family history suggestive of hereditary diffuse gastric cancer (HDGC) syndrome Establishing a diagnosis of HDGC syndrome allowing for targeted cancer surveillance based on associated risks Identifying genetic variants associated with increased risk for HDGC syndrome allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(6) Variants are classified based on known, predicted, or

possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Kaurah P, Huntsman DG. Hereditary diffuse gastric cancer. In: Adams MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews (Internet). University of Washington, Seattle; 2002. Updated March 22, 2018. Accessed September 10, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1139/ 2. Lindor NM, McMaster ML, Lindor CJ, Greene MH. Concise handbook of familial cancer susceptibility syndromes-second edition. J Natl Cancer Inst Monogr. 2008;(38):1-93. doi:10.1093/jncimonographs/Ign001 3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30 4. Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Oncol. 2020;21(8):e386-e397 5. Ajani JA, D'Amico TA, Almhanna K, et al. Gastric Cancer, Version 3.2016. NCCN clinical practice guidelines in Oncology. J Natl Compr Canc Netw. 2016;14(10):1286-1312 6. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

ENDCP
614578

Hereditary Endocrine Cancer Panel, Varies

Clinical Information: Tumors occurring within the endocrine and neuroendocrine systems, including thyroid/parathyroid tumors, pituitary tumors, pheochromocytomas (PCC), and paragangliomas (PGL), may occasionally be caused by an underlying hereditary predisposition. Suspicion may be raised for a hereditary cause in families with a strong history of endocrine cancers, patients diagnosed with an endocrine cancer at an early age, patients with multiple primary endocrine cancer diagnoses, and patients with specific histological subtypes, such as medullary thyroid cancer. The most common endocrine-related malignancy is thyroid cancer, with a lifetime risk of approximately 1.2%.(1,2) Papillary thyroid cancers are typically sporadic but can be seen in individuals or families with familial adenomatous polyposis (FAP) syndrome, caused by variants within the APC gene (cribriform-morular variant). Additionally, about 5% of cases of isolated papillary thyroid cancer cluster in a familial pattern; however, in most cases, no underlying genetic predisposition has yet been identified.(3-6) Follicular and/or papillary thyroid cancers may be seen in families with PTEN hamartoma tumor syndrome (PHTS). Individuals with disease-causing PTEN variants have a 70-fold increased incidence of thyroid cancer compared to the general population.(7) Thyroid cancers with follicular or papillary features can also be seen in individuals with disease-causing DICER1 variants, as well as individuals with Carney complex, which is caused by disease-causing variants within the PRKAR1A gene.(8,9) Approximately 25% of cases of medullary thyroid cancer (MTC) are caused by an inherited RET variant.(10) Some disease-causing RET variants are associated with only familial MTC, while others cause a syndrome called multiple endocrine neoplasia type 2 (MEN2). Individuals with MEN2 have a high risk for MTC and may also have other tumors of the endocrine/neuroendocrine system, including PGL, PCC, and parathyroid tumors.(11) Parathyroid and pituitary tumors may be caused by disease-causing variants within MEN1, CDKN1B, and CDC73. The AIP gene is associated with hereditary predisposition for isolated pituitary adenomas. PCC and PGL are rare neuroendocrine tumors, 30% of which may have an underlying hereditary predisposition.(12) The genes most frequently associated with increased risk for PGL/PCC are the succinate dehydrogenase-associated genes: SDHA, SDHAF2, SDHB, SDHC, and SDHD. Germline alterations in the MAX gene are typically associated with increased risk for PCC, although some individuals have been identified with PGL. MAX variants occur in approximately 1% of patients with hereditary PGL/PCC syndromes.(13) TMEM127 variants are most frequently associated with PCC and rarely PGL.(12) Alterations of TMEM127 account for approximately 2% of individuals with hereditary PGL/PCC.(13) Recent evidence suggests that disease-causing variants in FH increase risk for PGL/PCC.(14,15) Individuals with disease-causing FH variants

also have a significantly increased risk for cutaneous or uterine leiomyomata and renal tumors.(16) Alterations in VHL, NF1, and RET also increase risk for PGL/PCC in addition to other features and tumor types.(17) The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with hereditary endocrine tumor syndromes.(17,18)

Useful For: Evaluating patients with a personal or family history suggestive of a hereditary endocrine tumor syndrome Establishing a diagnosis of a hereditary endocrine tumor syndrome, allowing for targeted surveillance based on associated risks Identifying genetic variants associated with increased risk for endocrine tumors, allowing for predictive testing and appropriate screening of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(19) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Geeta L, O'Dorisio T, McDougall R, Weigel RJ. Cancer of the endocrine system: Thyroid cancer. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, eds. Abeloff's Clinical Oncology. 4th ed. Churchill Livingston; 2008 2. Surveillance Epidemiology and End Results Program: Cancer stat facts: Thyroid cancer. National Cancer Institute; 2018. Accessed April 26, 2024. Available at http://seer.cancer.gov/statfacts/html/thyro.html 3. Houlston RS, Stratton MR. Genetics of non-medullary thyroid cancer. QJM. 1995;88(10):685-693 4. Loh KC. Familial nonmedullary thyroid carcinoma: a meta-review of case series. Thyroid. 1997;7(1):107-113. doi:10.1089/thy.1997.7.107 5. Malchoff CD, Malchoff DM. Familial nonmedullary thyroid carcinoma. Semin Surg Oncol. 1999;16(1):16-18 6. Malchoff CD, Malchoff DM. The genetics of hereditary nonmedullary thyroid carcinoma. J Clin Endocrinol Metab. 2002;87(6):2455-2459 7. Ngeow J, Mester J, Rybicki LA, Ni Y, Milas M, Eng C. Incidence and clinical characteristics of thyroid cancer in prospective series of individuals with Cowden and Cowden-like syndrome characterized by germline PTEN, SDH, or KLLN alterations. J Clin Endocrinol Metab. 2011;96(12):E2063-71 8. Stratakis CA, Raygada M. Carney complex. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated September 21, 2023. Accessed April 26, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1286/ 9. Schultz KAP, Stewart DR, Kamihara J, et al. DICER1 tumor predisposition. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2014. Updated April 30, 2020. Accessed April 26, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK196157/ 10. Shepet K, Alhefdhi A, Lai N, Mazeh H, Sippel R, Chen H. Hereditary medullary thyroid cancer: age-appropriate thyroidectomy improves disease-free survival. Ann Surg Oncol. 2013;20(5):1451-1455 11. Eng C. Multiple endocrine neoplasia type 2. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated August 10, 2023. Accessed April 26, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1257/ 12. Else T, Greenberg S, Fishbein L. Hereditary paraganglioma-pheochromocytoma syndromes. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2008, Updated September 21, 2023. Accessed April 26, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1548/ 13. Bausch B, Schiavi F, Ni Y, et al. European-American-Asian Pheochromocytoma-Paraganglioma Registry Study Group. Clinical characterization of the pheochromocytoma and paraganglioma susceptibility genes SDHA, TMEM127, MAX, and SDHAF2 for gene-informed prevention. JAMA Oncol. 2017;3(9):1204-1212 14. Udager AM, Magers MJ, Goerke DM, et al. The utility of SDHB and FH immunohistochemistry in patients evaluated for hereditary paraganglioma-pheochromocytoma syndromes. Hum Pathol. 2018;71:47-54. doi:10.1016/j.humpath.2017 15. Castro-Vega LJ, Buffet A, De Cubas AA, et al. Germline mutations in FH confer predisposition to malignant pheochromocytomas and paragangliomas. Hum Mol Genet. 2014;23(9):2440-2446 16. Kamihara J, Schultz KA, Rana HQ. FH Tumor predisposition syndrome. In:

Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated August 13, 2020. Accessed April 26, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1252/ 17. Shah MH, Goldner WS, Halfdanarson TR, et al. NCCN Guidelines Insights: Neuroendocrine and Adrenal Tumors, Version 2.2018. J Natl Compr Canc Netw. 2018;16(6):693-702 18. Haddad RI, Nasr C, Bischoff L, et al. NCCN Guidelines Insights: Thyroid Carcinoma, Version 2.2018. J Natl Compr Canc Netw. 2018;16(12):1429-1440 19. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

NHEM
618991

Hereditary Erythrocytosis Focused Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Next-generation sequencing is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene variants can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. Erythrocytosis (ie, increased red blood cell [RBC] mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with neoplasia (ie, pheochromocytoma and/or paraganglioma formation). It is caused by variations in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new variants to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor (EPOR) and oxygen-sensing pathway enzymes (hypoxia-inducible factor [HIF2A/EPAS1], prolyl hydroxylase domain 2 [PHD2/EGLN1], and von Hippel Lindau [VHL]) can result in hereditary erythrocytosis. High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF2A, PHD2, and VHL have normal p50 results. The true prevalence of hereditary erythrocytosis-causing variants is unknown. Due to high homology, hemoglobin genes, HBA1/HBA2 and HBB, are not interrogated in this panel. The oxygen-sensing pathway functions through an enzyme, HIF, which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place, and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO. HIF-alpha is regulated by VHL protein-mediated ubiquitination and proteasomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the PHD2 (EGLN1) gene. Variations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants, in PHD2/EGLN1 and HIF2A/EPAS1, have also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating variants in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known variants have been localized to exon 8 and are heterozygous truncating variants. EPOR variants are associated with decreased EPO levels and normal p50 values. Gain of function variants in EPO have also been associated with hereditary erythrocytosis.

Useful For: Focused evaluation of an individual with JAK2-V617F negative erythrocytosis associated with lifelong sustained increased red blood cell (RBC) mass, hemoglobin, or hematocrit Providing a focused genetic evaluation for patients with a personal or family history suggestive of hereditary erythrocytosis Establishing a diagnosis of a hereditary erythrocytosis or related disorder, allowing for appropriate management and surveillance of disease features based on the gene involved

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Patnaik MM, Tefferi A. The complete evaluation of erythrocytosis: congenital and acquired. Leukemia. 2009;23(5):834-844. doi:10.1038/leu.2009.54 3. Prchal JF, Prchal JT: Polycythemia Vera. In: Kaushansky K, Lichtman MA, Prchal JT, Levi MM, Press OW, Burns LJ, Caligiuri M. eds. Williams Hematology, 9e. McGraw Hill; 2015 4. Oliveira JL, Coon LM, Frederick LA, et al. Genotype-Phenotype Correlation of Hereditary Erythrocytosis Mutations, a single center experience. Am J Hematol. 2018;10.1002/ajh.25150. doi:10.1002/ajh.25150 5. Zhuang Z, Yang C, Lorenzo F, et al. Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. N Engl J Med. 2012;367(10):922-930. doi:10.1056/NEJMoa1205119 6. Tarade D, Robinson CM, Lee JE, Ohh M. HIF-2a-pVHL complex reveals broad genotype-phenotype correlations in HIF-2a-driven disease. Nat Commun. 2018;9(1):3359. doi:10.1038/s41467-018-05554-1 7. Oliveira JL. Algorithmic evaluation of hereditary erythrocytosis: Pathways and caveats. Int J Lab Hematol. 2019;41 Suppl 1:89-94. doi:10.1111/ijlh.13019 8. Gangat N, Oliveira JL, Porter TR, et al. Erythrocytosis associated with EPAS1(HIF2A), EGLN1(PHD2), VHL, EPOR or BPGM mutations: The Mayo Clinic experience. Haematologica. 2022;107(5):1201-1204. doi:10.3324/haematol.2021.280516 9. Camps C, Petousi N, Bento C, et al. Gene panel sequencing improves the diagnostic work-up of patients with idiopathic erythrocytosis and identifies new mutations. Haematologica. 2016;101(11):1306-1318. doi:10.3324/haematol.2016.144063

NHEP
619019

Hereditary Erythrocytosis Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Next-generation sequencing is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene variants can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. Erythrocytosis (ie, increased red blood cell [RBC] mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders, including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, kidney cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases are associated with neoplasia (eg, pheochromocytoma or paraganglioma formation). It is caused by variations in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these

cases, although it is possible for new variants to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor (EPOR) and oxygen-sensing pathway enzymes (hypoxia-inducible factor [HIF2A/EPAS1], prolyl hydroxylase domain 2 [PHD2/EGLN1], and von Hippel Lindau [VHL]) can result in hereditary erythrocytosis. High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF2A, PHD2, and VHL have normal p50 results. The true prevalence of hereditary erythrocytosis-causing variants is unknown. Due to high homology, the hemoglobin genes, HBA1/HBA2 and HBB, are not interrogated in this panel. The oxygen-sensing pathway functions through an enzyme, HIF, which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place, and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes, including EPO. HIF-alpha is regulated by VHL protein-mediated ubiquitination and proteasomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the PHD2 (EGLN1) gene. Variations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants, in PHD2/EGLN1 and HIF2A/EPAS1, has also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating variants in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known variants have been localized to exon 8 and are heterozygous truncating variants. EPOR variants are associated with decreased EPO levels and normal p50 values. Gain-of-function variants in EPO have also been associated with hereditary erythrocytosis. However, the cause of erythrocytosis remains unknown in greater than 70% of cases after testing genes most associated with hereditary erythrocytosis. Therefore, additional genes associated with erythropoiesis are also interrogated in this assay. These include additional oxygen sensing erythrocytosis pathway genes (EGLN2, EGLN3, HIF1A, HIF1AN, HIF3A), some genes associated with myeloid proliferation (JAK2, SH2B3, SOCS3), and those associated with other conditions that also variably present with erythrocytosis (ANKRD26, PFKM, PIEZO1, PKLR), or methemoglobinemia (CYB5A, CYB5R3). In addition, genes identified by whole genome studies (ACO1, GFI1B, KDM6A, and BHLHE41) are included.(1)

Useful For: Evaluating an individual with JAK2-V617F negative erythrocytosis associated with lifelong sustained increased red blood cell (RBC) mass, elevated RBC count, hemoglobin, or hematocrit Providing an extensive genetic evaluation for patients with a personal or family history suggestive of hereditary erythrocytosis Comprehensive testing for patients in whom previous targeted gene variant analyses were negative for a specific hereditary erythrocytosis Establishing a diagnosis of a hereditary erythrocytosis or related disorder, allowing for appropriate management and surveillance of disease features based on the gene involved

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(2) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:

An interpretive report will be provided.

Clinical References: 1. Camps C, Petousi N, Bento C. Gene panel sequencing improves the diagnostic work-up of patients with idiopathic erythrocytosis and identifies new mutations. Haematologica. 2016;101(11):1306-1318. doi:10.3324/haematol.2016.144063 2. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 3. Patnaik MM, Tefferi A. The complete evaluation of erythrocytosis: congenital and acquired. Leukemia. 2009;23(5):834-844. doi:10.1038/leu.2009.54 4. Prchal JF, Prchal JT. Polycythemia vera. In: Kaushansky K, Lichtman MA, Prchal JT, eds. Williams Hematology. 9th ed. McGraw Hill; 2015 5. Oliveira JL, Coon LM, Frederick LA, et al. Genotype-phenotype correlation of hereditary erythrocytosis mutations, a single center experience. Am J Hematol. 2018 May 23. doi:10.1002/ajh.25150 6. Zhuang Z, Yang C, Lorenzo F, et al. Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. N Engl J Med. 2012;367(10):922-930. doi:10.1056/NEJMoa1205119 7. Tarade D, Robinson CM, Lee JE, Ohh M. HIF-2 alpha-pVHL complex reveals broad genotype-phenotype correlations in HIF-2 alpha-driven disease. Nat Commun. 2018;9(1):3359. doi:10.1038/s41467-018-05554-1 8. Oliveira JL. Algorithmic evaluation of hereditary erythrocytosis: Pathways and caveats. Int J Lab Hematol. 2019;41 Suppl 1:89-94. doi:10.1111/ijlh.13019 9. Gangat N, Oliveira JL, Porter TR, et al. Erythrocytosis associated with EPAS1(HIF2A), EGLN1(PHD2), VHL, EPOR or BPGM mutations: The Mayo Clinic experience. Haematologica. 2022;107(5):1201-1204. doi:10.3324/haematol.2021.280516 10. Iolascon A, Bianchi P, Andolfo I, et al. Recommendations for diagnosis and treatment of methemoglobinemia. Am J Hematol. 2021;96(12):1666-1678. doi:10.1002/ajh.26340

HEMP
61337

Hereditary Erythrocytosis Mutations, Whole Blood

Clinical Information: Erythrocytosis (ie, increased red blood cell [RBC] mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, kidney cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases are associated with pheochromocytoma or paraganglioma formation. Hereditary erythrocytosis is caused by variations in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new variants to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor(EPOR) and oxygen-sensing pathway enzymes (hypoxia-inducible factor[HIF/EPAS1], prolyl hydroxylase domain [PHD2/EGLN1], and von Hippel Lindau [VHL]) can result in hereditary erythrocytosis (see Table). The true prevalence of hereditary erythrocytosis-causing variants is unknown. The hemoglobin genes, HBA1/HBA2 and HBB are not assayed in this profile. Table. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum EPO JAK2 V617F Acquired Decreased JAK2 exon 12 Acquired Decreased EPOR Dominant Decreased PHD2/EGLN1 Dominant Normal level BPGM Recessive Normal level Beta globin Dominant Normal level to increased Alpha globin Dominant Normal level to increased HIF2A/EPAS1 Dominant Normal level to increased VHL Recessive Normal to increased The oxygen-sensing pathway functions

through an enzyme, HIF, which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by VHL protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the PHD2 (EGLN1) gene. Variations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants in PHD2/EGLN1 and HIF2A/EPAS1 have also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating variants in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known variants have been localized to exon 8 and are heterozygous truncating variants. EPOR variants are associated with decreased EPO levels (see Table).

Useful For: Definitive evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased red blood cell (RBC) mass, elevated RBC count, hemoglobin, or hematocrit This test is not intended for prenatal diagnosis.

Interpretation: An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any variants in the gene. If positive, the variant will be correlated with clinical significance, if known.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Patnaik MM, Tefferi A: The complete evaluation of erythrocytosis: congenital and acquired. Leukemia. 2009 May;23(5):834-844. doi: 10.1038/leu.2009.54 2. McMullin MF: The classification and diagnosis of erythrocytosis. Int J Lab Hematol. 2008 Dec;30(6):447-459. doi: 10.1111/j.1751-553X.2008.01102.x 3. Percy MJ, Lee FS: Familial erythrocytosis: molecular links to red blood cell control. Haematologica. 2008 Jul;93(7):963-967. doi: 10.3324/haematol.13250 4. Huang LJ, Shen YM, Bulut GB: Advances in understanding the pathogenesis of primary familial and congenital polycythaemia. Br J Haematol. 2010 Mar;148(6):844-852. doi: 10.1111/j.1365-2141.2009.08069.x 5. Maran J, Prchal J: Polycythemia and oxygen sensing. Patho Biol. 2004 Jun;52(5):280-284. doi: 10.1016/j.patbio.2004.02.006 6. Lee F: Genetic causes of erythrocytosis and the oxygen-sensing pathway. Blood Rev. 2008 Nov;22(6):321-332. doi: 10.1016/j.blre.2008.04.003 7. Merchant SH, Oliveira JL, Hoyer JD, Viswanatha DS: Erythrocytosis. In: His ED, ed. Hematopathology. 2nd ed. Elsevier Saunders; 2012:22-723 8. Zhuang Z, Yang C, Lorenzo F, et al: Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. N Engl J Med. 2012 Sep 6;367(10):922-930. doi: 10.1056/NEJMoa1205119 9. Ladroue C, Carcenac R, Leporrier M, et al: PHD2 mutation and congenital erythrocytosis with paraganglioma. N Engl J Med. 2008 Dec 18;359(25):2685-2692. doi: 10.1056/NEJMoa0806277 10. Lorenzo FR, Yang C, Ng Tang Fui M, et al: A novel EPAS1/HIF2A germline mutation in congenital polycythemia with paraganglioma. J Mol Med. 2013 Apr;91(4):507-512. doi: 10.1007/s00109-012-0967-z 11. Tarade D, Robinson CM, Lee JE, Ohh M: HIF-2alpha-pVHL complex reveals broad genotype-phenotype correlations in HIF-2aalpha-driven disease. Nat Commun. 2018 Aug;9(1):3359. doi: 10.1038/s41467-018-05554-1 12. Oliveira JL: Algorithmic evaluation of hereditary erythrocytosis: Pathways and caveats. Int J Lab Hematol. 2019 May;41 Suppl 1:89-94. doi: 10.1111/ijlh.13019

XCP 614318 Hereditary Expanded Cancer Panel, Varies

Clinical Information: Hereditary cancer syndromes explain about 5% to 10% of cancer cases.(1,2) Determining if there is a genetic risk factor contributing to cancer in an individual or family can be useful for tailoring surveillance plans, consideration of prophylactic risk reducing interventions, targeted cancer treatments, and determining risk for family members.(3) This panel evaluates 87 genes associated with an increased risk for the following cancers: breast, colon, gastric, ovarian, pancreatic, prostate, renal, skin, thyroid, and endometrial cancers, as well as paragangliomas, pheochromocytomas, and Wilms tumor. The risk for developing cancer associated with these syndromes varies. Several of the of the genes on this panel have established cancer risk and National Comprehensive Cancer Network (NCCN) or expert group guidelines and recommendations for management.(4-9) Indications for testing include but are not limited to: -Individuals with multiple primary cancers -Individuals with cancer diagnosed at young age -Individuals with a family history of multiple relatives with cancer -Individuals whose family history of cancer may seem to overlap with more than one hereditary cancer syndrome

Useful For: Evaluating hereditary cancer in patients with a personal or family history suggestive of a hereditary cancer syndrome using a panel of 87 genes Establishing a diagnosis of a hereditary cancer syndrome allowing for targeted cancer surveillance based on associated risks Identifying genetic variants associated with increased risk for cancer, allowing for predictive testing and appropriate screening of at-risk family members Therapeutic eligibility with poly adenosine diphosphate-ribose polymerase (PARP) inhibitors based on certain gene alterations (eg, BRCA1, BRCA2) in selected tumor types

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(10) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review. 1975-2018. National Cancer Institute. Updated April 15, 2021. Accessed March 18, 2025. Available at: https://seer.cancer.gov/csr/1975_2018/ 2. Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. Oncogene. 2004;23(38):6445-6470 3. Samadder NJ, Riegert-Johnson D, Boardman L, et al. Comparison of universal genetic testing vs guideline-directed targeted testing or patients with hereditary cancer syndrome. JAMA Oncol. 2021;7(2):230-237 4. Daly MB, Pal T, Berry MP, et al. Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(1):77-102 5. Gupta S, Provenzale D, Llor X, et al. NCCN Guidelines Insights: Genetic/familial high-risk assessment: colorectal, version 2.2019. J Natl Compr Canc Netw. 2019;17(9):1032-1041 6. Coit DG, Thompson JA, Albertini MR, et al. Cutaneous melanoma, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(4):367-402 7. Haddad RI, Nasr C, Bischoff L, et al. NCCN Guidelines Insights: Thyroid carcinoma, Version 2.2018. J Natl Compr Canc Netw. 2018;16(12):1429-1440 8. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007;57(2):75-89 9. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2019;69(3):184-210 10. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

CRCGP
614571

Hereditary Gastrointestinal Cancer Panel, Varies

Clinical Information: Colorectal cancer occurs in approximately 4% to 6% of individuals in the

general population.(1) In some cases, individuals with a personal or family history of colorectal cancer, gastric cancer, or polyposis may be at increased risk of cancer due to a hereditary cancer syndrome.(2,3) Evaluation of the genes on this panel may be useful for families with a history of colorectal cancer, gastric cancer, polyposis, or gastrointestinal cancers to determine cancer risk, surveillance recommendations, and targeted treatments.(2-4) The most common hereditary colon cancer syndrome is Lynch syndrome, accounting for about 2% to 4% of all colon cancer cases.(2) Lynch syndrome is associated with germline variants in the mismatch repair genes, MLH1, MSH2, MSH6, PMS2, or deletions of the EPCAM gene.(2,3) It is predominantly characterized by significantly increased risks for colorectal and endometrial cancer.(2,3) The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved.(2,3) Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and upper tract urothelial carcinomas, and small bowel cancer.(2,3) Although rare, individuals and families with polyposis may also be at risk for a hereditary polyposis syndrome, such as familial adenomatous polyposis (FAP).(2) FAP is caused by variants in the APC gene and characterized by numerous adenomatous polyps.(2) The presence of extracolonic manifestations is variable and includes gastric and duodenal polyps, ampullary polyps, osteomas, dental abnormalities (unerupted teeth), congenital hypertrophy of the retinal pigment epithelium (CHRPE), benign cutaneous lesions, desmoid tumors, hepatoblastoma, and extracolonic cancers.(2) Other genes are also known to cause to hereditary colorectal cancer, gastric cancer, polyposis, and gastrointestinal cancers.(2) The risk for developing cancer associated with these syndromes varies.(2) Some individuals with a disease-causing variant in one of these genes develop multiple primary cancers.(2) The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with hereditary gastrointestinal cancer syndromes.(2,4)

Useful For: Evaluating patients with a personal or family history suggestive of a hereditary gastrointestinal cancer or hereditary polyposis syndrome Establishing a diagnosis of a hereditary gastrointestinal cancer syndrome or hereditary polyposis syndrome allowing for targeted cancer surveillance based on associated risks Identifying genetic variants associated with increased risk for gastrointestinal cancer and polyposis, allowing for predictive testing and appropriate screening of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Howlader N, Noone AM, Krapcho M, et al: SEER Cancer Statistics Review. 1975-2018. National Cancer Institute; Updated April 15, 2021. Accessed September 12, 2024. Available at: https://seer.cancer.gov/csr/1975_2018/ 2. Gupta S, Provenzale D, Llor X, et al. NCCN Guidelines Insights: Genetic/familial high-risk assessment: colorectal, version 2.2019. J Natl Compr Canc Netw. 2019 1;17(9):1032-1041 3. Idos G, Valle L: Lynch syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated February 4, 2021. Accessed September 12, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1211/ 4. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2019;69(3):184-210 5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

HFET 614573 Hereditary Hemochromatosis, HFE Variant Analysis, Varies

Clinical Information:

Useful For: Establishing or confirming the clinical diagnosis of hereditary hemochromatosis (HH) in adults Testing of individuals with increased serum transferrin-iron saturation and ferritin Predictive testing of individuals who have a family history of HH, in coordination with appropriate genetic counseling This test is not recommended for population screening.

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
An interpretative report will be provided.

Clinical References: 1. Barton JC, Edwards CQ. HFE Hemochromatosis. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated April 11, 2024. Accessed March 24, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1440/ 2. Kowdley KV, Brown KE, Ahn J, Sundaram V. ACG Clinical Guideline: Hereditary Hemochromatosis. Am J Gastroenterol. 2019;114(8):1202-1218 3. Porto G, Brissot P, Swinkels DW, Zoller H, et al. EMQN best practice guidelines for the molecular genetic diagnosis of hereditary hemochromatosis (HH). Eur J Hum Genet. 2016;24(4):479-495 4. Hollerer I, Bachmann A, Muckenthaler MU. Pathophysiological consequences and benefits of HFE mutations: 20 years of research. Haematologica. 2017;102(5):809-817

NHHA
619033

Hereditary Hemolytic Anemia Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Next-generation sequencing is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene variants can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. Hereditary hemolytic anemias are caused by defects in one or more of the genes that control red blood cell (RBC) production, metabolism, or structure, resulting in faulty erythropoiesis, cell membranes, or enzymes required for normal RBC function. This panel aids in the diagnosis and treatment for hereditary (congenital) hemolytic anemia.(1,2) The panel includes genes known to cause hereditary anemia, including those implicated in RBC enzyme,(3) RBC membrane/RBC hydration,(4,5) and congenital dyserythropoietic anemia(6) disorders. This panel can aid in the differential diagnosis of early onset and lifelong myopathic or neurologic syndromes, especially if associated with hemolysis. Specifically, this panel analyzes genes associated with hereditary spherocytosis, hereditary elliptocytosis, hereditary pyropoikilocytosis, Southeast Asian ovalocytosis, hereditary stomatocytosis (both overhydrated and dehydrated/hereditary xerocytosis subtypes), and cryohydrocytosis. Hereditary stomatocytosis is an RBC membrane permeability disorder that can manifest as the more common dehydrated hereditary stomatocytosis, also known as hereditary xerocytosis, and the rarer overhydrated hereditary stomatocytosis subtypes. These disorders are important to confirm or exclude as splenectomy has been associated with an increased risk for serious venous thrombosis and thromboembolism events and is contraindicated in published guidelines.(2) It also includes genes associated with RBC enzymopathies, ranging from the common glucose 6-phosphate dehydrogenase and pyruvate kinase deficiencies to the rarer disorders of adenylate kinase, hexokinase, phosphofructokinase, phosphoglycerate kinase, pyruvate kinase, glutathione pathway, and triosephosphate isomerase. This panel also includes multiple genes associated with congenital dyserythropoietic anemia (CDA), types 1a, 1b, 2, 3, and 4. CDA is a disorder of ineffective erythropoiesis associated with distinctive bone marrow morphologic changes.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary hemolytic anemias, including red blood cell (RBC) membrane/hydration disorders, RBC enzymopathies, and congenital dyserythropoietic anemia Comprehensive testing for

patients in whom previous targeted gene variant analyses were negative for a specific hereditary hemolytic anemia Establishing a diagnosis of a hereditary hemolytic anemia or related disorder, allowing for appropriate management and surveillance of disease features based on the gene involved, especially if splenectomy is a consideration(2) Identifying variants within genes associated with phenotypic severity, allowing for predictive testing and further genetic counseling

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Orkin SH, Nathan DG, Ginsburg D, et al, eds. Nathan and Oski's Hematology of Infancy and Childhood. 7th ed. Saunders Elsevier; 2009:455-1108 2. Iolascon A, Andolfo I, Barcellini W, et al. Recommendations for splenectomy in hereditary hemolytic anemias. Haematologica. 2017;102(8):1304-1313. doi: 10.3324/haematol.2016.161166 3. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia - pathophysiology, clinical aspects, and laboratory diagnosis. Int J Lab Hematol. 2014;36(3):388-397. doi:10.1111/ijlh.12223 4. King MJ, Garcon L, Hoyer JD, et al. International Council for Standardization in Haematology. ICSH guidelines for the laboratory diagnosis of nonimmune hereditary red cell membrane disorders. Int J Lab Hematol. 2015;37(3):304-325. doi:10.1111/ijlh.12335 5. Andolfo I, Russo R, Gambale A, Iolascon A. Hereditary stomatocytosis: an underdiagnosed condition. Am J Hematol. 2018;93(1):107-121. doi: 10.1002/ajh.24929 6. Gambale A, Iolascon A, Andolfo I, Russo R. Diagnosis and management of congenital dyserythropoietic anemias. Expert Rev Hematol. 2016;9(3):283-296. doi:10.1586/17474086.2016.1131608 7. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30

HHTGG
617295

Hereditary Hemorrhagic Telangiectasia and Vascular Malformations Gene Panel, Varies

Clinical Information: Hereditary vascular malformation syndromes include a group of genetic conditions characterized by abnormal blood vessel development. These syndromes can be of germline or somatic origin. This gene panel is restricted to analysis of genes associated with vascular malformation syndromes of germline origin. Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal dominant vascular dysplasia characterized by the presence of arteriovenous malformations (AVM) of the skin, mucosa, and viscera. Small AVM, or telangiectasias, develop predominantly on the face, oral cavity, and hands, and spontaneous, recurrent epistaxis (nose bleeding) is a common presenting sign.(1) HHT has an estimated prevalence of 1:5000 and is primarily caused by heterozygous, disease-causing variants in the ACVRL1 and ENG genes. Rarely, HHT can be caused by disease-causing variants in the GDF2 gene (also known as BMP9). Additionally, SMAD4 disease-causing variants cause autosomal dominant juvenile polyposis/HHT syndrome, which includes features of juvenile polyposis syndrome and HHT.(2) An overlapping pulmonary arterial hypertension and HHT phenotype have also been reported in association with the BMPR2 gene.(3,4) Familial cerebral cavernous malformation (CCM) is an autosomal dominant condition characterized by structurally abnormal capillaries in the central nervous system leading to an increased risk of cerebral hemorrhage.(5) The estimated prevalence of familial CCM ranges from 1:3300 to 1:10,000,(5) and the condition displays age-related penetrance with up to 50% of individuals

remaining symptom free throughout their life.(5,6) Disease-causing variants in three genes have been associated with familial CCM: KRIT1, CCM2, and PDCD10. Capillary malformation-arteriovenous malformation syndrome (CM-AVM) is an autosomal dominant condition primarily characterized by capillary malformations localized to the dermis of the face and limbs, AVM or arteriovenous fistulas of the skin, muscle, bone, spine, and brain, and Parkes Weber syndrome.(6) The prevalence of CM-AVM has been estimated in Northern European cohorts at approximately 1:100,000, with penetrance estimated at 90% to 99%.(6) Approximately 60% of cases of CM-AVM can be attributed to disease-causing variants in the EPHB4 and RASA1 genes. The genetic etiology remains unknown in approximately 40% of cases.(6) Hereditary glomuvenous malformation is a rare autosomal dominant condition characterized by multiple venous malformations within the glomerulus of the kidney. The condition is associated with germline disease-causing variants in the GLMN gene. However, it is thought that a second, somatic (acquired) variant on the second allele, or acquired uniparental disomy, is required for the development of venous malformations.(7,8) Multiple cutaneous and mucosal venous malformations (also known as cutaneomucosal venous malformation: VMCM) is an autosomal dominant condition characterized by small multifocal cutaneous and mucosal vascular malformations that typically present at birth.(9) These lesions are usually asymptomatic but may become painful if they are large enough to impact the underlying muscle tissue. The prevalence of this condition is unknown but thought to be rare. VMCM is associated with disease-causing variants in the TEK gene, and penetrance is estimated at 90% in individuals with a known genetic etiology.(9)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of hereditary hemorrhagic telangiectasia (HHT), cerebral cavernous malformation (CCM), capillary malformation-arteriovenous malformation syndrome (CV-AVM), or other hereditary vascular malformation syndromes of germline origin Establishing a diagnosis of HHT, CCM, CM-AVM, or other hereditary vascular malformation syndromes of germline origin

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(10) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Faughnan ME, Mager JJ, Hetts SW, et al. Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. Ann Intern Med. 2020;173(12):989-1001. doi:10.7326/M20-1443 2. McDonald J, Stevenson DA. Hereditary hemorrhagic telangiectasia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds: GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated November 24, 2021. Accessed December 5, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1351/ 3. Rigelsky CM, Jennings C, Lehtonen R, Minai OA, Eng C, Aldred MA. BMPR2 mutation in a patient with pulmonary arterial hypertension and suspected hereditary hemorrhagic telangiectasia. Am J Med Genet A. 2008;146A(19):2551-2556. doi:10.1002/ajmg.a.32468 4. Ye F, Jiang W, Lin W, et al. A novel BMPR2 mutation in a patient with heritable pulmonary arterial hypertension and suspected hereditary hemorrhagic telangiectasia: A case report. Medicine (Baltimore). 2020;99(31):e21342. doi:10.1097/MD.0000000000021342 5. Zafar A, Quadri SA, Farooqui M, et al. Familial cerebral cavernous malformations. Stroke. 2019;50(5):1294-1301. doi:10.1161/STROKEAHA.118.022314 6. Bayrak-Toydemir P, Stevenson DA. Capillary malformation-arteriovenous malformation syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2011. Updated September 12, 2019. Accessed December 5, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK52764/ 7. Brouillard P, Boon LM, Mulliken JB, et al. Mutations in a novel factor, glomulin, are responsible for glomuvenous malformations ("glomangiomas"). Am J Hum Genet. 2002;70(4):866-874. doi:10.1086/339492 8. Amyere M, Aerts V, Brouillard P, et al. Somatic uniparental isodisomy explains multifocality of glomuvenous malformations. Am J Hum Genet. 2013;92(2):188-196. doi:10.1016/j.ajhg.2012.12.017 9. Seront E, Boon LM, Vikkula

M. TEK-Related venous malformations. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2008. Updated March 2, 2023. Accessed December 5, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1967/ 10. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30

LRCCZ 614583 Hereditary Leiomyomatosis and Renal Cell Cancer Syndrome, FH, Full Gene Analysis, Varies

Clinical Information:

Useful For: Evaluating patients with a personal or family history suggestive of hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome or fumarate hydratase deficiency (FHD) Establishing a diagnosis of HLRCC or FHD allowing for targeted surveillance based on associated risks Identifying genetic variants associated with increased risk for HLRCC syndrome allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Kamihara J, Schultz KA, Rana HQ: FH tumor predisposition syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews. [Internet]. University of Washington, Seattle; 2006. Updated August 13, 2020. Accessed April 24, 2025. Available at: www.ncbi.nlm.nih.gov/books/NBK1252/ 2. Coman D, Kranc KR, Christodoulou J: Fumarate hydratase deficiency. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews. [Internet]. University of Washington, Seattle; 2006. Updated April 23, 2020. Accessed April 24, 2025. Available at: www.ncbi.nlm.nih.gov/books/NBK1506/ 3. Zhang L, Walsh MF, Jairam S, et al. Fumarate hydratase FH c.1431_1433dupAAA (p.Lys477dup) variant is not associated with cancer including renal cell carcinoma. Hum Mutat. 2020;41(1):103-109. doi:10.1002/humu.23900 4. Menko FH, Maher ER, Schmidt LS, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. Fam Cancer. 2014;13(4):637-644. 10.1007/s10689-014-9735-2 5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

PANCP 614574 Hereditary Pancreatic Cancer Panel, Varies

Clinical Information:

Useful For: Evaluating patients with a personal or family history suggestive of a hereditary pancreatic cancer syndrome Establishing a diagnosis of a hereditary pancreatic cancer syndrome, allowing for targeted cancer surveillance based on associated risks Identifying genetic variants associated with increased risk for pancreatic cancer, allowing for predictive testing and appropriate screening of at-risk family members Therapeutic eligibility with poly adenosine diphosphate-ribose

polymerase (PARP) inhibitors based on certain gene alterations (eg, BRCA1, BRCA2)

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review. 1975-2018. National Cancer Institute. Updated April 2021. Accessed September, 11, 2024. Available at: https://seer.cancer.gov/csr/1975_2018 2. Daly MB, Pal T, Berry M, et al. Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(1):77-102 3. Gupta S, Provenzale D, Llor X, et al. NCCN guidelines insights: Genetic/familial high-risk assessment: colorectal, version 2.2019. J Natl Compr Canc Netw. 2019;17(9):1032-1041 4. Petrucelli N, Daly MB, Pal T, et al. BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. In: Adams MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated September 21, 2023. Accessed September 11, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1247/ 5. Idos G, Valle L. Lynch syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated February 4, 2021. Accessed September 11, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1211/ 6. McGarrity TJ, Amos CI, Baker MJ. Peutz-Jeghers syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2001. Updated September 2, 2021. Accessed September 11, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1266/ 7. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2019;69(3):184-210 8. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

HPANP
619844

Hereditary Pancreatitis Gene Panel, Varies

Clinical Information: Hereditary pancreatitis (HP) is defined as 2 or more individuals in a family affected with pancreatitis involving at least 2 generations.(1) Variants in several genes, including PRSS1, CFTR, CTRC, and SPINK1 have demonstrated genetic susceptibility to chronic pancreatitis. Disease susceptibility may be monogenic, as is the case with PRSS1, digenic or multigenic, and multifactorial in which multiple genes and environmental factors play a role in disease expression. PRSS1: The most common monogenic cause of HP is the presence of a variant in the cationic trypsinogen (PRSS1) gene. Variants in the PRSS1 gene are inherited in an autosomal dominant manner. It has been reported that as many as 80% of patients with symptomatic hereditary pancreatitis have a causative PRSS1 variant.(1) HP cannot be clinically distinguished from other forms of pancreatitis. However, PRSS1 variants are generally restricted to individuals with a family history of pancreatitis and are infrequently found in patients with alcohol-induced pancreatitis. Although several variants have been identified, the p.R122H, p.N29I, and p.A16V variants are the most common disease-causing variants in PRSS1 associated with HP.(2) Patients with HP are also at an increased risk for developing pancreatic cancer. Studies have estimated the lifetime risk of developing pancreatic cancer to be as high as 40%.(3) SPINK1: Biallelic variants in the SPINK1 gene have been associated with increased susceptibility to chronic pancreatitis especially in families without PRSS1 variants; however, it is unknown if biallelic variants alone are sufficient to cause chronic pancreatitis. Additionally, heterozygous SPINK1 variants appear to modify disease severity when observed in combination with variants in other genes.(1,2,4) Unlike PRSS1

variants, SPINK1 variants have been associated with alcohol-induced pancreatitis.(4) CFTR: Pancreatitis is a known manifestation of an atypical CFTR-related disorder, which results from biallelic disease-causing variants in the CFTR gene. However, CFTR variants can also cooccur with variants in CTRC, SPINK1, or CASR to confer pancreatitis disease susceptibility.(1-4) When observed in the context of a SPINK1 variant, for example, heterozygous variants in CFTR are associated with a 2- to 5-fold increased risk for pancreatitis as compared to the general population.(4) CTRC: Variants in CTRC have been observed in individuals with chronic pancreatitis in association with other risk factors, such as variants in CFTR or SPINK1 or specific environmental risk factors. Thus, chronic pancreatitis may be attributable to the presence of CTRC variants in the context of other risk factors as opposed to CTRC variants alone.(1)

Useful For: Confirming a suspected clinical diagnosis of familial or hereditary pancreatitis in patients with chronic pancreatitis Identifying gene variants contributing to pancreatitis in an individual or family Identifying gene variants to allow for predictive and diagnostic testing in family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

HPGLP
614579

Hereditary Paraganglioma/Pheochromocytoma Panel, Varies

Clinical Information: Paragangliomas (PGL)and pheochromocytomas (PCC) are rare neuroendocrine tumors that arise from autonomous ganglia. Tumors located within the adrenal medulla (the largest sympathetic ganglion) are called pheochromocytomas, while those that stem from either parasympathetic or sympathetic ganglia are designated paragangliomas. Paragangliomas and pheochromocytomas have a germline genetic basis in up to 30% of cases.(1) The genes implicated in hereditary PGL/PCC syndrome include MAX, TMEM127, FH, and the SDHx genes. The genes most frequently associated with hereditary PGL/PCC syndromes are the succinate dehydrogenase-associated genes SDHA, SDHAF2, SDHB, SDHC, and SDHD. Germline alterations in the MAX gene are typically associated with increased risk for PCC, although some individuals have been identified with PGL. MAX variants occur in approximately 1% of patients with hereditary PGL/PCC syndromes.(2) TMEM127 variants are associated most frequently with PCC and rarely PGL.(1) Alterations of TMEM127 account for approximately 2% of individuals with hereditary PGL/PCC.(2) Recent evidence suggests that disease-causing variants in FH also increase risk for PGL/PCC.(3,4) Individuals with disease-causing FH variants carry a significantly increased risk for cutaneous or uterine leiomyomata and renal tumors.(5) Alterations in VHL, NF1, and RET also increase risk for PGL/PCC, in addition to other types of tumors.(6) Disease-causing variants in the VHL gene are associated with a syndrome called von Hippel Lindau (VHL) syndrome. In addition to PGL/PCC, individuals with VHL syndrome are at increased risk for hemangioblastomas, renal cell carcinoma, pancreatic cysts, neuroendocrine tumors, endolymphatic sac and epididymal tumors.(7) NF1 gene variants are associated with neurofibromatosis type I (NF1). Individuals with NF1 are at increased risk for pheochromocytomas in addition to neurofibromas and central nervous system gliomas, such as optic nerve gliomas. NF1 is also characterized by other features such as cafe-au lait macules, axillary/inguinal freckling and Lisch nodules.(8) Disease-causing RET variants result in a syndrome called multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid cancer (FMTC). In addition to an increased risk for PGL/PCC, individuals with MEN2/FMTC have a very high risk of developing medullary thyroid cancer.

Individuals with MEN2 may also have other features, such as primary hyperparathyroidism, mucosal neuromas, ganglioneuromatosis, and distinctive facial features.(9) The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with hereditary PGL/PCC syndromes.(10)

Useful For: Evaluating patients with a personal or family history suggestive of a hereditary paraganglioma and pheochromocytoma (PGL/PCC) syndrome Establishing a diagnosis of a hereditary PGL/PCC, allowing for targeted surveillance based on associated risks Identifying genetic variants associated with increased risk for PGL/PCC, allowing for predictive testing and appropriate screening of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(11) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Else T, Greenberg S, Fishbein L. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. Hereditary paraganglioma-pheochromocytoma syndromes. GeneReviews [Internet]. University of Washington, Seattle; 2008. Updated September 21, 2023. Accessed January 7, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1548/ 2. Bausch B, Schiavi F, Ni Y, et al. European-American-Asian Pheochromocytoma-Paraganglioma Registry Study Group. Clinical characterization of the pheochromocytoma and paraganglioma susceptibility genes SDHA, TMEM127, MAX, and SDHAF2 for gene-informed prevention. JAMA Oncol. 2017;3(9):1204-1212 3. Udager AM, Magers MJ, Goerke DM, et al. The utility of SDHB and FH immunohistochemistry in patients evaluated for hereditary paraganglioma-pheochromocytoma syndromes. Hum Pathol. 2018;71:47-54 4. Castro-Vega LJ, Buffet A, De Cubas AA, et al. Germline mutations in FH confer predisposition to malignant pheochromocytomas and paragangliomas. Hum Mol Genet. 2014;23(9):2440-2446. doi:10.1093/hmg/ddt639 5. Kamihara J, Schultz KA, Rana HQ. FH tumor predisposition syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated August 13, 2020. Accessed January 7, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1252/ 6. Shah MH, Goldner WS, Halfdanarson TR, et al. NCCN Guidelines Insights: Neuroendocrine and Adrenal Tumors, Version 2.2018. J Natl Compr Canc Netw. 2018;16(6):693-702 7. van Leeuwaarde RS, Ahmad S, Links TP, et al. Von Hippel-Lindau syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated February 29, 2024. Accessed January 7, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1463/ 8. Friedman JM. Neurofibromatosis 1. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated April 21, 2022. Accessed January 7, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1109/ 9. Eng C. Multiple Endocrine Neoplasia Type 2. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated August 10, 2023. Accessed January 7, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1257/ 10. Benn DE, Gimenez-Roqueplo AP, Reilly JR, et al. Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. J Clin Endocrinol Metab. 2006;91(3):827-836 11. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

PRS8P
614576

Hereditary Prostate Cancer Panel, Varies

Clinical Information: Hereditary prostate cancer accounts for approximately 5% to 10% of all

prostate cancer cases and up to half of all early-onset prostate cancer cases.(1-3) Evaluation of the genes on this panel may be useful for families with a history of prostate cancer to determine cancer risk, surveillance recommendations, and targeted treatments (such as poly adenosine diphosphate-ribose polymerase [PARP] inhibitor therapy).(4,5) The 2 most common hereditary prostate cancer syndromes are hereditary breast and ovarian cancer (HBOC) syndrome and Lynch syndrome.(3-5) HBOC syndrome is caused by disease-causing variants in the BRCA1 and BRCA2 genes. Individuals with HBOC syndrome are also at increased risk for multiple cancer types, including prostate cancer.(5) Lynch syndrome is caused by variants in the MLH1, MSH2, MSH6, and PMS2 mismatch-repair genes and deletions of the EPCAM gene. A subset of these patients presents with prostate cancer.(3-5) This panel includes other genes known to increase prostate cancer risk.(3-5) The risk of developing cancer associated with these syndromes varies. Some individuals with a disease-causing variant in one of these genes develop multiple primary cancers.(4) The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with hereditary prostate cancer syndromes.(4,5)

Useful For: Evaluating patients with a personal or family history suggestive of a hereditary prostate cancer syndrome Establishing a diagnosis of a hereditary prostate cancer syndrome allowing for targeted cancer surveillance based on associated risks Identifying genetic variants associated with increased risk for prostate cancer, allowing for predictive testing and appropriate screening of at-risk family members Therapeutic eligibility with poly adenosine diphosphate-ribose polymerase (PARP) inhibitors based on certain gene alterations (eg, BRCA1, BRCA2)

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71(1):7-33 2. Lange EM, Salinas CA, Zuhlke KA, et al. Early onset prostate cancer has a significant genetic component. Prostate. 2012;72(2):147-156 3. Pritchard CC, Mateo J, Walsh M, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med. 2016;375(5):443-453. doi:10.1056/NEJMoa1603144 4. Schaeffer E, Srinivas S, Antonarakis ES, et al. NCCN guidelines insights: Prostate cancer, version 1.2021. J Natl Compr Canc Netw. 2021;19(2):134-143 5. Daly MB, Pal T, Berry MP, et al. Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2021;19(1):77-102 6. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

RENCP
614575

Hereditary Renal Cancer Panel, Varies

Clinical Information: Lifetime risk for developing renal cancer in the United States is approximately 1% to 2%.(1) Of these cases, about 3% to 5% are associated with an underlying hereditary predisposition.(2,3) Suspicion for a hereditary association may be raised in cases of early age of onset, multifocal/bilateral lesions, or a family or personal history of renal or other tumors. Clear cell type renal cancers can be seen in individuals with disease-causing variants in BAP1, PTEN, and VHL. BAP1 variants also associated with an increased risk for melanomas, mesothelioma, and epithelioid atypical Spitz tumors. PTEN variants are also associated with significantly increased risk for breast,

thyroid, and uterine cancer. VHL variants are associated with von Hippel Lindau syndrome and are associated with an increased risk for several types of tumors, including hemangioblastomas, pancreatic cysts, neuroendocrine tumors, endolymphatic sac, and epididymal tumors.(4) Risk for renal cancer is also increased by disease-causing variants in the succinate dehydrogenase-associated genes: SDHAF2, SDHA, SDHB, SDHC and SDHD.(5-8) Variants in the SDH genes are also associated with an increased risk for paragangliomas and pheochromocytomas. Hereditary papillary renal cancer may be caused by variants in the MET gene, while alterations in the FH gene cause a syndrome called hereditary leiomyomatosis and renal cell cancer (HLRCC). Individuals with HLRCC also have an increased risk of developing cutaneous or uterine leiomyomas.(2) Birt-Hogg-Dube syndrome is caused by disease-causing variants in the FLCN gene. Individuals with Birt-Hogg-Dube syndrome have an increased risk for oncocytic or chromophobe renal cancers and often exhibit other features such as fibrofolliculomas, lung cysts, and pneumothorax. Angiomyolipomas and morphologically heterogenous renal tumors may be seen in individuals with tuberous sclerosis complex (TS), caused by variants in the TSC1 or TSC2 genes.(9) Individuals with TS are also at increased risk for subependymal giant cell astrocytomas and may exhibit several other features, including facial angiofibromas, lymphangioleiomyomatosis, cardiac rhabdomyomas, hypomelanocytic macules, shagreen patches, and ungual/periungual fibromas.(10) Disease-causing DICER1 variants are associated with an increased risk of developing kidney tumors called cystic nephromas, although some individuals with DICER1 variants have developed high-grade renal sarcomas.(11) DICER1 tumor predisposition syndrome is also characterized by risk for pleuropulmonary blastoma, pulmonary cysts, thyroid tumors, and ovarian tumors, in addition to other features.(12) A specific variant within the MITF gene, p.E318K, is associated with increased risk for melanoma as well as renal cancer.(13) Lastly, disease-causing variants within the SMARCA4 and SMARCB1 genes cause a hereditary cancer syndrome called rhabdoid tumor predisposition syndrome, characterized by a significantly increased risk for aggressive, childhood-onset rhabdoid tumors, including rhabdoid tumors of the kidney.(14) The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with hereditary renal cancer syndromes.(15)

Useful For: Evaluating patients with a personal or family history suggestive of a hereditary renal cancer syndrome Establishing a diagnosis of a hereditary renal cancer syndrome allowing for targeted cancer surveillance based on associated risks Identifying genetic variants associated with increased risk for renal and/or other cancers, allowing for predictive testing and appropriate screening of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(16) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

GNHTC
619341

Hereditary Thrombocytopenia Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Platelets have essential roles in primary hemostasis. Patients with either hereditary or acquired platelet disorders usually have bleeding diathesis, which can potentially be life-threatening. They may also have issues with the development and/or functioning of major organs.(2) Inherited platelet disorders can be syndromic (ie, associated with current or future development of other organ system defects) or non-syndromic (ie, isolated to thrombocytopenia with no other organ system defects). A reliable laboratory diagnosis of a platelet disorder can significantly impact patients' and, potentially, their family members' clinical management and outcome. Identification of an alteration that is known or suspected to cause disease aids in confirmation of the diagnosis and potentially provides

prognostic information, especially in syndromic inherited platelet disorders. This panel evaluates 36 genes associated with a variety of hereditary thrombocytopenia disorders, including macrothrombocytopenia; sitosterolemia with macrothrombocytopenia; Baraitser-Winter syndrome 1 with macrothrombocytopenia; autosomal dominant thrombocytopenia 2; Scott syndrome; platelet abnormalities with eosinophilia and immune-mediated inflammatory disease; Takenouchi-Kosaki syndrome with thrombocytopenia; autosomal dominant thrombocytopenia 4; macrothrombocytopenia and sensorineural hearing loss; thrombocytopenia and susceptibility to cancer; Paris-Trousseau-Jacobson syndrome; syndrome with macrothrombocytopenia; thrombocytopenia 3; X-linked thrombocytopenia with dyserythropoiesis; GATA2 deficiency; myopathy associated with thrombocytopenia; amegakaryocytic thrombocytopenia with radioulnar synostoses 1 and 2; thrombocytopenia and erythrokeraderma; autosomal thrombocytopenia with normal platelets; thrombocytopenia anemia and myelofibrosis; congenital amegakaryocytic thrombocytopenia; May-Hegglin disorder/anomaly; Sebastian syndrome; MYH9-related disorders; autosomal dominant tubular aggregate myopathy-2; Quebec platelet disorder; platelet-type bleeding disorder 19; thrombocytopenia-absent radius (TAR) syndrome; familial platelet disorder with predisposition to acute myeloid leukemia; platelet-type bleeding disorder 20; Stormorken syndrome; York platelet syndrome; thrombocytopenia progressing to trilineage bone marrow failure; and Wiskott-Aldrich syndrome. The risk for developing bleeding or other phenotypic features associated with these disorders and syndromes varies. Several of the genes on this panel have established bleeding, thrombocytopenia, or other hematologic or non-hematologic disease associations. Several of the genes on this panel also have expert group guidelines.(1,3-5) It is recommended that genetic testing be offered to all patients suspected of having a heritable platelet disorder since some patients may have normal platelet laboratory testing results.(1,6)

Useful For: Evaluating hereditary thrombocytopenia disorders in patients with a personal or family history suggestive of a hereditary thrombocytopenia disorder Diagnosing hereditary thrombocytopenia disorders for patients in whom phenotypic testing is nondiagnostic but there is a strong clinical suspicion of the hereditary thrombocytopenia disorder Confirming a hereditary thrombocytopenia disorder diagnosis with the identification of a known or suspected disease-causing alteration in one or more of 36 genes associated with a variety of hereditary thrombocytopenia disorders Determining the disease-causing alterations within one or more of these 36 genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of a thrombocytopenia disorder Identifying the causative alteration for genetic counseling purposes Prognosis and risk assessment based on the genotype-phenotype correlations Providing a prognosis in syndromic hereditary thrombocytopenia disorders Carrier testing for close family members of an individual with a hereditary thrombocytopenia disorder diagnosis This test is not intended for prenatal diagnosis.

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Gomez K, Anderson J, Baker P, et al: Clinical and laboratory diagnosis of heritable platelet disorders in adults and children: a British Society for Haematology Guideline. Brit J Haematol. 2021 Oct;195(1):46-72 2. Nurden AT, Freson K, Selifsohn U: Inherited platelet disorders. Haemophilia. 2012 July;18 Suppl 4:154-160 3. International Society on Thrombosis and Haemostasis: Bleeding Thrombotic and Platelet Disorder TIER1 genes. ISTH; 2018. Updated July 2022. Accessed November 23, 2022. Available at: www.isth.org/page/GinTh_GeneLists 4. Megy K, Downes K, Simeoni I, et al: Curated disease-causing genes for bleeding, thrombotic, and platelet disorders: Communication from the SSC of the ISTH. J Thromb Haemost. 2019 Aug;17(8):1253-1260 5. Bolton-Maggs PHB, Chalmers EA, Collins PW, et al: A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. Brit J Haematol. 2006 Dec;135(5):603-633 6. Watson

SP, Lowe GC, Lordkipanidze M, Morgan NV, GAPP consortium: Genotyping and phenotyping of platelet function disorders. J Thromb Haemost. 2013 June;11(Suppl. 1):351-363 7. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

GNADM 619229 Hereditary Thrombotic Thrombocytopenic Purpura, ADAMTS13 Gene, Next-Generation Sequencing, Varies

Clinical Information: Hereditary thrombotic thrombocytopenic purpura (TTP), also known as Upshaw-Schulman syndrome or congenital TTP (cTTP), is a rare blood condition associated with germline variants in the ADAMTS13 gene. It is inherited in an autosomal recesssive manner with variable expressivity.(4) Hereditary TTP is characterized by a severe deficiency of the ADAMTS-13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif 13) protease resulting in the abnormal accumulation of ultra-large von Willebrand factor multimers, which are thought to aggregate with platelets to form occlusive microvascular platelet-rich thrombi.(3-5) Systemic platelet thrombi lead to the classic pentad of TTP findings: thrombocytopenia, microangiopathic hemolytic anemia (intravascular hemolysis and presence of peripheral blood schistocytes), fever, neurologic symptoms (ischemic attack and stroke), and kidney dysfunction. While some individuals with hereditary TTP may have symptoms that present at birth, others can remain asymptomatic for decades. Although patients are at significant risk for complications of microvascular thrombosis throughout their lives, two periods appear to be associated with particularly severe risk: the first days of life and pregnancy.(5,6) Acquired, immune-mediated TTP (caused by the presence of autoantibodies to ADAMTS-13) is more common than hereditary TTP and can be distinguished through ADAMTS-13 antibody or inhibitor assays.(3) Several other non-TTP causes of thrombotic microangiopathy and severe ADAMTS-13 deficiency should be excluded prior to genetic testing, including hemolytic uremic syndrome, hematopoietic stem cell and solid-organ transplantation, liver disease, disseminated intravascular coagulation, malignancy, viral infection (eg, HIV), sepsis, pregnancy (preeclampsia/eclampsia or HELLP [hemolysis, elevated liver enzymes and low platelets] syndrome), and medications, such as antiplatelet agents, calcineurin inhibitors, and certain chemotherapeutics.(3,7,8)

Useful For: Evaluating hereditary thrombotic thrombocytopenic purpura (TTP) in patients with a personal or family history suggestive of thrombotic microangiopathy Confirming a hereditary TTP diagnosis with the identification of known or suspected disease-causing alteration(s) in the ADAMTS13 gene Determining the disease-causing alterations within the ADAMTS13 gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of hereditary TTP Identifying the causative alterations for genetic counseling purposes Prognosis and risk assessment based on the genotype-phenotype correlations Carrier testing for close family members of an individual with a diagnosis of hereditary TTP This test is not intended for prenatal diagnosis.

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(10) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Bendapudi PK, Hurwitz S, Fry A, et al: Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. Lancet Haematol. 2017 Apr;4(4):e157-e164 2. Scully M, Cataland S, Coppo P, et al; International

Working Group for Thrombotic Thrombocytopenic Purpura: Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J Thromb Haemost. 2017 Feb;15(2):312-322 3. Mackie I, Mancini I, Muia J, et al: International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of ADAMTS13. Int J Lab Hematol. 2020 Dec;42(6):685-696 4. Alwan F Vendramin C, Liesner R, et al: Characterization and treatment of congenital thrombotic thrombocytopenic purpura. Blood. 2019 Apr 11;133(15):1644-1651 5. Smock KJ: ADAMTS13 testing update: Focus on laboratory aspects of difficult thrombotic thrombocytopenic purpura diagnoses and effects of new therapies. Int J Lab Hematol. 2021 Jul;43 Suppl 1:103-108 6. Hovinga JAK, George JN: Hereditary thrombotic thrombocytopenic purpura. N Engl J Med. 2019 Oct 24;381(17):1653-1662 7. Saha M, McDaniel JK, Zheng XL: Thrombotic thrombocytopenic purpura: pathogenesis, diagnosis and potential novel therapeutics. J Thromb Haemost. 2017 Oct;15(10):1889-1900 8. Zuno JAN: Thrombotic thrombocytopenic purpura evaluation and management. In: Khaddour K, ed. StatPearls [Internet]. StatPearls Publishing; 2021. Updated July 25, 2022. Accessed November 28, 2022. Available at www.statpearls.com/articlelibrary/viewarticle/30113 9. George JN: Thrombotic thrombocytopenic purpura: From 1972 to 2022 and beyond. Semin Thromb Hemost. 2022 Nov;48(8):926-936 10. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

THYRP
614580

Hereditary Thyroid Cancer Panel, Varies

Clinical Information: The lifetime risk to develop thyroid cancer is approximately 1.2%.(1) Rarely, a predisposition to thyroid cancer may be inherited in families with certain genetic alterations. Most of these genetic alterations are syndromic, meaning individuals who inherit them are usually at risk for other types of cancers or features, in addition to thyroid cancer. Papillary thyroid cancers are typically sporadic but can be seen in individuals or families with familial adenomatous polyposis (FAP) syndrome, caused by variants within the APC gene (cribriform morular variant). Individuals with FAP are at also very high risk for colonic polyposis and colorectal cancer. Follicular or papillary thyroid cancers may be seen in families with PTEN hamartoma tumor syndrome (PHTS). Individuals with disease-causing PTEN variants have a 70-fold increased incidence of thyroid cancer compared to the general population and are at increased risk to develop breast and endometrial cancer.(2) Thyroid cancers with follicular or papillary features can also be seen in individuals with disease-causing DICER1 variants, as well as individuals with Carney complex, which is caused by disease-causing variants within the PRKAR1A gene.(3,4) Approximately 25% of cases of medullary thyroid cancer (MTC) are caused by an inherited RET variant.(5) Some disease-causing RET variants are associated with only isolated, familial MTC, while others cause a syndrome called multiple endocrine neoplasia type 2 (MEN2). Individuals with MEN2 have a high risk for MTC and may also have other tumors of the endocrine/neuroendocrine system, including paragangliomas, mucosal neuromas, pheochromocytomas, and parathyroid tumors.(6) The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with hereditary thyroid cancer syndromes.(7)

Useful For: Evaluating patients with a personal or family history suggestive of a hereditary thyroid cancer syndrome Establishing a diagnosis of a hereditary thyroid cancer syndrome, allowing for targeted surveillance based on associated risks Identifying genetic variants associated with increased risk for thyroid and other cancers, allowing for predictive testing and appropriate screening of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known

significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Surveillance Epidemiology and End Results Program: Cancer Stat Facts: Thyroid cancer. National Cancer Institute; 2018. Accessed April 25, 2024. Available at http://seer.cancer.gov/statfacts/html/thyro.html 2. Ngeow J, Mester J, Rybicki LA, Ni Y, Milas M, Eng C. Incidence and clinical characteristics of thyroid cancer in prospective series of individuals with Cowden and Cowden-like syndrome characterized by germline PTEN, SDH, or KLLN alterations. J Clin Endocrinol Metab. 2011;96(12):E2063-E2071 3. Stratakis CA, Raygada M. Carney complex. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated September 21, 2023. Accessed April 25, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1286/ 4. Schultz KAP, Stewart DR, Kamihara J, et al. DICER1 tumor predisposition. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2014. Updated April 30, 2020. Accessed April 25, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK196157/ 5. Shepet K, Alhefdhi A, Lai N, Mazeh H, Sippel R, Chen H. Hereditary medullary thyroid cancer: age-appropriate thyroidectomy improves disease-free survival. Ann Surg Oncol. 2013;20(5):1451-1455 6. Eng C. Multiple endocrine neoplasia type 2. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated August 10, 2023. Accessed April 25, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1257/ 7. Haddad RI, Nasr C, Bischoff L, et al. NCCN Guidelines Insights: Thyroid carcinoma, Version 2.2018. J Natl Compr Canc Netw. 2018;16(12):1429-1440 8. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

WILMP
614577

Hereditary Wilms Tumor Panel, Varies

Clinical Information: Hereditary predisposition to Wilms tumor encompasses a heterogeneous group of syndromic and nonsyndromic conditions. A comprehensive diagnostic genetic test is useful to help determine a molecular etiology for Wilms tumor and, therefore, identify other potential risks and ascertain the inheritance pattern and recurrence risk within a family. Approximately 10% to 15% of individuals with Wilms tumor have a genetic etiology that can be identified.(1) The most common genetic cause of Wilms tumor is disease-causing variants in the WT1 gene.(1) There are several other genes that also can increase Wilms tumor risk, including BLM, BUB1B, CDC73, DIS3L2, GPC3, REST, TP53, and TRIP13. Individuals with syndromic Wilms tumor may have involvement of other organs.(1)

Useful For: Evaluating isolated and syndromic causes of Wilms tumor Establishing a diagnosis to guide management for individuals with Wilms tumor Identifying a familial variant allowing for predictive testing and appropriate screening of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(2) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Turner JT, Brzezinski J. Dome JS. Wilms tumor predisposition. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle;

2003. Updated March 24, 2022. Accessed September 10, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1294/ 2. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

LHSVZ
800315

Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV), Molecular Detection, PCR, Varies

Clinical Information: Herpes simplex virus (HSV) types 1 and 2 are members of the Herpesviridae family and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using PCR or viral culture. HSV causes various clinical syndromes. Anatomic sites infected include skin, lips and oral cavity, eyes, genital tract, and central nervous system.(1) Varicella-zoster virus (VZV) causes both varicella (chickenpox) and herpes zoster (shingles). VZV produces a generalized vesicular rash on the dermis (chickenpox) in normal children, usually before age 10. After primary infection with VZV, the virus persists in latent form and may emerge (usually in adults age 50 and older) clinically to cause a unilateral vesicular eruption, generally in a dermatomal distribution (shingles).

Useful For: Rapid diagnosis of herpes simplex virus and varicella-zoster virus infections

Interpretation: Herpes Simplex Virus (HSV) PCR: This is a qualitative assay; results are reported either as negative, positive, or indeterminate for HSV type 1 or HSV type 2. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus. Varicella-Zoster Virus (VZV) PCR: Detection of VZV DNA in clinical specimens supports the clinical diagnosis of infection due to this virus. VZV DNA is not detected in cerebrospinal fluid from patients without central nervous system disease caused by this virus. This LightCycler PCR assay does not yield positive results with other herpesvirus gene targets (cytomegalovirus, Epstein-Barr virus).

Reference Values:

HERPES SIMPLEX VIRUS (HSV) PCR
Negative

VARICELLA-ZOSTER VIRUS PCR
Negative

Clinical References: 1. Schiffer JT, Corye L. New concepts in understanding genital herpes. Curr Infect Dis Rep. 2009;11(6):457-464 2. Espy MJ, Uhl JR, Svien KA. Laboratory diagnosis of herpes simplex virus infections in the clinical laboratory by LightCycler PCR. J Clin Microbiol. 2000;38(2):795-799 3. Espy MJ, Ross TK, Teo R. Evaluation of LightCycler PCR for implementation of laboratory diagnosis of herpes simplex virus infections. J Clin Microbiol. 2000;38(8):3116-3118 4. Sauerbrei A, Eichhorn U, Hottenrott G, Wutzler P. Virological diagnosis of herpes simplex encephalitis. J Clin Virol. 2000;17(1):31-36 5. Mitchell PS, Espy MJ, Smith TF, et al. Laboratory diagnosis of central nervous system infections with herpes simplex virus by PCR performed with cerebrospinal fluid specimens. J Clin Microbiol. 1997;35(11):2873-2877 6. Yi-Wei T, Mitchell PS, Espy MJ, Smith TF, Persing DH. Molecular diagnosis of herpes simplex virus infections in the central nervous system. J

Clin Microbiol. 1999;37(7):2127-2136 7. Cinque P, Bossolasco S, Vago L, et al. Varicella-zoster virus (VZV) DNA in cerebrospinal fluid of patients infected with human immunodeficiency virus: VZV disease of the central nervous system or subclinical reactivation of VZV infection? Clin Infect Dis. 1997;25(3):634-639 8. Brown M, Scarborough M, Brink N, et al: Varicella zoster virus-associated neurological disease in HIV-infected patients. Int J STD AIDS. 2001;12(2):79-83 9. Studahl M, Hagberg L, Rekabdar E, Bergstrom T. Herpesvirus DNA detection in cerebrospinal fluid: differences in clinical presentation between alpha-, beta-, and gamma-herpesviruses. Scand J Infect Dis. 2000;32(3):237-248 10. Iten A, Chatelard P, Vuadens P, et al. Impact of cerebrospinal fluid PCR on the management of HIV-infected patients with varicella-zoster virus infection of the central nervous system. J Neurovirol. 1999;5(2):172-180

HSVG
84429

Herpes Simplex Virus (HSV) Type 1- and Type 2-Specific Antibodies, IgG, Serum

Clinical Information: Herpes simplex virus (HSV) types 1 and 2 are members of the Herpesviridae family and produce infections that range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing, primarily using polymerase chain reaction to detect viral DNA. However, in instances of subclinical or unrecognized HSV infection, serologic testing for IgG-class antibodies to type-specific HSV glycoprotein G may be useful. There are several circumstances where it may be important to distinguish between infection caused by HSV types 1 and 2 (eg, risk of reactivation). In addition, the results of HSV type-specific IgG testing are sometimes used during pregnancy to identify risks of congenital HSV disease and allow for focused counseling prior to delivery.

Useful For: Determining whether a patient has been previously exposed to herpes simplex virus (HSV) types 1 and 2 Distinguishing between infection caused by HSV types 1 and 2, especially in patients with subclinical or unrecognized HSV infection This test should not be used to diagnose active or recent infection.

Interpretation: This assay detects IgG-class antibodies to type-specific herpes simplex virus (HSV) glycoprotein G and may allow for the differentiation of infection caused by HSV types 1 and 2. The presence of IgG-class antibodies to HSV types 1 or 2 indicates previous exposure, and does not necessarily indicate that HSV is the causative agent of an acute illness.

Reference Values:
Negative

Clinical References: 1. Ashley RL, Wald A. Genital herpes: review of the epidemic and potential use of type-specific serology. Clin Microbiol Rev. 1999;12(1):1-8 2. Ashley RL, Wu L, Pickering JW, et al. Premarket evaluation of a commercial glycoprotein G-based enzyme immunoassay for herpes simplex virus type-specific antibodies. J Clin Microbiol. 1998;36(1):294-295 3. Brown ZA, Selke S, Zeh J, et al. The acquisition of herpes simplex virus during pregnancy. N Engl J Med 1997;337(8):509-515 4. Lafferty WE, Coombs RW, Benedetti J, et al. Recurrences after oral and genital herpes simplex infection. Influence of site of infection and viral type. N Engl J Med. 1987;316(23):1444-1449 5. Binnicker MJ, Jespersen DJ, Harring JA. Evaluation of three multiplex flow immunoassays to enzyme immunoassay for the detection and differentiation of IgG class antibodies to herpes simplex virus types 1 and 2. Clin Vaccine Immunol. 2010;17(2):253-257 6. Nath P, Kabir MA, Doust SK, Ray A. Diagnosis of herpes

simplex virus: Laboratory and point-of-care techniques. Infect Dis Rep. 2021;13(2):518-539

LHSVB
802067

Herpes Simplex Virus (HSV), Molecular Detection, PCR, Blood

Clinical Information: Herpes simplex virus (HSV) types 1 and 2 cause a variety of clinical syndromes. Anatomic sites infected include the skin, lips, oral cavity, eyes, genital tract, and central nervous system. Systemic disease may also occur, in which the virus may be detectable in the bloodstream. The detection of HSV-1 or HSV-2 DNA from blood specimens may help support the diagnosis of disseminated disease associated with this virus.

Useful For: Aiding in the rapid diagnosis of disseminated disease due to herpes simplex virus (HSV) Qualitative detection of HSV DNA This test should not be used to screen asymptomatic patients.

Interpretation: This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1 or HSV type 2. An Indeterminate result means that HSV DNA was detected, but the assay was unable to differentiate between HSV type 1 and HSV type 2. If typing is required, it is recommended that a new sample be collected and tested by an alternate method. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus.

Reference Values:
HERPES SIMPLEX VIRUS (HSV)-1
Negative

HERPES SIMPLEX VIRUS (HSV)-2
Negative

Reference values apply to all ages.

Clinical References: 1. Schiffer JT, Corey L: New concepts in understanding genital herpes. Curr Infect Dis Rep. Nov 2009 Nov;11(6):457-464 2. Espy MJ, Uhl JR, Svien KA, et al: Laboratory diagnosis of herpes simplex virus infections in the clinical laboratory by LightCycler PCR. J Clin Microbiol. 2000 Feb;38(2):795-799 3. Espy MJ, Ross TK, Teo R, et al: Evaluation of LightCycler PCR for implementation of laboratory diagnosis of herpes simplex virus infections. J Clin Microbiol. 2000 Aug;38(8):3116-3118 4. Sauerbrei A, Eichhorn U, Hottenrott G, Wutzler P: Virological diagnosis of herpes simplex encephalitis. J Clin Virol. 2000 Jun;17(1):31-36 5. Mitchell PS, Espy MJ, Smith TF, et al: Laboratory diagnosis of central nervous system infections with herpes simplex virus by PCR performed with cerebrospinal fluid specimens. J Clin Microbiol. 1997 Nov;35(11):2873-2877 6. Yi-Wei T, Mitchell PS, Espy MJ, Smith TF, Persing DH: Molecular diagnosis of herpes simplex virus infections in the central nervous system. J Clin Microbiol. 1999 Jul;37(7):2127-2136 7. Schiffer JT, Corey L: Herpes simplex virus. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:1828-1848

HSVPB
618308

Herpes Simplex Virus (HSV), Molecular Detection, PCR, Blood

Clinical Information: Herpes simplex virus (HSV) types 1 and 2 cause a variety of clinical syndromes. Anatomic sites infected include the skin, lips, oral cavity, eyes, genital tract, and central nervous system. Systemic disease may also occur, in which the virus may be detectable in the bloodstream. The detection of HSV-1 or HSV-2 DNA from blood specimens may help support the diagnosis of disseminated disease associated with this virus.

Useful For: Aiding in the rapid diagnosis of disseminated disease due to herpes simplex virus (HSV) Qualitative detection of HSV DNA This test should not be used to screen asymptomatic patients.

Interpretation: This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1, HSV type 2, or HSV type indeterminate. Results can also be reported as invalid. An indeterminate result means that HSV DNA was detected but the assay was unable to differentiate between HSV type 1 and HSV type 2. If typing is required, it is recommended that a new specimen be collected and tested by an alternate method. An invalid result points to the inability to determine presence or absence of HSV-1 or HSV-2 DNA in the sample. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus.

Reference Values:
HERPES SIMPLEX VIRUS (HSV)-1
Negative

HERPES SIMPLEX VIRUS (HSV)-2
Negative

Clinical References: 1. Binnicker MJ, Espy MJ, Duresko B, Irish C, Mandrekar J. Automated processing, extraction and detection of herpes simplex virus types 1 and 2: A comparative evaluation of three commercial platforms using clinical specimens. J Clin Virol. 2017;89:30-33 2. Schiffer JT, Corye L. New concepts in understanding genital herpes. Curr Infect Dis Rep. 2009;11(6):457-464 3. Espy MJ, Uhl JR, Svien KA, et al. Laboratory diagnosis of herpes simplex virus infections in the clinical laboratory by LightCycler PCR. J Clin Microbiol. 2000;38(2):795-799 4. Espy MJ, Ross TK, Teo R, et al. Evaluation of LightCycler PCR for implementation of laboratory diagnosis of herpes simplex virus infections. J Clin Microbiol. 2000;38(8):3116-3118 5. Sauerbrei A, Eichhorn U, Hottenrott G, Wutzler P. Virological diagnosis of herpes simplex encephalitis. J Clin Virol. 2000;17(1):31-36 6. Mitchell PS, Espy MJ, Smith TF, et al. Laboratory diagnosis of central nervous system infections with herpes simplex virus by PCR performed with cerebrospinal fluid specimens. J Clin Microbiol. 1997;35(11):2873-2877 7. Yi-Wei T, Mitchell PS, Espy MJ, Smith TF, Persing DH. Molecular diagnosis of herpes simplex virus infections in the central nervous system. J Clin Microbiol. 1999;37(7):2127-2136

HSVC
63434

Herpes Simplex Virus (HSV), Molecular Detection, PCR, Spinal Fluid

Clinical Information: Herpes simplex virus (HSV)-1 and HSV-2 are members of the Alpha herpesviridae subfamily. HSV is an enveloped virus with a capsid containing viral DNA. Although HSV-1 and HSV-2 are closely related, the 2 viruses are serologically and genetically distinct.(1,2) HSV-1 and -2 are common causes of dermal and genital infections; however, in some cases, infection with HSV may result in central nervous system (CNS) disease that is considered a medical emergency. HSV infection of the CNS may result in encephalitis (more commonly associated with HSV-1) or meningitis (more commonly associated with HSV-2). Encephalitis is inflammation of the brain associated with clinical evidence of neurologic dysfunction. Of the pathogens reported to cause encephalitis, the majority are viruses.(3) In general, the most frequently identified etiologies in the United States are HSV, West Nile virus, and the enteroviruses, followed by other herpesviruses.(3) HSV causes about 5% to 10% of all encephalitis cases and is one of the most common causes of identified sporadic encephalitis globally.(3) HSV encephalitis occurs in all ages, and during all seasons. HSV-1 encephalitis is more common in adults, and HSV-2 encephalitis is more common in neonates.(3) One study reported a neonatal herpes rate of 1 case per 3200 live births in the United States.(4) Clinical features involved with HSV encephalitis include fever, hemicranial headache, language and behavioral abnormalities, memory impairment, and seizures.(3)

Useful For: Aiding in the rapid diagnosis of herpes simplex virus (HSV)-1 and HSV-2 infections of the central nervous system

Interpretation: A positive result suggests the presence of herpes simplex virus (HSV)-1 and/or HSV-2 DNA in the cerebrospinal fluid (CSF) sample. A negative result suggests that HSV-1 and HSV-2 DNA are not present in the CSF sample. An invalid result points to the inability to determine presence or absence of HSV-1 or HSV-2 DNA in the CSF sample.

Reference Values:
Negative

Clinical References: 1. Lawrence C. Herpes Simplex virus. In: Mandell GL, Bennet JE, Dolin R, eds. Principles and Practice of Infectious Diseases. 6th ed. Elsevier, Churchill and Livingstone; 2004:1762-1780 2. Szpara ML, Parsons L, Enquist LW. Sequence variability in clinical and laboratory isolates of herpes simplex virus 1 reveals new mutations. J Virol. 2010;84(10):5303-5313 3. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2008;47(3):303-327 4. Brown ZA, Wald A, Morrow RA, et al. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA. 2003;289(2):203-209 5. Clinical Management Guidelines for Obstetrician-Gynecologists. ACOG Practice Bulletin No. 57, 104 (5 pt 1). 2004;1111-1118 6. Binnicker MJ, Espy MJ, Irish CL. Rapid and direct detection of herpes simplex virus in cerebrospinal fluid using a commercial real-time PCR assay. J Clin Microbiol. 2014;52(12):4361-4362

LHSV
800143

Herpes Simplex Virus (HSV), Molecular Detection, PCR, Varies

Clinical Information: Herpes simplex virus (HSV) types 1 and 2 are members of the Herpesviridae family and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using polymerase chain reaction or viral culture.

Useful For: Aiding in the rapid diagnosis of herpes simplex virus (HSV) infections, including qualitative detection of HSV DNA in nonblood clinical specimens This test should not be used to screen asymptomatic patients.

Interpretation: This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1, HSV type 2, or HSV type indeterminate. An Indeterminate result indicates that HSV DNA was detected, but the assay is unable to differentiate between HSV-1 and HSV-2. If typing is required, it is suggested that a new sample be collected for testing by an alternate method. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus.

Reference Values:
HERPES SIMPLEX VIRUS (HSV)-1
Negative

HERPES SIMPLEX VIRUS (HSV)-2

Negative

Reference values apply to all ages.

Clinical References: 1. Schiffer JT, Corye L. New concepts in understanding genital herpes. Curr Infect Dis Rep. 2009;11(6):457-464 2. Espy MJ, Uhl JR, Mitchell PS, et al. Diagnosis of herpes simplex virus infections in the clinical laboratory by LightCycler PCR. J Clin Microbiol. 2000;38(2):795-799 3. Espy MJ, Ross TK, Teo R, et al. Evaluation of LightCycler PCR for implementation of laboratory diagnosis of herpes simplex virus infections. J Clin Microbiol. 2000;38(8):3116-3118 4. Sauerbrei A, Eichhorn U, Hottenrott G, Wutzler P. Virological diagnosis of herpes simplex encephalitis. J Clin Virol. 2000;17(1):31-36 5. Mitchell PS, Espy MJ, Smith TF, et al. Laboratory diagnosis of central nervous system infections with herpes simplex virus by PCR performed with cerebrospinal fluid specimens. J Clin Microbiol. 1997;35(11):2873-2877 6. Tang YW, Mitchell PS, Espy MJ, Smith TF, Persing DH. Molecular diagnosis of herpes simplex virus infections in the central nervous system. J Clin Microbiol. 1999;37(7):2127-2136 7. Schiffer JT, Corey L. Herpes simplex virus. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:1828-1848

HSVPV
618307

Herpes Simplex Virus (HSV), Molecular Detection, PCR, Varies

Clinical Information: Herpes simplex virus (HSV) types 1 and 2 are members of the Herpesviridae family and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using polymerase chain reaction or viral culture.

Useful For: Aiding in the rapid diagnosis of herpes simplex virus (HSV) infections, including qualitative detection of HSV DNA in nonblood clinical specimens This test should not be used to screen asymptomatic patients.

Interpretation: This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1, HSV type 2, or HSV type indeterminate. Results can also be reported as invalid. An indeterminate result indicates that HSV DNA was detected but the assay is unable to differentiate between HSV-1 and HSV-2. If typing is required, it is suggested that a new specimen be collected for testing by an alternate method. An invalid result points to the inability to determine presence or absence of HSV-1 or HSV-2 DNA in the sample. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus.

Reference Values:
HERPES SIMPLEX VIRUS (HSV)-1
Negative

HERPES SIMPLEX VIRUS (HSV)-2
Negative

Clinical References: 1. Binnicker MJ, Espy MJ, Duresko B, Irish C, Mandrekar J. Automated processing, extraction and detection of herpes simplex virus types 1 and 2: A comparative evaluation of

three commercial platforms using clinical specimens. J Clin Virol. 2017;89:30-33 2. Schiffer JT, Corye L. New concepts in understanding genital herpes. Curr Infect Dis Rep. 2009;11(6):457-464 3. Espy MJ, Uhl JR, Svien KA, et al. Laboratory diagnosis of herpes simplex virus infections in the clinical laboratory by LightCycler PCR. J Clin Microbiol. 2000;38(2):795-799 4. Espy MJ, Ross TK, Teo R, et al. Evaluation of LightCycler PCR for implementation of laboratory diagnosis of herpes simplex virus infections. J Clin Microbiol. 2000;38(8):3116-3118 5. Sauerbrei A, Eichhorn U, Hottenrott G, Wutzler P. Virological diagnosis of herpes simplex encephalitis. J Clin Virol. 2000;17(1):31-36 6. Mitchell PS, Espy MJ, Smith TF, et al. Laboratory diagnosis of central nervous system infections with herpes simplex virus by PCR performed with cerebrospinal fluid specimens. J Clin Microbiol. 1997;35(11):2873-2877 7. Tang YW, Mitchell PS, Espy MJ, Smith TF, Persing DH. Molecular diagnosis of herpes simplex virus infections in the central nervous system. J Clin Microbiol. 1999;37(7):2127-2136

HRPSV
70467

Herpes Simplex Virus, I and II (HSV I and II) Immunostain, Technical Component Only

Clinical Information: Immunoperoxidase staining for herpes simplex virus (HSV) I and II produces nuclear and granular cytoplasmic staining of virus infected cells. HSV I and II are part of the herpes virus family that also includes Epstein Barr virus, herpes zoster, and cytomegalovirus. HSV are among the most common infectious agents of man and usually are transmitted through close personal contact. The manifestations of infection can be localized (oral lesions HSV I; genital lesions HSV II) or can cause life-threatening systemic infection in immunocompromised patients.

Useful For: Identification of herpes simplex virus I and II infection

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Molina-Ruiz AM, Santonja C, Rutten A, Cerroni L, Kutzner H, Requena L. Immunohistochemistry in the diagnosis of cutaneous viral infections-part I. Cutaneous viral infections by herpesviruses and papillomaviruses. Am J Dermatopathol. 2015;37(1):1-4. doi:10.1097/DAD.0000000000000203 2. Lloyd J, Copaciu R, Yahyabeik A, et al. Characterization of polyclonal antibodies to herpes simplex virus types 1 and 2. J Histotechnol. 2019;42(4):202-214. doi:10.1080/01478885.2019.1683132 3. Zhang DH, Zhang QY, Hong CQ, Chen JY, Shen ZY, Zhu Y. Prevalence and association of human papillomavirus 16, Epstein-Barr virus, herpes simplex virus-1 and cytomegalovirus infection with human esophageal carcinoma: a case-control study. Oncol Rep. 2011;25(6):1731-1738. doi:10.3892/or.2011.1234 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FHHV6
91311

Herpes Virus 6 (HHV-6) DNA, Qualitative Real-Time PCR

Clinical Information:

Reference Values:
Not Detected

FHV7P
75755

Herpesvirus 7 (HHV-7) DNA, Quantitative Real-Time PCR

Reference Values:
Not Detected

FH7GM
57487

Herpesvirus 7 IgG and IgM Antibody Panel, IFA

Reference Values:
Reference Range:

IgG	<1:320
IgM	<1:20

Human Herpesvirus 7 (HHV-7), a close relative of HHV-6, is found in >85% of the population, with transmission occurring in early childhood. Like HHV-6, HHV-7 is a cause of exanthem subitum (roseola infantum). Due to the ubiquitous nature of HHV-7 infection, >80% of individuals in the general population exhibit HHV-7 IgG titers >or=1:20; however, only 5% of these individuals exhibit titers >1:320. Thus, HHV-7 IgG titers > 1:320 are suggestive of recent HHV-7 infection. Detection of HHV-7 specific IgM is also indicative of recent infection.

FHV8P
75756

Herpesvirus 8 (HHV-8) DNA, Quantitative Real-Time PCR

Clinical Information: Herpesvirus 8 (HHV-8) DNA, Quantitative Real-Time PCR-Human herpesvirus-8 (HHV-8) is associated with the development of all forms of Kaposi's sarcoma, as well as some other rare lymphoproliferative diseases, such as primary effusion lymphoma and multicentric Castleman's disease. Quantitative PCR may be used to monitor the level of viremia in a patient, often in the context of therapy.

Reference Values:
Not Detected

HERR
82823

Herring, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to herring Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists

or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

HEXLA
617974

Hexagonal Lupus Anticoagulant, Plasma

Clinical Information: Lupus anticoagulant (LA) is one of several antibodies referred to as antiphospholipid antibodies (APA). Lupus anticoagulants are immunoglobulins (IgG, IgM, IgA, or a combination of these) that interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of one or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time [aPTT]; dilute Russell's viper venom time due to inhibition). The characteristic in vitro inhibition caused by the presence of LA inhibitors can be overcome by additional phospholipid, which can be used to confirm the presence of LA. However, the most common in-vivo clinical manifestations of presence of APA are vascular thrombosis and recurrent miscarriage, among other organ manifestations. The combination of clinical manifestations and persistent presence of APA satisfies the criteria for APA syndrome. The hexagonal LA assay system enhances the sensitivity and specificity of aPTT-based LA detection by employing: 1. A partial thromboplastin that is more responsive to LA than many other reagents. 2. Inverted hexagonal phase phospholipid for neutralization of LA inhibition.

Useful For: Confirming or excluding the presence of a lupus anticoagulant (LA), in conjunction with other appropriate coagulation tests Differentiating between deficiencies or inhibitors of specific coagulation factors and LA inhibitors Evaluating a prolonged activated partial thromboplastin time resulting from inhibition

Interpretation: The diagnosis of a lupus anticoagulant (LA) requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LAs. Consequently, a combination or panel of coagulation tests are performed, including the activated partial thromboplastin time (aPTT) and the dilute Russell's viper venom time (dRVVT). If the aPTT or dRVVT is prolonged, additional testing may include mixing tests with normal plasma (to demonstrate inhibition) and the use of excess phospholipid in appropriate assay systems to confirm the presence of LA. Interpretation of hexagonal LA testing is complex and must be done within the context of several additional laboratory tests (eg, aPTT with reflexive aPTT mixing study and platelet neutralization procedure [PNP]; and dRVVT with reflexive mixing study and confirmatory procedure). Hexagonal LA is effective in evaluating a prolonged aPTT resulting from inhibition. The assay involves the addition of a reaction mixture with and without hexagonal phase phospholipid to the patient's platelet-poor plasma. A silica-based aPTT is done on both mixtures and the clotting times are compared. Plasma containing a LA will demonstrate significant shortening of the aPTT with addition of hexagonal phase phospholipid (by at least 13 seconds), when compared to aPTT without hexagonal phase phospholipid. Additional phospholipid supplied by the hexagonal phase phospholipid reagent can absorb LA antibody (anti-protein/phospholipid), thereby diagnostically shortening the aPTT. A hexagonal LA delta of less than 13 indicates LA negative and greater or equal to 13 seconds is LA positive for this assay. Per manufacturer studies hexagonal LA compared to Staclot LA data demonstrated positive percent agreement of 95.6% (95% CI, 91-98%), negative percent agreement of 95.2% (95% CI, 92%-97%), and overall agreement of 95.3% (95% CI, 93%-97%).

Reference Values:

Only orderable as part of a reflex. For more information see:
-AATHR / Thrombophilia Profile, Plasma and Whole Blood
-ACBL / Bleeding Diathesis Profile, Comprehensive, Plasma
-ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma
-ALBLD / Bleeding Diathesis Profile, Limited, Plasma
-ALUPP / Lupus Anticoagulant Profile, Plasma
-APROL / Prolonged Clot Time Profile, Plasma

<13 seconds

Clinical References: 1. Sammaritano LR. Antiphospholipid syndrome. Best Pract Res Clin Rheumatol. 2020;34(1):101463 2. Brandt JT, Triplett DA, Alving B, Sharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost. 1995;74(4):1185-1190 3. Blanco AN, Cardozo MA, Candela M, Santarelli MT, Bianco RP, Lazzari MA. Anti-factor VIII inhibitors and lupus anticoagulants in haemophilia A patients. Thromb Haemost, 1997;77(4):656-659 4. Rauch J, Tannenbaum M, Janoff AS. Distinguishing plasma lupus anticoagulants from anti-factor antibodies using hexagonal (II) phase phospholipids. Thromb Haemost. 1989;62(3):892-896

FHEXA
91442

Hexagonal Phospholipid Neutralization

Reference Values:

All ages: 0-11 sec

This is a qualitative assay and is therefore reported as positive for lupus anticoagulant or negative. The quantitative value is provided as an aid in diagnosis.

HKC
608420

Hexokinase Enzyme Activity, Blood

Clinical Information: Hexokinase (HK) is the first enzymatic step in glycolysis, converting glucose to glucose-6-phosphate. Hexokinase deficiency (OMIM 235700) is a rare cause of chronic nonspherocytic hemolytic anemia and its inheritance is autosomal recessive. Clinically significant HK deficiency manifests in early onset anemia with variable severity ranging from mild to severe. Some patients show neurologic impairment of which the mechanism is unclear.

Useful For: The evaluation of individuals with Coombs-negative chronic hemolysis

Interpretation: Clinical correlation or genetic confirmation may be required to establish hexokinase (HK) deficiency as a cause of hemolytic anemia as the assayed activity level in confirmed cases can vary from markedly decreased to borderline normal levels due to a compensated increase in enzyme by reticulocytes. Comparison of HK activity levels to other red blood cell enzyme activity can be very useful. Heterozygous individuals have moderately decreased to low normal HK levels and are expected to be clinically unaffected. Increased HK activity may be seen when reticulocytes are increased and is not supportive of a diagnosis of HK deficiency.

Reference Values:
Only available as part of a profile. For more information see:
-HAEV1 / Hemolytic Anemia Evaluation, Blood
-EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation, Blood

> or =12 months: 0.7-1.7 U/g Hb
Reference values have not been established for patients who are younger than 12 months.

Clinical References: 1. Koralkova P, Mojzikova R, van Oirschot B, et al: Molecular characterization of six new cases of red blood cell hexokinase deficiency yields four novel mutations in HK1. Blood Cells Mol Dis. 2016 Jul;59:71-76 2. Koralkova P, van Solinge WW, van Wijk R: Rare hereditary red blood cell enzymopathies associated with hemolytic anemia-pathophysiology, clinical aspects and laboratory diagnosis. Int J Lab Hematol. 2014;36:388-397

HK1
607461

Hexokinase Enzyme Activity, Blood

Clinical Information: Hexokinase (HK) is the first enzymatic step in glycolysis, converting glucose to glucose 6-phosphate. Hexokinase deficiency (OMIM 235700) is a rare cause of chronic nonspherocytic hemolytic anemia, and its inheritance is autosomal recessive. Clinically significant HK deficiency manifests in early onset anemia with variable severity ranging from mild to severe. Some patients show neurologic impairment of which the mechanism is unclear.

Useful For: The evaluation of individuals with Coombs-negative chronic hemolysis

Interpretation: Clinical correlation or genetic confirmation may be required to establish hexokinase (HK) deficiency as a cause of hemolytic anemia as the assayed activity level in confirmed cases can vary from markedly decreased to borderline normal levels due to a compensated increase in enzyme by reticulocytes. Comparison of HK activity levels to other RBC enzyme activity can be very useful. Heterozygotes have moderately decreased to low normal HK levels and are expected to be clinically unaffected. Increased HK activity may be seen when reticulocytes are increased and is not supportive of a diagnosis of HK deficiency.

Reference Values:

> or = 12 months: 0.7-1.7 U/g Hb
Reference values have not been established for patients who are younger than12 months.

Clinical References: 1. Koralkova P, Mojzikova R, van Oirschot B, et al: Molecular characterization of six new cases of red blood cell hexokinase deficiency yields four novel mutations in HK1. Blood Cells Mol Dis. 2016 Jul;59:71-76 2. Koralkova P, van Solinge WW, van Wijk R: Rare hereditary red blood cell enzymopathies associated with hemolytic anemia-pathophysiology, clinical aspects and laboratory diagnosis. Int J Lab Hematol. 2014;36:388-397

NAGW
8775

Hexosaminidase A and Total Hexosaminidase, Leukocytes

Clinical Information: Tay-Sachs and Sandhoff diseases, also referred to as GM2 gangliosidoses, are lysosomal storage disorders caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids result in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs and Sandhoff diseases are autosomal recessive conditions. Tay-Sachs disease results from 2 variants in HEXA, which encodes for the alpha subunit of hexosaminidase and causes a deficiency of hexosaminidase A enzyme. An increased carrier frequency for Tay-Sachs disease is observed in individuals of Ashkenazi Jewish, Celtic, and French-Canadian ancestry. Patients with Sandhoff disease have 2 variants in HEXB, which encodes for the beta subunit of hexosaminidase and results in deficiencies in both hexosaminidase A and hexosaminidase B enzymes. Sandhoff disease does not exhibit an increased carrier frequency in any specific population. Clinical Phenotypes: Phenotypically, patients with Tay-Sachs and Sandhoff diseases are virtually indistinguishable. Variability is observed with respect to age of onset and clinical symptoms. Enzyme analysis is generally required to distinguish between the 2 disorders. The acute infantile forms of Tay-Sachs and Sandhoff diseases typically present with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by 1 year of age. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past 5 years of age. The juvenile or subacute forms often present between 2 and 10 years of age with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively get worse, and death typically occurs 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs and Sandhoff diseases. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria, and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. Testing Options: Several tests are available for the detection of carriers of, and individuals affected with, Tay-Sachs and Sandhoff diseases (see Table, Ordering Guidance, and Testing Algorithm). The recommended test for both diagnostic and carrier testing is NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood. Testing begins with enzyme analysis and when indicated reflexes to the appropriate molecular analysis (either HEXA or HEXB gene), which includes sequencing and deletion/duplication analysis. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier, possible carrier, or affected ranges. This differentiates between nondisease causing pseudodeficiency alleles and disease-causing variants. In addition, molecular analysis allows for the facilitation of carrier testing and prenatal diagnosis for at-risk individuals. Table. Test ID Test Name Tay-Sachs disease Sandhoff disease Reflexes to molecular genetic testing Use during pregnancy or hormonal contraception Preferred use Carrier Affected Carrier Affected NAGR Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood Yes Yes Yes Yes Yes Yes Diagnostic or carrier testing NAGW Hexosaminidase A and Total Hexosaminidase, Leukocytes Yes Yes Yes Yes No Yes Diagnostic or carrier testing NAGS

Hexosaminidase A and Total Hexosaminidase, Serum Yes Yes Yes Yes No No Diagnostic MUGS* Hexosaminidase A, Serum Yes Yes No No No No Diagnostic, secondary only *MUGS testing should be utilized only when one of the other assays indicates normal, indeterminate, or carrier results and the clinical suspicion of Tay-Sachs disease remains high.

Useful For: Carrier detection and diagnosis of Tay-Sachs disease Carrier detection and diagnosis of Sandhoff disease

Interpretation: Interpretation is provided with report.

Reference Values:
Hexosaminidase total
< or =15 years: > or =20 nmol/min/mg
> or =16 years: 16.4-36.2 nmol/min/mg

Hexosaminidase percent A
< or =15 years: 20-80% of total
> or =16 years: 63-75% of total

Clinical References: 1. Triggs-Raine BL, Feigenbaum ASJ, Natowicz M, et al. Screening for carriers of Tay-Sachs disease among Ashkenazi Jews-A comparison of DNA-based and enzyme-based tests. N Engl J Med. 1990;323(1):6-12 2. Delnooz CCS, Lefeber DJ, Langemeijer SMC, et al. New cases of adult-onset Sandhoff disease with a cerebellar or lower motor neuron phenotype. J Neurol Neurosurg Psychiatry. 2010;81(9):968-972 3. Vallance H, Morris TJ, Coulter-Mackie M, Lim-Steele J, Kaback M. Common HEXB polymorphisms reduce serum HexA and HexB enzymatic activities, potentially masking Tay-Sachs disease carrier identification. Mol Genet Metab. 2006;87(2):122-127 4. Toro C, Shirvan L, Tifft C: HEXA disorders. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated October 1, 2020. Accessed September 10, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1218/ 5.Leal AF, Benincore-Florez E, Solano-Galarza D, et al. GM2 Gangliosidoses: Clinical Features, Pathophysiological Aspects, and Current Therapies. Int J Mol Sci. 2020;21(17):6213. Published 2020 Aug 27. doi:10.3390/ijms21176213. 6. Gravel RA, Kaback MM, Proia RL, Sandhoff K, Suzuki K, Suzuki K, The GM2 gangliosidoses. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed July 17, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225547784

NAGS
8774

Hexosaminidase A and Total Hexosaminidase, Serum

Clinical Information: Tay-Sachs and Sandhoff diseases, also referred to as GM2 gangliosidoses, are lysosomal storage disorders caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids result in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs and Sandhoff diseases are autosomal recessive conditions. Tay-Sachs disease results from 2 variants in HEXA, which encodes for the alpha subunit of hexosaminidase and causes a deficiency of hexosaminidase A enzyme. An increased carrier frequency for Tay-Sachs disease is observed in individuals of Ashkenazi Jewish, Celtic, and French-Canadian ancestry. Patients with Sandhoff disease have 2 variants in HEXB, which encodes for the beta subunit of hexosaminidase and results in deficiencies in both hexosaminidase A and hexosaminidase B enzymes. Sandhoff disease does not exhibit an increased carrier frequency in any specific population. Clinical Phenotypes: Phenotypically,

patients with Tay-Sachs and Sandhoff diseases are virtually indistinguishable. Variability is observed with respect to age of onset and clinical symptoms. Enzyme analysis is generally required to distinguish between the 2 disorders. The acute infantile forms of Tay-Sachs and Sandhoff diseases typically present with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by 1 year of age. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past 5 years of age. The juvenile or subacute forms often present between 2 and 10 years of age with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively get worse, and death typically occurs 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs and Sandhoff diseases. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria, and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. Testing Options: Several tests are available for the detection of carriers of, and individuals affected with, Tay-Sachs and Sandhoff diseases (see Table, Ordering Guidance, and Testing Algorithm). The recommended test for both diagnostic and carrier testing is NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood. Testing begins with enzyme analysis and when indicated reflexes to the appropriate molecular analysis (either HEXA or HEXB gene), which includes sequencing and deletion/duplication analysis. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier, possible carrier, or affected ranges. This differentiates between nondisease causing pseudodeficiency alleles and disease-causing variants. In addition, molecular analysis allows for the facilitation of carrier testing and prenatal diagnosis for at-risk individuals. Table. Test ID Test Name Tay-Sachs disease Sandhoff disease Reflexes to molecular genetic testing Use during pregnancy or hormonal contraception Preferred use Carrier Affected Carrier Affected NAGR Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood Yes Yes Yes Yes Yes Yes Diagnostic or carrier testing NAGW Hexosaminidase A and Total Hexosaminidase, Leukocytes Yes Yes Yes Yes No Yes Diagnostic or carrier testing NAGS Hexosaminidase A and Total Hexosaminidase, Serum Yes Yes Yes Yes No No Diagnostic MUGS* Hexosaminidase A, Serum Yes Yes No No No No Diagnostic, secondary only *MUGS testing should be utilized only when one of the other assays indicates normal, indeterminate, or carrier results and the clinical suspicion of Tay-Sachs disease remains high.

Useful For: Carrier detection and diagnosis of Tay-Sachs disease and Sandhoff disease Ruling out I-cell disease This test is not useful for pregnant females or those treated with hormonal contraception.

Interpretation: Interpretation is provided with report.

Reference Values:
Hexosaminidase total
< or =15 years: > or =20 nmol/min/mL
> or =16 years: 10.4-23.8 nmol/min/mL

Hexosaminidase percent A
< or =15 years: 20-90%
> or =16 years: 56-80%

Clinical References: 1. Delnooz CCS, Lefeber DJ, Langemeijer SMC, et al. New cases of adult-onset Sandhoff disease with a cerebellar or lower motor neuron phenotype. J Neurol Neurosurg Psychiatry. 2010;81(9):968-972 2. Gravel RA, Kaback MM, Proia RL, Sandhoff K, Suzuki K, Suzuki K: The GM2 gangliosidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed September 10, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225547784 3. Toro C, Shirvan L, Tifft C. HEXA Disorders. In: Adam MP, Everman DB, Mirzaa GM, et al, eds.

GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated October 1, 2020. Accessed September 10, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1218/ 4. Hall P, Minnich S, Teigen C, Raymond K. Diagnosing lysosomal storage disorders: the GM2 gangliosidoses. Curr Protoc Hum Genet. 2014;83:17.16.1-8. doi:10.1002/0471142905.hg1716s83 5. Leal AF, Benincore-Florez E, Solano-Galarza D, et al. GM2 Gangliosidoses: Clinical Features, Pathophysiological Aspects, and Current Therapies. Int J Mol Sci. 2020;21(17):6213. Published 2020 Aug 27. doi:10.3390/ijms21176213

NAGR
82943

Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood

Clinical Information: Tay-Sachs and Sandhoff diseases, also referred to as GM2 gangliosidoses, are lysosomal storage disorders caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids result in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs and Sandhoff diseases are autosomal recessive conditions. Tay-Sachs disease results from 2 variants in HEXA, which encodes for the alpha subunit of hexosaminidase and causes a deficiency of hexosaminidase A enzyme. An increased carrier frequency for Tay-Sachs disease is observed in individuals of Ashkenazi Jewish, Celtic, and French-Canadian ancestry. Patients with Sandhoff disease have 2 variants in HEXB, which encodes for the beta subunit of hexosaminidase and results in deficiencies in both hexosaminidase A and hexosaminidase B enzymes. Sandhoff disease does not exhibit an increased carrier frequency in any specific population. Clinical Phenotypes: Phenotypically, patients with Tay-Sachs and Sandhoff diseases are virtually indistinguishable. Variability is observed with respect to age of onset and clinical symptoms. Enzyme analysis is generally required to distinguish between the 2 disorders. The acute infantile forms of Tay-Sachs and Sandhoff diseases typically present with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by 1 year of age. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past 5 years of age. The juvenile or subacute forms often present between 2 and 10 years of age with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively get worse, and death typically occurs 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs and Sandhoff diseases. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria, and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. Testing Options: Several tests are available for the detection of carriers of, and individuals affected with, Tay-Sachs and Sandhoff diseases (see Table, Ordering Guidance, and Testing Algorithm). This test is the recommended test for both diagnostic and carrier testing. Testing begins with enzyme analysis and when indicated reflexes to the appropriate molecular analysis (either HEXA or HEXB gene), which includes next-generation sequencing to detect single nucleotide and copy number variants. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier, possible carrier, or affected ranges. This differentiates between nondisease causing pseudodeficiency alleles and disease-causing variants. In addition, molecular analysis allows for the facilitation of carrier testing and prenatal diagnosis for at-risk individuals. Table Test ID Test Name Tay-Sachs disease Sandhoff disease Reflexes to molecular genetic testing Use during pregnancy or hormonal contraception Preferred use Carrier Affected Carrier Affected NAGR Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood Yes Yes Yes Yes Yes Yes Diagnostic or carrier testing NAGW Hexosaminidase A and Total Hexosaminidase,

Leukocytes Yes Yes Yes Yes No Yes Diagnostic or carrier testing NAGS Hexosaminidase A and Total Hexosaminidase, Serum Yes Yes Yes Yes No No Diagnostic MUGS* Hexosaminidase A, Serum Yes Yes No No No No Diagnostic, secondary only *MUGS testing should be utilized only when one of the other assays indicates normal, indeterminate, or carrier results and the clinical suspicion of Tay-Sachs disease remains high.

Useful For: Carrier detection and diagnosis of Tay-Sachs disease Carrier detection and diagnosis of Sandhoff disease

Interpretation: Interpretation is provided with report.

Reference Values:
HEXOSAMINIDASE TOTAL
< or =15 years: > or =20 nmol/min/mg
> or =16 years: 16.4-36.2 nmol/min/mg

HEXOSAMINIDASE PERCENT A
< or =15 years: 20-80% of total
> or =16 years: 63-75% of total

Clinical References: 1. Triggs-Raine BL, Feigenbaum ASJ, Natowicz M, et al. Screening for carriers of Tay-Sachs disease among Ashkenazi Jews-A comparison of DNA-based and enzyme-based tests. N Engl J Med. 1990323(1):6-12 2. Delnooz CCS, Lefeber DJ, Langemeijer SMC, et al. New cases of adult-onset Sandhoff disease with a cerebellar or lower motor neuron phenotype. J Neurol Neurosurg Psychiatry. 2010;81(9):968-972 3. Vallance H, Morris TJ, Coulter-Mackie M, Lim-Stelle J, Kaback M. Common HEXB polymorphisms reduce serum HexA and HexB enzymatic activities, potentially masking Tay-Sachs disease carrier identification. Mol Genet Metab. 2006;87(2):122-127 4. Toro C, Shirvan L, Tifft C: HEXA disorders. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated October 1, 2020. Accessed September 10, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1218/ 5. Neudorfer O, Pastores GM, Zeng BJ, Gianutsos J, Zaroff CM, Kolodny EH. Late-onset Tay-Sachs disease: phenotypic characterization and genotypic correlations in 21 affected patients. Genet Med. 2005;7(2):119-123 6. Sutton VR. Tay-Sachs disease screening and counseling families at risk for metabolic disease. Obstet Gynecol Clin North Am. 2002;29(2):287-296 7. Gravel RA, Kaback MM, Proia RL, Sandhoff K, Suzuki K, Suzuki K: The GM2 gangliosidoses. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill. Accessed September 10, 2024. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225547784 8. D'Souza G, McCann CL, Hedrick J, et al. Tay-Sachs disease carrier screening: a 21-year experience. Genet Test. 2000;4(3):257-263. doi:10.1089/10906570050501470

MUGS
80350

Hexosaminidase A, Serum

Clinical Information: Tay-Sachs and Sandhoff diseases, also referred to as GM2 gangliosidoses, are lysosomal storage disorders caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids result in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs and Sandhoff diseases are autosomal recessive conditions. Tay-Sachs disease results from 2 variants in HEXA, which encodes for the alpha subunit of hexosaminidase and causes a deficiency of hexosaminidase A enzyme. An increased carrier frequency for Tay-Sachs disease is observed in individuals of Ashkenazi Jewish, Celtic,

and French-Canadian ancestry. Patients with Sandhoff disease have 2 variants in HEXB, which encodes for the beta subunit of hexosaminidase and results in deficiencies in both hexosaminidase A and hexosaminidase B enzymes. Sandhoff disease does not exhibit an increased carrier frequency in any specific population. Clinical Phenotypes: Phenotypically, patients with Tay-Sachs and Sandhoff diseases are virtually indistinguishable. Variability is observed with respect to age of onset and clinical symptoms. Enzyme analysis is generally required to distinguish between the 2 disorders. The acute infantile forms of Tay-Sachs and Sandhoff diseases typically present with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by 1 year of age. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past 5 years of age. The juvenile or subacute forms often present between 2 and 10 years of age with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively get worse, and death typically occurs 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs and Sandhoff diseases. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria, and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. Testing Options: Several tests are available for the detection of carriers of, and individuals affected with, Tay-Sachs and Sandhoff diseases (see table below, Ordering Guidance, and Testing Algorithm). The recommended test for both diagnostic and carrier testing is NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood. Testing begins with enzyme analysis and, when indicated, reflexes to the appropriate molecular analysis (either HEXA or HEXB gene), which includes sequencing and deletion/duplication analysis. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier, possible carrier, or affected ranges. This differentiates between nondisease-causing pseudodeficiency alleles and disease-causing variants. In addition, molecular analysis allows for the facilitation of carrier testing and prenatal diagnosis for at-risk individuals. Test ID Test Name Tay-Sachs disease Sandhoff disease Reflexes to molecular genetic testing Use during pregnancy or hormonal contraception Preferred use Carrier Affected Carrier Affected NAGR Hexosaminidase A and Total, Leukocytes/Molecular Reflex, Whole Blood Yes Yes Yes Yes Yes Yes Diagnostic or carrier testing NAGW Hexosaminidase A and Total Hexosaminidase, Leukocytes Yes Yes Yes Yes No Yes Diagnostic or carrier testing NAGS Hexosaminidase A and Total Hexosaminidase, Serum Yes Yes Yes Yes No No Diagnostic MUGS* Hexosaminidase A, Serum Yes Yes No No No No Diagnostic, secondary only *MUGS testing should be utilized only when one of the other assays indicates normal, indeterminate, or carrier results and the clinical suspicion of Tay-Sachs disease remains high.

Useful For: Second-order test for diagnosing the B1 variant of Tay-Sachs disease This test is not useful for testing for Sandhoff disease.

Interpretation: Interpretation is provided with report.

Reference Values:
1.23-2.59 U/L (Normal)
1.16-1.22 U/L (Indeterminate)
0.58-1.15 U/L (Carrier)

Clinical References: 1. Tutor JC. Biochemical characterization of the GM2 gangliosidosis B1 variant. Braz J Med Biol Res. 2004;37(6):777-783 2. Gravel RA, Kaback MM, Proia RL, Sandhoff K, Suzuki K, Suzuki K. The GM2 gangliosidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 10, 2024. Available at: http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225547784 3. Toro C, Shirvan L,

Tifft C: HEXA disorders. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated October 1, 2020. Accessed September 10, 2024. Available at: www.ncbi.nlm.nih.gov/books/NBK1218/ 4. Leal AF, Benincore-Florez E, Solano-Galarza D, et al. GM2 Gangliosidoses: Clinical Features, Pathophysiological Aspects, and Current Therapies. Int J Mol Sci. 2020;21(17):6213. Published 2020 Aug 27. doi:10.3390/ijms21176213

FSHAG
57950

Hickory Shagbark (Carya ovata) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >=49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

HMGA
70460

High Mobility Group A2 (HMGA2) Immunostain, Technical Component Only

Clinical Information: High mobility group (HMG) proteins are nonhistone chromatin factors expressed during embryonic development that function to regulate transcription and cellular differentiation. When expression of HMGA2 is deregulated in cells of adult tissues, this oncofetal protein promotes neoplastic transformation. Abnormal HMGA2 expression has been observed in a wide variety of neoplasms, including uterine leiomyomas, ovarian serous carcinomas, lipomatous tumors, lymphangiomyomatosis, and pancreatic carcinomas. Normal spermatids express HMGA2. This immunostain may be useful in the differential diagnosis of lower genital tract mesenchymal tumors, showing positivity in the majority of aggressive angiomyxomas.

Useful For: Identification of abnormal expression of the high mobility group protein, HMGA2

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Ding X, Wang Y, Ma X, et al: Expression of HMGA 2 in bladder cancer and its association with epithelial-to-mesenchymal transition. Cell Prolif. 2014; 7(2):146-151. doi: 10.1111/cpr.12096 2. Lu B, Shi H, Zhang X: Myxoid leiomyosarcoma of the uterus: a clinicopathological and immunohistochemical study of 10 cases. Human Pathol. 2017; 59:139-146. doi: 10.1016/j.humpath.2016.09.014 3. Gong J, Wang Y, Jiang B, et al: Impact of high-mobility-group A2 overexpression on epithelial-mesenchymal transition in pancreatic cancer. Cancer Manag Res. 2019;11:4075-4084. doi: 10.2147/CMAR.S199289

HPLC
65615

High-Performance Liquid Chromatography (HPLC) Hemoglobin Variant, Blood

Clinical Information: A large number of variants of hemoglobin have been recognized. Although many do not result in clinical or hematologic effects, clinical symptoms that can be associated with

hemoglobin disorders include microcytosis, sickling disorders, hemolysis, erythrocytosis/polycythemia, cyanosis/hypoxia, anemia (chronic, compensated, or episodic), and increased methemoglobin or sulfhemoglobin results (M-hemoglobins). For common, and many of the uncommon, hemoglobin variants, protein studies will be sufficient for definitive identification. High-performance liquid chromatography is a method that provides useful and supplementary information on most hemoglobin variants.

Useful For: Providing additional information, which aids in the identification of hemoglobin variants

H1083
618598

HIK1083 Immunostain, Technical Component Only

Clinical Information: HIK1083 is useful to support a diagnosis of gastric-type endocervical adenocarcinoma. HIK1083 is an antibody that recognizes the peripheral alpha-linked N-acetylglucosamine residue present in the carbohydrate moiety of the mucin molecule. This test is intended to identify the presence of HIK1083 protein.

Useful For: Diagnosis of gastric-type endocervical adenocarcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Hodgson A, Parra-Herran C, Mirkovic J. Immunohistochemical expression of HIK1083 and MUC6 in endometrial carcinomas. Histopathology. 2019;75(4):552-558 2. Semczuk A, Tomaszewski J, Gogacz M, et al. Well-differentiated mucinous uterine adenocarcinoma predominantly diagnosed as adenoma malignum: a case report with an immunohistochemical analysis. Int J Clin Exp Pathol. 2015;8(6):7600-7604 3. Stolnicu S, Barsan I, Hoang L, et al. Diagnostic algorithmic proposal based on comprehensive immunohistochemical evaluation of 297 invasive endocervical adenocarcinomas. Am J Surg Pathol. 2018;42(8):989-1000 4. Pirog EC: Diagnosis of HPV-negative, gastric-type adenocarcinoma of the endocervix. Methods Mol Biol. 2015;1249:213-219 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HIPA
9756

Hippuric Acid, Urine

Reference Values:

FHSPL
57533

Histamine Plasma

Reference Values:
<1.0 ng/mL

FHI24
75835

Histamine, 24-Hour Urine

Clinical Information: Histamine is a mediator of the allergic response. Histamine release causes itching, flushing, hives, vomiting, syncope, and even shock. In addition, some patients with gastric

carcinoids may exhibit high concentrations of histamine.

Reference Values:
0.006-0.131 mg/24 h

FHSTW 57368 Histamine, Whole Blood

Reference Values:
180 - 1800 nmol/L

HG34W 604697 Histone 3.3 G34W (H3F3A G34W) Immunostain, Technical Component Only

Clinical Information: H3F3A is a member of the histone H3 family and is located on chromosome 1. Histone H3 G34W is expressed in the nuclei of the mononuclear cell population of H3F3A altered giant cell tumor of bone (GCTB).

Useful For: Aiding in the diagnosis of giant cell tumor of bone

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Cleven A, Hocker S, Briaire-de Bruijn I, Szuhai K, Cleton-Jansen AM, Bovee JVMG. Mutation analysis of H3F3A and H3F3B as a diagnostic tool for giant cell tumor of bone and chondroblastoma. Am J Surg Pathol. 2015;39(11):1576-1583 2. Fernanda A, Bersha F, Ye H, et al. H3F3A (Histone 3.3) G34W immunohistochemistry a reliable marker defining benign and malignant giant cell tumor of one. Am J Surg Pathol. 2017;41(8):1059-1068 3. Luke J, Von Baer A, Schreiber J, et al. H3F3A mutation in giant cell tumour of the bone is detected by immunohistochemistry using a monoclonal antibody against the G34W mutated site of histone H3/3 variant. Histopathology. 2017;71(4):125-133 4. Yamamoto H, Iwasaki T, Yuichi Y, et al. Diagnostic utility of histone H3.3 G34W, G34R, and G34V mutant-specific antibodies for giant cell tumors of bone. Hum Pathol. 2018;73(3):41-50 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HISGT 619586 Histone Genes Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information: H3-3A (previously known as H3F3A) and H3-3B (previously known as H3F3B) genes encode H3.3 replication-independent histone proteins. H3C2 (previously known as HIST1H3B) and H3C3 (previously known as HIST1H3C) encode H3.1 replication-dependent histone proteins. H3C14 (previously known as HIST2H3C) encodes H3.2 replication-dependent histone protein. Mutations in H3-3A and H3-3B genes primarily involve codons K28 (also known as K27) and G35 (also known as G34), whereas mutations in H3C2, H3C3 and H3C14 involve codon K28 (also known as K27). In central nervous system tumors, H3-3A, H3C2, H3C3 and H3C14 mutations are a diagnostic molecular biomarker for diffuse midline glioma, H3 K27-altered and diffuse hemispheric glioma, H3 G34-mutant.

Among bone/soft tissue tumors, H3-3A mutations are a hallmark of giant cell tumour of bone and mutations in H3-3B and H3-3A genes are typical of chondroblastoma.

Useful For: Identifying specific mutations within the H3-3A, H3-3B, H3C2, H3C3 and H3C14 genes that assist in tumor diagnosis/classification

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. Horbinski C, Nabors LB, Portnow J, et al. NCCN Guidelines Insights: Central Nervous System Cancers, Version 2.2022. J Natl Compr Canc Netw. 2023;21(1):12-20 4. WHO Classification of Tumours Editorial Board. Central nervous system tumours. 5th ed. World Health Organization; 2022. WHO Classification of Tumours. Vol 6 5. Sturm D, Witt H, Hovestadt V, et al: Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. Cancer Cell. 2012 Oct 16;22(4):425-437 6. Wu G, Broniscer A, McEachron TA, et al. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. Nat Genet. 2012 Jan:44(3):251-253 7. Schwartzentruber J, Korshunov A, Liu XY, et al: Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature. 2012 Jan 29;482(7384):226-231 8. Behjati S, Tarpey PS, Presneau N, et al: Distinct H3F3A and H3F3B driver mutations define chondroblastoma and giant cell tumor of bone. Nat Genet. 2013 Dec;45(12):1479-82

HK27M
604989

Histone H3 K27M Mutant (H3 K27M) Immunostain, Technical Component Only

Clinical Information: Histone H3 K27M is an alteration in the H3F3A gene, encoding for histone H3.3. This alteration is characteristic of "diffuse midline glioma, H3 K27M-mutant," a new entity in the classification of central nervous system tumors, which carries a poor prognosis. H3 K27M-mutant diffuse midline glioma occurs most commonly in young children but, less frequently, can occur in adults. The most common locations include the brain stem, thalamus, and spinal cord. The term brain stem glioma and diffuse intrinsic pontine glioma were previously used to indicate tumors occurring in the brain stem and pons respectively.

Useful For: Identifying the presence of altered H3 K27M protein

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Venneti S, Santi M, Felicella MM, et al. A sensitive and specific histopathologic prognostic marker for H3F3A K27M mutant pediatric glioblastomas. Acta Neuropathol. 2014;128:743-753 2. Bechet D, Gielen GG, Korshunov A, et al. Specific detection of methionine 27

mutation in histone 3 variants (H3K27M) in fixed tissue from high-grade astrocytomas. Acta Neuropathol. 2014;128:733-741 3. Korshunov A, Ryzhova M, Hovestadt V, et al. Integrated analysis of pediatric glioblastoma reveals a subset of biologically favorable tumors with associated molecular prognostic markers. Acta Neuropathol. 2015;129:669-678 4. Schwartzentruber J, Korshunov A, Liu XY, et al. Driver mutations in histone H3.3 and chromatin remodeling genes in paediatric glioblastoma. Nature. 2012;482:226-231 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HK36M
604699

Histone H3 K36M Mutant (H3F3 K36M) Immunostain, Technical Component Only

Clinical Information: H3F3B is a member of the histone H3 family and is located on chromosome 17. Histone H3 K36M is expressed in the nuclei of the mononuclear cell population of H3F3B altered chondroblastoma.

Useful For: Diagnosis of chondroblastoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Cleven A, Hocker S, Briaire-de Bruijn I, Szuhai K, Cleton-Jansen AM, Bovee JVMG. Mutation analysis of H3F3A and H3F3B as a diagnostic tool for giant cell tumor of bone and chondroblastoma. Am J Surg Pathol. 2015;39(11):1576-1583 2. Lu C, Jain S, Hoelper D, et al. Histone H3K36 mutations promote sarcomagenesis through altered histone methylation landscape. Science. 2016;352(6287):844-849 3. Chen W, DiFrancesco LM. Chondroblastoma: An update. Arch Pathol Lab Med. 2017;141(6):867-871 4. Amary MF, Berisha F, Mozela R, et al. The H3F3 K36M mutant antibody is a sensitive and specific marker for the diagnosis of chondroblastoma. Histopathology. 2016;69(2):121-127 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HISME
72127

Histone H3 Trimethyl K27 Immunostain, Technical Component Only

Clinical Information: Histone H3 trimethyl-K27 is a bivalent epigenetic regulator that silences or represses the gene. Evaluation of H3 trimethyl-K27 immunohistochemical expression is a helpful biomarker in the diagnosis of diffuse midline gliomas H3 K27M-mutant, which most frequently occur in children and with less frequency in adults. These tumors typically occur along the midline and include intrinsic pontine gliomas (DIPG), thalamic, and spinal cord diffuse gliomas. H3 K27M mutations lead to global reduction in H3 trimethyl-K27 and result in H3 trimethyl-K27 loss of expression. Histologic mimics can be distinguishable from malignant peripheral nerve sheath tumors that show H3 trimethyl-K27 loss of expression.

Useful For: Diagnosis of malignant peripheral nerve sheath tumors and diffuse midline gliomas H3 K27M-mutant

Interpretation: This test does not include pathologist interpretation, only technical performance of the

stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Prieto-Granada CN, Wiesner T, Messina JL, et al. Loss of H3K27me3 Expression Is a Highly Sensitive Marker for Sporadic and Radiation-induced MPNST. Am J Surg Pathol. 2016;40(4):479-489 2. Schaefer IM, Fletcher C, Hormick JL. Loss of H3K27 trimethylation distinguishes malignant peripheral nerve sheath tumors from histologic mimics. Mod Pathol. 2016;29:4-13 3. Lee W, Teckie S, Wiesner T, et al. PRC2 is recurrently inactivated through EED or SUZ12 loss in malignant peripheral nerve sheath tumors. Nat Gene. 2014;46(11):1227-1232 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HIBAG
618715

Histoplasma and Blastomyces Antigen, Enzyme Immunoassay, Serum

Clinical Information: Blastomyces dermatitidis and Histoplasma capsulatum are dimorphic fungal agents with increasingly overlapping endemicity throughout the Midwestern, South Central, and Southeastern United States, particularly in regions around the Ohio and Mississippi River valleys, the Great Lakes, and the Saint Lawrence River. These agents are also found in regions of Canada. These 2 fungi maintain a yeast form in the host at body temperature but are maintained as molds in the environment, which release spores that are inhaled by individuals leading to infection. Through phylogenetic analysis, B dermatitidis has been separated into 2 distinct species: B dermatitidis and Blastomyces gilchristii, both able to cause blastomycosis. B dermatitidis infections are frequently associated with dissemination, particularly in older patients, smokers, and immunocompromised hosts, while B gilchristii has primarily been associated with pulmonary and constitutional symptoms. Additional species of Blastomyces have recently been discovered and characterized; however, the performance characteristics of this assay for these species are unknown. Approximately half of patients infected with Blastomyces will develop symptoms that are frequently nonspecific, including fever, cough, night sweats, myalgia or arthralgia, weight loss, dyspnea, chest pain, and fatigue. Symptoms may appear anywhere from 3 weeks to 3 months following infection. For Histoplasma infections, clinical manifestations are largely dependent on the fungal burden at the time of exposure and the patient's underlying immune status. While the vast majority (>90%) of exposed individuals will remain asymptomatic, individuals seeking medical attention can present with a diverse set of symptoms ranging from a self-limited pulmonary illness to severe, disseminated disease. Individuals at risk of severe infection include those with impaired cellular immunity or have undergone organ transplantation, are HIV positive, or have a hematologic malignancy. Diagnosis of blastomycosis and histoplasmosis relies on a combination of assays, including culture and molecular testing performed on appropriate specimens, and serologic evaluation for both antibodies to, and antigen released from, the organism. Although culture remains the gold standard method and is highly specific, these organisms can take several days to weeks to grow, and sensitivity is diminished in cases of acute or localized disease. Similarly, molecular testing offers high specificity and a rapid turnaround time, however sensitivity is imperfect. Detection of an antibody response to Blastomyces or Histoplasma offers high specificity; however, results may be falsely negative in patients who are acutely ill or are immunosuppressed.

Useful For: Diagnosing Histoplasma capsulatum or Blastomyces dermatitidis infection, without differentiation between the organisms, using serum specimens Monitor antigen levels following initiation of antifungal treatment

Interpretation:

Reference Values:
Histoplasma/Blastomyces Antigen Result:
Not detected

Histoplasma/Blastomyces Antigen Value:
Not detected
Detected: <1.5 ng/mL
Detected: 1.5-25.0 ng/mL
Detected: >25.0 ng/mL

Reference values apply to all ages.

Clinical References: 1. McBride JA, Gauthier GM, Klein BS. Clinical manifestations and treatment of Blastomycosis. Clin Chest Med. 2017;38(3):435-449 2. Chapman SW, Dismukes WE, Proia LA, et al: Clinical practice guidelines for the management of blastomycosis. Clin Infect Dis. 2008;46(12):1801-1812 3. Wheat LJ, Freifeld AG, Kleiman MB, et al: Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45(7):807-825

UHBAG 621248 Histoplasma and Blastomyces Antigen, Enzyme Immunoassay, Urine

Clinical Information: Blastomyces dermatitidis and Histoplasma capsulatum are dimorphic fungal agents with increasingly overlapping endemicity throughout the Midwestern, South Central, and Southeastern United States, particularly in regions around the Ohio and Mississippi River valleys, the Great Lakes, and the Saint Lawrence River. These agents are also found in regions of Canada. These 2 fungi maintain a yeast form in the host at body temperature but are maintained as molds in the environment, which release spores that are inhaled by individuals leading to infection. Through phylogenetic analysis, B dermatitidis has been separated into 2 distinct species: B dermatitidis and Blastomyces gilchristii, both able to cause blastomycosis. B dermatitidis infections are frequently associated with dissemination, particularly in older patients, smokers, and immunocompromised hosts, while B gilchristii has primarily been associated with pulmonary and constitutional symptoms. Additional species of Blastomyces have recently been discovered and characterized; however, the performance characteristics of this assay for these species are unknown. Approximately half of patients infected with Blastomyces will develop symptoms that are frequently nonspecific, including fever, cough, night sweats, myalgia or arthralgia, weight loss, dyspnea, chest pain, and fatigue. Symptoms may appear anywhere from 3 weeks to 3 months following infection. For Histoplasma infections, clinical manifestations are largely dependent on the fungal burden at the time of exposure and the patient's underlying immune status. While the vast majority (>90%) of exposed individuals will remain asymptomatic, individuals seeking medical attention can present with a diverse set of symptoms ranging from a self-limited pulmonary illness to severe, disseminated disease. Individuals at risk of severe infection include those with impaired cellular immunity or have undergone organ transplantation, are HIV positive, or have a hematologic malignancy. Diagnosis of blastomycosis and histoplasmosis relies on a combination of assays, including culture and molecular testing performed on appropriate specimens, and serologic evaluation for both antibodies to, and antigen released from, the organism. Although culture remains the gold standard method and is highly specific, these organisms can take several days to weeks to grow, and sensitivity is diminished in cases of acute or localized disease. Similarly, molecular testing offers high specificity and a rapid turnaround time, however sensitivity is imperfect. Detection of an antibody response to Blastomyces or Histoplasma offers high specificity; however, results may be falsely negative in patients who are acutely ill or are immunosuppressed.

Useful For: Diagnosing Histoplasma capsulatum or Blastomyces dermatitidis infection, without differentiation between the organisms, using random urine specimens Monitor antigen levels following initiation of antifungal treatment

Interpretation: Not detected: No antigen from Histoplasma or Blastomyces detected. False-negative results may occur depending on the extent of disease or site of infection. Repeat testing on a new specimen if clinically indicated. Detected: Antigen from Histoplasma or Blastomyces (unable to differentiate) was detected, below the limit of quantification (<1.3 ng/mL). Definitive identification requires additional testing, including serology, culture, histopathology, and/or molecular methods. Results should be correlated with clinical presentation and exposure history. Detected: Antigen from Histoplasma or Blastomyces (unable to differentiate) detected. Definitive identification requires additional testing, including serology, culture, histopathology, and/or molecular methods. Results should be correlated with clinical presentation and exposure history. Detected: Antigen from Histoplasma or Blastomyces (unable to differentiate) detected, above the limit of quantification (>20.0 ng/mL). Definitive identification requires additional testing, including serology, culture, histopathology, and/or molecular methods. Results should be correlated with clinical presentation and exposure history.

Reference Values:

Histoplasma/Blastomyces Antigen Result:
Not detected

Histoplasma/Blastomyces Antigen Value:
Not detected: 0.0 ng/mL
Detected: <1.3 ng/mL
Detected: 1.3-20.0 ng/mL
Detected: >20.0 ng/mL

Reference values apply to all ages.

Clinical References: 1. McBride JA, Gauthier GM, Klein B. Clinical manifestations and treatment of blastomycosis. Clin Chest Med. 2017;38(3):435-449 2. Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis. Clin Infect Dis. 2008;46(12):1801-1812 3. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45(7):807-825 4. Granger D, Streck NT, Theel ES. Detection of Histoplasma capsulatum and Blastomyces dermatitidis antigens in serum using a single quantitative enzyme immunoassay. J Clin Microbiol. 2024;62(1):e0121323. doi:10.1128/jcm.01213-23

HISER 621213 Histoplasma Antibody Complement Fixation and Immunodiffusion, Serum

Clinical Information: Histoplasma capsulatum is a dimorphic fungus endemic to the Midwestern United States, particularly along the Mississippi River and Ohio River valleys. Infection occurs following inhalation of fungal microconidia, and subsequent clinical manifestations are largely dependent on the fungal burden at the time of exposure and the patient's underlying immune status. While the vast majority (>90%) of exposed individuals will remain asymptomatic, individuals seeking medical attention can present with a diverse set of symptoms ranging from a self-limited pulmonary illness to severe, disseminated disease. Individuals at risk for severe infection include those with impaired cellular immunity, who have undergone organ transplantation, who are HIV positive, or who have a hematologic malignancy. The available laboratory methods for the diagnosis of H capsulatum infection include fungal culture, molecular techniques, serologic testing, and antigen detection. While culture remains the gold standard diagnostic test and is highly specific, prolonged incubation is often

required, and sensitivity decreases (9%-34%) in cases of acute or localized disease. Similarly, molecular methods offer high specificity but decreased sensitivity. Serologic testing likewise offers high specificity; however, results may be falsely negative in immunosuppressed patients or those who present with acute disease. Also, antibodies may persist for years following disease resolution, thereby limiting the clinical specificity.

Useful For: Aiding in the diagnosis of active histoplasmosis

Interpretation: Complement fixation (CF) titer results of 1:32 or higher indicate active disease. A rising CF titer is associated with progressive infection. Patients infected with Histoplasma capsulatum demonstrate a serum antibody with a rising titer within 6 weeks of infection. A rising titer is associated with progressive infection. Specific antibody persists for a few weeks to a year, regardless of clinical improvement. The presence of H and/or M bands on immunodiffusion tests is considered a positive result for the presence of antibodies to Histoplasma. Presence of an H band suggests recent infection.

Reference Values:
Anti-Yeast Antibody by Complement Fixation:
Negative (positive results reported as titer)

Antibody by Immunodiffusion:
Negative (positive results reported as band present)

Clinical References: 1. Kaufman L, Kovacs JA, Reiss E. Clinical immunomycology. In: Rose NR, de Macario ED, Folds JD, Lane HC, Nakamura RM, eds. Manual of Clinical and Laboratory Immunology. 5th ed. ASP Press; 1997 2. Deepe GS. Histoplasma capsulatum histoplasmosis. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3162-3176

HICSF 621216 Histoplasma Antibody Complement Fixation and Immunodiffusion, Spinal Fluid

Clinical Information: Histoplasma capsulatum is a dimorphic fungus endemic to the Midwestern United States, particularly along the Mississippi River and Ohio River valleys. Infection occurs following inhalation of fungal microconidia, and subsequent clinical manifestations are largely dependent on the fungal burden at the time of exposure and the patient's underlying immune status. While the vast majority (>90%) of exposed individuals will remain asymptomatic, individuals seeking medical attention can present with a diverse set of symptoms ranging from a self-limited pulmonary illness to severe, disseminated disease. Individuals at risk for severe infection include those with impaired cellular immunity, who have undergone organ transplantation, who are HIV positive, or who have a hematologic malignancy. The available laboratory methods for the diagnosis of H capsulatum infection include fungal culture, molecular techniques, serologic testing, and antigen detection. While culture remains the gold standard diagnostic test and is highly specific, prolonged incubation is often required, and sensitivity decreases (9%-34%) in cases of acute or localized disease. Similarly, molecular methods offer high specificity but decreased sensitivity. Serologic testing likewise offers high specificity; however, results may be falsely negative in immunosuppressed patients or those who present with acute disease. Also, antibodies may persist for years following disease resolution, thereby limiting the clinical specificity.

Useful For: Aiding in the diagnosis of Histoplasma meningitis using spinal fluid specimens

Interpretation: Any positive serologic result in spinal fluid is significant. Simultaneous appearance of the H and M precipitin bands indicates active histoplasmosis. The M band alone indicates active or

chronic disease or a recent skin test for histoplasmosis.

Reference Values:
Anti-Yeast Antibody by Complement Fixation
Negative (positive results reported as titer)

Antibody by Immunodiffusion
Negative (positive results reported as band present)

Clinical References: 1. Kaufman L, Kovacs JA, Reiss E. Clinical immunomycology. In: Rose NR, de Macario ED, Folds JD, Lane HC, Nakamura RM, eds. Manual of Clinical Laboratory Immunology. ASM Press; 1997 2. Deepe GS. Histoplasma capsulatum Histoplasmosis. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3162-3176

HBRP 60213 Histoplasma capsulatum/Blastomyces species, Molecular Detection, PCR, Varies

Clinical Information:

Useful For: Rapid detection of Histoplasma capsulatum and Blastomyces dermatitidis DNA Aiding in the rapid diagnosis of histoplasmosis and blastomycosis

Interpretation: A positive result for Histoplasma capsulatum indicates presence of Histoplasma DNA; a positive result for Blastomyces dermatitidis/gilchristii indicates presence of Blastomyces DNA. A negative result indicates absence of detectable H capsulatum and B dermatitidis/gilchristii DNA. Fungal culture has increased sensitivity over this polymerase chain reaction (PCR) assay and should always be performed when the PCR is negative.

Reference Values:
Not applicable

Clinical References: 1.Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C: Histoplasmosis. Infect Dis Clin North Am. 2016 Mar;30(1):207-227. doi: 10.1016/j.idc.2015.10.009 2.Azar MM, Loyd JL, Relich RF, Wheat LJ, Hage CA: Current concepts in the epidemiology, diagnosis, and management of Histoplasmosis syndromes. Semin Respir Crit Care Med. 2020 Feb;41(1):13-30. doi: 10.1055/s-0039-1698429 3.Linder KA, Kauffman CA, Miceli MH: Blastomycosis: A review of mycological and clinical aspects. J Fungi (Basel). 2023 Jan 14;9(1):117. doi: 10.3390/jof9010117 4.Smith DJ, Williams SL; Endemic Mycoses State Partners Group; Benedict KM, Jackson BR, Toda M: Surveillance for Coccidioidomycosis, Histoplasmosis, and Blastomycosis - United States, 2019. MMWR Surveill Summ. 2022 Aug 19;71(7):1-14. doi: 10.15585/mmwr.ss7107a1

HIBC 621305 Histoplasma/Blastomyces Panel, Spinal Fluid

Clinical Information: Histoplasma Histoplasma capsulatum is a dimorphic fungus endemic to the Midwestern United States, particularly along the Mississippi River and Ohio River valleys. Infection occurs following inhalation of fungal microconidia, and subsequent clinical manifestations are largely dependent on the fungal burden at the time of exposure and the patient's underlying immune status. While the vast majority (>90%) of exposed individuals will remain asymptomatic, individuals seeking medical attention can present with a diverse set of symptoms ranging from a self-limited pulmonary

illness to severe, disseminated disease. Individuals at risk for severe infection include those with impaired cellular immunity, who have undergone organ transplantation, who are HIV positive, or who have a hematologic malignancy. The available laboratory methods for the diagnosis of H capsulatum infection include fungal culture, molecular techniques, serologic testing, and antigen detection. While culture remains the gold standard diagnostic test and is highly specific, prolonged incubation is often required, and sensitivity decreases (9%-34%) in cases of acute or localized disease. Similarly, molecular methods offer high specificity but decreased sensitivity. Serologic testing likewise offers high specificity; however, results may be falsely negative in immunosuppressed patients or those who present with acute disease. Also, antibodies may persist for years following disease resolution, thereby limiting the clinical specificity. Blastomyces Blastomyces dermatitidis is endemic throughout the Midwestern, south central, and Southeastern United States, particularly in regions around the Ohio and Mississippi river valleys, the Great Lakes, and the Saint Lawrence River. It is also found in regions of Canada. Blastomyces species are dimorphic fungi, preferring moist soil and decomposing organic matter, which produces fungal spores that are released and inhaled by humans. At body temperature, spores mature into yeast, which may remain in the lungs or disseminate through the bloodstream to other parts of the body. Through phylogenetic analysis, B. dermatitidis has been separated into 2 distinct species: B dermatitidis and Blastomyces gilchristii, both able to cause blastomycosis. B dermatitidis infections are frequently associated with dissemination, particularly in older patients, smokers, and immunocompromised hosts, while B gilchristii has primarily been associated with pulmonary and constitutional symptoms. Additional species of Blastomyces have recently been discovered and characterized, however the performance characteristics of this assay for these species are unknown. Approximately half of patients infected with Blastomyces will develop symptoms, which are frequently nonspecific, including fever, cough, night sweats, myalgia or arthralgia, weight loss, dyspnea, chest pain, and fatigue. Symptoms may appear anywhere from 3 weeks to 3 months following infection. Diagnosis of blastomycosis relies on a combination of assays, including culture and molecular testing performed on appropriate specimens, and serologic evaluation for both antibodies to and antigen released from Blastomyces. Although culture remains the gold standard method and is highly specific, the organism can take several days to weeks to grow and sensitivity is diminished in cases of acute or localized disease. Similarly, molecular testing offers high specificity and a rapid turnaround time, however sensitivity is imperfect. Detection of an antibody response to Blastomyces offers high specificity, however results may be falsely negative in patients who are acutely ill or are immunosuppressed.

Useful For: Aiding in the diagnosis of histoplasmosis or blastomycosis meningitis

Interpretation: Histoplasma: -Any positive serologic result in spinal fluid is significant. -Simultaneous appearance of the H and M precipitin bands suggests active histoplasmosis. -The M band alone indicates active or chronic disease or a recent skin test for histoplasmosis. Blastomyces: A positive result is suggestive of infection, but the results cannot distinguish between active disease and prior exposure. Furthermore, detection of antibodies in cerebrospinal fluid (CSF) may reflect intrathecal antibody production or may occur due to passive transfer or introduction of antibodies from the blood during lumbar puncture. Routine fungal culture of clinical specimens (eg, CSF) is recommended in cases of suspected blastomycosis involving the central nervous system.

Reference Values:

HISTOPLASMA ANTIBODY
Anti-Yeast antibody by Complement Fixation: Negative (positive results reported as titer)
Antibody by Immunodiffusion: Negative (positive results reported as titer)

BLASTOMYCES ANTIBODY IMMUNODIFFUSION
Negative

Clinical References: Histoplasma Both immunodiffusion (ID) and compliment fixation (CF) tests are used to detect antibodies to Histoplasma capsulatum. For ID, the antigen is a culture filtrate, histoplasmin. H and M precipitin bands are identified. For the CF test, the antigens are histoplasmin and a

yeast form of H capsulatum; the latter is more sensitive.(Roberts GD: Fungi. In: Washington II JA, ed. Laboratory Procedures in Clinical Microbiology. 2nd ed. Springer-Verlag, 1985; In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020) Blastomyces The ID test is a qualitative test employed for the detection of precipitating antibodies present in the specimen. Soluble antigens of the fungus are placed in wells of an agarose gel-filled Petri dish, and the patient's specimen and a control (positive) are placed in adjoining wells. If present, specific precipitate antibody will form precipitin lines between the wells. Their comparison to the control establishes the results. When performing the ID test, only precipitin bands of identity with the reference bands are significant.(Kaufman L, McLaughlin DW, Clark MJ, Blumer S: Specific immunodiffusion test for blastomycosis. Appl Microbiol. 1973;26:244-247, Williams JE, Murphy R, Standard PG, Phan JP: Serologic response in blastomycosis: diagnostic value of double immunodiffusion assay. Am Res Resp Dis. 1981;123:209-212; Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020)

HIVSP
48393

HIV Antigen and Antibody Prenatal Routine Screen, Plasma

Clinical Information: AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS or AIDS-related complex and in asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa and has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed, but HIV p24 antigen should be detectable and yield reactive results with the HIV antigen-antibody combination detection assays. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with an HIV-1/-2 antigen and/or antibody screening test, which may be performed by various US Food and Drug Administration-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods.

Useful For: Screening for HIV-1 and HIV-2 infection in nonsymptomatic pregnant patients This test should not be used as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative HIV-1/-2 antigen and antibody screening test results usually indicate absence of HIV-1 and HIV-2 infection. However, such negative results do not rule-out acute HIV infection. If acute HIV-1 or HIV-2 infection is suspected, detection of HIV RNA (HPP12 / HIV-1/HIV-2 RNA Detection Prenatal, Plasma) is recommended. Reactive HIV-1/-2 antigen and antibody screening test results suggest the presence of HIV-1 and/or HIV-2 infection, but it is not diagnostic for HIV infection and should be considered preliminary. A reactive result does not differentiate among reactivity with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody. Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV antibody confirmation/differentiation test (automatically added to all samples with reactive screen test results at an additional charge). All initially positive supplemental or confirmatory HIV test results (by serologic or molecular test methods) should be verified by submitting a second plasma specimen for repeat testing. Such positive HIV test results are required under laws in many states in the United States to be reported to the departments of health of the respective states where the patients reside. The following algorithms are available: -HIV Prenatal Testing Algorithm, Including Follow-up of Reactive Rapid Serologic Test Results -HIV Testing Algorithm (Fourth Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results

Reference Values:
Negative

Clinical References:

HVPRS 617827 HIV Antigen and Antibody Prenatal Routine Screen, Serum

Clinical Information: AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS or AIDS-related complex and in asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa and has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed, but HIV p24 antigen should be detectable and yield reactive results with the HIV antigen-antibody combination detection assays. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with an HIV-1/-2 antigen and/or antibody screening test, which may be performed by various US Food and Drug Administration-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods.

Useful For: Screening for HIV-1 and HIV-2 infection in nonsymptomatic pregnant patients This test should not be used as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative HIV-1/-2 antigen and antibody screening test results usually indicate absence of HIV-1 and HIV-2 infection. However, such negative results do not rule-out acute HIV infection. If acute HIV-1 or HIV-2 infection is suspected, detection of HIV RNA (HPS12 / HIV-1/HIV-2 RNA Detection, Prenatal, Serum) is recommended. Reactive HIV-1/-2 antigen and antibody screening test results suggest the presence of HIV-1 and/or HIV-2 infection, but it is not diagnostic for HIV infection and should be considered preliminary. A reactive result does not differentiate among reactivity with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody. Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV antibody confirmation/differentiation test (automatically added to all samples with reactive screen test results at an additional charge). All initially positive supplemental or confirmatory HIV test results (by serologic or molecular test methods) should be verified by submitting a second plasma specimen for repeat testing. Such positive HIV test results are required under laws in many states in the United States to be reported to the departments of health of the respective states where the patients reside. For more information see HIV Prenatal Testing Algorithm, Including Follow-up of Reactive Rapid Serologic Test Results

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention. 2018 Quick reference guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. CDC; January 2018. Accessed October 16, 2023. Available at https://stacks.cdc.gov/view/cdc/50872 2. Centers for Disease Control and Prevention. Technical update: Use of the Determine HIV 1/2 Ag/Ab combo test with serum or plasma in the laboratory algorithm for HIV diagnosis. CDC; October 4, 2017. Accessed October 16, 2023. Available at https://stacks.cdc.gov/view/cdc/48472 3. Muhlbacher A, Sauleda S, Piron M, et al. A multicentre evaluation of the Elecsys HIV Duo assay. J Clin Virol. 2019;112:45-50 4. Duncan D, Duncan

J, Kramer B, et al. An HIV diagnostic testing algorithm using the cobas HIV-1/HIV-2 qualitative assay for HIV type differentiation and confirmation. J Clin Microbiol. 2021;59(7):e03030-20. doi:10.1128/JCM.03030-20

HV1CD 83628 HIV-1 and HIV-2 Antibodies for Cadaveric or Hemolyzed Specimens, Serum

Clinical Information: Epidemiological data indicate that AIDS is caused by at least 2 types of HIV. The first virus, HIV-1, has been isolated from patients with AIDS or AIDS-related complex and from asymptomatic infected individuals at high risk for AIDS. HIV-1 is transmitted by sexual contact, exposure to infected blood or blood products, or from an infected mother to her fetus or infant. A second HIV virus, HIV-2, was isolated from patients in West Africa in 1986. HIV-2 appears to be endemic only in West Africa, but it has also been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detected until 6 to 12 weeks following exposure and are almost always detected by 12 months. Antibodies may fall into undetectable levels in the terminal stage of AIDS. For more information see HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results.

Useful For: Diagnosing HIV-1 and/or HIV-2 infection in cadaveric or hemolyzed serum specimens from symptomatic patients with or without risk factors for HIV infection This test is not offered as a screening or confirmatory test for blood donor specimens.

Interpretation:

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention (CDC), Association of Public Health Laboratories: Laboratory testing for the diagnosis of HIV infection. CDC; Updated June 27, 2014. Accessed December 23, 2024. Available at: stacks.cdc.gov/view/cdc/23447 2. Centers for Disease Control and Prevention (CDC), Association of Public Health Laboratories: 2018 Quick reference guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. CDC; Updated January 2018. Accessed December 23, 2024. Available at https://stacks.cdc.gov/view/cdc/50872 3. Hariri S, McKenna MT: Epidemiology of human immunodeficiency virus in the United States. Clin Microbiol Rev. 2007 Jul;20(3):478-4884 4. Owen SM, Yang C, Spira T, et al: Alternative algorithms for human immunodeficiency virus infection diagnosis using tests that are licensed in the United States. J Clin Microbiol. 2008;46(5):1588-1595

HVPPS 617828 HIV-1 and HIV-2 Antibody Confirmation and Differentiation Prenatal, Serum

Clinical Information: AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS or AIDS-related complex and in asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12

weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with an HIV-1/-2 antigen and/or antibody screening test, which may be performed by various US Food and Drug Administration-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers' instructions for use.

Useful For: Confirmation and differentiation of HIV-1 and HIV-2 antibodies in serum specimens from prenatal patients who show reactive results with 3rd- (HIV-1/-2 antibody only) and 4th-generation (HIV antigen and antibody) HIV serologic assays This test is not useful as a screening test for HIV infection in symptomatic or asymptomatic individuals. This test should not be used as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative results for both HIV-1 and HIV-2 antibodies usually indicate the absence of HIV-1 and HIV-2 infection. However, negative results do not rule-out acute or early HIV infection in patients with reactive initial combined HIV-1/-2 antigen and antibody test results. HPS12 / HIV-1/HIV-2 RNA Detection Prenatal, Serum reflex test will be performed automatically per testing algorithm. Positive HIV-1 antibody but negative HIV-2 antibody results indicate the presence of HIV-1 infection. Together with reactive initial combined HIV-1/-2 antigen and antibody test results, individuals with such results are presumed to have HIV-1 infection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection. Additional testing with a newly submitted plasma specimen for HIQNP / HIV-1 RNA Detection and Quantification, Prenatal, Plasma is recommended to determine the baseline HIV-1 viral load prior to initiating antiretroviral treatment. Positive HIV-1 antibody but indeterminate HIV-2 antibody results indicate the presence of HIV-1 infection, with probable cross-reactivity of HIV-1 antibodies with HIV-2 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection by submitting a new plasma specimen for HIV-1 RNA quantification (HIQNP). Indeterminate HIV-1 antibody but negative HIV-2 antibody results suggest either very early HIV-1 infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' serum specimens and HIV-1 antigens on the assay strip. HPS12 will be performed automatically per testing algorithm. Negative HIV-1 antibody, but indeterminate HIV-2 antibody results, may be due to acute HIV-1 infection, very early HIV-2 infection (in individuals with risk factors), or presence of nonspecific cross-reactivity between the patients' serum specimens and HIV-2 antigens on the assay strip. HPS12 will be performed automatically per testing algorithm. Positive results for both HIV-1 and HIV-2 antibodies suggest probable presence of HIV-1 and HIV-2 coinfection. However, such results may be rarely due to HIV-1 infection with HIV-2 antibody cross-reactivity, or HIV-2 infection with HIV-1 antibody cross-reactivity (eg, absence of HIV-1 p24 and p31 bands). Verification of a first-time positive test result is recommended for the diagnosis of HIV infection. HPS12 will be performed automatically per testing algorithm. Indeterminate results for both HIV-1 and HIV-2 antibodies indicate either very early HIV infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV antigens on the assay strip. Nonspecific cross-reactivity may be due to recent non-HIV infections, hypergammaglobulinemic states, connective tissue disorders, or pregnancy (alloantibodies). HPS12 will be performed automatically per testing algorithm. Negative HIV-1 antibody but positive HIV-2 antibody results indicate the presence of HIV-2 infection. Together with a reactive initial HIV-1/-2 antigen and antibody screening test results, individuals with such results are presumed to have HIV-2 infection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a new whole blood specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. Reactive HIV-1 antibody but positive HIV-2 antibody results usually indicate the presence of HIV-2 infection with HIV-1 antibody cross-reactivity (eg, presence of only HIV-1 gp41 and/or gp160 band). However, such results may be rarely due to HIV-1 and HIV-2 coinfection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a new whole blood specimen for FHV2Q Indeterminate HIV-1 antibody but positive HIV-2 antibody results indicate the presence of HIV-2 infection, with probable cross-

reactivity of HIV-2 antibodies with HIV-1 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a new whole blood specimen for FHV2Q. For more information see HIV Prenatal Testing Algorithm, Including Follow-up of Reactive Rapid Serologic Test Results

Reference Values:
Negative

Clinical References: 1. Branson BM, Owen SM, Wesolowski LG, et al. Laboratory testing for the diagnosis of HIV infection: Updated recommendations. Centers for Disease Control and Prevention; June 27, 2014. Accessed December 27, 2024. Available at http://stacks.cdc.gov/view/cdc/23447 2. Malloch L, Kadivar K, Putz J, et al. Comparative evaluation of the Bio-Rad Geenius HIV-1/2 confirmatory assay and the Bio-Rad Multispot HIV-1/2 rapid test as an alternative differentiation assay for CLSI M53 algorithm-I. J Clin Virol. 2013;58 Suppl. 1:e85-e91 3. Montesinos I, Eykmans J, Delforge ML. Evaluation of the Bio-Rad Geenius HIV-1/2 test as confirmatory assay. J Clin Virol. 2014;60(4):399-401 4. Abbate I, Pergola C, Pisciotta M, et al. Evaluation in a clinical setting of the performances of a new rapid confirmatory assay for HIV-1/2 serodiagnosis. J Clin Virol. 2014;61(1):166-169 5. Duncan D, Duncan J, Kramer B, et al. An HIV diagnostic testing algorithm using the cobas HIV-1/HIV-2 qualitative assay for HIV type differentiation and confirmation. J Clin Microbiol. 2021;59(7):e03030-20. doi:10.1128/JCM.03030-20

HVDIP
601758

HIV-1 and HIV-2 Antibody Confirmation and Differentiation, Plasma

Clinical Information: AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS or AIDS-related complex and in asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various US Food and Drug Administration-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers' instructions for use.

Useful For: Confirmation and differentiation of HIV-1 and HIV-2 antibodies in plasma specimens that show reactive results with third-(HIV-1/-2 antibody only) and 4th-generation (HIV antigen and antibody) HIV serologic assays This test is not useful as a screening test for HIV infection in symptomatic or asymptomatic individuals. This test is not to be used as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative results for both HIV-1 and HIV-2 antibodies usually indicate the absence of HIV-1 and HIV-2 infection. However, in patients with reactive initial combined HIV-1/-2 antigen and antibody test results, such negative results do not rule-out acute or early HIV infection. HIP12 / HIV-1/HIV-2 RNA Detection, Plasma will be performed automatically per testing algorithm. Positive HIV-1 antibody but negative HIV-2 antibody results indicate the presence of HIV-1 infection. Together with reactive initial combined HIV-1/-2 antigen and antibody test results, individuals with such results

are presumed to have HIV-1 infection. HIVQN / HIV-1 RNA Detection and Quantification, Plasma will be performed automatically per testing algorithm. Positive HIV-1 antibody but indeterminate HIV-2 antibody results indicate the presence of HIV-1 infection with probable cross-reactivity of HIV-1 antibodies with HIV-2 antigens on the assay strip. HIVQN will be performed automatically per testing algorithm. Indeterminate HIV-1 antibody but negative HIV-2 antibody results suggest either very early HIV-1 infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV-1 antigens on the assay strip. HIP12 will be performed automatically per testing algorithm. Negative HIV-1 antibody but indeterminate HIV-2 antibody results may be due to acute HIV-1 infection, very early HIV-2 infection (in individuals with risk factors), or the presence of nonspecific cross-reactivity between the patients' specimens and HIV-2 antigens on the assay strip. HIP12 will be performed automatically per testing algorithm. Positive results for both HIV-1 and HIV-2 antibodies suggest probable presence of HIV-1 and HIV-2 coinfection. However, such results may be rarely due to either HIV-1 infection with HIV-2 antibody cross-reactivity or HIV-2 infection with HIV-1 antibody cross-reactivity (eg, absence of HIV-1 p24 and p31 bands). Verification of a first-time positive test result is recommended for the diagnosis of HIV infection. HIP12 will be performed automatically per testing algorithm. Indeterminate results for both HIV-1 and HIV-2 antibodies indicate either very early HIV infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV antigens on the assay strip. Nonspecific cross-reactivity may be due to recent non-HIV infections, hypergammaglobulinemic states, connective tissue disorders, or pregnancy (alloantibodies). HIP12 will be performed automatically per testing algorithm. Negative HIV-1 antibody but positive HIV-2 antibody results indicate the presence of HIV-2 infection. Together with a reactive initial HIV-1/-2 antigen and antibody screening test results, individuals with such results are presumed to have HIV-2 infection. Additional testing with a newly submitted whole blood specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR is recommended to verify and confirm the diagnosis of HIV-2 infection prior to initiating antiretroviral treatment. Reactive HIV-1 antibody but positive HIV-2 antibody results usually indicate the presence of HIV-2 infection with HIV-1 antibody cross-reactivity (eg, presence of only HIV-1 gp41 and/or gp160 band). However, such results may be rarely due to HIV-1 and HIV-2 coinfection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection by submitting a whole blood specimen for FHV2Q. Indeterminate HIV-1 antibody but positive HIV-2 antibody results indicate the presence of HIV-2 infection with probable cross-reactivity of HIV-2 antibodies with HIV-1 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection by submitting a whole blood specimen for FHV2Q. For more information see HIV Testing Algorithm (Fourth Generation Screening Assay), Including Neonatal Testing and Follow-up of Reactive Rapid Serologic Test Results.

Reference Values:

Negative

Clinical References: 1. Branson BM, Owen SM, Wesolowski LG, et al. Laboratory testing for the diagnosis of HIV infection: updated recommendations. Centers for Disease Control and Prevention; June 27, 2014. Accessed December 26, 2024. Available at https://stacks.cdc.gov/view/cdc/23447 2. Malloch L, Kadivar K, Putz J, et al. Comparative evaluation of the Bio-Rad Geenius HIV-1/2 confirmatory assay and the Bio-Rad Multispot HIV-1/2 rapid test as an alternative differentiation assay for CLSI M53 algorithm-I. J Clin Virol. 2013;58(Suppl 1):e85-e91 3. Montesinos I, Eykmans J, Delforge ML. Evaluation of the Bio-Rad Geenius HIV-1/2 test as confirmatory assay. J Clin Virol. 2014;60(4):399-401 4. Abbate I, Pergola C, Pisciotta M, et al. Evaluation in a clinical setting of the performances of a new rapid confirmatory assay for HIV-1/2 serodiagnosis. J Clin Virol. 2014;61(1):166-169 5. Centers for Disease Control and Prevention. 2018 Quick Reference Guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. CDC; January 2018. Accessed December 26, 2024. Available at https://stacks.cdc.gov/view/cdc/50872 6. Duncan D, Duncan J, Kramer B, et al. An HIV diagnostic testing algorithm using the cobas HIV-1/HIV-2 qualitative assay for HIV type differentiation and confirmation. J Clin Microbiol. 2021;59(7):e03030-20. doi:10.1128/JCM.03030-20

HVDSP
601759

HIV-1 and HIV-2 Antibody Confirmation and Differentiation, Prenatal, Plasma

Clinical Information: AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS or AIDS-related complex and in asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with an HIV-1/-2 antigen and/or antibody screening test, which may be performed by various US Food and Drug Administration approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers' instructions for use.

Useful For: Confirmation and differentiation of HIV-1 and HIV-2 antibodies in plasma specimens from prenatal patients who show reactive results with 3rd- (HIV-1/-2 antibody only) and 4th-generation (HIV antigen and antibody) HIV serologic assays This test is not useful as a screening test for HIV infection in symptomatic or asymptomatic individuals. This test should not be used as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative results for both HIV-1 and HIV-2 antibodies usually indicate the absence of HIV-1 and HIV-2 infection. However, in patients with reactive initial combined HIV-1/-2 antigen and antibody test results, such negative results do not rule-out acute or early HIV infection. HPP12 / HIV-1/HIV-2 RNA Detection, Prenatal, Plasma will be performed automatically per testing algorithm. Positive HIV-1 antibody but negative HIV-2 antibody results indicate the presence of HIV-1 infection. Together with reactive initial combined HIV-1/-2 antigen and antibody test results, individuals with such results are presumed to have HIV-1 infection. HIQNP / HIV-1 RNA Detection and Quantification, Prenatal, Plasma will be performed automatically per testing algorithm. Positive HIV-1 antibody but indeterminate HIV-2 antibody results indicate the presence of HIV-1 infection with probable cross-reactivity of HIV-1 antibodies with HIV-2 antigens on the assay strip. HIQNP will be performed automatically per testing algorithm. Indeterminate HIV-1 antibody but negative HIV-2 antibody results suggest either very early HIV-1 infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV-1 antigens on the assay strip. HPP12 will be performed automatically per testing algorithm. Negative HIV-1 antibody but indeterminate HIV-2 antibody results may be due to acute HIV-1 infection, very early HIV-2 infection (in individuals with risk factors), or the presence of nonspecific cross-reactivity between the patients' specimens and HIV-2 antigens on the assay strip. HPP12 will be performed automatically per testing algorithm. Positive results for both HIV-1 and HIV-2 antibodies suggest probable presence of HIV-1 and HIV-2 coinfection. However, such results may be rarely due to either an HIV-1 infection with HIV-2 antibody cross-reactivity or an HIV-2 infection with HIV-1 antibody cross-reactivity (eg, absence of HIV-1 p24 and p31 bands). Verification of a first-time positive test result is recommended for the diagnosis of HIV infection. HPP12 will be performed automatically per testing algorithm. Indeterminate results for both HIV-1 and HIV-2 antibodies indicate either very early HIV infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV antigens on the assay strip. Nonspecific cross-reactivity may be due to recent non-HIV infections, hypergammaglobulinemic states, connective tissue disorders, or pregnancy (alloantibodies). HPP12 will be performed automatically per testing algorithm. Negative HIV-1 antibody but positive HIV-2 antibody results indicate the presence of HIV-2 infection. Together with a reactive initial HIV-1/-2 antigen and antibody screening test results, individuals with such results are

presumed to have HIV-2 infection. Additional testing with a newly submitted whole blood specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR is recommended to verify and confirm the diagnosis of HIV-2 infection prior to initiating antiretroviral treatment. Reactive HIV-1 antibody but positive HIV-2 antibody results usually indicate the presence of HIV-2 infection with HIV-1 antibody cross-reactivity (eg, presence of only HIV-1 gp41 and/or gp160 band). However, such results may be rarely due to HIV-1 and HIV-2 coinfection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection by submitting a whole blood specimen for FHV2Q. Indeterminate HIV-1 antibody but positive HIV-2 antibody results indicate the presence of HIV-2 infection, with probable cross-reactivity of HIV-2 antibodies with HIV-1 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection by submitting a whole blood specimen for FHV2Q. The following algorithms are available: -HIV Prenatal Testing Algorithm, Including Follow-up of Reactive Rapid Serologic Test Results -HIV Testing Algorithm (Fourth Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results

Reference Values:
Negative

Clinical References: 1. Branson BM, Owen SM, Wesolowski LG, et al. Laboratory testing for the diagnosis of HIV infection: Updated recommendations. Centers for Disease Control and Prevention; June 27, 2014. Accessed December 23, 2024. Available at https://stacks.cdc.gov/view/cdc/23447 2. Malloch L, Kadivar K, Putz J, et al. Comparative evaluation of the Bio-Rad Geenius HIV-1/2 confirmatory assay and the Bio-Rad Multispot HIV-1/2 rapid test as an alternative differentiation assay for CLSI M53 algorithm-I. J Clin Virol. 2013;58(Suppl. 1):e85-e91 3. Montesinos I, Eykmans J, Delforge ML. Evaluation of the Bio-Rad Geenius HIV-1/2 test as confirmatory assay. J Clin Virol. 2014;60(4):399-401 4. Abbate I, Pergola C, Pisciotta M, et al. Evaluation in a clinical setting of the performances of a new rapid confirmatory assay for HIV-1/2 serodiagnosis. J Clin Virol. 2014;61(1):166-169 5. Centers for Disease Control and Prevention and Association of Public Health Laboratories. 2018 Quick Reference Guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. January 2018. Accessed December 23, 2024. Available at https://stacks.cdc.gov/view/cdc/50872 6. Duncan D, Duncan J, Kramer B, et al. An HIV diagnostic testing algorithm using the cobas HIV-1/HIV-2 Qualitative Assay for HIV type differentiation and confirmation. J Clin Microbiol. 2021; 59(7):e03030-20. doi:10.1128/JCM.03030-20

HIVDI
62421

HIV-1 and HIV-2 Antibody Confirmation and Differentiation, Serum

Clinical Information: AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS or AIDS-related complex and in asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various US Food and Drug Administration-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers' instructions for use.

Useful For: Confirmation and differentiation of HIV-1 and HIV-2 antibodies in serum specimens that show reactive results with third-(HIV-1/-2 antibody only) and 4th-generation (HIV antigen and antibody) HIV serologic assays Confirmation and differentiation of HIV-1 and HIV-2 antibodies in cadaveric blood or hemolyzed serum specimens that show reactive results with initial HIV serologic screening assays This test is not useful as a screening test for HIV infection in symptomatic or asymptomatic individuals. It is not to be used as a screening or confirmatory test for blood donor specimens. This test is not useful for maternal or newborn HIV screening for specimens originating in New York State.

Interpretation: Negative results for both HIV-1 and HIV-2 antibodies usually indicate the absence of HIV-1 and HIV-2 infection. However, negative results do not rule-out acute or early HIV infection in patients with reactive initial combined HIV-1/-2 antigen and antibody test results. HIS12 / HIV-1/HIV-2 RNA Detection, Serum will be performed automatically per testing algorithm. Positive HIV-1 antibody but negative HIV-2 antibody results indicate the presence of HIV-1 infection. Together with reactive initial combined HIV-1/-2 antigen and antibody test results, individuals with these results are presumed to have HIV-1 infection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection. Additional testing with a newly submitted plasma specimen for HIVQN / HIV-1 RNA Detection and Quantification, Plasma. HIV-1 RNA quantification in plasma is recommended to determine the baseline HIV-1 viral load prior to initiating antiretroviral treatment. Positive HIV-1 antibody but indeterminate HIV-2 antibody results indicate the presence of HIV-1 infection with probable cross-reactivity of HIV-1 antibodies with HIV-2 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection by submitting a plasma specimen for HIV-1 RNA quantification (HIVQN). Indeterminate HIV-1 antibody but negative HIV-2 antibody results suggest either very early HIV-1 infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patient serum specimen and HIV-1 antigens on the assay strip. HIS12 will be performed automatically per testing algorithm. Negative HIV-1 antibody but indeterminate HIV-2 antibody results may be due to acute HIV-1 infection, very early HIV-2 infection (in individuals with risk factors), or the presence of nonspecific cross-reactivity between the patient serum specimen and HIV-2 antigens on the assay strip. HIS12 will be performed automatically per testing algorithm. Positive results for both HIV-1 and HIV-2 antibodies suggest the probable presence of HIV-1 and HIV-2 coinfection. However, such results may rarely be due to either HIV-1 infection with HIV-2 antibody cross-reactivity or HIV-2 infection with HIV-1 antibody cross-reactivity (eg, absence of HIV-1 p24 and p31 bands). Verification of a first-time positive test result is recommended for the diagnosis of HIV infection. HIS12 will be performed automatically per testing algorithm. Indeterminate results for both HIV-1 and HIV-2 antibodies indicate either very early HIV infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV antigens on the assay strip. Nonspecific cross-reactivity may be due to recent non-HIV infections, hypergammaglobulinemic states, connective tissue disorders, or pregnancy (alloantibodies). HIS12 will be performed automatically per testing algorithm. Negative HIV-1 antibody but positive HIV-2 antibody results indicate the presence of HIV-2 infection. Together with a reactive initial HIV-1/-2 antigen and antibody screening test results, individuals with such results are presumed to have HIV-2 infection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection by submitting a new whole blood specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. Reactive HIV-1 antibody but positive HIV-2 antibody results usually indicate the presence of HIV-2 infection with HIV-1 antibody cross-reactivity (eg, presence of only HIV-1 gp41 and/or gp160 band). However, such results may rarely be due to HIV-1 and HIV-2 coinfection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection by submitting a new whole blood specimen for FHV2Q. Indeterminate HIV-1 antibody but positive HIV-2 antibody results indicate the presence of HIV-2 infection with probable cross-reactivity of HIV-2 antibodies with HIV-1 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection by submitting a new whole blood specimen for FHV2Q. For more information see HIV Testing Algorithm (Fourth Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: Updated recommendations. June 27, 2014. Accessed December 23, 2024. Available at https://stacks.cdc.gov/view/cdc/23447 2. Malloch L, Kadivar K, Putz J, et al. Comparative evaluation of the Bio-Rad Geenius HIV-1/2 confirmatory assay and the Bio-Rad Multispot HIV-1/2 rapid test as an alternative differentiation assay for CLSI M53 algorithm-I. J Clin Virol. 2013;58(Suppl 1):e85-e91 3. Montesinos I, Eykmans J, Delforge ML. Evaluation of the Bio-Rad Geenius HIV-1/2 test as confirmatory assay. J Clin Virol. 2014;60(4):399-401 4. Abbate I, Pergola C, Pisciotta M, et al. Evaluation in a clinical setting of the performances of a new rapid confirmatory assay for HIV-1/2 serodiagnosis. J Clin Virol. 2014;61(1):166-169 5. Duncan D, Duncan J, Kramer B, et al. An HIV diagnostic testing algorithm using the cobas HIV-1/HIV-2 qualitative assay for HIV type differentiation and confirmation. J Clin Microbiol. 2021;59(7):e03030-20. doi:10.1128/JCM.03030-20

HV1CM
60357

HIV-1 and HIV-2 Antibody Screen for Hemolyzed Specimens, Serum

Clinical Information: Epidemiological data indicate that AIDS is caused by at least 2 types of HIV. The first virus, HIV-1, has been isolated from patients with AIDS or AIDS-related complex and from asymptomatic infected individuals at high risk for AIDS. HIV-1 is transmitted by sexual contact, exposure to infected blood or blood products, or from an infected mother to her fetus or infant. A second HIV virus, HIV-2, was isolated from patients in West Africa in 1986. HIV-2 appears to be endemic only in West Africa, but it also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detected until 6 to 12 weeks following exposure and are almost always detected by 12 months. Antibodies may fall into undetectable levels in the terminal stage of AIDS. For more information see HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results.

Useful For: Screening cadaveric or hemolyzed serum specimens for HIV-1 and/or HIV-2 infection in nonsymptomatic patients with or without risk factors for HIV infection This test is not offered as a screening or confirmatory test for blood donor specimens.

Interpretation: A reactive HIV-1/-2 antibody screen result obtained by enzyme immunoassay (EIA) suggests the presence of HIV-1 and/or HIV-2 infection. However, it does not differentiate between HIV-1 and HIV-2 antibody reactivity. Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV antibody confirmation/differentiation test (automatically reflexed on all samples with reactive screen test results at an additional charge). All presumptive antibody-positive test results should be verified by submitting a second serum specimen for retesting. A negative HIV-1/-2 antibody EIA screen result usually indicates the absence of HIV-1 or HIV-2 infection. However, for specimens reactive by the rapid HIV antibody tests, confirmatory testing is recommended, even if the EIA results are negative.

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention (CDC), Association of Public Health Laboratories: Laboratory testing for the diagnosis of HIV infection. CDC; Updated June 27, 2014. Accessed December 23, 2024. Available at: stacks.cdc.gov/view/cdc/23447 2. Centers for Disease

Control and Prevention (CDC), Association of Public Health Laboratories: 2018 Quick reference guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. CDC; Updated January 2018. Accessed December 23, 2024. Available at https://stacks.cdc.gov/view/cdc/50872 3. Hariri S, McKenna MT: Epidemiology of human immunodeficiency virus in the United States. Clin Microbiol Rev. 2007 Jul;20(3):478-4884 4. Owen SM, Yang C, Spira T, et al: Alternative algorithms for human immunodeficiency virus infection diagnosis using tests that are licensed in the United States. J Clin Microbiol. 2008;46(5):1588-1595

HIVDX
48392

HIV-1 and HIV-2 Antigen and Antibody Diagnostic Evaluation, Plasma

Clinical Information: AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS or AIDS-related complex and in asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed, but HIV p24 antigen should be detectable and yield reactive results with the HIV antigen-antibody combination detection assays. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with an HIV-1/-2 antigen and/or antibody screening test, which may be performed by various US Food and Drug Administration approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods.

Useful For: Detecting HIV-1 and HIV-2 infection in symptomatic patients older than 2 years Follow-up testing of symptomatic individuals with reactive rapid HIV test results This test should not be used as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative HIV-1/-2 antigen and antibody screening test results usually indicate the absence of HIV-1 and HIV-2 infection. However, such negative results do not rule-out acute HIV infection. If acute HIV-1 or HIV-2 infection is suspected, detection of HIV RNA (HIP12 / HIV-1/HIV-2 RNA Detection, Plasma) is recommended. Reactive HIV-1/-2 antigen and antibody screening test results suggest the presence of HIV-1 and/or HIV-2 infection, but it is not diagnostic for HIV infection and should be considered preliminary. A reactive result does not differentiate among reactivity with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody. Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV antibody confirmation/differentiation test (automatically added to all samples with reactive screen test results at an additional charge). All initially positive supplemental or confirmatory HIV test results (by serologic or molecular test methods) should be verified by submitting a second plasma specimen for repeat testing. Such positive HIV test results are required under laws in many states in the United States to be reported to the departments of health of the respective states where the patients reside. For more information see HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results

Reference Values:
Negative

Clinical References:

HIVDS
617825

HIV-1 and HIV-2 Antigen and Antibody Diagnostic Evaluation, Serum

Clinical Information:

Useful For: Detecting HIV-1 and HIV-2 infection in symptomatic patients older than 2 years Follow-up testing of symptomatic individuals with reactive rapid HIV test results This test should not be used as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative HIV-1/-2 antigen and antibody screening test results usually indicate the absence of HIV-1 and HIV-2 infection. However, such negative results do not rule-out acute HIV infection. If acute HIV-1 or HIV-2 infection is suspected, detection of HIV RNA (HIS12 / HIV-1/HIV-2 RNA Detection, Serum) is recommended. Reactive HIV-1/-2 antigen and antibody screening test results suggest the presence of HIV-1 and/or HIV-2 infection, but it is not diagnostic for HIV infection and should be considered preliminary. A reactive result does not differentiate among reactivity with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody. Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV antibody confirmation/differentiation test (automatically added to all samples with reactive screen test results at an additional charge). All initially positive supplemental or confirmatory HIV test results (by serologic or molecular test methods) should be verified by submitting a plasma specimen for repeat testing. Such positive HIV test results are required under laws in many states in the United States to be reported to the departments of health of the respective states where the patients reside. For more information see HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results.

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention. 2018 Quick reference guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. CDC; January 2018. Accessed October 16, 2023. Available at https://stacks.cdc.gov/view/cdc/50872 2. Centers for Disease Control and Prevention. Technical update: Use of the Determine HIV 1/2 Ag/Ab combo test with serum or plasma in the laboratory algorithm for HIV diagnosis. CDC; October 4, 2017. Accessed October 16, 2023. Available at https://stacks.cdc.gov/view/cdc/48472 3. Muhlbacher A, Sauleda S, Piron M, et al. A multicentre evaluation of the Elecsys HIV Duo assay. J Clin Virol 2019;112:45-50 4. Duncan D, Duncan J, Kramer B, et al. An HIV diagnostic testing algorithm using the cobas HIV-1/HIV-2 Qualitative Assay for HIV type differentiation and confirmation. J Clin Microbiol. 2021;59(7):e03030-20. doi:10.1128/JCM.03030-20

HVCOP
48341

HIV-1 and HIV-2 Antigen and Antibody Routine Screen, Plasma

Clinical Information: AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS or AIDS-related complex and in asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed, but HIV p24 antigen should be detectable and yield reactive results with the HIV antigen-antibody combination detection assays. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with an HIV-1/-2 antigen and/or antibody screening test, which may be performed by

various US Food and Drug Administration-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods.

Useful For: Screening for HIV-1 and HIV-2 infection in nonsymptomatic, nonpregnant individuals older than 2 years This test should not be used as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative HIV-1/-2 antigen and antibody screening test results usually indicate absence of HIV-1 and HIV-2 infection. However, such negative results do not rule out acute HIV infection. If acute HIV-1 or HIV-2 infection is suspected, detection of HIV RNA (HIP12 / HIV-1/HIV-2 RNA Detection, Plasma) is recommended. Reactive HIV-1/-2 antigen and antibody screening test results suggest the presence of HIV-1 and/or HIV-2 infection, but it is not diagnostic for HIV infection and should be considered preliminary. A reactive result does not differentiate among reactivity with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody. Diagnosis of HIV infection must be based on results of supplemental tests, such as the HIV antibody confirmation/differentiation test (automatically added to all samples with reactive screen test results at an additional charge). All initially positive supplemental or confirmatory HIV test results (by serologic or molecular test methods) should be verified by submitting a second plasma specimen for repeat testing. Such positive HIV test results are required under laws in many states in the United States to be reported to the departments of health of the respective states where the patients reside. For more information see HIV Testing Algorithm (Fourth Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention: 2018 Quick Reference Guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. CDC; January 2018. Accessed October 16, 2023. Available at https://stacks.cdc.gov/view/cdc/50872 2. Centers for Disease Control and Prevention: Technical update: Use of the Determine HIV 1/2 Ag/Ab combo test with serum or plasma in the laboratory algorithm for HIV diagnosis. CDC; October 4, 2017. Accessed October 16, 2023. Available at https://stacks.cdc.gov/view/cdc/48472 3. Muhlbacher A, Sauleda S, Piron M, et al. A multicentre evaluation of the Elecsys HIV Duo assay. J Clin Virol. 2019;112:45-50 4. Duncan D, Duncan J, Kramer B, et al. An HIV diagnostic testing algorithm using the cobas HIV-1/HIV-2 qualitative assay for HIV type differentiation and confirmation. J Clin Microbiol. 2021;59(7):e03030-20. doi:10.1128/JCM.03030-20

HIVSS
617826

HIV-1 and HIV-2 Antigen and Antibody Routine Screen, Serum

Clinical Information: AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS or AIDS-related complex, and in asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed, but HIV p24 antigen should be detectable and yield reactive results with the HIV antigen-antibody combination detection assays. Routine serologic screening of patients at risk for

HIV-1 or HIV-2 infection usually begins with an HIV-1/-2 antigen and/or antibody screening test, which may be performed by various US Food and Drug Administration approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods.

Useful For: Screening for HIV-1 and HIV-2 infection in nonsymptomatic, nonpregnant individuals older than 2 years This test should not be used as a screening or confirmatory test for blood donor specimens.

Interpretation: Negative HIV-1/-2 antigen and antibody screening test results usually indicate absence of HIV-1 and HIV-2 infection. However, such negative results do not rule-out acute HIV infection. If acute HIV-1 or HIV-2 infection is suspected, detection of HIV RNA (HIS12 / HIV-1/HIV-2 RNA Detection, Serum) is recommended. Reactive HIV-1/-2 antigen and antibody screening test results suggest the presence of HIV-1 and/or HIV-2 infection, but it is not diagnostic for HIV infection and should be considered preliminary. A reactive result does not differentiate among reactivity with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody. Diagnosis of HIV infection must be based on results of supplemental tests, such as the HIV antibody confirmation/differentiation test (automatically added to all samples with reactive screen test results at an additional charge). All initially positive supplemental or confirmatory HIV test results (by serologic or molecular test methods) should be verified by submitting a plasma specimen for repeat testing. Such positive HIV test results are required under laws in many states in the United States to be reported to the departments of health of the respective states where the patients reside. For more information, see HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Follow-up of Reactive Rapid Serologic Test Results.

Reference Values:
Negative

Clinical References:

HIVDR
616052

HIV-1 Genotypic Drug Resistance to Reverse Transcriptase, Protease, and Integrase Inhibitors, Plasma

Clinical Information: Antiviral resistance may compromise the efficacy of antiretroviral therapy (ART) in patients receiving such therapy for HIV1 infection. When combination therapy fails, detection and analysis of antiviral drug resistance-associated viral genotypic mutations can guide necessary changes to ART to suppress viral replication (ie, reduce viral load), thereby improving patient outcome. HIV-1 is an RNA virus that infects cells and is then converted to complementary DNA by the action of the viral reverse transcriptase (RT) gene product. RT has little proofreading capacity and therefore, incorporates errors in the proviral DNA. These errors are transcribed into infectious viral particles when the proviral DNA is transcribed into RNA. Similarly, the enzyme protease catalyzes a polyprotein to produce peptides necessary for active viral replication. Although ART (combination of nucleoside and nonnucleoside reverse-transcriptase inhibitors, protease inhibitors, and/or integrase strain transfer inhibitors) may be effective in reducing the viral load, genotypic mutations arising in the drug-targeted HIV-1 genome due to selective pressure from antiviral therapy will result in antiviral resistance that may compromise such therapy. Amplification and analysis of drug-targeted HIV-gene sequence allows identification of changes in nucleotide bases and associated amino acid codons that may cause antiviral drug resistance. Such genotypic changes are deemed as variants by comparing the sequence data of the patient's HIV strain to those of a wild-type HIV strain. The significance of these genotypic mutations in relation to antiviral resistance is then determined by a set of interpretive rules developed by a consensus panel of leading experts in the field of HIV-1 resistance. Relevant data presented at a recognized scientific conference or published in peer-reviewed journals are considered by the consensus panel in developing these rules.

When necessary, reliable unpublished drug resistance data known to consensus panel members may be considered in the process. The interpretive rules are updated by the consensus panel annually after reviewing newly published data on HIV-1 genotypic drug resistance mutations.

Useful For: Identifying HIV-1 genotypic mutations associated with resistance to nucleotide and non-nucleoside reverse-transcriptase inhibitors, protease inhibitors, and integrase strain transfer inhibitors Guiding initiation or change of combination antiretroviral therapy in individuals, including children, with HIV-1 infection

Interpretation: Detectable HIV-1 genotypic mutations conferring resistance to an antiviral drug are reported as amino acid codon changes (eg, M184V) resulting from the nucleic acid base alterations, according to the interpretative algorithm of the Stanford HIV Database program. The codon mutations are categorized and interpreted in relation to previously published data of phenotypic antiviral susceptibility tests on virus that harbor such mutations. Each codon mutation is assigned a drug penalty score. The total score generated from all mutations relevant to the specific antiviral drug is used to estimate the level of resistance to that drug. These interpretive rules may be updated periodically by the Stanford HIV Database Team after reviewing newly published data on HIV-1 genotypic drug resistance-associated codon mutations. Susceptible (SUSC) indicates that the codon mutations present in patient's HIV-1 strain have not been associated with resistance to the specific drug (Stanford HIVdb total score 0 to 9). Potential Low-Level Resistance (PLR) indicates that codon mutations detected have been associated with possible reduction in susceptibility to the specific drug (Stanford HIVdb score 10 to 14). Low-Level Resistance (LR) indicates that codon mutations detected have been associated with reduction in susceptibility to the specific drug (Stanford HIVdb score 15 to 29). Intermediate Resistance (IR) indicates that codon mutations detected have been associated with reduction in susceptibility to the specific drug (Stanford HIVdb score 30 to 59). High-level Resistant (HR) indicates that codon mutations detected have been associated with maximum reduction in susceptibility to the specific drug (Stanford HIVdb > or = 60). Unable to genotype indicates that the sequence data obtained are of poor quality to determine the presence or absence of resistance-associated codon mutations in the patient's HIV-1 strain. Probable causes of such poor sequence data include polymorphism in the region of the sequencing primers interfering with primer binding and subsequent sequencing reaction, or low viral load (ie, <1000 copies/mL). Inconclusive indicates inability of the assay to reliably determine antiviral resistance because of the presence of polymerase chain reaction inhibitors or ambiguous or incomplete viral target sequences generated from the assay.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Weber J, Volkova I, Sahoo MK, Tzou PL, Shafer RW, Pinsky BA. Prospective evaluation of the Vela Diagnostics next-generation sequencing platform for HIV-1 genotypic resistance testing. J Mol Diagn. 2019;21(6): 961-970. doi:10.1016/j.jmoldx.2019.06.003 2. Avila-Rios S, Parkin N, Swanstrom R, et al. Next-generation sequencing for HIV drug resistance testing: laboratory, clinical, and implementation considerations. Viruses. 2020;12(6):617.doi: 10.3390/v12060617 3. Raymond S, Nicot F, Abravanel F, et al: Performance evaluation of the Vela Dx Sentosa next-generation sequencing system for HIV-1 DNA genotypic resistance. J Clin Virol. 2020;122:104229. doi:10.1016/j.jcv.2019.104229 4. Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. US Department of Health and Human Services. Updated September 12, 2024. Accessed March 27, 2025. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf

HIVQN 113581 HIV-1 RNA Detection and Quantification, Plasma

Clinical Information: Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS or AIDS-related complex, and from asymptomatic infected individuals at high-risk for AIDS. Accounting for more than 99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa, and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of individuals living with HIV-1. HIV serologic tests may be unreliable for infants born to HIV-infected mothers. In infants up to 2 years, positive serologic test results can be due to the presence of maternal HIV antibodies. Therefore, the US Department of Health and Human Services Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children recommends the use of HIV RNA or proviral DNA tests for the detection of HIV infection in infants born to HIV-infected mothers.

Useful For: Quantifying plasma HIV-1 RNA levels (viral load) in individuals living with HIV-1: -Before initiating antiretroviral therapy to obtain baseline viral load -Who may have developed HIV-1 drug resistance while on antiretroviral therapy -Who may be noncompliant with antiretroviral therapy Monitoring HIV-1 disease progression before or during antiretroviral drug therapy

Interpretation: This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA in the plasma specimen tested. A result of "<20 copies/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load below 20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, <3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ">10,000,000 copies/mL" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level" indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For monitoring a patient's response to antiretroviral therapy, the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load above 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-drug interactions, and patient adherence.

Reference Values:
Undetected

Clinical References: 1. Branson BM, Owen SM, Wesolowski LG, et al. Laboratory testing for the diagnosis of HIV infection: Updated recommendations. Centers for Disease Control and Prevention; June 27, 2014. Accessed January 29, 2025. Available at http://stacks.cdc.gov/view/cdc/23447 2. Gunthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA Panel. JAMA. 2016;316(2):191-210 3. Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. US Department of Health and Human Services; October 17,

2017. Updated September 12, 2024. Accessed January 29, 2025. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf

HIQNP
65567

HIV-1 RNA Detection and Quantification, Prenatal, Plasma

Clinical Information: Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS or AIDS-related complex, and from asymptomatic infected individuals at high-risk for AIDS. Accounting for more than 99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of HIV-1-infected patients.

Useful For: Diagnosis of HIV-1 infection in pregnant individuals with acute or early HIV-1 infection Quantifying plasma HIV-1 RNA levels (viral load) in pregnant individuals living with HIV-1: -Before initiating anti-HIV-1 drug therapy (baseline viral load) -Who may have developed HIV-1 drug resistance while on anti-HIV-1 therapy -Who may be noncompliant with anti-HIV-1 drug therapy Monitoring HIV-1 disease progression before or during antiretroviral drug therapy in pregnant individuals

Interpretation: This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA in the plasma specimen tested. A result of "<20 copies/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load less than 20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, <3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ">10,000,000 copies/mL" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level" indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patient's response to antiretroviral therapy, the United States Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load of above 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-drug interactions, and patient adherence.

Reference Values:
Undetected

Clinical References: 1. Branson BM, Owen SM, Wesolowski LG, et al. Laboratory testing for the diagnosis of HIV infection: Updated recommendations. Centers for Disease Control and Prevention; June 27, 2014. Accessed January 28, 2025. Available at http://stacks.cdc.gov/view/cdc/23447 2.

Gunthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA Panel. JAMA. 2016;316(2):191-210 3. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission: Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. US Department of Health and Human Services. October 26, 2016. Updated December 19, 2024. Accessed January 28, 2025. Available at https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new-guidelines

PSHIV
65819

HIV-1 RNA Patient Source, Plasma

Clinical Information: Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS or AIDS-related complex, and from asymptomatic infected individuals at high-risk for AIDS. Accounting for more than 99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of individuals living with HIV-1. HIV serologic tests may be unreliable for infants born to HIV-infected mothers. In infants up to 2 years, positive serologic test results can be due to the presence of maternal HIV antibodies. Therefore, the US Department of Health and Human Services Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children recommends the use of HIV RNA or proviral DNA tests for the detection of HIV infection in infants born to HIV-infected mothers.

Useful For: Detection and diagnosis of HIV-1 infection in an acutely or early infected individual (including infants of <2 years of age) who is the source of blood or body fluid in an occupational exposure event

Interpretation: This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA in the plasma specimen tested. A result of "<20 copies/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load below 20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, <3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ">10,000,000 copies/mL" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level" indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patient's response to antiretroviral therapy, the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load above 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay

Reference Values:
Undetected

Clinical References: 1. Kuhar DT, Henderson DK, Struble KA, et al. Updated U.S. Public Health Service Guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2013. Updated May 23, 2018. Accessed January 28, 2025. Available at http://stacks.cdc.gov/view/cdc/20711 2. Branson BM, Owen SM, Wesolowski LG, et al. Laboratory testing for the diagnosis of HIV infection: Updated recommendations. Centers for Disease Control and Prevention; June 27, 2014. Accessed January 28, 2025. Available at http://stacks.cdc.gov/view/cdc/23447 3. Gunthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA Panel. JAMA. 2016;316(2):191-210 4. Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. U.S. Department of Health and Human Services. Updated September 12, 2024. Accessed January 28, 2025. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf

HIQDR
616917

HIV-1 RNA Quantification with Reflex to Genotypic Drug Resistance to Reverse Transcriptase, Protease, and Integrase Inhibitors, Plasma

Clinical Information: Human immunodeficiency virus-1 (HIV-1) is an RNA virus that infects human host cells and is then converted to complementary DNA by the action of viral reverse transcriptase. HIV-1 is the causative agent of AIDS, a severe, life-threatening condition, and the virus has been isolated from asymptomatic, infected individuals at high-risk for AIDS. Accounting for over 99% of HIV infections in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast feeding. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of HIV-1-infected patients. Studies have identified a number of mutations associated with antiviral resistance. Genotypic analysis allows identification of nucleotide changes associated with HIV drug resistance. When combination therapy fails, genotyping for drug resistance mutations may help direct appropriate changes in antiretroviral therapy and may result in at least a short-term benefit, as evidenced by viral load reduction.

Useful For: Quantifying plasma HIV-1 RNA levels (viral load) in individuals (including children) with known HIV-1 infection, followed by identification of HIV-1 genotypic mutations associated with resistance to nucleotide and non-nucleoside reverse-transcriptase inhibitors protease inhibitors, and integrase strain transfer inhibitors Guiding initiation or change of combination antiretroviral therapy in individuals, including children, with HIV-1 infection

Interpretation: HIV-1 RNA Quantification: This assay has a HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL) in plasma. An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA within the plasma specimen. A result of "<20 copies/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load below 20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, <3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive result). A result of ">10,000,000" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA

above this level" indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patient's response to antiretroviral therapy, the US Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load of greater than 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-to-drug interactions, and patient adherence. If the viral load is greater than or equal to 1000 copies/mL, genotypic antiviral drug resistance mutation analysis is performed automatically at an additional charge. Genotypic Drug Resistance: Codon sequences of the reverse transcriptase, protease and integrase coding region of the HIV-1 genome are compared with those in the Stanford HIV database of known antiretroviral resistance-associated mutations determined with the assay software application. Results are provided on the interpretation of those codon changes associated with resistance to individual antiretroviral drugs. Susceptible (SUSC) indicates that the codon mutations present in patient's HIV-1 strain have not been associated with resistance to the specific drug (Stanford HIVdb total score 0 to 9). Potential Low-Level Resistance (PLR) indicates that codon mutations detected have been associated with possible reduction in susceptibility to the specific drug (Stanford HIVdb score 10 to 14). Low-Level Resistance (LR) indicates that codon mutations detected have been associated with reduction in susceptibility to the specific drug (Stanford HIVdb score 15 to 29). Intermediate Resistance (IR) indicates that codon mutations detected have been associated with reduction in susceptibility to the specific drug (Stanford HIVdb score 30 to 59). High-level Resistant (HR) indicates that codon mutations detected have been associated with maximum reduction in susceptibility to the specific drug (Stanford HIVdb > or =60). Unable to genotype indicates that the sequence data obtained are of poor quality to determine the presence or absence of resistance-associated codon mutations in the patient's HIV-1 strain. Probable causes of such poor sequence data include polymorphism in the region of the sequencing primers interfering with primer binding and subsequent sequencing reaction, or low viral load (ie, <1000 copies/mL). Inconclusive indicates inability of the assay to reliably determine antiviral resistance because of the presence of polymerase chain reaction inhibitors or ambiguous or incomplete viral target sequences generated from the assay.

Reference Values:
Undetected

Clinical References:

HPP12
615817

HIV-1/HIV-2 RNA Detection Prenatal, Plasma

Clinical Information: Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS or AIDS-related complex, and from asymptomatic infected individuals at high-risk for AIDS. Accounting for more than 99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa, and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in overall genomic structure and ability to cause AIDS, but viral load tends to lower in HIV-2 than HIV-1 infection.

Useful For: Diagnosis of HIV-1 and/or HIV-2 infection in pregnant individuals with indeterminate or inconclusive HIV serologic test results Diagnosis of HIV-1 and/or HIV-2 infection in pregnant individuals in the acute or early phase of HIV-1 and/or HIV-2 infection

Interpretation: A "Detected" result indicates that the presence of RNA of the specific virus in the

plasma specimen tested, consistent with the presence of this viral infection. For example, a "Detected" result for HIV-1 RNA by this assay is indicative of HIV-1 infection in the tested individual. A follow-up plasma specimen should be collected from this individual to both verify the diagnosis and quantify the HIV RNA prior to initiation of antiviral therapy. An "Undetected" result indicates that the assay was unable to detect RNA of the specific virus in the plasma specimen tested. An "Inconclusive" result indicates that the presence or absence of viral RNA could not be determined with certainty after repeat testing in the laboratory, possibly due to presence of inhibitory substances in the plasma specimen tested. Collection of a new plasma for testing is recommended.

Reference Values:
Undetected

Clinical References: 1. Centers for Disease Control and Prevention. 2018 Quick reference guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. CDC; January 2018. Accessed July 22, 2024. Available at https://stacks.cdc.gov/view/cdc/50872 2. Branson BM, Owen SM, Wesolowski LG, et al. Laboratory testing for the diagnosis of HIV infection: Updated recommendations. Centers for Disease Control and Prevention; June 27, 2014. Accessed July 22, 2024. Available at https://stacks.cdc.gov/view/cdc/23447 3. Duncan D, Duncan J, Kramer B, et al. An HIV diagnostic testing algorithm using the cobas HIV-1/HIV-2 Qualitative Assay for HIV type differentiation and confirmation. J Clin Microbiol. 2021;59(7):e03030-20. doi:10.1128/JCM.03030-20 4. U.S. Department of Health and Human Services, Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs during pregnancy and interventions to reduce perinatal HIV transmission in the United States. HHS; January 31, 2023. Accessed July 22, 2024. Available at https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new

HPS12
615818

HIV-1/HIV-2 RNA Detection Prenatal, Serum

Clinical Information: Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS or AIDS-related complex, and from asymptomatic infected individuals at high-risk for AIDS. Accounting for more than 99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa, and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in overall genomic structure and ability to cause AIDS, but viral load tends to lower in HIV-2 than HIV-1 infection.

Useful For: Diagnosis of HIV-1 and/or HIV-2 infection in pregnant individuals with indeterminate or inconclusive HIV serologic test results Diagnosis of HIV-1 and/or HIV-2 infection in pregnant individuals in the acute or early phase of HIV-1 and/or HIV-2 infection

Interpretation: A "Detected" result indicates that the presence of RNA of the specific virus in the plasma specimen tested, consistent with the presence of this viral infection. For example, a "Detected" result for HIV-1 RNA by this assay is indicative of HIV-1 infection in the tested individual. A follow-up plasma specimen should be collected from this individual to both verify the diagnosis and quantify the HIV RNA prior to initiation of antiviral therapy. An "Undetected" result indicates that the assay was unable to detect RNA of the specific virus in the plasma specimen tested. An "Inconclusive" result indicates that the presence or absence of viral RNA could not be determined with certainty after repeat testing in the laboratory, possibly due to presence of inhibitory substances in the plasma specimen tested. Collection of a new plasma for testing is recommended.

Reference Values:
Undetected

Clinical References: 1. Centers for Disease Control and Prevention. 2018 Quick reference guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. CDC; January 2018. Accessed July 22, 2024. Available at https://stacks.cdc.gov/view/cdc/50872 2. Branson BM, Owen SM, Wesolowski LG, et al. Laboratory testing for the diagnosis of HIV infection: Updated recommendations. Centers for Disease Control and Prevention; June 27, 2014. Accessed July 22, 2024. Available at https://stacks.cdc.gov/view/cdc/23447 3. Duncan D, Duncan J, Kramer B, et al. An HIV diagnostic testing algorithm using the cobas HIV-1/HIV-2 Qualitative Assay for HIV type differentiation and confirmation. J Clin Microbiol. 2021;59(7):e03030-20. doi:10.1128/JCM.03030-20 4. U.S. Department of Health and Human Services, Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission: Recommendations for the use of antiretroviral drugs during pregnancy and interventions to reduce perinatal HIV transmission in the United States. HHS; January 31, 2024. Accessed July 22, 2024. Available at https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new

HIP12
615815

HIV-1/HIV-2 RNA Detection, Plasma

Clinical Information: Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS or AIDS-related complex, and from asymptomatic infected individuals at high-risk for AIDS. Accounting for more than 99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa, and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in overall genomic structure and ability to cause AIDS, but viral load tends to lower in HIV-2 than HIV-1 infection.

Useful For: Diagnosis of HIV-1 and/or HIV-2 infection in individuals with indeterminate or inconclusive HIV serologic test results Diagnosis of HIV-1 and/or HIV-2 infection in individuals with acute or early HIV-1 and/or HIV-2 infection Diagnosis of HIV-1 and/or HIV-2 infection in infants under 18 months of age who are born to HIV-infected mothers

Interpretation: A "Detected" result indicates that the presence of RNA of the specific virus in the plasma specimen tested, consistent with the presence of this viral infection. For example, a "Detected" result for HIV-1 RNA by this assay is indicative of HIV-1 infection in the tested individual. A follow-up plasma specimen should be collected from this individual to both verify the diagnosis and quantify the HIV RNA prior to initiation of antiviral therapy. An "Undetected" result indicates that the assay was unable to detect RNA of the specific virus in the plasma specimen tested. An "Inconclusive" result indicates that the presence or absence of viral RNA could not be determined with certainty after repeat testing in the laboratory, possibly due to presence of inhibitory substances in the plasma specimen tested. Collection of a new plasma for testing is recommended.

Reference Values:
Undetected

Clinical References: 1. Centers for Disease Control and Prevention and Association of Public Health Laboratories. 2018 Quick Reference Guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. CDC; January 2018. Accessed July 22, 2024. Available at https://stacks.cdc.gov/view/cdc/50872 2. Branson BM, Owen SM, Wesolowski LG, et al. Laboratory testing for the diagnosis of HIV infection: Updated recommendations. Centers for Disease Control and

Prevention; June 27, 2014. Accessed July 22, 2024. Available at https://stacks.cdc.gov/view/cdc/23447 3. Duncan D, Duncan J, Kramer B, et al. An HIV diagnostic testing algorithm using the cobas HIV-1/HIV-2 Qualitative Assay for HIV type differentiation and confirmation. J Clin Microbiol. 2021;59(7):e0303020. doi:10.1128/JCM.03030-20 4. US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. HHS; March 23, 2023. Accessed July 22, 2024. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf 5. US Department of Health and Human Services Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV: Guidelines for the use of antiretroviral agents in pediatric HIV infection. HSS; April 11, 2023. Accessed July 22, 2024. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf

HIS12
615816

HIV-1/HIV-2 RNA Detection, Serum

Clinical Information: Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS or AIDS-related complex, and from asymptomatic infected individuals at high-risk for AIDS. Accounting for more than 99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa, and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in overall genomic structure and ability to cause AIDS, but viral load tends to lower in HIV-2 than HIV-1 infection.

Useful For: Diagnosis of HIV-1 and/or HIV-2 infection in individuals with indeterminate or inconclusive HIV serologic test results Diagnosis of HIV-1 and/or HIV-2 infection in individuals with acute or early HIV-1 and/or HIV-2 infection Diagnosis of HIV-1 and/or HIV-2 infection in infants under 18 months who are born to HIV-infected mothers

Interpretation: A "Detected" result indicates that the presence of RNA of the specific virus in the specimen tested, consistent with the presence of this viral infection. For example, a "Detected" result for HIV-1 RNA by this assay is indicative of HIV-1 infection in the tested individual. A follow-up specimen should be collected from this individual to both verify the diagnosis and quantify the HIV RNA prior to initiation of antiviral therapy. An "Undetected" result indicates that the assay was unable to detect RNA of the specific virus in the specimen tested. An "Inconclusive" result indicates that the presence or absence of viral RNA could not be determined with certainty after repeat testing in the laboratory, possibly due to presence of inhibitory substances in the specimen tested. Collection of a new specimen for testing is recommended.

Reference Values:
Undetected

Clinical References: 1. Centers for Disease Control and Prevention: 2018 Quick reference guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. CDC; January 2018. Accessed July 22, 2024. Available at https://stacks.cdc.gov/view/cdc/50872 2. Branson BM, Owen SM, Wesolowski LG, et al: Laboratory testing for the diagnosis of HIV infection: Updated recommendations. Centers for Disease Control and Prevention; June 27, 2014. Accessed July 22, 2024. Available at https://stacks.cdc.gov/view/cdc/23447 3. Duncan D, Duncan J, Kramer B, et al. An HIV diagnostic testing algorithm using the cobas HIV-1/HIV-2 qualitative assay for HIV type differentiation and confirmation. J Clin Microbiol. 2021;59(7):e03030-20. doi:10.1128/JCM.03030-20 4. US Department of Health and Human Services, Panel on Antiretroviral Guidelines for Adults and

Adolescents: Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. HHS. Updated February 27, 2024. Accessed July 22, 2024. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf 5. US Department of Health and Human Services, Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV: Guidelines for the use of antiretroviral agents in pediatric HIV infection. HSS. Updated June 27, 2024. Accessed July 22, 2024. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf

FHV2Q
91490

HIV-2 DNA/RNA Qualitative Real-Time PCR

Reference Values:
Reference Range: Not Detected

FHLAA
91498

HLA A High Resolution

Reference Values:
Testing is complete. Final report has been sent to the referring laboratory.

FHLAB
91499

HLA B High Resolution

Reference Values:
Testing is complete. Final report has been sent to the referring laboratory.

FHLAC
91500

HLA C High Resolution

Reference Values:
Testing is complete. Final report has been sent to the referring laboratory.

HL57R
610054

HLA-B*57:01 Genotype, Pharmacogenomics, Varies

Clinical Information: The human leukocyte antigen (HLA) genes help the immune system recognize and respond to foreign substances (such as viruses and bacteria). The HLA-B gene encodes a class I HLA molecule in the major histocompatibility complex (MHC), which acts by presenting peptides to immune cells. There are more than 1500 different HLA-B alleles identified, one of which is the HLA-B*57:01 allele. Frequency of the HLA-B*57:01 allele varies with ethnicity, with a frequency of 6% to 7% in European populations and up to 20% in Southwest Asian populations. The HLA-B*57:01 allele has been associated with hypersensitivity to abacavir, a highly effective nucleoside analog reverse-transcriptase inhibitor used to treat HIV infection and AIDS. Per the Clinical Pharmacogenomics Implementation Consortium (CPIC) dosing guidelines for abacavir and HLA-B, individuals who are positive for the HLA-B*57:01 allele are at an increased risk for abacavir hypersensitivity, and it is not recommended for use in treating these individuals. Hypersensitivity reactions, which generally occur during the first 6 weeks of treatment, are often nonspecific and include skin rashes, gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, and abdominal pain), and respiratory symptoms. Fatalities have been reported with abacavir hypersensitivity. Prospective testing for the HLA-B*57:01 genotype and excluding HLA-B*57:01-positive individuals from treatment with abacavir decreases the incidence of abacavir hypersensitivity. Pazopanib is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma and advanced soft tissue sarcoma who have received prior chemotherapy. In clinical

trials with pazopanib, hepatotoxicity was observed, manifested as increases in serum transaminases such as alanine aminotransferase (ALT), aspartate aminotransferase , and bilirubin. This hepatotoxicity can be severe and fatal. Patients older than 65 years are at greater risk for hepatotoxicity. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). Patients who are HLA-B*57:01 carriers and are taking pazopanib are at increased risk of elevated ALT levels.(1,2) According to the FDA label for pazopanib, in an analysis of data from 31 clinical studies of pazopanib administered as either monotherapy or in combination with other agents, elevation in ALT to levels greater than 3 times the upper limit of normal occurred in 32% (42/133) of HLA-B*57:01 allele carriers as compared to 19% (397/2101) of noncarriers. Furthermore, elevation in ALT to levels greater than 5 times the upper limit of normal occurred in 19% (25/133) of HLA-B*57:01 allele carriers and in 10% (213/2101) of noncarriers. All patients taking pazopanib should have hepatic function monitored, regardless of HLA-B*57:01 carrier status, and administration of pazopanib should be interrupted, reduced, or discontinued according to recommendations in the FDA label if hepatic function is impaired. UGT1A1 genotype is also relevant to pazopanib-induced hyperbilirubinemia and testing may also be warranted. For more information see U1A1Q / UDP-Glucuronosyltransferase 1A1 TA Repeat Genotype, UGT1A1, Varies.

Useful For:

Interpretation: Positivity for human leukocyte antigen allele HLA-B*57:01 confers high risk for hypersensitivity to abacavir and higher risk of elevated alanine aminotransferase (ALT) levels in patient taking pazopanib. For more information see Abacavir Hypersensitivity Testing and Initial Patient Management Algorithm. For additional information regarding pharmacogenomic genes and their associated drugs, see the. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:

Negative
An interpretive report will be provided.

Clinical References: 1. Xu CF, Johnson T, Wang X, et al: HLA-B*57:01 confers susceptibility to pazopanib-associated liver injury in patients with cancer. Clin Cancer Res. 2016 Mar 15;22(6):1371-1377 2. Pazopanib. Package insert. Novartis Pharmaceuticals; Updated February 2022. Accessed June 29, 2022. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=eeaaaf38-fb86-4d9f-a19d-0f61daac2fd7 3. Saag M, Balu R, Brachman P, et al: High sensitivity of HLA-B*5701 in whites and blacks in immunologically-confirmed cases of abacavir hypersensitivity. Fourth IAS Conference on HIV Pathogenesis, Treatment, and Prevention. July 22-25, 2007. Sydney. Abstract WEAB305 4. Martin M, Klein T, Dong B, Pirmohamed M, Haas DW, Kroetz DL: Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B genotype and abacavir dosing. Clin Pharmacol Ther. 2012 Apr;91(4):734-738 5. Martin M, Hoffman J, Freimuth R, et al: Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B genotype and abacavir dosing: 2014 update. Clin Pharmacol Ther. 2014 May;95(5):499-500 6. Faruki H, Heine U, Brown T, Koester R, Lai-Goldman M: HLA-B*5701 clinical testing: early experience in the United States. Pharmacogenet Genomics. 2007 Oct;17(10):857-860 7. Sun HY, Hung CC, Lin PH, et al: Incidence of abacavir hypersensitivity and its relationship with HLA-B*5701 in HIV-infected patients in Taiwan. J Antimicrob Chemother. 2007 Sep60(3):599-604. doi: 10.1093/jac/dkm243

HL58R
610055

HLA-B*5801 Genotype, Allopurinol Hypersensitivity, Varies

Clinical Information: The human leukocyte antigen (HLA) genes help the immune system recognize and respond to foreign substances (such as viruses and bacteria). The HLA-B gene encodes a

class 1 HLA molecule in the major histocompatibility complex (MHC), which acts by presenting peptides to immune cells. There are more than 1500 different HLA-B alleles identified, one of which is the HLA-B*58:01 allele. The frequency of the HLA-B*58:01 allele varies with ethnicity, with a frequency of 10% to 17% in Han Chinese, 6% in Korean, 6% to 8% in Thai, and 3% to 6% in African American populations. This allele is present at a lower frequency (approximately 1%-2%) among the White and Hispanic populations.(1) Allopurinol is a drug widely used for hyperuricemia-related diseases such as gout, Lesch-Nyhan syndrome, and recurrent urate kidney stones. Allopurinol has been associated with severe cutaneous adverse reactions (SCAR), including drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, Stevens-Johnson syndrome, and allopurinol hypersensitivity syndrome (AHS). These reactions have a reported mortality rate of 20% to 25%. The HLA-B*58:01 allele is associated with a markedly elevated risk for SCAR/AHS. Guidelines from the Clinical Pharmacogenomics Implementation Consortium recommend HLA-B*58:01 genotyping be performed when considering prescribing allopurinol, and that allopurinol should not be prescribed to patients who test positive for the allele due to the increased risk of SCAR.(2) In addition, the 2020 American College of Rheumatology Guideline for the Management of Gout recommends testing for the HLA-B*58:01 allele prior to initiation of allopurinol in patients of Southeast Asian descent (eg, Han Chinese, Korean, Thai) and for African American patients.(3)

Useful For: Identifying individuals with an increased risk of severe cutaneous adverse reactions to allopurinol based on the presence of the human leukocyte antigen HLA-B*58:01 allele

Interpretation: Positivity for HLA-B*58:01 confers increased risk for hypersensitivity to allopurinol. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Gonzalez-Galarza FF, McCabe A, Santos EJ, et al: Allele Frequency Net Database (AFND) 2020 update: gold-standard data classification, open access genotype data, and new query tools. Nucleic Acid Res. 2020;48:D783-D788 2. Saito Y, Stamp L, Caudle K, et al: Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. Clin Pharmacol Ther. 2016 Jan;99(1):36-37. doi: 10.1002/cpt.161 3. FitzGerald JD, Dalbeth N, Mikuls T, et al: 2020 American College of Rheumatology Guideline for the management of gout. Arthritis Rheumatol. 2020 Jun;72(6):879-895 4. Hershfield MS, Callaghan JT, Tassaneeyakul W, et al: Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. Clin Pharmacol Ther. 2013 Feb;93(2):153-158 5. Chung WH, Hung SI, Chen YT: Human leukocyte antigens and drug hypersensitivity. Curr Opin Allergy Clin Immunol. 2007;7:317-323

LY27B
9648

HLA-B27, Blood

Clinical Information: This major histocompatibility coded class I antigen is associated with ankylosing spondylitis, juvenile rheumatoid arthritis, and reactive arthritis. The mechanism of the association is not understood but probably is that of linkage disequilibrium. There is an increased prevalence of human leukocyte antigen (HLA)-B27 in certain rheumatic diseases, particularly ankylosing spondylitis. Studies have demonstrated that the HLA-B*27:06 allele, which is present in a small percentage of individuals of Asian ethnicity, may not be associated with ankylosing spondylitis.

Useful For: Assisting in the diagnostic process of ankylosing spondylitis, juvenile rheumatoid arthritis, and reactive arthritis

Interpretation: Approximately 8% of the normal population carries the human leukocyte antigen (HLA)-B27. HLA-B27 is present in approximately 89% of patients with ankylosing spondylitis, 79% of patients with reactive arthritis, and 42% of patients with juvenile rheumatoid arthritis. However, lacking other data, it is not diagnostic for these disorders.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Profaizer T, Dibb K, Bethers H, et al. Comparison of next-generation sequencing-based human leukocyte antigen typing with clinical flow cytometry and allele-specific PCR melting assays for HLA-B27 genotyping. J Appl Lab Med. 2021;6(5):1221-1227. doi:10.1093/jalm/jfab046 2. Skalska U, Kozakiewicz A, Maslinski W, Jurkowska M. HLA-B27 detection - comparison of genetic sequence-based method and flow cytometry assay. Reumatologia. 2015;53(2):74-78. doi:10.5114/reum.2015.51506 3. Brewerton DA, Hart FD, Nicholls A, Caffrey M, James DC, Sturrock RD. Ankylosing spondylitis and HL-A27. Lancet. 1973;1(7809):904-907 4. Albrecht J, Muller HA. HLA-B27 typing by use of flow cytofluorometry. Clin Chem. 1987;33(9):1619-1623

HMB45
70459

HMB45 Immunostain, Technical Component Only

Clinical Information: The HMB45 immunostain identifies an antigen that is associated with a pre-melanosomal glycoprotein found in activated and neoplastic melanocytes. Most melanomas (approximately 90%) react with HMB45. HMB45 staining is cytoplasmic and is usually diffuse but may be focal. Benign nevi (moles) and other tumors that have melanin production (such as peripheral nerve sheath tumors) also stain positively.

Useful For: Identification of activated and neoplastic melanocytes

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Uguen A, Uguen M, Gujbourg B, Talagas M, Marcorelles P, De Braekeleer M. The p16-Ki-67-HMB45 immunohistochemistry scoring system is highly concordant with the fluorescent in situ hybridization test to differentiate between melanocytic nevi and melanomas. Appl Immunohistochem Mol Morphol. 2018;26(6):361-367. doi:10.1097/PAI.0000000000000428 2. Kriegsmann M, Kriegsmann M, Kriegsmann K, et al. Expression of HMB45, melanA and SOX10 is rare in non-small cell lung cancer. Diagn Pathol. 2018;13(1):68. doi:10.1186/s13000-018-0751-7 3. Garola R, Singh V: Utility of p16-Ki-67-HMB45 score in sorting benign from malignant Spitz tumors. Pathol Res Pract. 2019;215(10):152550. doi:10.1016/j.prp.2019.152550 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HCMM
89047

Homocysteine (Total), Methylmalonic Acid, and Methylcitric Acid, Blood Spot

Clinical Information: Homocystinuria is an autosomal recessive disorder caused by a deficiency of the enzyme cystathionine beta-synthase. The incidence of homocystinuria is approximately 1 in 200,000

to 335,000 live births. Classical homocystinuria is characterized by a normal presentation at birth followed by failure to thrive and developmental delay. Untreated homocystinuria can lead to ophthalmological problems, intellectual disability, seizures, thromboembolic episodes, and skeletal abnormalities. The biochemical phenotype is characterized by increased plasma concentrations of methionine and homocysteine (free and total) along with decreased concentrations of cystine. Methylmalonic acidemia (MMA) and propionic acidemia (PA) are defects of propionate metabolism caused by deficiencies in methylmalonyl-CoA mutase and propionyl-CoA carboxylase, respectively. The clinical phenotype includes vomiting, hypotonia, lethargy, apnea, hypothermia, and coma. The biochemical phenotype for MMA includes elevations of propionyl carnitine, methylmalonic acid, and methylcitric acid. Patients with PA will have elevations of propionyl carnitine and methylcitric acid with normal methylmalonic acid concentrations as the enzymatic defect is upstream of methylmalonic-CoA mutase. Newborn screening for inborn errors of methionine and propionic acid metabolism relies on elevations of methionine and propionyl carnitine. These analytes are not specific for these conditions and are prone to false-positive results, leading to increased cost, stress, and anxiety for families who are subjected to follow-up testing. Homocysteine, methylmalonic acid, and methylcitric acid are more specific markers for inborn errors of methionine and propionic acid metabolism. Molecular genetic testing can be used to confirm a biochemical diagnosis for homocystinuria, methylmalonic acidemia, and propionic acidemia.

Useful For: Second-tier assay of newborn screening specimens when abnormal propionyl carnitine or methionine concentrations are identified in a primary newborn screen

Interpretation: Elevated homocysteine, methylcitric acid, or methylmalonic acid concentrations are indicative of an underlying metabolic disorder.

Reference Values:
Homocysteine:
<9.0 nmol/mL

Methylmalonic Acid:
<4.0 nmol/mL

Methylcitric Acid:
<1.0 nmol/mL

An interpretive report will also be provided.

Clinical References: 1. Pasquali M, Longo N. Newborn screening and inborn errors of metabolism. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1697-1730 2. Tortorelli S, Turgeon CT, Lim JS, et al. Two-tier approach to the newborn screening of methylenetetrahydrofolate reductase deficiency and other remethylation disorders with tandem mass spectrometry. J Pediatr. 2010;157(2):271-275 3. Fenton WA, Gravel RA, Rosenblatt DS. Disorders of propionate and methylmalonate metabolism. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Accessed October 07, 2024. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225086103 4. Harvey Mudd S, Levy HL, Kraus JP. Disorders of transsulfuration. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed October 7, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225084718

HCYSP
80379

Homocysteine, Total, Plasma

Clinical Information: Homocysteine is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinemia or homocystinuria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine remethylation. Genetic defects in vitamin cofactors (vitamins B6, B12, and folate) and nutritional deficiency of vitamin B12 and folate also lead to abnormal homocysteine accumulation. Homocysteine concentration is an indicator of acquired folate or cobalamin deficiency and is a contributing factor in the pathogenesis of neural tube defects. Homocysteine was once thought to be an independent predictor of cardiovascular disease (atherosclerosis, heart disease, thromboembolism), as early observational studies prior to the year 2000 linked homocysteine to cardiovascular risk and morbidity and mortality. However, following US Food and Drug Administration mandated folic acid supplementation in 1998, homocysteine concentrations decreased by approximately 10% without a similar change in cardiovascular or ischemic events. Currently, the use of homocysteine for assessment of cardiovascular risk is uncertain and controversial. Based on several meta-analyses, at present, homocysteine may be regarded as a weak risk factor for coronary heart disease, and there is a lack of direct causal relationship between hyperhomocysteinemia and cardiovascular disease. It is most likely an indicator of poor lifestyle and diet. This test should be used in conjunction with plasma amino acids, quantitative acylcarnitines, methylmalonic acid, and urine organic acids to aid in the biochemical screening for primary and secondary disorders of methionine metabolism.

Useful For: An aid for screening patients suspected of having an inherited disorder of methionine metabolism including: -Cystathionine beta-synthase deficiency (homocystinuria) -Methylenetetrahydrofolate reductase deficiency and its thermolabile variants -Methionine synthase deficiency -Cobalamin (Cbl) metabolism -Combined methyl-Cbl and adenosyl-Cbl deficiencies: Cbl C2, Cbl D2, and Cbl F3 deficiencies -Methyl-Cbl specific deficiencies: Cbl D-Var1, Cbl E, and Cbl G deficiencies -Transcobalamin II deficiency -Adenosylhomocysteinase deficiency -Glycine N-methyltransferase deficiency -Methionine adenosyltransferase I/III deficiency Screening and monitoring patients suspected of, or confirmed with, an inherited disorder of methionine metabolism using plasma specimens Evaluating individuals with suspected deficiency of vitamin B12 or folate

Interpretation: Elevated homocysteine concentrations are considered informative in patients evaluated for suspected nutritional deficiencies (vitamin B12, folate) and inborn errors of metabolism. Measurement of methylmalonic acid (MMA) distinguishes between vitamin B12 (cobalamin) and folate deficiencies, as MMA is only elevated in vitamin B12 deficiency. Treatment response can be evaluated by monitoring plasma homocysteine concentrations over time.

Reference Values:

Age	Total homocysteine (nmol/mL)
Female	Male
0-11 months	3.1-8.3
12-23 months	3.2-8.3
24-35 months	3.2-8.2
3 years	3.2-8.2
4 years	3.3-8.2
5 years	3.4-8.1
6 years	3.5-8.1
7 years	3.5-8.1

8 years	3.6-8.2
9 years	3.7-8.2
10 years	3.8-8.3
11 years	3.9-8.4
12 years	3.9-8.6
13 years	4.0-8.7
14 years	4.1-8.8
15 years	4.2-8.9
16 years	4.2-9.1
17 years	4.3-9.2
18 years	4.3-9.3
19 years	4.4-9.5
20 years	4.4-9.6
21 years	4.4-9.8
22 years	4.4-9.9
23 years	4.4-10.1
24 years	4.4-10.3
25 years	4.4-10.4
26 years	4.4-10.6
27 years	4.3-10.8
28 years	4.3-11.0
29 years	4.3-11.2
30 years	4.3-11.4
31 years	4.4-11.6
32 years	4.4-11.8
33 years	4.4-11.9
34 years	4.5-12.1
35 years	4.5-12.2
36 years	4.6-12.4
37 years	4.6-12.5
38 years	4.7-12.7
39 years	4.7-12.8
40 years	4.8-13.0
41 years	4.8-13.2
42 years	4.8-13.4
43 years	4.9-13.5
44 years	4.9-13.7

45 years	4.9-13.9
46 years	4.9-14.0
47 years	4.9-14.2
48 years	5.0-14.3
49 years	5.0-14.4
50 years	5.0-14.5
51 years	5.1-14.6
52 years	5.1-14.7
53 years	5.1-14.8
54 years	5.2-14.9
55 years	5.2-15.0
56 years	5.3-15.0
57 years	5.3-15.1
58 years	5.3-15.2
59 years	5.4-15.2
60 years	5.4-15.3
61 years	5.4-15.4
62 years	5.5-15.4
63 years	5.5-15.5
64 years	5.6-15.5
65 years	5.6-15.6
66 years	5.7-15.6
67 years	5.7-15.7
68 years	5.8-15.7
69 years	5.9-15.7
70 years	6.0-15.8
71 years	6.1-15.8
72 years	6.2-15.8
73 years	6.3-15.9
74 years	6.4-15.9
75 years	6.5-15.9
76 years	6.6-15.9
77 years	6.7-16.0
78 years	6.8-16.0
79 years	6.9-16.0
80 years	7.0-16.0
81 years	7.1-16.0

82 years	7.2-16.0
83 years	7.2-16.0
84 years	7.3-16.0
85 years	7.3-16.0
>85 years	7.4-16.0

Clinical References: 1. Mudd SH, Levy HL, Kraus JP: Disorders of transsulfuration. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill, 2019. Accessed December 2, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225084718&bookid=2709 2. Chrysant SG, Chrysant GS. The current status of homocysteine as a risk factor for cardiovascular disease: a mini review. Expert Rev Cardiovasc Ther. 2018;16(8):559-565. doi:10.1080/14779072.2018.1497974 3. Refsum H, Smith AD, Ueland PM, et al. Facts and recommendations about total homocysteine determinations: an expert opinion. Clin Chem. 2004;50(1):3-32 4. Turgeon CT, Magera MJ, Cuthbert CD, et al. Determination of total homocysteine, methylmalonic acid, and 2-methylcitric acid in dried blood spots by tandem mass spectrometry. Clin Chem. 2010;56(11):1686-1695 5. Sacharow SJ, Picker JD, Levy HL. Homocystinuria caused by cystathionine beta-synthase deficiency. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated May 18, 2017. Accessed December 2, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1524/

HCYSS
35836

Homocysteine, Total, Serum

Clinical Information: Homocysteine is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinemia or homocystinuria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine remethylation. Genetic defects in vitamin cofactors (vitamins B6, B12, and folate) and nutritional deficiency of vitamin B12 and folate also lead to abnormal homocysteine accumulation. Homocysteine concentration is an indicator of acquired folate or cobalamin deficiency and is a contributing factor in the pathogenesis of neural tube defects. Homocysteine was once thought to be an independent predictor of cardiovascular disease (atherosclerosis, heart disease, thromboembolism), as early observational studies prior to the year 2000 linked homocysteine to cardiovascular risk and morbidity and mortality. However, following US Food and Drug Administration mandated folic acid supplementation in 1998, homocysteine concentrations decreased by approximately 10% without a similar change in cardiovascular or ischemic events. Currently, the use of homocysteine for assessment of cardiovascular risk is uncertain and controversial. Based on several meta-analyses, at present, homocysteine may be regarded as a weak risk factor for coronary heart disease, and there is a lack of direct causal relationship between hyperhomocysteinemia and cardiovascular disease. It is most likely an indicator of poor lifestyle and diet. This test should be used in conjunction with plasma amino acids, quantitative acylcarnitines, methylmalonic acid, and urine organic acids to aid in the biochemical screening for primary and secondary disorders of methionine metabolism.

Useful For: An aid for screening patients suspected of having an inherited disorder of methionine metabolism including: -Cystathionine beta-synthase deficiency (homocystinuria) -Methylenetetrahydrofolate reductase deficiency and its thermolabile variants: -Methionine synthase deficiency -Cobalamin (Cbl) metabolism -Combined methyl-Cbl and adenosyl-Cbl deficiencies: Cbl C2, Cbl D2, and Cbl F3 deficiencies -Methyl-Cbl specific deficiencies: Cbl D-Var1, Cbl E, and Cbl G deficiencies -Transcobalamin II deficiency -Adenosylhomocysteinase deficiency -Glycine N-methyltransferase deficiency -Methionine adenosyltransferase I/III deficiency Screening and monitoring patients suspected of, or confirmed with, an inherited disorder of methionine metabolism using serum

specimens Evaluating individuals with suspected deficiency of vitamin B12 or folate

Interpretation: Elevated homocysteine concentrations are considered informative in patients evaluated for suspected nutritional deficiencies (vitamin B12, folate) and inborn errors of metabolism. Measurement of methylmalonic acid (MMA) distinguishes between vitamin B12 (cobalamin) and folate deficiencies, as MMA is only elevated in vitamin B12 deficiency. Treatment response can be evaluated by monitoring serum homocysteine concentrations over time.

Reference Values:

Age	Total Homocysteine (nmol/mL)
Female	Male
0-11 months	3.1-8.3
12-23 months	3.2-8.3
24-35 months	3.2-8.2
3 years	3.2-8.2
4 years	3.3-8.2
5 years	3.4-8.1
6 years	3.5-8.1
7 years	3.5-8.1
8 years	3.6-8.2
9 years	3.7-8.2
10 years	3.8-8.3
11 years	3.9-8.4
12 years	3.9-8.6
13 years	4.0-8.7
14 years	4.1-8.8
15 years	4.2-8.9
16 years	4.2-9.1
17 years	4.3-9.2
18 years	4.3-9.3
19 years	4.4-9.5
20 years	4.4-9.6
21 years	4.4-9.8
22 years	4.4-9.9
23 years	4.4-10.1
24 years	4.4-10.3
25 years	4.4-10.4
26 years	4.4-10.6

27 years	4.3-10.8
28 years	4.3-11.0
29 years	4.3-11.2
30 years	4.3-11.4
31 years	4.4-11.6
32 years	4.4-11.8
33 years	4.4-11.9
34 years	4.5-12.1
35 years	4.5-12.2
36 years	4.6-12.4
37 years	4.6-12.5
38 years	4.7-12.7
39 years	4.7-12.8
40 years	4.8-13.0
41 years	4.8-13.2
42 years	4.8-13.4
43 years	4.9-13.5
44 years	4.9-13.7
45 years	4.9-13.9
46 years	4.9-14.0
47 years	4.9-14.2
48 years	5.0-14.3
49 years	5.0-14.4
50 years	5.0-14.5
51 years	5.1-14.6
52 years	5.1-14.7
53 years	5.1-14.8
54 years	5.2-14.9
55 years	5.2-15.0
56 years	5.3-15.0
57 years	5.3-15.1
58 years	5.3-15.2
59 years	5.4-15.2
60 years	5.4-15.3
61 years	5.4-15.4
62 years	5.5-15.4
63 years	5.5-15.5

64 years	5.6-15.5
65 years	5.6-15.6
66 years	5.7-15.6
67 years	5.7-15.7
68 years	5.8-15.7
69 years	5.9-15.7
70 years	6.0-15.8
71 years	6.1-15.8
72 years	6.2-15.8
73 years	6.3-15.9
74 years	6.4-15.9
75 years	6.5-15.9
76 years	6.6-15.9
77 years	6.7-16.0
78 years	6.8-16.0
79 years	6.9-16.0
80 years	7.0-16.0
81 years	7.1-16.0
82 years	7.2-16.0
83 years	7.2-16.0
84 years	7.3-16.0
85 years	7.3-16.0
>85 years	7.4-16.0

Clinical References: 1. Mudd SH, Levy HL, Kraus JP. Disorders of transsulfuration. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill, 2019. Accessed December 2, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225084718&bookid=2709 2. Chrysant SG, Chrysant GS. The current status of homocysteine as a risk factor for cardiovascular disease: a mini review. Expert Rev Cardiovasc Ther. 2018;16(8):559-565. doi:10.1080/14779072.2018.1497974 3. Refsum H, Smith AD, Ueland PM, et al. Facts and recommendations about total homocysteine determinations: an expert opinion. Clin Chem. 2004;50(1):3-32 4. Turgeon CT, Magera MJ, Cuthbert CD, et al. Determination of total homocysteine, methylmalonic acid, and 2-methylcitric acid in dried blood spots by tandem mass spectrometry. Clin Chem. 2010;56(11):1686-1695 5. Sacharow SJ, Picker JD, Levy HL. Homocystinuria caused by cystathionine beta-synthase deficiency. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated May 18, 2017. Accessed December 2, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1524/

HVA
9253

Homovanillic Acid, 24 Hour, Urine

Clinical Information: Homovanillic acid (HVA) and other catecholamine metabolites

(vanillylmandelic acid [VMA] and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). HVA and VMA levels may also be useful in monitoring patients who have been treated as a result of the above-mentioned tumors. HVA levels may also be altered in disorders of catecholamine metabolism; monoamine oxidase-A deficiency can cause decreased urinary HVA values, while a deficiency of dopamine beta-hydrolase (the enzyme that converts dopamine to norepinephrine) can cause elevated urinary HVA values.

Useful For: Screening children for catecholamine-secreting tumors using a 24-hour urine collection when requesting homovanillic acid only Monitoring neuroblastoma treatment Screening patients with possible inborn errors of catecholamine metabolism

Interpretation: Vanillylmandelic acid or homovanillic acid (HVA) concentrations are elevated in over 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated HVA values are suggestive of a deficiency of dopamine beta-hydrolase, a neuroblastoma, a pheochromocytoma, or may reflect administration of L-dopa. Decreased urinary HVA values may suggest monoamine oxidase-A deficiency.

Reference Values:
<1 year: <35.0 mg/g creatinine
1 year: <30.0 mg/g creatinine
2-4 years: <25.0 mg/g creatinine
5-9 years: <15.0 mg/g creatinine
10-14 years: <9.0 mg/g creatinine
> or =15 years (adults): <8.0 mg/24 hours

Clinical References: 1. Eisenhofer G. Monoamine-producing tumors. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:765 2. Ormazabal A, Molero-Luis M, Garcia-Cazorla A, Artuch R. Biomarkers for the study of catecholamine and serotonin genetic diseases. In: Garg U, Smith LD, eds. Biomarkers in Inborn Errors of Metabolism: Clinical Aspects and Laboratory Determination. Elsevier; 2017:301-329 3. Strenger V, Kerbl R, Dornbusch HJ, et al. Diagnostic and prognostic impact of urinary catecholamines in neuroblastoma patients. Pediatr Blood Cancer. 2007;48(5):504-509 4. Barco S, Gennai I, Reggiardo G, et al. Urinary homovanillic and vanillylmandelic acid in the diagnosis of neuroblastoma: report from the Italian Cooperative Group for Neuroblastoma. Clin Biochem. 2014;47(9):848-852 5. Matthay KK, Maris JM, Schleiermacher G, et al. Neuroblastoma. Nat Rev Dis Primers. 2016;2:16078. doi: 10.1038/nrdp.2016.78

HVAR
60275

Homovanillic Acid, Random, Urine

Clinical Information: Homovanillic acid (HVA) and other catecholamine metabolites (vanillylmandelic acid [VMA] and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). HVA and VMA levels may also be useful in monitoring patients who have been treated as a result of the above-mentioned tumors. HVA levels may also be altered in disorders of catecholamine metabolism; monoamine oxidase-A deficiency can cause decreased urinary HVA values, while a deficiency of dopamine beta-hydrolase (the enzyme that converts dopamine to norepinephrine) can cause elevated urinary HVA values.

Useful For: Screening children for catecholamine-secreting tumors using a random urine collection when requesting homovanillic acid only Monitoring neuroblastoma treatment Screening patients with possible inborn errors of catecholamine metabolism

Interpretation: Vanillylmandelic acid and/or homovanillic acid (HVA) concentrations are elevated in

over 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated HVA values are suggestive of a deficiency of dopamine beta-hydrolase, a neuroblastoma, a pheochromocytoma, or may reflect administration of L-dopa. Decreased urinary HVA values may suggest monoamine oxidase-A deficiency.

Reference Values:

<1 year: <35.0 mg/g creatinine
1 year: <30.0 mg/g creatinine
2-4 years: <25.0 mg/g creatinine
5-9 years: <15.0 mg/g creatinine
10-14 years: <9.0 mg/g creatinine
> or =15 years (adults): <8.0 mg/g creatinine

Clinical References: 1. Eisenhofer G. Monoamine-producing tumors. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:765 2. Ormazabal A, Molero-Luis M, Garcia-Cazorla A, Artuch R. Biomarkers for the study of catecholamine and serotonin genetic diseases. In: Garg U, Smith LD, eds. Biomarkers in Inborn Errors of Metabolism: Clinical Aspects and Laboratory Determination. Elsevier; 2017:301-329 3. Strenger V, Kerbl R, Dornbusch HJ, et al. Diagnostic and prognostic impact of urinary catecholamines in neuroblastoma patients. Pediatr Blood Cancer. 2007;48(5):504-509 4. Barco S, Gennai I, Reggiardo G, et al. Urinary homovanillic and vanillylmandelic acid in the diagnosis of neuroblastoma: report from the Italian Cooperative Group for Neuroblastoma. Clin Biochem. 2014;47(9):848-852 5. Matthay KK, Maris JM, Schleiermacher G, et al. Neuroblastoma. Nat Rev Dis Primers. 2016;2:16078. doi:10.1038/nrdp.2016.78

HBV
82551

Honeybee Venom, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to honeybee venom Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with

the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

HBEA
82484

Hornbeam, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to hornbeam Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

HRSPF
616095

Horse Dander, IgE with Reflex to Horse Dander Component, IgE, Serum

Clinical Information: Horse (equine) allergen sensitization occurs in approximately 5 to 15% of individuals exposed to horses in occupational settings. The assessment of allergy to horses is dependent upon the presence of compatible clinical symptoms in the context of exposure, with support from identification of potential equine-specific IgE allergen antibodies, either by skin testing or in vitro serology testing. In vitro testing has generally focused on assessing for the presence of IgE antibodies to total horse allergen extracts. There is a correlation between total horse IgE allergen antibodies and an increased likelihood of a clinical allergic response. Once an elevated antibody response to total horse dander IgE extract is established, assessment for the presence of specific IgE antibodies to the major equine component will be performed. This may yield additional, potentially useful information for the clinical assessment of allergy and sensitization. During horse component allergen IgE antibody testing, the presence of IgE antibodies specific for the potential allergenic individual protein, namely Equ c 1, is assessed. The determination of the relative amount of IgE antibody to specific component can aid in assessment of the potential strength and type of allergenic response. While several horse allergens have been described, the lipocalin Equ c 1 is the major horse allergen, and antibodies to this allergen are present in 76% of individuals exhibiting allergy to horses. The main source of exposure of Equ c 1 is inhalation. However, individuals can be exposed by contact with contaminated clothing and, potentially, through horse bites. Mattresses containing horsehair may also be a potential route of exposure. Individuals who are allergic to horses may exhibit allergic rhinitis, conjunctivitis, asthma, anaphylaxis, and allergy to other foods and animals.(1) To date, the existence of completely hypoallergenic horse breeds has not been verified. Sensitization to horses may also occur through cross-reactivity, with as many as 30% of individuals with pet allergy also reporting allergic reaction to horses. As many as 50% of individuals with cross-reactive allergen sensitization are caused by cross reactive to horse lipocalin as represented by Equ c 1. Cross-reactivity has been shown to exist between horse lipocalin allergen Equ c 1, cat lipocalin allergen Fel d4, and dog lipocalin allergen Can f 6.

Useful For: Evaluating patients with suspected horse dander allergy

Interpretation: When detectable total horse dander IgE antibody is present (> or =0.10 IgE kUa/L), additional specific component IgE antibody testing will be performed. If the specific allergenic horse dander component IgE is detectable (> or =0.10 IgE kUa/L), an interpretative report will be provided. When the sample is negative for total horse dander IgE antibody (<0.10 IgE kUa/L), additional testing for specific horse dander component IgE antibodies will not be performed. Negative IgE results for total horse dander antibody may indicate a lack of sensitization to potential horse dander allergenic components.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Arseneau AM, Hrabak TM, Waibel KH. Inhalant horse allergens and allergies: a review of the literature. Mil Med. 2012;177(7):877-882 2.Salo PM, Arbes SJ Jr, Jaramillo R, et al: Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol. 2014;134(2):350-359. doi:10.1016/j.jaci.2013.12.1071 3.Guida G, Nebiolo F, Heffler E, Bergia R, Rolla G: Anaphylaxis after a horse bite. Allergy. 2005;60(8):1088-1089 4.Saarelainen S, Rytkonen-Nissinen M, Rouvinen J, et al: Animal-derived lipocalin allergens exhibit immunoglobulin E cross-reactivity. Clin Exp Allergy. 2008 Feb;38(2):374-381 5.Chan SK, Leung DYM: Dog and cat allergies: Current state of diagnostic approaches and challenges. Allergy Asthma Immunol Res. 2018 Mar;10(2):97-105. doi: 10.4168/aair.2018.10.2.97 6.Chruszcz M, Mikolajczak K, Mank N, Majorek KA, Porebski PJ, Minor W: Serum albumins-unusual allergens. Biochim Biophys Acta. 2013;1830(12):5375-81 7.Nwaru BI, Suzuki S, Ekerljung L, et al: Furry animal allergen component sensitization and clinical outcomes in adult asthma and rhinitis. J Allergy Clin Immunol Pract..2019 Apr;7(4):1230-1238.e4 8.Hilger C, van Hage M, Kuehn A: Diagnosis of allergy to mammals and fish: Cross-reactive vs. specific markers. Curr Allergy Asthma Rep. 2017 Aug 22;17(9):64

HORS
82874

Horse Dander, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants

and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to horse dander Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

HFSF
82608

Horsefly/Stablefly, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to horsefly/stablefly Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FHORS
57934

Horseradish (Armoracia rusticana/A.lapathifolia)IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

DF
82905

House Dust Mites/Dermatophagoides farinae, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to

allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to house dust mites/Dermatophagoides farinae Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

DP
82904

House Dust Mites/Dermatophagoides pteronyssinus, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend

upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to house dust mites/Dermatophagoides pteronyssinus Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

HD1
81877

House Dust Panel, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants

and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to cockroach, Dermatophagoides farinea, Dermatophagoides pteronyssinus, and house dust/H-S lab Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

HDG
82906

House Dust/Greer Lab, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to

inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to house dust/Greer lab Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

HDHS
82903

House Dust/H-S Lab, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to house dust/H-S lab Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FHTL
91491

HTLV I/II DNA, Qualitative Real-Time PCR

Reference Values:
Not Detected

FHAM
57856

Human Anti-mouse Antibody (HAMA)

Reference Values:
< or = 74 ng/mL

HCG
70455

Human Chorionic Gonadotropin (hCG) Immunostain, Technical Component Only

Clinical Information: Human chorionic gonadotropin (hCG) is produced by the syncytiotrophoblasts of the placenta and has the same biologic properties as pituitary luteinizing hormone (LH). hCG stimulates androgen and progesterone production in women and helps maintain the corpus luteum of pregnancy. hCG is a heterodimeric hormone of 36kD with subunits designated alpha and beta. Many neoplasms including choriocarcinomas and adenocarcinomas may express hCG.

Useful For: Identification human chorionic gonadotropin expression in neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Lenhard M, Tsvilina A, Schumacher L, et al. Human chorionic gonadotropin and its relation to grade, stage and patient survival in ovarian cancer. BMC Cancer. 2012;12:2. doi:10.1186/1471-2407-12-2 2. Mustafa A, Bozdag Z, Tepe NB, Ozcan HC. An unexpected reason for elevated human chorionic gonadotropin in a young woman. Cervical squamous carcinoma. Saudi Med J. 2016;37(8):905-907. doi:10.15537/2016.8.14529 3. Khattri S, Vivekanandarajah A, Varma S, Kong F. Secretion of beta-human chorionic gonadotropin by non-small cell lung cancer: a case report. J Med Case Rep. 2011;5:19. doi:10.1186/1752-1947-5-19 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

THCG
80678

Human Chorionic Gonadotropin (hCG), Quantitative, Pregnancy, Serum

Clinical Information: Human chorionic gonadotropin (hCG) is a glycoprotein hormone that consists of 2 subunits (alpha and beta chains) that are associated to comprise the intact hormone. The alpha subunit is similar to those of luteinizing hormone, follicle-stimulating hormone, and thyrotropin (formerly thyroid-stimulating hormone). The beta subunit of hCG differs from other pituitary glycoprotein hormones, which results in its unique biochemical and immunological properties. This method quantitates the sum of intact hCG plus the beta subunit. hCG is produced in the placenta during pregnancy. In nonpregnant individuals, it can also be produced by tumors of the trophoblast, germ cell tumors with trophoblastic components, and some nontrophoblastic tumors. The biological action of hCG serves to maintain the corpus luteum during pregnancy. It also influences steroid production. The serum in pregnant individuals contains mainly intact hCG. Measurement of the hCG concentration permits the diagnosis of pregnancy as early as 1 week after conception.

Useful For: Early detection of pregnancy Investigation of suspected ectopic pregnancy or other pregnancy-related complications Monitoring in vitro fertilization patients This test is not useful for detecting or monitoring tumors or gestational trophoblastic disease.

Interpretation: Values in pregnancy should double every 2 to 3 days for the first 6 weeks. Elevated concentrations of human chorionic gonadotropin (hCG) measured in the first trimester of pregnancy are observed in normal pregnancy but may serve as an indication of chorionic carcinoma, hydatiform mole, or multiple pregnancy. Decreasing hCG concentrations indicate threatened or missed abortion, recent termination of pregnancy, ectopic pregnancy, gestosis, or intrauterine death. Both normal and ectopic pregnancies generally yield positive results of pregnancy tests. The comparison of quantitative hCG measurements with the results of transvaginal ultrasonography (TVUS) may aid in the diagnosis of ectopic pregnancy. When an embryo is first large enough for the gestation sac to be visible on TVUS, the patient generally will have hCG concentrations between 1000 and 2000 IU/L. (These are literature values.

Definitive values for this method have not been established at this time.) If the hCG value is this high and no sac is visible in the uterus, ectopic pregnancy is suggested. Elevated values will also be seen with choriocarcinoma and hydatiform mole. Peri- and postmenopausal females may have detectable hCG concentrations (< or = to 14 IU/L) due to pituitary production of hCG. Serum follicle-stimulating hormone measurement may aid in ruling-out pregnancy in this population. Cutoffs of greater than 20 to 45 IU/L have been suggested and are method dependent.

Reference Values:
Negative: <5 IU/L

Clinical References: 1. Snyder JA, Haymond S, Parvin CA, et al: Diagnostic considerations in the measurement of human chorionic gonadotropin in aging women. Clin Chem. 2005 Oct;51(10):1830-1835. doi: 10.1373/clinchem.2005.053595 2. Nerenz RD, Braga JA: Pregnancy and its disorders. In: Rifai N, Chiu RWK, Young I, Burnham ACD, Wittwer CT eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 59

HE4
62137

Human Epididymis Protein 4, Serum

Clinical Information: Human epididymis (HE) protein 4 belongs to the family of whey acidic four-disulfide core (WFDC) proteins. Currently, the biologic function of HE4 is unknown. Human epididymis protein 4 has been shown to be overexpressed in 93% of serous, 100% of endometrioid, and 50% of clear cell ovarian carcinomas. In a study of 233 patients with a pelvic mass, including 67 with epithelial ovarian cancer, HE4 had a higher sensitivity for ovarian cancer detection than cancer antigen (CA) 125, 72.9% versus 43.3%, respectively, at a specificity of 95%. Researchers also found HE4 to be elevated in more than half of the ovarian cancer patients who did not have elevated CA 125 levels; therefore, the combination of markers provided slightly improved cancer diagnostic sensitivity for the detection of ovarian cancer. The main established application of HE4 is in post-therapy monitoring of ovarian cancer patients, who had elevated pretreatment levels. In this setting, it complements CA 125 measurement and facilitates follow-up of patients with little or no CA 125 pretreatment elevations. Certain histological types of ovarian cancer (mucinous or germ cell tumors) rarely express HE4, therefore the use of HE4 is not recommended for monitoring of patients with these types of ovarian cancer.

Useful For: Aiding in monitoring patients with treated epithelial ovarian cancer for recurrence or progression This test should not be used as a screening test for ovarian cancer.

Interpretation: Increase in human epididymis protein 4 (HE4) suggests recurrence or disease progression, while a decrease suggests therapeutic response. A change in serum HE4 concentration of greater than or equal to 20% is considered significant.

Reference Values:
Females: < or =140 pmol/L
Males: Not applicable

Clinical References: 1. Moore RG, Brown AK, Miller MC, et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. Gynecol Oncol. 2008;108(2):402-408 2. Ferraro S, Braga F, Lanzoni M, Boracchi P, Biganzoli EM, Panteghini M. Serum human epididymis protein 4 vs carbohydrate antigen 125 for ovarian cancer diagnosis: a systematic review. J Clin Pathol. 2013;66(4):273-281 3. Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. J Ovarian Res. 2019;12(1):28. Published 2019 Mar 27. doi:10.1186/s13048-019-0503-7

HRPV8
70458

Human Herpes Virus, Type 8 (HHV-8) Immunostain, Technical Component Only

Clinical Information: Human herpes virus type 8 infection can lead to the development of lymphoproliferative diseases or other neoplasms, especially in the setting of HIV. These neoplasms include the plasma cell variant of Castleman disease, Kaposi sarcoma, and primary effusion lymphoma.

Useful For: Identification of human herpes virus type 8 infection

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Beukes CA, Thiart J. The incidence of human herpes virus-8 expression in lymph node biopsies from human immunodeficiency virus-positive patients. Histopathology. 2012;61(5):942-944. doi:10.1111/j.1365-2559.2012.04291.x 2. Roe CJ, Siddiqui MT, Lawson D, Cohen C. RNA In Situ Hybridization for Epstein-Barr Virus and Cytomegalovirus: Comparison With In Situ Hybridization and Immunohistochemistry. Appl Immunohistochem Mol Morphol. 2019;27(2):155-159. doi:10.1097/PAI.0000000000000568 3. Speicher DJ, Wanzala P, D'Lima M, et al. Diagnostic challenges of oral and cutaneous Kaposi's sarcoma in resource-constrained settings. J Oral Pathol Med. 2015;44(10):842-849. doi:10.1111/jop.12315 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

QHV6P
619925

Human Herpesvirus-6 A and B DNA Detection and Quantification, PCR, Plasma

Clinical Information: Human herpesvirus-6 (HHV-6) is a member of the Herpesviridae family. These DNA viruses contain a capsid surrounded by a lipid envelope. Among members of this group, this virus is most closely related to cytomegalovirus (CMV) and HHV-7. As with other members of the herpesvirus group (herpes simplex virus [HSV]-1, HSV-2, varicella-zoster virus, CMV, Epstein-Barr virus, HHV-7, HHV-8), HHV-6 may cause primary and reactivated infections.(1) Infection with HHV-6 occurs early in childhood. Most adults (80%-90%) have been infected with this virus. Human herpesvirus-6 was first linked with exanthem subitum (roseola infantum) in 1998; since then, the virus has been associated with central nervous system disease almost exclusively in patients who are immunocompromised.(1) HHV-6 is commonly detected in patients post transplantation. Clinical symptoms associated with this viral infection include febrile illness, pneumonitis, hepatitis, and encephalitis. However, most HHV-6 infections are asymptomatic.(2) Human herpesvirus-6 is designated as variant A (HHV-6A) or variant B (HHV-6B) depending on restriction enzyme digestion patterns and its reaction with monoclonal antibodies. Generally, variant B has been associated with exanthem subitum, whereas variant A has been found in many immunosuppressed patients.(3) Infection with HHV-6 is very common, approaching 100% seroprevalence in developed countries.(4) In about 1% of the population, HHV-6 can integrate into the host genome. Often asymptomatic in immunocompetent hosts, reactivation can cause serious disease in immunocompromised individuals, particularly those with AIDS and transplant recipients, which can cause rejection of the transplanted organ and even death.(1) This assay will be used to assist with diagnosis and monitoring of HHV-6 disease in patients who are suspected of having disease due to HHV-6 infection. It will also be used as an initial indicator of infection versus chromosomally-integrated HHV-6.

Useful For: As an adjunct in the rapid diagnosis of human herpesvirus-6 infection using plasma specimens This test should not be used to screen asymptomatic patients

Interpretation: The quantification range of this assay is 500 to 5,000,000 copies/mL (2.70 log to 6.70 log copies/mL) An "Undetected" test result indicates the absence of human herpesvirus-6 (HHV-6) DNA in plasma. A test result of "<500 copies/mL (<2.70 log copies/mL)" indicates that HHV-6 DNA is detected in the plasma, but the assay cannot accurately quantify the level of HHV-6 DNA. A test result of ">5,000,000 copies/mL (>6.70 log copies/mL)" indicates that the HHV-6 DNA level present in plasma is above 5,000,000 copies/mL (6.70 log copies/mL), and the assay cannot accurately quantify the level of HHV-6 DNA. A viral load above 5,000,000 copies/mL should raise suspicion for chromosomally-integrated HHV-6 (ciHHV-6), and additional testing to rule out ciHHV-6 may be needed. An "Inconclusive" result indicates that the presence or absence of HHV-6 DNA in the plasma specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to inhibition or the presence of an interfering substance. If clinically indicated, submission of a new specimen for testing is recommended.

Reference Values:
Undetected

Clinical References: 1. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. Clin Microbiol Rev. 2015;28(2):313-335 2. De Bolle L, Naesens L, De Clercq E. Update on human herpesvirus 6 biology, clinical features, and therapy. Clin Microbiol Rev. 2005;18(1):217-245 3. Dockrell DH, Paya CV. Human herpesvirus-6 and -7 in transplantation. Rev Med Virol. 2001;11(1):23-36 4. Campadelli-Fiume G, Mirandola P, Menotti L. Human herpesvirus 6: An emerging pathogen. Emerging Infectious Diseases. 1999;5(3):353-366. doi:10.3201/eid0503.990306 5. Abdel-Haq NM, Asmar BI. Human herpesvirus 6 (HHV6) infection. Indian J Pediatr. 2004;71(1):89-96 6. Dockrell DH, Smith TF, Paya CV. Human herpesvirus 6. Mayo Clin Proc. 1999;74(2):163-170 7. Pellet Madan RP, Hand J; AST Infectious Diseases Community of Practice. Human herpesvirus 6, 7, and 8 in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant, 2019;33(9):e13518. doi:10.1111/ctr.13518 8. Pawlowski AB, Karras NA, Liu H, et al. Reactivation of human herpesvirus 6 in pediatric allogeneic hematopoietic stem cell transplant recipients. Transpl Infect Dis. 2021;23(1):e13453. doi:10.1111/tid.13453 9. Yip CCY, Sridhar S, Cheng AKW, et al. Comparative evaluation of a laboratory developed real-time PCR assay and the RealStar HHV-6 PCR Kit for quantitative detection of human herpesvirus 6. J Virol Methods. 2017;246:112-116

QHV6C 619924 Human Herpesvirus-6 A and B DNA Detection and Quantification, PCR, Spinal Fluid

Clinical Information: Human herpesvirus-6 (HHV-6) is a member of the Herpesviridae family. These DNA viruses contain a capsid surrounded by a lipid envelope. Among members of this group, this virus is most closely related to cytomegalovirus (CMV) and HHV-7. As with other members of the herpesvirus group (herpes simplex virus [HSV]-1, HSV-2, varicella-zoster virus, CMV, Epstein-Barr virus, HHV-7, HHV-8), HHV-6 may cause primary and reactivated infections.(1) Infection with HHV-6 occurs early in childhood. Most adults (80%-90%) have been infected with this virus. Human herpesvirus-6 was first linked with exanthem subitum (roseola infantum) in 1998; since then, the virus has been associated with central nervous system disease almost exclusively in patients who are immunocompromised.(1) HHV-6 is commonly detected in patients post transplantation. Clinical symptoms associated with this viral infection include febrile illness, pneumonitis, hepatitis, and encephalitis. However, most HHV-6 infections are asymptomatic.(2) Human herpesvirus-6 is designated as variant A (HHV-6A) or variant B (HHV-6B) depending on restriction enzyme digestion patterns and its reaction with monoclonal antibodies. Generally, variant B has been associated with

exanthem subitum, whereas variant A has been found in many immunosuppressed patients.(3) Infection with HHV-6 is very common, approaching 100% seroprevalence in developed countries.(4) In about 1% of the population, HHV-6 can integrate into the host genome. Often asymptomatic in immunocompetent hosts, reactivation can cause serious disease in immunocompromised individuals, particularly those with AIDS and transplant recipients, which can cause rejection of the transplanted organ and even death.(1) This assay will be used to assist with diagnosis and monitoring of HHV-6 disease in patients who are suspected of having disease due to HHV-6 infection. It will also be used as an initial indicator of infection versus chromosomally-integrated HHV-6.

Useful For: As an adjunct in the rapid diagnosis of human herpesvirus-6 infection using cerebrospinal fluid specimens This test should not be used to screen asymptomatic patients.

Interpretation:

Reference Values:
Undetected

Clinical References:

1DIS 609354 Human Leukocyte Antigens (HLA) A-B-C Disease Association Typing Low Resolution, Blood

Clinical Information: Human leukocyte antigens (HLA) are regulators of the immune response. HLA class I typing is used to identify HLA-matched platelets for alloimmunized refractory patients and identify presence of HLA antigens associated with a number of diseases or as drug hypersensitivity markers class I HLA antigens include A, B, and C loci.

Useful For: Determining class I human leukocyte antigens (HLA) on specimens for those patients who have become refractory to platelet transfusions and identify potential disease associations or markers for drug hypersensitivity

Interpretation: Interpretation depends on the rationale for ordering the test.

Reference Values:
Not applicable

Clinical References: 1. Terasaki PI, Bernoco D, Park MS, Ozturk G, Iwaki Y. Microdroplet testing for HLA-A, -B, -C, and -D antigens. The Phillip Levine Award Lecture. Am J Clin Pathol. 1978;69(2):103-120 2. Colinas RJ, Bellisario R, Pass KA. Multiplexed genotyping of beta-globin variants from PCR-amplified newborn blood spot DNA by hybridization with allele-specific oligodeoxynucleotides coupled to an array of fluorescent microspheres. Clin Chem. 2000;46(7):996-998 3. Kennedy AE, Ozbek U, Dorak MT. What has GWAS done for HLA and disease associations?. Int J Immunogenet. 2017;44(5):195-211. doi:10.1111/iji.12332 4. Caillat-Zucman S. New insights into the understanding of MHC associations with immune-mediated disorders. HLA. 2017;89(1):3-13. doi: 10.1111/tan.12947 5. Howell WM. HLA and disease: guilt by association. Int J Immunogenet. 2014;41(1):1-12. doi:10.1111/iji.12088 6. Profaizer T, Pole A, Monds C, Delgado JC, Lazar-Molnar E. Clinical utility of next generation sequencing based HLA typing for disease association and pharmacogenetic testing. Hum Immunol. 2020;81(7):354-360

DIS 618568

Human Leukocyte Antigens (HLA) Class I and II Disease Association Typing, Low Resolution, Blood

Clinical Information: Human leukocyte antigens (HLA) class I and II genes (A, B, C, DRB1, DRB3/4/5, DQB1, DQA1, DPB1, DPA1) are a part of the major histocompatibility gene complex that encodes for proteins involved in immune recognition and are regulators of the immune response.

Useful For: Identifying class I and II human leukocyte antigens (HLA) for potential disease associations or markers for drug hypersensitivity

Interpretation: Interpretation depends on the rationale for ordering the test.

Reference Values:
Not applicable

Clinical References: 1. Terasaki PI, Bernoco D, Park MS, Ozturk G, Iwaki Y. Microdroplet testing for HLA-A, -B, -C, and -D antigens. The Phillip Levine Award Lecture. Am J Clin Pathol. 1978;69(2):103-120 2. Colinas RJ, Bellisario R, Pass KA. Multiplexed genotyping of beta-globin variants from PCR-amplified newborn blood spot DNA by hybridization with allele-specific oligodeoxynucleotides coupled to an array of fluorescent microspheres. Clin Chem. 2000;46(7):996-998 3. Kennedy AE, Ozbek U, Dorak MT. What has GWAS done for HLA and disease associations?. Int J Immunogenet. 2017;44(5):195-211. doi:10.1111/iji.12332 4. Caillat-Zucman S. New insights into the understanding of MHC associations with immune-mediated disorders. HLA. 2017;89(1):3-13. doi:10.1111/tan.12947 5. Howell WM. HLA and disease: guilt by association. Int J Immunogenet. 2014;41(1):1-12. doi:10.1111/iji.12088 6. Profaizer T, Pole A, Monds C, Delgado JC, Lazar-Molnar E. Clinical utility of next generation sequencing based HLA typing for disease association and pharmacogenetic testing. Hum Immunol. 2020;81(7):354-360

2DIS
609356

Human Leukocyte Antigens (HLA)-DR-DQ Disease Association Typing Low Resolution, Blood

Clinical Information: Human leukocyte antigen (HLA) class II genes (HLA-DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPA1, -DPB1) are a part of the major histocompatibility gene complex that encodes for proteins involved in immune recognition.

Useful For: Determining class II human leukocyte antigens (HLA) to identify potential disease associations or markers for drug hypersensitivity

Interpretation: Interpretation depends on the rationale for ordering the test.

Reference Values:
Not applicable

Clinical References: 1. Terasaki PI, Bernoco D, Park MS, Ozturk G, Iwaki Y. Microdroplet testing for HLA-A, -B, -C, and -D antigens. The Phillip Levine Award Lecture. Am J Clin Pathol. 1978;69(2):103-120 2. Colinas RJ, Bellisario R, Pass KA. Multiplexed genotyping of beta-globin variants from PCR-amplified newborn blood spot DNA by hybridization with allele-specific oligodeoxynucleotides coupled to an array of fluorescent microspheres. Clin Chem. 2000;46(7):996-998 3. Kennedy AE, Ozbek U, Dorak MT. What has GWAS done for HLA and disease associations?. Int J Immunogenet. 2017;44(5):195-211. doi:10.1111/iji.12332 4. Caillat-Zucman S. New insights into the

understanding of MHC associations with immune-mediated disorders. HLA. 2017;89(1):3-13. doi:10.1111/tan.12947 5. Howell WM. HLA and disease: guilt by association. Int J Immunogenet. 2014;41(1):1-12. doi:10.1111/iji.12088 6. Profaizer T, Pole A, Monds C, Delgado JC, Lazar-Molnar E. Clinical utility of next generation sequencing based HLA typing for disease association and pharmacogenetic testing. Hum Immunol. 2020;81(7):354-360

SCHPV 621927 Human Papillomavirus (HPV) Detection and High-Risk Genotyping, Self-Collect, PCR, Vaginal

Clinical Information: Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer. The presence of HPV has been implicated in more than 99% of cervical cancers worldwide, including both cervical squamous cell carcinoma and cervical adenocarcinoma. Before development of invasive cancer, HPV infects the squamous mucosa cells and/or the glandular cells of the endocervix, leading to clonal expansion and morphologic changes. While the HPV-infected cells are restricted to their normal anatomic location, these changes are classified as cervical intraepithelial neoplasia (CIN). The severity of the morphologic changes and the degree to which those changes resemble the morphology of an invasive carcinoma are used to "grade" CIN. In general, high-grade CIN more closely resembles invasive carcinoma morphologically. HPV can also infect other mucosal cells in the anogenital region, such as the vaginal mucosa, leading to the development of HPV-associated intraepithelial neoplasia as well as invasive carcinoma not involving the cervix itself, although this is less common. Human papillomavirus is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs can infect the human anogenital mucosa. Only a very small percentage of patients who are exposed to HPV will develop CIN. Of those patients who develop CIN, only a small percentage will progress to invasive cervical cancer. Sexually transmission of HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without long-term health consequences. Both high-risk HPV genotypes (especially HPV-16 and 18), as well as persistent HPV infection (eg, an infection that is not cleared by the patient's immune system over time), are associated with an increased chance of progressing to high-grade CIN and invasive cancer. Data suggest that certain HPV genotypes (eg, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are high-risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers. In developed countries with cervical cancer screening programs, the Papanicolaou test (ie, Pap smear) has been used since the mid-1950s as the primary tool to morphologically detect CIN, the precursor to cervical cancer. Pap smear screening has decreased death rates due to cervical cancer dramatically, since in many cases CIN can be treated and eliminated (eg, by local excision) before it progresses to invasive carcinoma. Although Pap smears and other liquid-based cytology methods have many advantages, they also have limitations: they require subjective interpretation by a highly trained cytopathologist and misinterpretation can occur, morphologic changes that resemble HPV-associated CIN can be caused by other conditions (eg, inflammation), and Pap smear does not sample every cell within the cervix/anogenital region potentially leading to falsely negative results. Perhaps most importantly, Pap smear does not differentiate between HPV genotypes that are high or low risk for progression to cervical cancer and it does not detect very early infections, which may lack a morphological phenotype. Nucleic acid (DNA) testing by polymerase chain reaction has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may: 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women aged 30 years and older with normal cytology. 2) reduce the need for unnecessary colposcopy and treatment in patients aged 21 and older with cytology results showing atypical squamous cells of undetermined significance. Data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of

CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% CI 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes, and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV-negative women. Based in part on these data, the American Society for Colposcopy and Cervical Pathology now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.

Useful For: Human papillomavirus (HPV) screening for average-risk, asymptomatic individuals who are eligible for primary HPV testing, have barriers to a speculum exam for a clinician-collected cervical sample for screening, and who are able to self-collect a vaginal sample in a healthcare setting This test is not intended for symptomatic patients (eg, pelvic pain, abnormal uterine bleeding).

Interpretation: HPV 16 Positive: Human papillomavirus (HPV) 16 DNA detected. Referral for colposcopy indicated. HPV18 Positive: HPV18 DNA detected. Referral for colposcopy indicated. HPV High Risk Other Positive: HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and/or 68 DNA detected. Additional testing (Pap/cytology or dual stain) on a clinician-collected cervical/endocervical specimen indicated. HPV 16/18/HRO Negative: No HPV DNA detected. Repeat cervical cancer screening in 3 years. When providing management advice, take into consideration past test results as per current American Society for Colposcopy and Cervical Pathology guidelines.

Reference Values:
Negative for human papillomavirus (HPV) genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Clinical References: 1. US Preventive Services Task Force, Curry SJ, Krist AH, et al. Screening for Cervical Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2018;320(7):674-686. doi:10.1001/jama.2018.10897 2. Poljak M, Ostrbenk Valencak A, Cuschieri K, Bohinc KB, Arbyn M. 2023 Global inventory of commercial molecular tests for human papillomaviruses (HPV). J Clin Virol. 2024;172:1105671 3. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2020;24(2):102-131. doi:10.1097/LGT.0000000000000525

HPVP 62995 Human Papillomavirus (HPV) DNA Detection with Genotyping, High Risk Types by PCR with Papanicolaou Smear Reflex, ThinPrep, Varies

Clinical Information: Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer. The presence of HPV has been implicated in more than 99% of cervical cancers worldwide, including both cervical squamous cell carcinoma and cervical adenocarcinoma. Before the development of invasive cancer, HPV infects the squamous mucosa cells and/or the glandular cells of the endocervix, leading to clonal expansion and morphologic changes. While the HPV-infected cells are restricted to their normal anatomic location, these changes are classified as cervical intraepithelial neoplasia (CIN). The severity of the morphologic changes and the degree to which those changes resemble the morphology of an invasive carcinoma are used to "grade" CIN. In general, high-grade CIN more closely resembles invasive carcinoma morphologically. HPV can also infect other mucosal cells in the anogenital region, such as the vaginal mucosa, leading to the development of HPV-associated intraepithelial neoplasia as well as invasive carcinoma not involving the cervix itself, although this is less common. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV and approximately 40

different HPVs can infect the human anogenital mucosa. Only a very small percentage of patients who are exposed to HPV will develop CIN. Of those patients who develop CIN, only a small percentage will progress to invasive cervical cancer. Sexual transmission of HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without long-term health consequences. Both high-risk HPV genotypes (especially HPV-16 and 18) and persistent HPV infection (eg, an infection that is not cleared by the patient's immune system over time) are associated with an increased chance of progressing to high-grade CIN and invasive cancer. Data suggest that certain HPV genotypes (eg, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are high-risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to morphologically detect CIN, the precursor to cervical cancer. Pap smear screening has decreased death rates due to cervical cancer dramatically, since in many cases CIN can be treated and eliminated (eg, by local excision) before it progresses to invasive carcinoma. Although Pap smears and other liquid-based cytology methods have many advantages, they also have limitations: they require subjective interpretation by a highly trained cytopathologist and misinterpretation can occur, morphologic changes that resemble HIV-associated CIN can be caused by other conditions (eg, inflammation), and Pap smear does not sample every cell within the cervix/anogenital region potentially leading to false-negative results. Perhaps most importantly, a Pap smear does not differentiate between HPV genotypes that are high or low risk for progression to cervical cancer, and it does not detect very early infections, which may lack a morphological phenotype. Nucleic acid (DNA) testing by polymerase chain reaction has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may: 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance Data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% CI, 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for "other" HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women. Based in part on these data, the American Society for Colposcopy and Cervical Pathology now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology/Pap smear. Women who are found to be positive for HPV-16 and/or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and/or 18 may have repeat cytology and HR-HPV testing in 12 months. Recently, the US Food and Drug Administration approved the use of the Roche cobas HPV test for primary screening of cervical and endocervical samples collected in ThinPrep/PreservCyt media. In addition, the age at which patients may be screened by the HPV test has dropped from 30 to 25 years old.

Useful For: Screening for infection with high-risk human papillomavirus (HPV) associated with the development of cervical cancer Individual genotyping of HPV-16 and/or HPV-18 if present This testing is intended for use in clinical monitoring and management of patients. It is not intended for use in medical-legal applications. This test is not intended for women who have undergone hysterectomy. This test is not intended for use with samples other than those collected by a clinician using an endocervical brush or spatula and placed in the ThinPrep Pap test PreservCyt solution. This test is not intended for use in determining the need for treatment (ie, excisional or ablative treatment of the cervix) in the absence of high-grade cervical dysplasia. Patients who are HPV16/18 positive should be monitored carefully for the development of high-grade cervical dysplasia according to current practice guidelines.

Interpretation: Human papillomavirus with Genotyping Polymerase Chain Reaction: A positive result indicates the presence of human papillomavirus (HPV) DNA due to 1 or more of the following genotypes:

16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance Pap smear result and who are positive for high-risk-HPV, consider referral for colposcopy, if clinically indicated. For women 25 years and older who are positive for HPV-16 and/or HPV-18 but negative by Pap smear, consider referral for colposcopy, if clinically indicated. Cytology: Standard reporting, as defined by the Bethesda System (TBS) is utilized.

Reference Values:

Human papillomavirus (HPV) with Genotyping polymerase chain reaction: Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

ThinPrep Pap Test: Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

Clinical References: 1. Perkins RB, Guido RS, Castle PE, et al: 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors [published correction appears in J Low Genit Tract Dis. 2020 Oct;24(4):427]. J Low Genit Tract Dis. 2020;24(2):102-131. doi:10.1097/LGT.0000000000000525 2. Wright TC Jr, Stoler MH, Behrens CM, Apple R, Derion T, Wright TL. The ATHENA human papillomavirus study: design, methods, and baseline results. Am J Obstet Gynecol. 2012;206(1):46.e1-46.e11. doi:10.1016/j.ajog.2011.07.024 3. Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. Gynecol Oncol. 2015;136(2):189-197. doi:10.1016/j.ygyno.2014.11.076

SHPV
62599

Human Papillomavirus (HPV) DNA Detection with Genotyping, High-Risk Types by PCR, SurePath, Varies

Clinical Information: Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer. The presence of HPV has been implicated in more than 99% of cervical cancers worldwide, including both cervical squamous cell carcinoma and cervical adenocarcinoma. Before the development of invasive cancer, HPV infects the squamous mucosa cells and/or the glandular cells of the endocervix, leading to clonal expansion and morphologic changes. While the HPV-infected cells are restricted to their normal anatomic location, these changes are classified as cervical intraepithelial neoplasia (CIN). The severity of the morphologic changes and the degree to which those changes resemble the morphology of an invasive carcinoma are used to "grade" CIN. In general, high-grade CIN more closely resembles invasive carcinoma morphologically. HPV can also infect other mucosal cells in the anogenital region, such as the vaginal mucosa, leading to the development of HPV-associated intraepithelial neoplasia as well as invasive carcinoma not involving the cervix itself, although this is less common. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs can infect the human anogenital mucosa. Only a very small percentage of patients who are exposed to HPV will develop CIN. Of those patients, only a small percentage will progress to invasive cervical cancer. Sexual transmission of HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without long-term health consequences. Both high-risk HPV genotypes (especially HPV-16 and 18), as well as persistent HPV infection (eg, an infection that is not cleared by the patient's immune system over time), are associated with an increased chance of progressing to high-grade CIN and invasive cancer. Data suggest that certain HPV genotypes (eg, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are high risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all cervical

cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to morphologically detect CIN, the precursor to cervical cancer. Pap smear screening has decreased death rates due to cervical cancer dramatically, since in many cases CIN can be treated and eliminated (eg, by local excision) before it progresses to invasive carcinoma. Although Pap smears and other liquid-based cytology methods have many advantages, they also have limitations: they require subjective interpretation by a highly trained cytopathologist and misinterpretation can occur, morphologic changes that resemble HIV-associated CIN can be caused by other conditions (eg, inflammation), and Pap smear does not sample every cell within the cervix/anogenital region potentially leading to falsely negative results. Perhaps most importantly, Pap smear does not differentiate between HPV genotypes that are high or low risk for progression to cervical cancer and it does not detect very early infections, which may lack a morphological phenotype. Nucleic acid (DNA) testing by polymerase chain reaction has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may: 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance. Data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% CI, 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for "other" HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women. Based in part on these data, the American Society for Colposcopy and Cervical Pathology now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV, but negative by routine cytology/Pap smear. Women who are found to be positive for HPV-16 and/or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and/or 18 may have repeat cytology and HR HPV testing in 12 months.

Useful For: Detection of high-risk (HR) genotypes associated with the development of cervical cancer An aid in triaging women with abnormal Pap smear test results Individual genotyping of human papillomavirus (HPV)-16 and/or HPV-18, if present This testing is intended for use in clinical monitoring and management of patients. It is not intended for use in medical-legal applications.

Interpretation: A positive result indicates the presence of human papillomavirus (HPV) DNA from one or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. For patients with atypical squamous cells of undetermined significance Pap smear test result and who are positive for high-risk (HR) HPV, consider referral for colposcopy, if clinically indicated. A negative result indicates the absence of HPV DNA of the targeted genotypes. For women aged 30 years and older with a negative Pap smear test result but who are positive for HPV-16 and/or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear test result, positive HR HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR HPV test in 12 months.

Reference Values:
Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Clinical References: 1. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. J Low Genit Tract Dis. 2012;16(3):175-204. doi: 10.1097/LGT.0b013e31824ca9d5 2. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189:12-19. doi:10.1002/(SICI)1096-9896(199909)189:1 3. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11:1048-1056. doi:10.1016/S1470-2045(10)70230-8 4. Wright TC Jr, Stoler MH, Sharma A, et al. Evaluation of HPV-16 and HPV-18 genotyping for the triage of women

with high-risk HPV positive, cytology-negative results. Am J Clin Pathol. 2011;136(4):578-586. doi:10.1309/AJCPTUS5EXAS6DKZ

HPV
62598

Human Papillomavirus (HPV) DNA Detection with Genotyping, High-Risk Types by PCR, ThinPrep, Varies

Clinical Information: Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer. The presence of HPV has been implicated in more than 99% of cervical cancers worldwide, including both cervical squamous cell carcinoma and cervical adenocarcinoma. Before the development of invasive cancer, HPV infects the squamous mucosa cells and/or the glandular cells of the endocervix, leading to clonal expansion and morphologic changes. While the HPV-infected cells are restricted to their normal anatomic location, these changes are classified as cervical intraepithelial neoplasia (CIN). The severity of the morphologic changes and the degree to which those changes resemble the morphology of an invasive carcinoma are used to "grade" CIN. In general, high-grade CIN more closely resembles invasive carcinoma morphologically. HPV can also infect other mucosal cells in the anogenital region, such as the vaginal mucosa, leading to the development of HPV-associated intraepithelial neoplasia as well as invasive carcinoma not involving the cervix itself, although this is less common. HPV is a small, nonenveloped, double-stranded DNA virus with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV, and approximately 40 different HPVs can infect the human anogenital mucosa. Only a very small percentage of patients exposed to HPV will develop CIN. Of those patients who develop CIN, only a small percentage will progress to invasive cervical cancer. Sexual transmission of HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without long-term health consequences. Both high-risk HPV genotypes (especially HPV-16 and 18) and persistent HPV infection (eg, an infection that is not cleared by the patient's immune system over time) are associated with an increased chance of progressing to high-grade CIN and invasive cancer. Data suggest that certain HPV genotypes (eg, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are high-risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to morphologically detect CIN, the precursor to cervical cancer. Pap smear screening has decreased death rates due to cervical cancer dramatically, since in many cases CIN can be treated and eliminated (eg, by local excision) before it progresses to invasive carcinoma. Although Pap smears and other liquid-based cytology methods have many advantages, they also have limitations: they require subjective interpretation by a highly trained cytopathologist and misinterpretation can occur, morphologic changes that resemble HIV-associated CIN can be caused by other conditions (eg, inflammation), and Pap smear does not sample every cell within the cervix/anogenital region potentially leading to falsely negative results. Perhaps most importantly, a Pap smear does not differentiate between HPV genotypes that are high or low risk for progression to cervical cancer, and it does not detect very early infections, which may lack a morphological phenotype. Nucleic acid (DNA) testing by polymerase chain reaction has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may: 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology. 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance. Data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% CI 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes, and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV-negative women.(4)

Based on these data, the American Society for Colposcopy and Cervical Pathology now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 and/or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.

Useful For: Detecting high-risk (HR) genotypes associated with the development of cervical cancer Aiding in triaging women with abnormal Pap smear test results Individual genotyping of human papillomavirus (HPV)-16 and/or HPV-18 if present Results of HPV-16 and HPV-18 genotyping can aid in triaging women with positive HR-HPV but negative Pap smear results This testing is intended for use in clinical monitoring and management of patients. It is not intended for use in medical-legal applications. This test is not intended for use in determining the need for treatment (ie, excisional or ablative treatment of the cervix) in the absence of high-grade cervical dysplasia. Patients who are HPV16/18 positive should be monitored carefully for the development of high-grade cervical dysplasia according to current practice guidelines. This test is not intended for women who have undergone hysterectomy. This test is not intended for use with samples other than those collected by a clinician using an endocervical brush or spatula and placed in the ThinPrep Pap test PreservCyt solution.

Interpretation: A positive result indicates the presence of human papillomavirus (HPV) DNA from one or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance Pap smear result and who are positive for high-risk (HR) HPV, consider referral for colposcopy, if clinically indicated. For women 25 years and older with a negative Pap smear result but who are positive for HPV-16 and/or HPV-18, consider referral for colposcopy, if clinically indicated. For women 25 years and older with a negative Pap smear, positive-HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

Reference Values:
Negative for human papillomavirus (HPV) genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Clinical References: 1. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. J Low Genit Tract Dis. 2012;16(3):175-204. doi: 10.1097/LGT.0b013e31824ca9d5 2. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12-19. doi: 10.1002/(SICI)1096-9896(199909)189:1 3. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11(11):1048-1056. doi: 10.1016/S1470-2045(10)70230-8 4. Wright TC Jr, Stoler MH, Sharma A, Zhang G, Behrens C, Wright TL: Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV positive, cytology-negative results. Am J Clin Pathol. 2011;136(4):578-586. doi: 10.1309/AJCPTUS5EXAS6DKZ

HPVE6
71405

Human Papillomavirus (HPV) High-Risk E6/E7, RNA In Situ Hybridization

Clinical Information: This assay is intended to identify the presence of human papillomavirus (HPV) E6/E7 transcripts from high-risk genotypes. Patients with HPV-related oropharyngeal squamous cell carcinoma (OPSCC) have shown better disease-specific survival and overall survival when compared to HPV-negative cases of OPSCC. An indication for this test is p16 expression by immunohistochemistry.

Useful For: Stratification of oropharyngeal squamous cell carcinoma

Interpretation: This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

Reference Values:
Results are reported as positive or negative for types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82.

Clinical References: 1. Lindemann ML, Dominguez MJ, de Antonio JC, et al. Analytical comparison of the cobas HPV test with hybrid capture 2 for the detection of high-risk HPV genotypes. J Mol Diagn. 2012;14(1):65-70 2. Bishop JA, Ma XJ, Wang H, et al. Detection of transcriptionally active high-risk HPV in patients with head and neck squamous cell carcinoma as visualized by a novel E6/E7 mRNA in situ hybridization method. Am J Surg Pathol. 2012;36(12):1874-1882 3. Mirghani H, Casiraghi O, Guerlain J, et al. Diagnosis of HPV driven oropharyngeal cancers: Comparing p16 based algorithms with the RNAscope HPV-test. Oral oncology. 2016;62:101-108 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HPVHL 70464 Human Papillomavirus (HPV) High/Low Risk, In Situ Hybridization

Clinical Information: Human papillomavirus (HPV) infections with low-risk genotypes (6, 11) can cause benign hyperplasia such as condylomas and papillomas. Persistent infections with high-risk genotypes (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82) are associated with cervical, vaginal, vulvar, and head and neck malignancies. Patients with HPV-related oropharyngeal squamous cell carcinoma (OPSCC) have shown better disease-specific survival and overall survival when compared to HPV-negative cases of OPSCC.

Useful For: Detecting human papillomavirus for both low-risk (6, 11) and high-risk (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82.) genotypes

Interpretation: This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

Reference Values:
Results are reported as positive or negative for types 6 and 11 (low risk), and 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82(high risk).

Clinical References: 1. Lindemann ML, Dominguez MJ, de Antonio JC, et al: Analytical comparison of the cobas HPV test with hybrid capture 2 for the detection of high-risk HPV genotypes. J Mol Diagn. 2012 Jan;14(1):65-70 2. Bishop JA, Ma XJ, Wang H, et al: Detection of transcriptionally active high-risk HPV in patients with head and neck squamous cell carcinoma as visualized by a novel E6/E7 mRNA in situ hybridization method. Am J Surg Pathol. 2012 Dec;36(12):1874-1882 3. Mirghani H, Casiraghi O, Guerlain J, et al: Diagnosis of HPV driven oropharyngeal cancers: Comparing p16 based algorithms with the RNAscope HPV-test. Oral oncology. 2016;62:101-108

HPVLR 70465 Human Papillomavirus (HPV) Low Risk, In Situ Hybridization

Clinical Information: Human papillomavirus infections with low-risk genotypes (6, 11) can cause benign hyperplasia, such as condylomas and papillomas.

Useful For: Detection of human papillomavirus from low-risk genotypes (6, 11)

Interpretation: This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

Reference Values:
Results are reported as positive or negative for types 6 and 11.

Clinical References: 1. Lindemann ML, Dominguez MJ, de Antonio JC, et al. Analytical comparison of the cobas HPV test with hybrid capture 2 for the detection of high-risk HPV genotypes. J Mol Diagn. 2012;14(1):65-70 2. Bishop JA, Ma XJ, Wang H, et al. Detection of transcriptionally active high-risk HPV in patients with head and neck squamous cell carcinoma as visualized by a novel E6/E7 mRNA in situ hybridization method. Am J Surg Pathol. 2012;36(12):1874-1882 3. Mirghani H, Casiraghi O, Guerlain J, et al. Diagnosis of HPV driven oropharyngeal cancers: Comparing p16 based algorithms with the RNAscope HPV-test. Oral oncology. 2016;62:101-108 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

VHPV
619401

Human Papillomavirus (HPV) Vaginal Detection with Genotyping for High-Risk Types by PCR

Clinical Information: Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer. The presence of HPV has been implicated in more than 99% of cervical cancers worldwide, including both cervical squamous cell carcinoma and cervical adenocarcinoma. Before the development of invasive cancer, HPV infects the squamous mucosa cells and/or the glandular cells of the endocervix, leading to clonal expansion and morphologic changes. While the HPV-infected cells are restricted to their normal anatomic location, these changes are classified as cervical intraepithelial neoplasia (CIN). The severity of the morphologic changes and the degree to which those changes resemble the morphology of an invasive carcinoma are used to "grade" CIN. In general, high-grade CIN more closely resembles invasive carcinoma morphologically. HPV can also infect other mucosal cells in the anogenital region, such as the vaginal mucosa, leading to the development of HPV-associated intraepithelial neoplasia as well as invasive carcinoma not involving the cervix itself, although this is less common. Human papillomavirus is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs can infect the human anogenital mucosa. Only a very small percentage of patients who are exposed to HPV will develop CIN. Of those patients who develop CIN, only a small percentage will progress to invasive cervical cancer. Sexually transmission of HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without long-term health consequences. Both high-risk HPV genotypes (especially HPV-16 and 18), as well as persistent HPV infection (eg, an infection that is not cleared by the patient's immune system over time), are associated with an increased chance of progressing to high-grade CIN and invasive cancer. Data suggest that certain HPV genotypes (eg, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are high-risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to

morphologically detect CIN, the precursor to cervical cancer. Pap smear screening has decreased death rates due to cervical cancer dramatically, since in many cases CIN can be treated and eliminated (eg, by local excision) before it progresses to invasive carcinoma. Although Pap smears and other liquid-based cytology methods have many advantages, they also have limitations: they require subjective interpretation by a highly trained cytopathologist and misinterpretation can occur, morphologic changes that resemble HIV-associated CIN can be caused by other conditions (eg, inflammation), and Pap smear does not sample every cell within the cervix/anogenital region potentially leading to falsely negative results. Perhaps most importantly, Pap smear does not differentiate between HPV genotypes that are high or low risk for progression to cervical cancer and it does not detect very early infections, which may lack a morphological phenotype. Nucleic acid (DNA) testing by polymerase chain reaction has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may: 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology. 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance. Data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes, and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV-negative women. Based in part on these data, the American Society for Colposcopy and Cervical Pathology now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 and/or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.

Useful For: Detection of high-risk (HR) genotypes associated with the development of cervical cancer Aids in triaging women with abnormal Pap smear results Individual genotyping of human papillomavirus (HPV)-16 and/or HPV-18 if present Results of HPV-16 and HPV-18 genotyping can aid in triaging women with positive HR-HPV but negative Pap smear results This testing is intended for use in clinical monitoring and management of patients. It is not intended for use in medical-legal applications. This test is not intended for use in determining the need for treatment (ie, excisional or ablative treatment of the cervix) in the absence of high-grade cervical dysplasia. Patients who are HPV16/18 positive should be monitored carefully for the development of high-grade cervical dysplasia according to current practice guidelines.

Interpretation: A positive result indicates the presence of human papillomavirus (HPV) DNA from one or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. For patients with atypical squamous cells of undetermined significance Pap smear result and who are positive for high-risk (HR) HPV, consider referral for colposcopy, if clinically indicated. A negative result indicates the absence of HPV DNA of the targeted genotypes. For women aged 30 years and older with a negative Pap smear test result but who are positive for HPV-16 and/or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear test result, positive-HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

Reference Values:
Negative for human papillomavirus (HPV) genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Clinical References: 1. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. J Low Genit Tract Dis. 2012;16(3):175-204. doi:10.1097/LGT.0b013e31824ca9d5 2. Walboomers JM, Jacobs MV, Manos

MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12-19. doi:10.1002/(SICI)1096-9896(199909)189:1 3. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11(11):1048-1056. doi:10.1016/S1470-2045(10)70230-8 4. Wright TC Jr, Stoler MH, Sharma A, Zhang G, Behrens C, Wright TL. Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV positive, cytology-negative results. Am J Clin Pathol. 2011;136(4):578-586. doi:10.1309/AJCPTUS5EXAS6DKZ 5. US Preventive Services Task Force, Curry SJ, Krist AH, et al. Screening for cervical cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2018;320(7):674-686. doi:10.1001/jama.2018.10897 6. Poljak M, Balencak AO, Cuschieri K, Bohinc KB, Arbyn M. 2023 global inventory of commercial molecular tests for human papillomaviruses (HPV). J Clin Viro. 2024:172;105671 7. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2020;24(2):102-131. doi:10.1097/LGT.0000000000000525

FHPL
91178

Human Placental Lactogen (HPL)

Clinical Information: Human placental lactogen (hPL; chorionic somatomammotropin) is a 21,000 Da polypeptide produced during pregnancy by placental trophoblastic cells. The level of hPL in maternal serum is directly related to placental function and fetal well-being. Human placental lactogen is detected about 6 weeks after conception and its concentration increases gradually to peak levels (without decreases) until about the 34th week where it remains stable for the remainder of the pregnancy. Consistently low levels throughout pregnancy or a sudden drop in serial determinations are an indication of fetal distress. After normal delivery, the hPL concentration falls rapidly to an undetectable level. The hPL levels in serum of women with multiple placenta pregnancies generally exceeds that of single placenta pregnancies. This is generally noted from the 2nd trimester to delivery.

Reference Values:
Males and nonpregnant Women: 0.0-0.1 mcg/mL
1st Trimester of Pregnancy: 0.2-2.1 mcg/mL
2nd Trimester of Pregnancy: 0.5-6.7 mcg/mL
3rd Trimester of Pregnancy: 4.5-12.8 mcg/mL

HPL
70462

Human Placental Lactogen Immunostain, Technical Component Only

Clinical Information: Human placental lactogen (HPL) is a hormone secreted by the placenta during normal pregnancy. Detection of this hormone may help in diagnosis of placenta-related tumors such as trophoblastic tumors and choriocarcinomas.

Useful For: Aids in the identification of placenta-related tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Huang F, Zheng W, Liang Q, Yin T. Diagnosis and treatment of placental site trophoblastic tumor. Int J Clin Exp Pathol. 2013;6(7):1448-1451 2. Sung WJ, Shin HC, Kim MK,

Kim MJ. Epithelioid trophoblastic tumor: clinicopathologic and immunohistochemical analysis of three cases. Korean J Pathol. 2013;47(1):67-73 3. Luiza JW, Taylor SE, Gao FF, Edwards RP. Placental site trophoblastic tumor: Immunohistochemistry algorithm key to diagnosis and review of literature. Gynecol Oncol Case Rep. 2014;7:13-15 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HBZ
618481

Human T-cell Lymphotropic Virus Type 1 (HTLV-1) bZIP Factor (HBZ), In Situ Hybridization, Technical Component Only

Clinical Information: Adult T-cell leukemia/lymphoma (ATLL) is a T-cell malignancy induced by human T-cell lymphotropic virus 1 (HTLV-1) infection. This test is intended to identify the presence of HTLV-1 in formalin-fixed, paraffin-embedded tissue, which may be useful in the diagnosis of ATLL.

Useful For: Diagnosing adult T-cell leukemia/lymphoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

HTLLC
604935

Human T-Cell Lymphotropic Virus Types 1 and 2 (HTLV-1/-2) Antibody Confirmation, Spinal Fluid

Clinical Information: Human T-cell lymphotropic virus types 1 and 2 (HTLV-1 and HTLV-2) are closely related exogenous human retroviruses. HTLV-1 was first isolated in 1980 from a patient with a cutaneous T-cell lymphoma, while HTLV-2 was identified from a patient with hairy cell leukemia in 1982. HTLV-1 infection is endemic in southwestern Japan, Caribbean basin, Melanesia, and parts of Africa, where HTLV-1 seroprevalence rates are as high as 15% in the general population. In the United States, the combined HTLV-1 and HTLV-2 seroprevalence rate is about 0.016% among voluntary blood donors. About half of these infected blood donors are infected with HTLV-1, with most of them reporting a history of birth in HTLV-1-endemic countries or sexual contact with persons from the Caribbean or Japan. Smaller percentages report a history of either injection drug use or blood transfusion. Transmission of HTLV-1 occurs from mother to fetus, sexual contact, blood transfusion, and sharing of contaminated needles. Two diseases are known to be caused by HTLV-1 infection: adult T-cell leukemia or lymphoma and a chronic degenerative neurologic disease known as HTLV-1-associated myelopathy or tropical spastic paraparesis. Cases of polymyositis, chronic arthropathy, panbronchiolitis, and uveitis have also been reported in patients infected with HTLV-1. HTLV-2 is prevalent among injection drug users in the United States and Europe. More than 80% of HTLV infections in drug users in the United States are due to HTLV-2. HTLV-2 also appears to be endemic in Native American populations, including the Guaymi in Panama and Native Americans in Florida and New Mexico. HTLV-2-infected blood donors most often report either a history of injection drug use or a history of sexual contact with an injection drug user. A smaller percentage of infected individuals report a history of blood transfusion. HTLV-2 is transmitted similarly to HTLV-1, but much less is known about the specific modes and efficiency of transmission of HTLV-2. The virus can be transmitted by transfusion of cellular blood products (whole blood, red blood cells, and platelets). HTLV-2 infection has been associated with hairy-cell leukemia, but definitive evidence is lacking on a

viral etiologic role. HTLV-2 has also been linked with neurodegenerative disorders characterized by spastic paraparesis and variable degrees of ataxia. Infection by these viruses results in the appearance of specific antibodies against the viruses that can be detected by serologic tests, such as enzyme immunoassay. For accurate diagnosis of HTLV-1 or HTLV-2 infection, all initial screening test-reactive results should be verified by a confirmatory test, such as Western blot or line immunoassay.

Useful For: Confirmatory detection of human T-cell lymphotropic virus types 1 and 2 (HTLV-1 and HTLV-2)-specific IgG antibodies in spinal fluid specimens that are consistently reactive by initial screening tests Differentiating between HTLV-1- and HTLV-2-specific IgG antibodies present in spinal fluid

Interpretation: Negative confirmatory test results indicate the absence of both human T-cell lymphotropic virus types 1 and 2 (HTLV-1 and HTLV-2)-specific IgG antibodies in spinal fluid and a low probability of an HTLV-1/-2-associated neurologic disorder. A reactive screening (enzyme immunoassay) result with a negative or indeterminate confirmatory (line immunoassay) test result suggests either a false-reactive screening test result or a seroconverting HTLV infection. Repeat testing with a new specimen can clarify the final infection status. Persistently indeterminate confirmatory test results indicate an absence of HTLV infection. Positive results for HTLV-1 antibodies indicate the confirmed presence of HTLV-1 IgG antibodies in spinal fluid, based on 2 visible antibody bands that include gp21-I/-II band, or 3 or more bands, and the sum of the gp46-I and p19-I band intensity is greater than the gp46-II band intensity. Positive results for HTLV-2 antibodies indicate the confirmed presence of HTLV-2 IgG antibodies in spinal fluid, based on 2 visible antibody bands that include gp21-I/-II band, or 3 or more bands, and the gp46-II band intensity is a) greater than the gp46-I band intensity and b) greater than or equal to the sum of the gp46-I and p19-I band intensity. Indeterminate results indicate the presence of the gp21-I/-II band only or combination of any 2 bands without a detectable gp21-I/-II band. Patients with indeterminate test results with known risk factors for HTLV-1 or HTLV-2 infection should undergo repeat confirmatory antibody testing with a new specimen to determine final infection status. Differentiation of HTLV-1 and HTLV-2 infection is not possible (ie, nontypeable HTLV antibodies) when the band intensity pattern does not meet the criteria of positive HTLV-1 or HTLV-2 antibody band intensity pattern. Unreadable results indicate the presence of nonspecific background reactivity that is inhibiting the visualization of specific bands on the test strip. Repeat testing with a new specimen is recommended. Invalid results indicate that nonspecific band reactivity is present. Submit another specimen for retesting if clinically indicated.

Reference Values:
Negative

Clinical References: 1. Mahieux R, Gessain A. Adult T-cell leukemia/lymphoma and HTLV-I. Curr Hematol Malig Rep. 2007;2(4):257-264. doi:10.3390/v8060161 2. Yamano Y, Sato T. Clinical pathophysiology of human T-lymphotropic virus-type I-associated myelopathy/tropical spastic paraparesis. Front Microbiol. 2012;3:389. doi:10.3389/fmicb.2012.00389 3. Marrero Rolon RM, Yao JDC. Laboratory diagnosis of HTLV-1-associated myelopathy. Clin Microbiol Newslett. 2020;42(16)129-134. doi:10.1016/j.clinmicnews.2020.07.004

HTLVC 604934 Human T-Cell Lymphotropic Virus Types 1 and 2 (HTLV-1/-2) Antibody Screen with Confirmation, Spinal Fluid

Clinical Information:

Useful For: Qualitative screening detection of human T-cell lymphotropic virus types 1 and 2 (HTLV-1/-2) specific antibodies with confirmation and differentiation between HTLV-1 and HTLV-2 infection This test should not be used as a screening or confirmatory test for any specimen other than spinal fluid.

Interpretation: Negative screening results indicate the absence of both human T-cell lymphotropic virus types 1 and 2 (HTLV-1/-2)-specific IgG antibodies in spinal fluid. A reactive screening test result is suggestive of infection with either HTLV-1 or HTLV-2. However, this result does not confirm infection (eg, low specificity), and it cannot differentiate between HTLV-1 and HTLV-2 infection. Specimens with reactive screening test results will be tested automatically by the line immunoassay (LIA) confirmatory test. Positive LIA results provide confirmatory evidence of infection with HTLV-1 or HTLV-2. A reactive screening result with a negative or indeterminate confirmatory test result suggests either a false-reactive screening test result or a seroconverting HTLV infection. Repeat testing in 1 to 2 months can clarify the final infection status. Persistently indeterminate confirmatory test results indicate absence of HTLV infection.

Reference Values:
Negative

Clinical References: 1. Yamano Y, Sato T. Clinical pathophysiology of human T-lymphotropic virus-type I-associated myelopathy/tropical spastic paraparesis. Front Microbiol. 2012;3:389 2. Gessain A, Mahieux R. Tropical spastic paraparesis and HTLV-I associated myelopathy: clinical, epidemiological, virological, and therapeutic aspects. Rev Neurol (Paris). 2012;168(3):257-269 3. Marrero Rolon RM, Yao JDC. Laboratory diagnosis of HTLV-1-associated myelopathy. Clin Microbiol Newsl. 2020;42(16):129-134

HTLVL
83277

Human T-Cell Lymphotropic Virus Types I and II (HTLV-I/-II) Antibody Confirmation, Serum

Clinical Information: Human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II) are closely related exogenous human retroviruses. HTLV-I was first isolated in 1980 from a patient with a cutaneous T-cell lymphoma, while HTLV-II was identified from a patient with hairy cell leukemia in 1982. HTLV-I infection is endemic in southwestern Japan, the Caribbean basin, Melanesia, and parts of Africa, where HTLV-I seroprevalence rates are as high as 15% in the general population. In the United States, the combined HTLV-I and HTLV-II seroprevalence rate is about 0.016% among voluntary blood donors. About half of these infected blood donors are infected with HTLV-I, with most of them reporting a history of birth in HTLV-I-endemic countries or sexual contact with persons from the Caribbean or Japan. Smaller percentages report a history of either injection drug use or blood transfusion. Transmission of HTLV-I occurs from mother to fetus, sexual contact, blood transfusion, and sharing of contaminated needles. Two diseases are known to be caused by HTLV-I infection: adult T-cell leukemia or lymphoma and a chronic degenerative neurologic disease known as HTLV-I-associated myelopathy or tropical spastic paraparesis. Cases of polymyositis, chronic arthropathy, panbronchiolitis, and uveitis have also been reported in patients infected with HTLV-I. HTLV-II is prevalent among injection drug users in the United States and Europe. More than 80% of HTLV infections in drug users in the United States are due to HTLV-II. HTLV-II also appears to be endemic in Native American populations, including the Guaymi in Panama and Native Americans in Florida and New Mexico. HTLV-II-infected blood donors most often report either a history of injection drug use or a history of sexual contact with an injection drug user. A smaller percentage of infected individuals report a history of blood transfusion. HTLV-II is transmitted similarly to HTLV-I, but much less is known about the specific modes and efficiency of transmission of HTLV-II. The virus can be transmitted by transfusion of cellular blood products (whole blood, red blood cells, and platelets). HTLV-II infection has been associated with hairy-cell leukemia, but definitive evidence is lacking on a viral etiologic role. HTLV-II has also been linked with neurodegenerative disorders characterized by spastic paraparesis and variable degrees of ataxia. Infection by these viruses results in the appearance of specific antibodies against the viruses that can be detected by serologic tests, such as enzyme immunoassay. For accurate diagnosis of HTLV-I or HTLV-II infection, all initially screening test-reactive results should be verified by a confirmatory test, such as Western blot or line immunoassay.

Useful For: Confirmatory detection of human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II)-specific IgG antibodies in human serum specimens that are consistently reactive by initial screening tests Differentiating between HTLV-I- and HTLV-II-specific IgG antibodies

Interpretation: Negative confirmatory test results indicate the absence of both human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II)-specific IgG antibodies in serum. A reactive screening (enzyme immunoassay) result with a negative or indeterminate confirmatory (line immunoassay) test result suggests either a false-reactive screening test result or a seroconverting HTLV infection. Repeat testing with a new specimen can clarify the final infection status. Persistently indeterminate confirmatory test results indicate absence of HTLV infection. Positive results for HTLV-I antibodies indicate the confirmed presence of HTLV-I IgG antibodies in serum, based on 2 visible antibody bands that include gp21-I/-II band, or 3 or more bands, and the sum of the gp46-I and p19-I band intensity is greater than the gp46-II band intensity. Positive results for HTLV-II antibodies indicate the confirmed presence of HTLV-II IgG antibodies in serum, based on 2 visible antibody bands that include gp21-I/-II band, or 3 or more bands, and the gp46-II band intensity is a) greater than the gp46-I band intensity and b) greater than or equal to the sum of the gp46-I and p19-I band intensity. Indeterminate results indicate the presence of gp21-I/-II band only or combination of any 2 bands without a detectable gp21-I/-II band. Patients with indeterminate test results with known risk factors for HTLV-I or HTLV-II infection should undergo repeat confirmatory antibody testing with a new specimen to determine final infection status. Differentiation of HTLV-I and HTLV-II infection is not possible (ie, nontypeable HTLV antibodies) when the band intensity pattern does not meet the criteria of positive HTLV-I or HTLV-II antibody band intensity pattern. Unreadable results indicate the presence of nonspecific background reactivity that is inhibiting the visualization of specific bands on the test strip. Repeat testing with a new specimen is recommended. Invalid results indicate that nonspecific band reactivity is present. Submit another serum specimen for retesting if clinically indicated.

Reference Values:
Negative

Clinical References: 1. Gessain A, Mahieux R. Tropical spastic paraparesis and HTLV-I associated myelopathy: clinical, epidemiological, virological, and therapeutic aspects. Rev Neurol (Paris). 2012;168(3):257-269. doi:10.1016/j.neurol.2011.12.006 2. Mahieux R, Gessain A. Adult T-cell leukemia/lymphoma and HTLV-I. Curr Hematol Malig Rep. 2007;2(4):257-264. doi:10.3390/v8060161 3. Yamano Y, Sato T. Clinical pathophysiology of human T-lymphotropic virus-type I-associated myelopathy/tropical spastic paraparesis. Front Microbiol. 2012;3:389. doi:10.3389/fmicb.2012.00389 4. Marrero Rolon RM, Yao JDC. Laboratory diagnosis of HTLV-1-associated myelopathy. Clin Microbiol Newslett. 2020;42(16)129-134. doi:10.1016/j.clinmicnews.2020.07.004

HTLVI
9539

Human T-Cell Lymphotropic Virus Types I and II Antibody Screen with Confirmation, Serum

Clinical Information: Human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II) are closely related exogenous human retroviruses. HTLV-I was first isolated in 1980 from a patient with a cutaneous T-cell lymphoma, while HTLV-II was identified from a patient with hairy cell leukemia in 1982. Human T-cell lymphotropic virus type I infection is endemic in southwestern Japan, the Caribbean basin, Melanesia, and parts of Africa, where HTLV-I seroprevalence rates are as high as 15% in the general population. In the United States, the combined HTLV-I and HTLV-II seroprevalence rate is about 0.016% among voluntary blood donors. About half of these infected blood donors are infected with HTLV-I, with most of them reporting a history of birth in HTLV-I-endemic countries or sexual contact with persons from the Caribbean or Japan. Smaller percentages report a history of either injection drug use or blood transfusion. Transmission of HTLV-I occurs from mother to fetus, sexual contact, blood transfusion, and sharing of contaminated needles. Two diseases are known to be caused by HTLV-I

infection: adult T-cell leukemia or lymphoma, and a chronic degenerative neurologic disease known as HTLV-I-associated myelopathy or tropical spastic paraparesis. Cases of polymyositis, chronic arthropathy, panbronchiolitis, and uveitis also have been reported in patients with a HTLV-I infection. In the United States and Europe, HTLV-II is prevalent among persons who inject drugs (PWID). In the United States, over 80% of HTLV infections in drug users are due to HTLV-II. HTLV-II appears to be endemic in American indigenous populations, including the Guaymi tribe in Panama and Native Americans in Florida and New Mexico. HTLV-II-infected blood donors most often report either a history of injection drug use or a history of sexual contact with a PWID. A smaller percentage of infected individuals report a history of blood transfusion. HTLV-II is transmitted similarly to HTLV-I, but much less is known about the specific modes and efficiency of transmission of HTLV-II. The virus can be transmitted by transfusion of cellular blood products (whole blood, red blood cells, and platelets). HTLV-II infection has been associated with hairy-cell leukemia, but definitive evidence is lacking on a viral etiologic role. HTLV-II has also been linked with neurodegenerative disorders characterized by spastic paraparesis and variable degrees of ataxia. Infection by these viruses results in the appearance of specific antibodies against the viruses that can be detected by serologic tests such as enzyme immunoassay. For accurate diagnosis of HTLV-I or HTLV-II infection, all initially screening test-reactive results should be verified by a confirmatory test, such as Western blot or line immunoassay.

Useful For: Qualitative detection of human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II)-specific antibodies with confirmation and differentiation between HTLV-I and HTLV-II infection This test should not be used to screen blood, human cells, tissues, or solid-organ donors. This test is not intended for use on cord blood specimens.

Interpretation: Negative screening results indicate the absence of both human T-cell lymphotropic virus types I and II (HTLV-I- and HTLV-II)-specific IgG antibodies in serum. A reactive screening test result is suggestive of infection with either HTLV-I or HTLV-II. However, this result does not confirm infection (eg, low specificity), and it cannot differentiate between HTLV-I and HTLV-II infection. Specimens with reactive screening test results will be tested automatically by the line immunoassay (LIA) confirmatory test. Positive LIA results provide confirmatory evidence of infection with HTLV-I or HTLV-II. A reactive screening result with a negative or indeterminate confirmatory test result suggests either a false-reactive screening test result or a seroconverting HTLV infection. Repeat testing in 1 to 2 months can clarify the final infection status. Persistently indeterminate confirmatory test results indicate absence of HTLV infection.

Reference Values:
Negative

Clinical References: 1. Yamano Y, Sato T. Clinical pathophysiology of human T-lymphotropic virus-type I-associated myelopathy/tropical spastic paraparesis. Front Microbiol. 2012;3:389 2. Gessain A, Mahieux R. Tropical spastic paraparesis and HTLV-I associated myelopathy: clinical, epidemiological, virological, and therapeutic aspects. Rev Neurol (Paris). 2012;168(3):257-269 3. Marrero Rolon RM, Yao JDC. Laboratory diagnosis of HTLV-1-associated myelopathy. Clin Microbiol Newsl. 2020;42(16):129-134. doi:10.1016/j.clinmicnews.2020.07.004

FHTGF
75825

Human Transforming Growth Factor beta 1 (TGF-b1)

Clinical Information: Transforming growth factor (TGF) play a crucial role in tissue regeneration, cell differentiation, embryonic development, and regulation of the immune system. Transforming growth factor beta is found in hematopoietic (blood-forming) tissue and initiates a signaling pathway that suppresses the early development of cancer cells. It enhances the deposition of extracellular matrix and may play potential role in wound healing and cirrhosis formation. Many cells synthesize TGF-b and

almost all of them have specific receptors for this peptide.

Reference Values:
0-22,062 pg/mL

MPS2Z
35463

Hunter Syndrome, Full Gene Analysis, Varies

Clinical Information: Mucopolysaccharidosis type II (MPS-II), also known as Hunter syndrome, is a rare X-linked condition caused by variants in the IDS gene. MPS-II is characterized by reduced or absent activity of the iduronate 2-sulfatase enzyme. The clinical features and severity of symptoms of MPS-II are widely variable, ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, joint contractures, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. Female carriers are usually asymptomatic. The IDS gene is located on the X chromosome and has 9 exons and is the only known gene to be associated with MPS-II. The recommended first-tier test for mucopolysaccharidosis type II is biochemical testing that measures iduronate 2-sulfatase enzyme activity in blood: I2SW / Iduronate-2-Sulfatase, Whole Blood or blood spots: I2SBS / Iduronate-2-Sulfatase, Blood Spot. Individuals with decreased or absent enzyme activity are more likely to have a variant in the IDS gene identifiable by molecular genetic testing. However, enzymatic testing is not reliable to detect carriers. Additionally, measurement of mucopolysaccharides in blood can aid in diagnosis and ongoing therapeutic monitoring (MPSBS / Mucopolysaccharidosis, Blood Spot).

Useful For: Confirmation of a diagnosis of mucopolysaccharidosis type II (Hunter syndrome) Carrier testing when there is a family history of mucopolysaccharidosis type II (Hunter syndrome), but disease-causing variants have not been previously identified

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 2. Martin R, Beck M, Eng C, et al: Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). Pediatrics. 2008;121(2):e377-386 3. Wraith JE, Scarpa M, Beck M, et al: Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy. Eur J Pediatr. 2008;167(3):267-277

HAD
35452

Huntington Disease, Molecular Analysis, Varies

Clinical Information: Huntington disease (HD) is an autosomal dominant progressive neurodegenerative disorder associated with progressive involuntary and voluntary motor disturbances (chorea, dystonia, dysarthria, gait disturbance, postural instability, oculomotor dysfunction), cognitive decline leading to dementia, and a wide range of neuropsychiatric problems including apathy, depression, anxiety, and other behavioral disturbances. Onset occurs typically in the late 30's to early 40's, but rare individuals may present with juvenile onset. Huntington disease is caused by a CAG (cystine, adenine,

guanine) repeat expansion in the HTT gene and is associated with genetic anticipation, whereby repeat sizes may expand with transmission to subsequent generations. Correlation exists between the size of the CAG repeat and disease onset and severity, with larger alleles associated with earlier onset and more severe disease presentation. Full penetrance HTT expansions are greater than 39 repeats, while normal alleles are less than 27 repeats. Allele sizes between 36 and 39 repeats are associated with reduced penetrance of clinical HD symptoms. Intermediate alleles (27-35 repeats) are not typically associated with clinical symptoms; however, both reduced penetrance and intermediate alleles may expand into the full penetrance range with transmission to offspring. Identification of a disease-associated repeat expansion has important implications for family members. Testing of at-risk individuals is possible, but it is recommended that predictive testing be performed in conjunction with appropriate pre- and post-test counseling. Additionally, presymptomatic testing of minors is strongly discouraged.

Useful For: Molecular confirmation of clinically suspected cases of Huntington disease (HD)
Presymptomatic testing for individuals with a family history of HD and a documented expansion in the HTT gene

Interpretation: The provided interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
Normal alleles: <27 CAG repeats
Intermediate alleles: 27-35 CAG repeats
Reduced penetrance: 36-39 CAG repeats
Full penetrance: >39 CAG repeats
An interpretive report will be provided.

Clinical References: 1. Bean L, Bayrak-Toydemir P. American College of Medical Genetics and Genomics Standards and Guidelines for Clinical Genetics Laboratories, 2014 edition: technical standards and guidelines for Huntington disease. Genet Med. 2014;16(12):e2. doi:10.1038/gim.2014.146 2. Testa C, Jankovic J. Huntington disease: A quarter century of progress since the gene discovery. J Neurol Sci. 2019:396:52-68. doi:10.1016/j.jns.2018.09.022

MPS1Z
35465

Hurler Syndrome, Full Gene Analysis, Varies

Clinical Information: Mucopolysaccharidosis type I (MPS-I) can be categorized into 3 syndromes, Hurler syndrome, Scheie syndrome, and Hurler-Scheie syndrome. MPS-I, inherited in an autosomal recessive manner, is caused by variants in the IDUA gene. Furthermore, MPS-I is characterized by reduced or absent activity of the alpha-L-iduronidase enzyme. Hurler syndrome (severe MPS-I) has early onset and consists of skeletal deformities, coarse facial features, corneal clouding, hepatosplenomegaly, cardiac involvement, hearing loss, and respiratory tract infections. Developmental delay is noticed as early as 12 months with death occurring usually before 10 years of age. Hurler-Scheie syndrome and Scheie syndrome (attenuated MPS-I) have onset between 3 to 10 years of age and consist of corneal clouding, cardiac involvement, moderate-to-severe hearing loss, and progressive pulmonary disease. Typically skeletal and joint involvement is the most significant source of discomfort for attenuated MPS-I. Intellect with attenuated MPS-I is typically normal or nearly normal. The IDUA gene is located on chromosome 4 and has 14 exons. IDUA is the only known gene to be associated with MPS-I, and the 3 syndromes appear to be caused by different combinations of variants. The recommended first-tier test for MPS-I is biochemical testing that measures alpha-L-iduronidase enzyme activity in blood: IDUAW / Alpha-L-Iduronidase, Leukocytes or PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot. Individuals with decreased or absent enzyme activity are more likely to have 2 identifiable variants in the IDUA gene by molecular genetic testing. However, enzymatic testing is not reliable to detect carriers. Additionally, measurement of mucopolysaccharides

in blood can aid in diagnosis and ongoing therapeutic monitoring (MPSBS / Mucopolysaccharidosis, Blood Spot).

Useful For: Identifying variants within the IDUA gene Confirmation of a diagnosis of mucopolysaccharidosis type I (MPS-I) Carrier testing when there is a family history of MPS- I, but disease-causing variants have not been previously identified

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(2) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Newborn Screening ACT Sheet [alpha-L-iduronidase deficiency with or without glycosaminoglycan (GAG) accumulation] Mucopolysaccharidosis Type I (MPS I). American College of Medical Genetics and Genomics; 2023. Updated November 2023. Accessed June 10, 2024. Available at www.acmg.net/PDFLibrary/MPSI-ACT-Sheet.pdf 2. Muenzer J, Wraith JE, Clarke LA, International Consensus Panel on Management and Treatment of Mucopolysaccharidosis I: Mucopolysaccharidosis I: management and treatment guidelines. Pediatrics. 2009 Jan;123(1):19-29 3. Scott HS, Bunge S, Gal A, Clarke LA, Morris CP, Hopwood JJ: Molecular genetics of mucopolysaccharidosis type I: diagnostic, clinical, and biological implications. Hum Mutat. 1995;6(4):288-302 4. Terlato NJ, Cox GF: Can mucopolysaccharidosis type I disease severity be predicted based on a patient's genotype? A comprehensive review of the literature. Genet Med. 2003 Jul-Aug;5(4):286-294 5. Vijay S, Wraith JE: Clinical presentation and follow-up of patients with the attenuated phenotype of mucopolysaccharidosis type I. Acta Paediatr. 2005 Jul;94(7):872-877

FHMTB
58081

Hydrocodone and metabolites

Reference Values:
Reference Range:

Hydrocodone, unconjugated: 10-100 ng/mL

Hydromorphone, unconjugated: 1-30 ng/mL

Dihydrocodeine, unconjugated: Not established ng/mL

HYDCU
62614

Hydrocodone with Metabolite Confirmation, Random, Urine

Clinical Information: Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the 6-beta hydroxymetabolites. Hydromorphone and norhydrocodone are both metabolites of hydrocodone. Dihydrocodeine is also a minor metabolite. Trace amounts of hydrocodone can also be found in the presence of approximately 100-fold higher concentrations of oxycodone or hydromorphone since it can be a pharmaceutical impurity in these medications. The presence of hydrocodone indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The presence of hydromorphone indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone; therefore, the presence of

hydromorphone could also indicate exposure to hydrocodone. The detection interval for the opiates is generally 2 to 3 days after last ingestion.

Useful For: Detection and quantification of hydrocodone, norhydrocodone, and hydromorphone in urine

Interpretation: This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

Reference Values:
Negative
Positive results are reported with a quantitative result.

Cutoff concentrations by-liquid chromatography tandem mass spectrometry:
Hydrocodone: 25 ng/mL
Norhydrocodone: 25 ng/mL
Hydromorphone: 25 ng/mL

Clinical References: 1. Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds. The Pharmacological Basis of Therapeutics. 11th ed. Goodman and Gilman's: McGraw-Hill Companies, Inc. 2006 Available at www.accessmedicine.com/content.aspx?aID=940653 2. Baselt RC, ed: Disposition of Toxic Drugs and Chemical in Man. 9th ed. Biomedical Publications; 2011 3. Hackett LP, Dusci LJ, Ilett KF, Chiswell GM. Optimizing the hydrolysis of codeine and morphine glucuronides in urine. Ther Drug Monit. 2002;24(5):652-657. doi:10.1097/00007691-200210000-00012 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

HYDMU
62615

Hydromorphone Confirmation, Random, Urine

Clinical Information: Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (eg, codeine, hydrocodone, hydromorphone, oxycodone). Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the 6-beta hydroxymetabolites. Hydromorphone is a metabolite of hydrocodone. The presence of hydrocodone indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The presence of hydromorphone indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone; therefore, the presence of hydromorphone could also indicate exposure to hydrocodone.

Useful For: Detection and quantification of hydromorphone in urine

Interpretation: This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

Reference Values:
Negative
Positive results are reported with a quantitative result.

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Hydromorphone: 25 ng/mL

Clinical References: 1. Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill; 2006:chap 21 2. Baselt RC, ed: Disposition of Toxic Drugs and Chemical in Man. 9th ed. Biomedical Publications; 2011 3. Hackett LP, Dusci LJ, Ilett KF, Chiswell GM. Optimizing the hydrolysis of codeine and morphine glucuronides in urine. Ther Drug Monit. 2002;24(5):652-657. doi:10.1097/00007691-200210000-00012 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

HCQ
64947

Hydroxychloroquine, Serum

Clinical Information: Hydroxychloroquine is an antimalarial drug used to treat or prevent malaria. It is highly effective against erythrocytic forms of Plasmodium but not effective against exoerythrocytic forms of parasites. Hydroxychloroquine is also used to treat symptoms of acute or chronic rheumatoid arthritis and systemic lupus erythematosus (SLE). Adult doses range from 400 mg/week for suppressive therapy to 1200 mg/day for acute malaria attacks. Typical daily doses of 200 to 600 mg are used for SLE and rheumatoid diseases. Hydroxychloroquine has a long terminal elimination half-life in blood (>40 days), which exceeds that in serum. The oral bioavailability averages 75%. Hydroxychloroquine accumulates in several organs, especially melanin-containing retina and skin. Mild to moderate overdose can result in gastrointestinal tract effects (ie, nausea, vomiting, and abdominal pain), headache, visual and hearing disturbances, and neuromuscular excitability. Acute hepatitis, cardiotoxicity, and retinopathy may occur with therapeutic doses. The effects of overdosage with hydroxychloroquine include headache, drowsiness, visual disturbances, convulsions, cardiovascular collapse, and respiratory arrest. Toxic retinopathy has also been associated with higher doses and longer duration of use.

Useful For: Monitoring serum hydroxychloroquine concentrations, assessing compliance, and adjusting dosage in patients

Interpretation: The serum concentration should be interpreted in the context of the patient's clinical response and may provide useful information in patients showing poor response, noncompliance, or adverse effects. Concentrations less than 106 ng/mL have been associated with noncompliance.

Reference Values:
For suppressive treatment of malaria, suggested plasma or serum concentrations should be >10 ng/mL.

For systemic lupus erythematosus, proposed serum target concentrations should be > or =500 ng/mL.

Clinical References: 1. McChesney EW BW, McAuliff JP: Laboratory studies on the 4-aminoquinoline antimalarials: II. Plasma levels of chloroquine and hydroxychloroquine in man after various oral dosage regimens. Antibiot Chemother (Northfield). 1962;12(9):583-594 2. Mok CC, Penn HJ, Chan KL, Tse SM, Langman LJ, Jannetto PJ. Hydroxychloroquine serum concentrations and flares of systemic lupus erythematosus: A longitudinal cohort analysis. Arthritis Care Res. 2016;68(9):1295-1302. doi:10.1002/acr.22837 3. Durcan L, Clarke WA, Magder LS, Petri M. Hydroxychloroquine blood levels in systemic lupus erythematosus: clarifying dosing controversies and improving adherence. J Rheumatol. 2015;42(11):2092-2097. doi:10.3899/jrheum.150379 4. Blanchet B, Jallouli M, Allard M, et al. Whole blood versus serum hydroxychloroquine levels for drug monitoring of patients with systemic lupus erythematosus: preliminary results of a pharmacological study. Ann Rheum Dis. 2019;78(2):1168-1169. Abstract SAT0188 5. Soichot M, Megarbane B, Houze P, et al. Development, validation and clinical application of a LC-MS/MS method for the simultaneous quantification of hydroxychloroquine and its active metabolites in human whole blood. J Pharm Biomed Anal. 2014;100:131-137. doi:10.1016/j.jpba.2014.07.009 6. Wang LZ, Ong RYL, Chin TM, et al. Method development and validation for rapid quantification of hydroxychloroquine in human blood using liquid chromatography-

tandem mass spectrometry. J Pharm Biomed Anal. 2012;61:86-92. doi:10.1016/j.jpba.2011.11.034 7. Disposition of Toxic Drugs and Chemicals in Man. 10th ed. Biomedical Publications; 2014 8. Tett SE, Cutler DJ, Day RO, Brown KF. A dose-ranging study of the pharmacokinetics of hydroxy-chloroquine following intravenous administration to healthy volunteers. Brit J Clin Pharmacol. 1988;26(3):303-313 9. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949. doi:10.1016/j.ijantimicag.2020.105949 10. Kim SH: Comparison of lopinavir/ritonavir or hydroxychloroquine in patients with mild coronavirus disease (COVID-19). US National Library of Medicine (NLM). 2020. Accessed April 23, 2024. Available at clinicaltrials.gov/ct2/show/NCT04307693 11. Lu H: Efficacy and safety of hydroxychloroquine for treatment of pneumonia caused by 2019-nCoV (HC-nCoV). US National Library of Medicine (NLM). 2020. Accessed April 23, 2024. Available at clinicaltrials.gov/ct2/show/NCT04261517 12. Post-exposure prophylaxis for SARS-coronavirus-2. US National Library of Medicine (NLM). 2020. Accessed April 23, 2024. Available at clinicaltrials.gov/ct2/show/NCT04308668

HGEM
62230

Hydroxyglutaric Acids, Glutaric Acid, Ethylmalonic Acid, and Methylsuccinic Acid, Blood Spot

Clinical Information: Acylcarnitine analysis is included in newborn screening blood tests and is utilized for detection of several inborn errors of metabolism, including fatty acid oxidation disorders (FAOD) and organic acidemias (OA). A limitation of this analytic method is its inability to differentiate between several isomers. Additional testing of 2-hydroxyglutaric acid (2OH-GA), 3-hydroxyglutaric acid (3OH-GA), glutaric acid (GA), methylsuccinic acid (MSA), and ethylmalonic acid (EMA) by liquid chromatography tandem mass spectrometry allows better differentiation among C4-acylcarnitine and glutarylcarnitine/C10-OH isomers. C4-acylcarnitine represents both butyrylcarnitine and isobutyrylcarnitine and is elevated in short-chain acyl Co-A dehydrogenase (SCAD) deficiency, isobutyryl-CoA dehydrogenase (IBDH) deficiency, and ethylmalonic encephalopathy (EE). SCAD deficiency is a condition affecting fatty acid metabolism with reported symptoms of hypoglycemia, lethargy, developmental delays, and failure to thrive. There is controversy on whether a biochemical diagnosis necessarily confers clinical symptoms. IBDH deficiency is characterized by cardiomyopathy, hypotonia, and developmental delays, although many individuals with IBDH deficiency are asymptomatic. EE is a rare progressive encephalopathy associated with hypotonia, seizures, and abnormal movements. Individuals with SCAD deficiency demonstrate elevated plasma EMA and MSA levels and individuals with EE show only elevations in EMA, while individuals with IBDH deficiency do not typically have elevations in either EMA or MSA. Glutarylcarnitine (C5-DC) is elevated in glutaric acidemia type I (GA1) but is not differentiated from C10-OH acylcarnitine. GA1 is caused by a deficiency of glutaryl-CoA dehydrogenase and is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by illness. Individuals with GA1 typically show elevations of GA and 3OH-GA, even in those considered to be "low excretors." Glutaric acidemia type II (GA2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is caused by defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. This disease can be severe and is often fatal in the first weeks of life with typical symptoms of hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA2 can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood and muscle weakness in childhood and adulthood. In addition to elevations in GA, individuals with GA2 can also show increased EMA, MSA, and 2OH-GA. The American College of Medical Genetics and Genomics Newborn Screening Work Group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information see www.acmg.net.

Useful For: Evaluation of patients with an abnormal newborn screen showing elevations of glutarylcarnitine (C5-DC) using dried blood spot specimens Evaluation of patients with abnormal

newborn screens showing elevations of C4-acylcarnitine to aid in the differential diagnosis of short-chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies Diagnosis of glutaric acidemia type 1 Aiding in diagnosis of glutaric acidemia type 2

Interpretation: Elevations of ethylmalonic acid (EMA) and methylsuccinic acid (MSA) are consistent with a diagnosis of short-chain acyl Co-A dehydrogenase (SCAD) deficiency. Elevation of EMA is consistent with a diagnosis of ethylmalonic encephalopathy. Normal levels of EMA in the context of elevated C4 is consistent with a diagnosis of isobutyryl-CoA dehydrogenase (IBDH) deficiency. Elevation of glutaric acid (GA) and 3-hydroxyglutaric acid (3OH-GA) are consistent with a diagnosis of glutaric acidemia type I (GA1). Elevation of GA, 2-hydroxyglutaric acid (2OH-GA), 3OH-GA, EMA, and MSA are consistent with a diagnosis of glutaric acidemia type II (GA2).

Reference Values:

2-OH Glutaric acid: < or =25 nmol/mL
3-OH Glutaric acid: < or =1.5 nmol/mL
Glutaric acid: < or =1.5 nmol/mL
Methylsuccinic acid: < or =0.45 nmol/mL
Ethylmalonic acid: < or =3.5 nmol/mL

Clinical References:

HGEMP 62300 Hydroxyglutaric Acids, Glutaric Acid, Ethylmalonic Acid, and Methylsuccinic Acid, Plasma

Clinical Information: Acylcarnitine analysis is included in newborn screening blood tests and is utilized for detection of several inborn errors of metabolism, including fatty acid oxidation disorders (FAOD) and organic acidemias (OA). A limitation of this analytic method is its inability to differentiate between several isomers. Additional testing of 2-hydroxyglutaric acid (2OH-GA), 3-hydroxyglutaric acid (3OH-GA), glutaric acid (GA), methylsuccinic acid (MSA), and ethylmalonic acid (EMA) by liquid chromatography tandem mass spectrometry allows better differentiation among C4 acylcarnitine and glutarylcarnitine/C10-OH isomers. C4 acylcarnitine represents both butyrylcarnitine and isobutyrylcarnitine and is elevated in short-chain acyl Co-A dehydrogenase (SCAD) deficiency, isobutyryl-CoA dehydrogenase (IBDH) deficiency, and ethylmalonic encephalopathy (EE). SCAD deficiency is a condition affecting fatty acid metabolism with reported symptoms of hypoglycemia, lethargy, developmental delays, and failure to thrive. There is controversy on whether a biochemical diagnosis necessarily confers clinical symptoms. IBDH deficiency is characterized by cardiomyopathy, hypotonia, and developmental delays, although many individuals with IBDH deficiency are asymptomatic. EE is a rare progressive encephalopathy associated with hypotonia, seizures, and abnormal movements. Individuals with SCAD deficiency demonstrate elevated plasma EMA and MSA levels and individuals with EE show only elevations in EMA, while individuals with IBDH deficiency do not typically have elevations in either EMA or MSA. Glutarylcarnitine (C5-DC) is elevated in glutaric acidemia type I (GA1) but is not differentiated from C10-OH acylcarnitine. GA1 is caused by a deficiency of glutaryl-CoA dehydrogenase and is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by illness. Individuals with GA1 typically show elevations of GA and 3OH-GA, even in those considered to be "low excretors." Glutaric acidemia type II (GA2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is caused by defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. This disease can be severe and is often fatal in the first weeks of life with typical symptoms of hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA2 can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood and muscle weakness in childhood and adulthood. In addition to elevations in GA, individuals with GA2 can also show increased EMA, MSA, and 2OH-GA. The

American College of Medical Genetics and Genomics Newborn Screening Work Group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information see www.acmg.net.

Useful For: Evaluation of patients with an abnormal newborn screen showing elevations of glutarylcarnitine (C5-DC) using plasma specimens Evaluation of patients with abnormal newborn screens showing elevations of C4- acylcarnitine to aid in the differential diagnosis of short chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies Diagnosis of glutaric acidemia type 1 Aiding in diagnosis of glutaric acidemia type 2

Interpretation: Elevations of ethylmalonic acid (EMA) and methylsuccinic acid (MSA) are consistent with a diagnosis of short chain acyl Co-A dehydrogenase (SCAD) deficiency. Elevation of EMA is consistent with a diagnosis of ethylmalonic encephalopathy. Normal levels of EMA in the context of elevated C4 is consistent with a diagnosis of isobutyryl-CoA dehydrogenase (IBDH) deficiency. Elevation of glutaric acid (GA) and 3-hydroxyglutaric acid (3OH-GA) are consistent with a diagnosis of glutaric acidemia type I (GA1). Elevation of GA, 2-hydroxyglutaric acid (2OH-GA), 3OH-GA, EMA, and MSA are consistent with a diagnosis of glutaric acidemia type II (GA2).

Reference Values:

2-OH Glutaric acid < or =4.5 nmol/mL
3-OH Glutaric acid < or =0.7 nmol/mL
Glutaric acid < or =0.8 nmol/mL
Methylsuccinic acid < or =0.3 nmol/mL
Ethylmalonic acid < or =1.5 nmol/mL

Clinical References:

HGEMS 62231 Hydroxyglutaric Acids, Glutaric Acid, Ethylmalonic Acid, and Methylsuccinic Acid, Serum

Clinical Information: Acylcarnitine analysis is included in newborn screening blood tests and is utilized for detection of several inborn errors of metabolism, including fatty acid oxidation disorders (FAOD) and organic acidemias (OA). A limitation of this analytic method is its inability to differentiate between several isomers. Additional testing of 2-hydroxyglutaric acid (2OH-GA), 3-hydroxyglutaric acid (3OH-GA), glutaric acid (GA), methylsuccinic acid (MSA), and ethylmalonic acid (EMA) by liquid chromatography tandem mass spectrometry allows better differentiation among C4 acylcarnitine and glutarylcarnitine/C10-OH isomers. C4 acylcarnitine represents both butyrylcarnitine and isobutyrylcarnitine and is elevated in short-chain acyl Co-A dehydrogenase (SCAD) deficiency, isobutyryl-CoA dehydrogenase (IBDH) deficiency and ethylmalonic encephalopathy (EE). SCAD deficiency is a condition affecting fatty acid metabolism with reported symptoms of hypoglycemia, lethargy, developmental delays, and failure to thrive; there is controversy on whether a biochemical diagnosis necessarily confers clinical symptoms. IBDH deficiency is characterized by cardiomyopathy, hypotonia, and developmental delays, although many individuals with IBDH deficiency are asymptomatic. EE is a rare progressive encephalopathy associated with hypotonia, seizures, and abnormal movements. Individuals with SCAD deficiency demonstrate elevated plasma EMA and MSA levels, and individuals with EE show only elevations in EMA, while individuals with IBDH deficiency do not typically have elevations in either EMA or MSA. Glutarylcarnitine (C5-DC) is elevated in glutaric acidemia type I (GA1) but is not differentiated from C10-OH acylcarnitine. GA1 is caused by a deficiency of glutaryl-CoA dehydrogenase and is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by illness. Individuals with GA1 typically show elevations of GA and 3OH-GA, even in those considered to be "low excretors." Glutaric acidemia type II (GA2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is caused by

defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. This disease can be severe and is often fatal in the first weeks of life with typical symptoms of hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA2 can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood, and muscle weakness in childhood and adulthood. In addition to elevations in GA, individuals with GA2 can also show increased EMA, MSA, and 2OH-GA. The American College of Medical Genetics and Genomics (ACMG) Newborn Screening Work Group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information see www.acmg.net.

Useful For: Evaluation of patients with an abnormal newborn screen showing elevations of glutarylcarnitine (C5-DC) using serum specimens Evaluation of patients with abnormal newborn screens showing elevations of C4- acylcarnitine to aid in the differential diagnosis of short chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies Diagnosis of glutaric acidemia type 1 Aiding in diagnosis of glutaric acidemia type 2

Interpretation: Elevations of ethylmalonic acid (EMA) and methylsuccinic acid (MSA) are consistent with a diagnosis of short chain acyl Co-A dehydrogenase (SCAD) deficiency. Elevation of EMA is consistent with a diagnosis of ethylmalonic encephalopathy. Normal levels of EMA in the context of elevated C4 is consistent with a diagnosis of isobutyryl-CoA dehydrogenase (IBDH) deficiency. Elevation of glutaric acid (GA) and 3-hydroxyglutaric acid (3OH-GA) are consistent with a diagnosis of glutaric acidemia type I (GA1). Elevation of GA, 2-hydroxy glutaric acid (2OH-GA), 3OH-GA, EMA, and MSA are consistent with a diagnosis of glutaric acidemia type II (GA2).

Reference Values:

2-OH Glutaric acid: < or =4.5 nmol/mL
3-OH Glutaric acid: < or =0.7 nmol/mL
Glutaric acid: < or =0.8 nmol/mL
Methylsuccinic acid: < or =0.3 nmol/mL
Ethylmalonic acid: < or =1.5 nmol/mL

Clinical References: 1. Rinaldo P, Cowan TM, Matern D. Acylcarnitine profile analysis. Genet Med. 2008;10(2):151-156 2. Vockley J, Zschocke J, Knerr I, Vockley C, Michael Gibson KK. Branched chain organic acidurias. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed April1, 2025. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225085758 3. Frerman FE, Goodman SI. Defects of electron transfer flavoprotein and electron transfer flavoprotein-ubiquinone oxidoreductase: Glutaric acidemia type II. n: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed April1, 2025. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225088261 4. Larson A, Goodman S. Glutaric acidemia type 1. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2019. Accessed April1, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK546575/ 5. Di Meo I, Lamperti C, Tiranti V. Ethylmalonic encephalopathy. In: Adam MP, Mirzaa GM,, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2017. Accessed December 30, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK453432/ 6. Wolfe L, Jethva R, Oglesbee D, Vockley J. Short-chain acyl-CoA dehydrogenase deficiency. In: Adam MP, Mirzaa GM, Pagon RA, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2011. Updated August 9, 2018. Accessed April1, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK63582/

FVIST 90121 Hydroxyzine (Vistaril, Atarax), Serum

Reference Values:
Reference Range: 10 - 100 ng/mL

HIESG
619816

Hyper-IgE Syndrome Gene Panel, Varies

Clinical Information: Hyper IgE syndrome (HIES) is characterized by an increased susceptibility to infection (particularly recurrent skin and pulmonary infections), eczema, and elevated serum IgE. There is variable expression among individuals and additional features may be present, including vascular, skeletal, and connective tissue pathology. While the incidence of HIES is estimated to be between 1:100,000 to 1,000,000 at birth, this may be an underestimate due to incomplete penetrance. Dominant negative variants in STAT3 were first identified as the genetic cause of HIES, which was referred to as Job syndrome. Now additional genes have been identified, and cases due to STAT3 variants are referred to as STAT3-HIES. Infection in STAT3-HIES is often due to Staphylococcus aureus and Candida species. While HIES may be inherited in an autosomal dominant pattern, many cases are de novo. Genetic variants in additional genes have been identified that result in HIES. ZNF341 (zinc finger protein 341) deficiency results in an autosomal recessive form of HIES, also known as AR-HIES. Partial deficiency of interleukin (IL) 6 signal transducer (IL6ST) has been reported in both autosomal recessive and autosomal dominant forms of HIES, while complete IL6ST deficiency is typically fatal in utero or early in the neonatal period. Additionally, variants in PGM3, CARD11, and other genes have been identified as causes of HIES. Furthermore, other distinct immunodeficiency disorders or other conditions may have overlapping features with HIES (eg, elevated IgE or severe infection), making the diagnosis challenging. While the phenotypes of disorders leading to elevated IgE and predisposition to infection are often similar, the therapeutic options and treatment strategies differ.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hyper-IgE syndrome (HIES) Establishing a diagnosis of HIES, allowing for appropriate management and surveillance for disease features based on the gene and/or variant involved Identifying variants within genes known to be associated with HIES, allowing for predictive testing of at-risk family members and/or determination of targeted management (anticipatory guidance, management changes, specific therapies)

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 2. Tsilifis C, Freeman AF, Gennery AR: STAT3 Hyper-IgE syndrome-an update and unanswered questions. J Clin Immunol. 2021 Jul;41(5):864-880 3. Asano T, Khourieh J, Zhang P, et al: Human STAT3 variants underlie autosomal dominant hyper-IgE syndrome by negative dominance. J Exp Med. 2021 Aug 2;218(8):e20202592. doi: 10.1084/jem.20202592 4. Hsu AP, Davis J, Puck JM, Holland SM, Freeman AF: STAT3 hyper IgE syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews.[Internet] University of Washington, Seattle; 2010. Updated March 26, 2020. Accessed January 23, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK25507/ 5. Tangye SG, Al-Herz W, Bousfiha A, et al: Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022 Oct;42(7):1473-1507. doi:

10.1007/s10875-022-01289-3

HCHLG
617267

Hypercholesterolemia Gene Panel, Varies

Clinical Information: Hypercholesterolemia, characterized by elevated cholesterol levels in the blood, can be an inherited (genetic) condition or can be acquired due to either lifestyle factors such as diet or exercise or an underlying medical condition. The genetic influence on cholesterol levels can be complex, with monogenic (single gene) or polygenic (many genes) etiologies. This gene panel assesses for only monogenic causes of hypercholesterolemia. Autosomal dominant familial hypercholesterolemia (FH) is the most common inherited hypercholesterolemia condition and is characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C), leading to increased risk of premature cardiovascular disease and myocardial infarction. Affected individuals may also exhibit xanthomas that worsen with age. The majority of cases of FH are due to loss-of-function variants in the LDLR gene, but FH can also be caused by loss-of-function variants in the APOB gene or gain-of-function variants in the PCSK9 gene.(1,2) The most common form of FH is autosomal dominant heterozygous familial hypercholesterolemia (heFH) caused by single, heterozygous variants in LDLR, APOB, or PCSK9. A more severe form of FH, homozygous FH (hoFH), results when an individual inherits two variants in one of the three associated genes, either in the homozygous or compound heterozygous state.(1,2) Recent studies suggest that the prevalence of heFH is as high as 1:200 to 1:250, and the prevalence of hoFH is between 1:160,000 to 1:250,000.(1,2) Autosomal recessive FH, due to biallelic (homozygous or compound heterozygous) variants in the LDLRAP1 gene is a rare form of inherited hypercholesterolemia and is typically characterized by LDL-C levels above 400 mg/dL as well as cutaneous and tendon xanthomas. While LDLRAP1-associated hypercholesterolemia is rare, emerging evidence suggests heterozygous carriers of disease-causing LDLRAP1 variants may also present with hypercholesterolemia.(3,4,5,6) Sitosterolemia is a rare, autosomal recessive inherited lipid metabolism disease caused by biallelic variants in the ABCG5 or ABCG8 genes. The condition is characterized by increased intestinal absorption of plant sterols and has similar clinical manifestations to familial hypercholesterolemia, including elevated LDL-C, xanthomas, increased risk of premature cardiovascular disease, and increased risk of myocardial infarction. The prevalence of sitosterolemia has not been well established.(7) Other, more rare genetic conditions that may present with elevated cholesterol levels include autosomal recessive lysosomal acid lipase deficiency due to variants in the LIPA gene; autosomal dominant hyperalphalipoproteinemia due to variants in the CETP gene; autosomal recessive lipoprotein lipase deficiency due to variants in the LPL gene; and atypical autosomal dominant hypercholesterolemia due to variants in the APOE gene.(8) In addition, emerging evidence suggests that the LRP6 gene may be associated with autosomal dominant coronary artery disease, a condition in which hypercholesterolemia is a feature.(9,10) Cerebrotendinous xanthomatosis is a rare, autosomal dominant condition caused by disease-causing variants in the CYP27A1 gene. Individuals with cerebrotendinous xanthomatosis do not typically have elevated plasma cholesterol levels but do have clinical manifestations that overlap with hypercholesterolemia conditions, including xanthomas and increased risk for premature cardiovascular disease and myocardial infarction.(11)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of familial hypercholesterolemia (FH), sitosterolemia, or other monogenic forms of inherited hypercholesterolemia Establishing a diagnosis of FH, sitosterolemia, or other monogenic forms of inherited hypercholesterolemia

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(12) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:

An interpretive report will be provided.

Clinical References: 1. Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for familial hypercholesterolemia: JACC Scientific Expert Panel. J Am Coll Cardiol. 2018;72(6):662-680. doi:10.1016/j.jacc.2018.05.044 2. Ison HE, Clarke SL, Knowles JW. Familial hypercholesterolemia. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2014. Updated July 7, 2022. Accessed March 31, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK174884/3. Garcia CK, Wilund K, Arca M, et al. Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. Science. 2001;292(5520):1394-1398 4. Norman D, Sun XM, Bourbon M, Knight BL, Naoumova RP, Soutar AK. Characterization of a novel cellular defect in patients with phenotypic homozygous familial hypercholesterolemia: J Clin Invest. 1999;104(5):619-628 5. Pisciotta L, Priore Oliva C, Pes GM, et al. Autosomal recessive hypercholesterolemia (ARH) and homozygous familial hypercholesterolemia (FH): a phenotypic comparison: Atherosclerosis. 2006;188(2):398-405 6. Junna N, Ruotsalainen S, Ripatti P, FinnGen, Ripatti S, Widen E. Novel Finnish-enriched variants causing severe hypercholesterolemia and their clinical impact on coronary artery disease: Atherosclerosis. 2023:117327 7. Tzavella E, Hatzimichael E, Kostara C, Bairaktari E, Elisaf M, Tsimihodimos V: Sitosterolemia: A multifaceted metabolic disorder with important clinical consequences. J Clin Lipidol. 2017;11(4):1095-1100. doi:10.1016/j.jacl.2017.04.116 8. Hegele RA, Boren J, Ginsberg HN, et al. Rare dyslipidaemias, from phenotype to genotype to management: a European Atherosclerosis Society task force consensus statement. Lancet Diabetes Endocrinol. 2020;8(1):50-67. doi:10.1016/S2213-8587(19)30264-5 9. Mani A, Radhakrishnan J, Wang H, et al. LRP6 mutation in a family with early coronary disease and metabolic risk factors [published correction appears in Science. 2013 Aug 30;341(6149):959]. Science. 2007;315(5816):1278-1282. doi:10.1126/science.1136370 10. Singh R, Smith E, Fathzadeh M, et al. Rare nonconservative LRP6 mutations are associated with metabolic syndrome. Hum Mutat. 2013;34(9):1221-1225. doi:10.1002/humu.22360 11. Nie S, Chen G, Cao X, Zhang Y. Cerebrotendinous xanthomatosis: a comprehensive review of pathogenesis, clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2014;9:179. doi:10.1186/s13023-014-0179-4 12. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

HYOX
86213

Hyperoxaluria Panel, Random, Urine

Clinical Information: Increased urinary oxalate frequently leads to kidney stone formation and kidney insufficiency. Identifying the cause of hyperoxaluria has important implications in therapy, management, and prognosis. Hyperoxalurias are classified as primary and secondary. Primary hyperoxaluria is an inherited disorder of oxalate metabolism, while secondary hyperoxaluria is an acquired condition resulting from either increased intake of dietary oxalate or altered intestinal oxalate absorption. Primary hyperoxalurias are classified into types 1, 2, and 3. Hyperoxaluria type 1 (PH1) is an autosomal recessive disorder resulting in a deficiency of peroxisomal alanine:glyoxylate aminotransferase due to variants in the AGXT gene. It is characterized by increased urinary oxalic, glyoxylic, and glycolic acids. PH1 is the most common type with manifestations that include deposition of calcium oxalate in the kidneys (nephrolithiasis, nephrocalcinosis) and kidney failure. Calcium oxalate deposits can be further deposited in other tissues, such as the heart and eyes, and lead to a variety of additional symptoms. Age of onset is variable with a small percentage of patients presenting in the first year of life with failure to thrive, nephrocalcinosis, and metabolic acidosis. Approximately half of affected individuals show manifestations of PH1 in late childhood or early adolescence, and the remainder present in adulthood with recurrent kidney stones. Some individuals with PH1 respond to supplemental pyridoxine therapy. Hyperoxaluria type 2 (PH2) is due to a defect in GRHPR gene resulting in a deficiency of the enzyme hydroxypyruvate reductase. PH2 is inherited in an autosomal recessive manner and is identified by an increase in urinary oxalic and glyceric acids. Like PH1, PH2 is

characterized by deposition of calcium oxalate in the kidneys (nephrolithiasis, nephrocalcinosis), and kidney failure. Most individuals have symptoms of PH2 during childhood, and it is thought that PH2 is less common than PH1. Hyperoxaluria type 3 (PH3), due to recessive variants in HOGA1 (formerly DHDPSL), occurs in a small percentage of individuals with primary hyperoxaluria. HOGA1 encodes a mitochondrial 4-hydroxy-2-oxoglutarate aldolase that catalyzes the 4th step in the hydroxyproline pathway. PH3 is characterized biochemically by increased urinary excretion of oxalate and 4-hydroxy-2-oxoglutarate (HOG). As with PH types 1 and 2, PH type 3 is characterized by calcium-oxalate deposition in the kidneys or kidney stone formation. Most individuals with PH3 have early onset disease with recurrent kidney stones and urinary tract infections as common symptoms. Kidney failure is not a characteristic of PH3. Of note, individuals with heterozygous variants in HOGA1 can have variable and intermittent elevations of urine oxalate. Secondary hyperoxalurias are due to hyperabsorption of oxalate (enteric hyperoxaluria); total parenteral nutrition in premature infants; ingestion of oxalate, ascorbic acid, or ethylene glycol; or pyridoxine deficiency, and may respond to appropriate therapy. A diagnostic workup in an individual with hyperoxaluria demonstrates increased concentration of oxalate in urinary metabolite screening. If glycolate, glycerate, or HOG is present, a primary hyperoxaluria is indicated. Confirmatory testing includes molecular analysis for PH1, PH2, or PH3 (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; refer to the Hyperoxaluria Diagnostic Algorithm for specific Gene List IDs).

Useful For: Distinguishing between primary and secondary hyperoxaluria Distinguishing between primary hyperoxaluria types 1, 2, and 3

Interpretation: Increased concentrations of oxalate and glycolate indicate type 1 hyperoxaluria. Increased concentrations of oxalate and glycerate indicate type 2 hyperoxaluria. Increased concentrations of oxalate and 4-hydroxy-2-oxoglutarate indicate type 3 hyperoxaluria. Increased concentrations of oxalate with normal concentrations of glycolate, glycerate, and 4-hydroxy-2-oxoglutarate indicate secondary hyperoxaluria.

Reference Values:

GLYCOLATE
< or =17 years: < or =75 mg/g creatinine
> or =18 years: < or =50 mg/g creatinine

GLYCERATE
< or =31 days: < or =75 mg/g creatinine
32 days - 4 years: < or =125 mg/g creatinine
5 - 10 years: < or =55 mg/g creatinine
> or =11 years: < or =25 mg/g creatinine

OXALATE
< or =6 months: < or =400 mg/g creatinine
7 months - 1 year: < or =300 mg/g creatinine
2 - 6 years: < or =150 mg/g creatinine
7 - 10 years: < or =100 mg/g creatinine
> or =11 years: < or =75 mg/g creatinine

4-HYDROXY-2-OXOGLUTARATE (HOG)
< or =10 mg/g creatinine

Clinical References: 1. Bhasin B, Urekli HM, Atta MG. Primary and secondary hyperoxaluria: Understanding the enigma. World J Nephrol. 2015;4(2):235-244. doi:10.5527/wjn.v4.i2.235 2. Lorenzo V, Torres A, Salido E. Primary hyperoxaluria. Nefrologia. 2014;34(3):398-412 3. Milliner DS, Harris PC, Cogal AG, et al. Primary hyperoxaluria type 1. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated February 10, 2022. Accessed

August 28, 2023. Available at: www.ncbi.nlm.nih.gov/books/NBK1283/ 4. Rumsby G, Hulton SA. Primary hyperoxaluria type 2. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2008. Updated December 21, 2017. Accessed August 28, 2023. Available at: www.ncbi.nlm.nih.gov/books/NBK2692/ 5. Milliner DS, Harris PC, Lieske JC. Primary hyperoxaluria type 3. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2015. Updated February 9, 2023. Accessed August 28, 2023. Available at: www.ncbi.nlm.nih.gov/books/NBK316514/ 6. Fraser AD: Importance of glycolic acid analysis in ethylene glycol poisoning. Clin Chem. 1998;44(8):1769

FAVI
91509

Hypersensitivity Pneumonitis Avian Panel

Clinical Information: A hypersensitivity pneumonitis (HP) due to the inhalation and sensitization to avian antigens. Immunodiffusion is used to evaluate the presence of precipitating antibodies in the sera of patients with HP due to the sensitization to various species of birds.

Reference Values:

This panel includes the following antigens:

Pigeon Sera
Pigeon DE
Cockatiel
Parakeet
Parrot

Results are reported as:
Negative
Weakly Positive
Positive
Strong Positive

This result must be correlated with patient's clinical response and should not solely be considered in the diagnosis.

FHSPP
75769

Hypersensitivity Pneumonitis Panel

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:

Alternaria tenuis/alternata IgG
Aspergillus fumigatus IgG
Aureobasidium pullulans IgG
Laceyella sacchari IgG
Micropolyspora faeni IgG
Penicillium

Chrysogenum/notatum IgG
Phoma betae IgG
Trchoderma viride IgG

HYPTG
617323

Hypertriglyceridemia Gene Panel, Varies

Clinical Information: Hypertriglyceridemia (HTG), or abnormally elevated triglyceride concentration in the blood, is present in approximately 30% of adults in the United States.(1) HTG is frequently associated with other abnormalities such as abdominal obesity, insulin resistance, low high-density lipoprotein (HDL), and hypertension, which are linked to coronary artery disease and metabolic syndrome. Severe hypertriglyceridemia is associated with an increased risk of acute pancreatitis. Hypertriglyceridemia can be classified into primary and secondary types. Primary hypertriglyceridemia accounts for less than 5% of cases and is due to rare, monogenic conditions with disease-causing variants resulting in disordered triglyceride metabolism.(2) The majority of hypertriglyceridemia is secondary hypertriglyceridemia, due to a combination of lifestyle factors such as high fat diet, obesity, diabetes, hypothyroidism, or certain medications, in addition to various common, low impact genetic variants that cumulatively have an impact on triglyceride metabolism. This test includes analysis of several genes associated with monogenic forms of primary hypertriglyceridemia and related conditions. Autosomal recessive conditions tested for by this panel include combined lipase deficiency (LMF1), hepatic lipase deficiency (LIPC), lysosomal acid lipase deficiency (also known as Wolman disease) and cholesteryl ester storage disease (LIPA), lecithin:cholesterol acyltransferase deficiency (also known as Norum disease or fish-eye disease) (LCAT), hyperlipoproteinemia type 1b (APOC2), transient infantile hypertriglyceridemia (GPD1), hyperlipoproteinemia type ID (GPIHBP1), and lipoprotein lipase deficiency (LPL). Autosomal dominant conditions tested for by this panel include familial hypertriglyceridemia and late onset hyperchylomicronemia (APOA5), hypertriglyceridemia 2 (CREB3L3), and familial combined hyperlipidemia (LPL). In addition, this test reports homozygous status for the APOE E2 allele, a risk allele for type III hyperlipoproteinemia.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of hereditary forms of primary hypertriglyceridemia and related conditions.

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Pejic RN and Lee DT. Hypertriglyceridemia. J Am Board Fam Med. 2006;19(3):310-316 2. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: its etiology, effects and treatment. CMAJ. 2007;176(8): 1113-1120 3. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

HCMGG
617281

Hypertrophic Cardiomyopathy Gene Panel, Varies

Clinical Information: Cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by either inherited, genetic factors or nongenetic (acquired) causes, such as infection or trauma.(1) When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. The hereditary form of hypertrophic cardiomyopathy (HCM) is characterized by left ventricular hypertrophy in the absence of other cardiac or systemic causes that may cause hypertrophy of the heart muscle, such as longstanding, uncontrolled hypertension or aortic stenosis. The incidence of HCM in the general population is approximately 1:200 to1:500, and it is estimated that 30% to 60% of cases can be attributed to a genetic etiology.(1) Hereditary forms of HCM are most often caused by genes encoding proteins of the cardiac sarcomere, the functional contractile unit of the heart muscle. The clinical presentation of HCM can be variable, even within the same family. HCM can be apparently asymptomatic in some individuals but can cause sudden, life-threatening arrhythmias, increasing the risk of sudden cardiac death. Additionally, HCM may also be a feature of an underlying systemic condition such as Noonan syndrome, a mitochondrial disorder, or a metabolic storage disorder.(2) Hereditary forms of HCM can follow autosomal dominant, autosomal recessive, and X-linked patterns of inheritance. Mitochondrial inheritance is also possible, however, genes associated with mitochondrial inheritance of HCM are not assessed on this panel.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of a hereditary form of hypertrophic cardiomyopathy Establishing a diagnosis of a hereditary form of hypertrophic cardiomyopathy

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Ommen SR, Mital S, Burke MA, et al: 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: Executive Summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. Circulation. 2020;142(25):e533-e557. doi: 10.1161/CIR.0000000000000938 2. Authors/Task Force members, Elliott PM, Anastasakis A, et al: 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014 Oct;35(39):2733-2779. doi: 10.1093/eurheartj/ehu284 3. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424. doi: 10.1038/gim.2015.30

HYPBG
617309

Hypobetalipoproteinemia Gene Panel, Varies

Clinical Information: Monogenic causes of hypobetalipoproteinemia include familial hypobetalipoproteinemia (FHBL), abetalipoproteinemia (ABL), chylomicron retention disease (CMRD), loss-of-function variants in PCSK9, and familial combined hypolipidemia (FCH). Familial hypobetalipoproteinemia is the most common form of hypobetalipoproteinemia and is characterized by apolipoprotein B (ApoB) levels below the 5th percentile and low-density lipoprotein cholesterol (LDL-C) concentrations in the range of 20 mg/dL to 50 mg/dL. FHBL displays codominant inheritance, whereby heterozygous individuals may be asymptomatic or have mild disease, and (rare) compound heterozygous and homozygous individuals develop more severe, early-onset disease. In cases of mild to

moderate FHBL with little or no liver involvement, prognosis is good and, in fact, may be associated with increased longevity. In severe disease, symptoms include fatty liver, which may progress to cirrhosis over time, symptoms of fat malabsorption, failure to thrive, and neurological and ocular dysfunction. FHBL is most commonly due to disease-causing truncating variants in the APOB gene resulting in reduced or nonfunctional protein. Abetalipoproteinemia is a rare (<1:1,000,000) condition characterized by triglyceride concentrations of less than 30 mg/dL, cholesterol concentrations of less than 30 mg/dL, and undetectable LDL and ApoB levels. Clinical presentation is similar to that described above for compound heterozygous and homozygous FHBL. ABL displays autosomal recessive inheritance and is caused by compound heterozygous or homozygous disease-causing variants in the MTTP gene. Chylomicron retention disease is a rare lipid malabsorption syndrome that typically presents in young infants with diarrhea, steatorrhea, abdominal distention, and failure to thrive. Laboratory findings include LDL-C and high-density lipoprotein cholesterol-C reduction of approximately 50% with normal triglyceride concentrations. CMRD displays autosomal recessive inheritance and is caused by compound heterozygous or homozygous disease-causing variants in the SAR1B gene. Heterozygous loss-of-function variants in the PCSK9 gene are associated with mild to moderate reduction in LDL-C and normal health with significantly lower prevalence of atherosclerotic heart disease. Rare individuals with biallelic loss-of-function variants in PCSK9 have been reported with extremely low levels of LDL-C (approximately 15 mg/dL), normal health and reproductive capacity, and no evidence of neurologic or cognitive dysfunction. Notably, heterozygous gain-of-function variants in PCSK9 are associated with familial hypercholesterolemia. Finally, FCH is a very rare condition of panhypolipidemia associated with normal health and significantly lower prevalence of atherosclerotic heart disease. This condition is caused by loss-of-function variants in the ANGPTL3 gene. Similar to FHBL and PCSK9, FCH displays codominant inheritance, with heterozygotes having normal HDL-C and LDL-C concentrations that are below the 25th percentile, while compound heterozygous and homozygous individuals display significant reductions in HDL-C levels as well.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of familial hypobetalipoproteinemia

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Shapiro MD and Feingold KR. Monogenic disorders causing hypobetalipoproteinemia. In: Feingold KR, Anawalt B, Boyce A, et al, eds. Endotext [Internet]. MDTest.com, Inc; 2000. Updated January 22, 2024. Accessed March 31, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK326744/

HYPOG
82439

Hypoglycemic Agent Screen, Serum

Clinical Information: The metabolic and hormonal profiles of insulinoma and sulfonylurea-induced hypoglycemia are identical. Therefore, in the evaluation of the hypoglycemic patient, the possible use of oral hypoglycemic agents as the cause for low blood glucose and elevated serum insulin must be considered. Absence of hypoglycemic drugs in serum during an episode of low blood glucose should be demonstrated before considering pancreatic exploration for suspected insulinoma.

Useful For: Evaluation of suspected insulinoma characterized by hypoglycemia and increased serum insulin concentration Detecting drugs that stimulate insulin secretion Drugs detected by this procedure are: -The first-generation sulfonylureas: chlorpropamide (Diabinese), tolazamide, and tolbutamide (Orinase) -The second-generation sulfonylureas: glimepiride (Amaryl), glipizide (Glucotrol), and glyburide (Glibenclamide) -The meglitinides: repaglinide (Prandin) and nateglinide (Starlix) -The thiazolidinediones: pioglitazone (Actos) and rosiglitazone (Avandia) This test is not intended for therapeutic drug monitoring but could be used to monitor compliance.

Interpretation: Use of hypoglycemic agents outside of the context of treatment of type 2 diabetes is likely to cause hypoglycemia associated with elevated serum insulin. Patients presenting with hypoglycemia due to ingestion of a first-, second-, or third-generation hypoglycemic agents will have drug present in serum greater than the minimum effective concentration (see Reference Values). Presence of drug indicates that the patient has recently ingested a hypoglycemic agent.

Reference Values:

Negative

Screening cutoff concentrations
Chlorpropamide: 100 ng/mL
Glimepiride: 20 ng/mL
Glipizide: 5 ng/mL
Glyburide: 5 ng/mL
Nateglinide: 5 ng/mL
Pioglitazone: 20 ng/mL
Repaglinide: 5 ng/mL
Rosiglitazone: 20 ng/mL
Tolazamide: 50 ng/mL
Tolbutamide: 20 ng/mL

Note: If a drug is detected at a concentration greater than the cutoff, the report will indicate that specific drug is positive. The test cutoff listed for each drug is lower than the concentration that will cause increased insulin and decreased glucose.

Clinical References: 1. Ben-Ami H, Nagachandran P, Mendelson A, Edoute Y. Drug-induced hypoglycemic coma in 102 diabetic patients. Arch Intern Med. 1999;159(3):281-284 2. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

HIF2A
61681

Hypoxia-Inducible Factor Alpha (EPAS1/HIF2A) Gene, Exons 9 and 12 Sequencing, Whole Blood

Clinical Information: Erythrocytosis (ie, increased red blood cell [RBC] mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, kidney cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases are associated with pheochromocytoma or paraganglioma formation. Hereditary erythrocytosis is caused by variants in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these

cases, although it is possible for new alterations to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF2A/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (see Table). The true prevalence of hereditary erythrocytosis-causing variants is unknown. The hemoglobin genes, HBA1/HBA2 and HBB are not assayed in this profile. Table. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum EPO JAK2 V617F Acquired Decreased JAK2 exon 12 Acquired Decreased EPOR Dominant Decreased PHD2/EGLN1 Dominant Normal level BPGM Recessive Normal level Beta Globin Dominant Normal level to increased Alpha Globin Dominant Normal level to increased HIF2A/EPAS1 Dominant Normal level to increased VHL Recessive Normal level to increased The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the PHD2 (EGLN1) gene. Genetic alterations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants in PHD2/EGLN1 and HIF2A/EPAS1 have also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating variants in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known variants have been localized to exon 8 and are heterozygous truncating variants. EPOR variants are associated with decreased to normal EPO levels (see Table).

Useful For: Assessing HIF2A/EPAS1 in the evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased red blood cell (RBC) mass, elevated RBC count, hemoglobin, or hematocrit

Interpretation: An interpretive report will be provided as a part of HEMP / Hereditary Erythrocytosis Mutations, Whole Blood and will include specimen information, assay information, and whether the specimen was positive for any variants in the gene. If positive, the variant will be correlated with clinical significance, if known.

Reference Values:
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations, Whole Blood.

An interpretive report will be provided.

Clinical References: 1. Patnaik MM, Tefferi A: The complete evaluation of erythrocytosis: congenital and acquired. Leukemia. 2009 May;23(5):834-844. doi: 10.1038/leu.2009.54 2. McMullin MF: The classification and diagnosis of erythrocytosis. Int J Lab Hematol. 2008 Dec;30(6):447-459 3. Percy MJ, Lee FS: Familial erythrocytosis: molecular links to red blood cell control. Haematologica. 2008 Jul;93(7):963-967. doi: 10.3324/haematol.13250 4. Huang LJ, Shen YM, Bulut GB: Advances in understanding the pathogenesis of primary familial and congenital polycythaemia. Br J Haematol. 2010 Mar;148(6):844-852 5. Maran J, Prchal J: Polycythemia and oxygen sensing. Pathologie Biologie. 2004 Jun;52(5):280-284 6. Lee F: Genetic causes of erythrocytosis and the oxygen-sensing pathway. Blood Rev. 2008 Nov;22(6):321-332 7. Merchant SH, Oliveira JL, Hoyer JD, Viswanatha DS: Erythrocytosis. In: His ED, ed. Hematopathology. 2nd ed. Elsevier Saunders; 2012:22-723 8. Zhuang Z, Yang C, Lorenzo

F, et al: Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. N Engl J Med. 2012 Sep 6;367(10):922-930 9. Ladroue C, Carcenac R, Leporrier M, et al: PHD2 mutation and congenital erythrocytosis with paraganglioma. N Engl J Med. 2008 Dec 18;359(25):2685-2692 10. Lorenzo FR, Yang C, Ng Tang Fui M, et al: A novel EPAS1/HIF2A germline mutation in congenital polycythemia with paraganglioma. J Mol Med. 2013 Apr;91(4):507-512 11. Tarade D, Robinson CM, Lee JE, Ohh M: HIF-2alpha-pVHL complex reveals broad genotype-phenotype correlations in HIF-2aalpha-driven disease. Nat Commun. 2018 Aug 22;9(1):3359 12. Oliveira JL: Algorithmic evaluation of hereditary erythrocytosis: Pathways and caveats. Int J Lab Hematol. 2019 May;41 Suppl 1:89-94.doi: 10.1111/ijlh.13019

FIBUP
57703

Ibuprofen (Motrin, Advil, Nuprin), serum

Reference Values:
Reference Range: 10.0 - 50.0 ug/mL

ICOSI
113518

ICOS (CD278), Immunostain, Technical Component Only

Clinical Information: ICOS (inducible T-cell costimulator or CD278: cluster of differentiation 278) is primarily expressed on activated CD4+ and CD8+ T cells where it regulates immune responses and plays a role in the regulation of T-follicular helper cells. ICOS is a sensitive marker for identifying T-cell lymphomas of follicular helper T-cell origin, especially certain patterns of angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphomas with T-follicular helper phenotype (PTCL-TFH).

Useful For: Classification of T-cell lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Baseggio L, Traverse-Glehen A, Berger F, et al. CD10 and ICOS expression by multiparametric flow cytometry in angioimmunoblastic T-cell lymphoma. Modern Pathology. 2011;24(7):993-1003 2. Tan LH, Tan SY. Aberrant immunoarchitecture distinguishes hyperplastic germinal centres in pattern 1 angioimmunoblastic T-cell lymphoma from reactive follicles. Hematol Oncol. 2014;32(3):145-154 3. Bosisio FM, Cerroni L. Expression of T-follicular helper markers in sequential biopsies of progressive mycosis fungoides and other primary cutaneous T-cell lymphomas. Am J Dermatopathol. 2015;37(2):115-121 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

RMALA
62258

Id MALDI-TOF Mass Spec Anaerobe (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

LCHB
60214

Id, Histoplasma/Blastomyces PCR (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

RMALD
60029

Ident by MALDI-TOF Mass Spec (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

LCCI
45463

Ident Rapid PCR Coccidioides (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

PCRID
64706

Identification by PCR (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

LCCA
610319

Identification, Candida auris, Rapid PCR (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

COMM
45070

Identification, Commercial Kit (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

ISNGS
609732

Identification, Next-Generation Sequencing (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IDHQ
615859

IDH1 (R132) and IDH2 (R140 and R172) Quantitative Detection,

Droplet Digital PCR, Varies

Clinical Information: Isocitrate dehydrogenase 1 (IDH1) is a cytosolic/peroxisomal enzyme involved in citric acid cycle and other cellular metabolic processes. It catalyzes the oxidative decarboxylation of isocitrate to alpha-ketoglutarate (a-KG), generating reduced nicotinamide adenine dinucleotide phosphate (NADPH) from NADP(+). Isocitrate dehydrogenase 2 (IDH2) is a mitochondrial NADP(+)-dependent enzyme that catalyzes the oxidative decarboxylation of isocitrate to a- KG, generating NADPH from NADP(+). Mutations in codon R132 of IDH1 or R140 or R172 in IDH2 confer an abnormal enzyme activity that converts a-KG to D-2- hydroxyglutarate (2-HG) resulting in elevation of 2-HG and a hypermethylation state, associated in myeloid neoplasms including acute myeloid leukemia (AML). IDH1 and IDH2 point mutations are seen in approximately 5% to 33% de novo AML and 7% to 25% secondary AML. The US Food and Drug Administration (FDA) has approved ivosidenib (AG-120) for the treatment of newly-diagnosed IDH1-mutated AML (patients 75 years of age and older or who have comorbidities that preclude the use of intensive induction chemotherapy) and relapsed/refractory AML in adult patients.(1) The FDA has also approved enasidenib (AG-221) for the treatment of IDH2-mutated relapsed/refractory AML.(2) IDH1 and IDH2 have also been shown to be suitable minimal residual disease markers for AML post-therapy.

Useful For: Detecting IDH1 R132 and IDH2 R140 and R172 mutations in acute myeloid leukemia patients at the time of diagnosis to guide targeted therapy Monitoring minimal residual disease during the clinical and therapeutic course

Interpretation: The assay is reported as positive or negative. In positive cases, the mutation and its variant allele fraction (VAF) are reported. VAF%= (mutant copy number)/(mutant copy number + wild-type number) The precision of this quantitative assay is excellent but interassay variability may occur such that result changes should not be considered significant if 2 single measurements differ by less than 0.5 log (3.16-folds).

Reference Values:
An interpretive report will be provided.

Clinical References: 1. US Food and Drug Administration (FDA): Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated September 23, 2024. January 15, 2025. Available at www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling 2. US Food and Drug Administration (FDA): FDA granted regular approval to enasidenib for the treatment of relapsed or refractory AML. FDA; August 1, 2017. Accessed January 15, 2025. Available at www.fda.gov/drugs/resources-information-approved-drugs/fda-granted-regular-approval-enasidenib-treatment-relapsed-or-refractory-aml 3. Duncavage EJ, Bagg A, Hasserjian RP, et al. Genomic profiling for clinical decision making in myeloid neoplasms and acute leukemia. Blood. 2022;140(21):2228-2247. doi:10.1182/blood.2022015853 4. Dohner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377. doi:10.1182/blood.2022016867 5. Pollyea DA. New drugs for acute myeloid leukemia inspired by genomics and when to use them. Hematology Am Soc Hematol Educ Program. 2018;2018(1):45-50 6. Stein EM, DiNardo CD, Pollyea DA, Fathi AT, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia Blood. 2017;130(6):722-731 7. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with Ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med. 2018;378(25):2386-2398 8. Ok CY, Loghavi S, Sui D, et al. Persistent IDH1/2 mutations in remission can predict relapse in patients with acute myeloid leukemia. Haematologica. 2019;104(2):305-311

IDHT
616498

IDH1 and IDH2 Mutation Analyses, Next-Generation

Sequencing, Tumor

Clinical Information: IDH1 and IDH2 (isocitrate dehydrogenase: IDH) genes encode enzymes involved in cellular glucose metabolism. Mutations in the IDH genes primarily involve codons R132 in IDH1 and R140 and R172 in IDH2 and lead to the neomorphic ability to generate oncometabolite R(-)-2-hydroxyglutarate, which contributes to tumorigenesis. In central nervous system (CNS) tumors, IDH mutations are a diagnostic molecular biomarker for diffuse gliomas and define two biologically distinct groups: IDH-mutant and IDH-wildtype tumors. IDH mutations are rarely observed in other CNS tumor types and are not seen in CNS reactive non-neoplastic processes. IDH mutations are also a molecular biomarker in non-CNS tumors, including acute myeloid leukemia, cholangiocarcinoma, and cartilaginous tumors. Clinically approved targeted therapies are available for a subset of patients with IDH-mutant acute myeloid leukemia and IDH-mutant cholangiocarcinoma.

Useful For: Identifying specific mutations within the IDH1 and IDH2 genes that assist in tumor diagnosis/classification and predict response to targeted therapy

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. US Food and Drug Administration (FDA): Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated February, 10, 2023, Accessed July 31, 2023. Available at www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling 4. WHO Classification of Tumours Editorial Board: Central nervous system tumours. 5th ed. World Health Organization; 2021. WHO Classification of Tumours. Vol 6. 5. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360(8):765-773 6. Cancer Genome Atlas Research Network, Brat DJ, Verhaak RG, et al. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med. 2015;372(26):2481-2498 7. Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med. 2015;372(26):2499-2508 8. Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. N Engl J Med. 2009;361(11):1058-1066 9. Jusakul A, Cutcutache I, Yong CH, et al. Whole-genome and epigenomic landscapes of etiologically distinct subtypes of cholangiocarcinoma. Cancer Discov. 20177(10):1116-1135 10. Amary MF, Bacsi K, Maggiani F, et al. IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. J Pathol. 2011;224(3):334-343

IDH1
70468

IDH1 Mutation (R132H) Immunostain, Technical Component Only

Clinical Information: Antihuman isocitrate dehydrogenase 1 (IDH1) R132H antibody binds to IDH1-mutated protein but does not bind the wild-type IDH1 protein. IDH1 R132H point mutations are frequently seen in World Health Organization grade II and III gliomas and are believed to constitute an early step in tumorigenesis. IDH1 R132H can be used as a diagnostic marker to help differentiate infiltrating gliomas from gliosis and as a prognostic marker for gliomas and secondary glioblastoma multiforme. IDH1 R132H antibody shows strong cytoplasmic staining and weaker nuclear staining in tumor cells with the R132H-mutated peptide. Diffuse staining of the fibrillary tumor matrix is also seen.

Useful For: Classification of gliomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Preusser M, Wohrer A, Stary S, Hoftberger R, Streubel B, Hainfellner JA. Value and limitations of immunohistochemistry and gene sequencing for detection of the IDH1-R132H mutation in diffuse glioma biopsy specimens. J Neuropathol Exp Neurol. 2011;70(8):715-723 2. Zou Y, Bai HX, Wang Z, Yang L. Comparison of immunohistochemistry and DNA sequencing for the detection of IDH1 mutations in gliomas. Neuro Oncol. 2015;17(3):477-478 3. Agarwal S, Sharma MC, Jha P, et al. Comparative study of IDH1 mutations in gliomas by immunohistochemistry and DNA sequencing. Neuro Oncol. 2013;15(6):718-726 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

IDTRT 619649 IDH1, IDH2, and TERT Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information: IDH1 and IDH2 (IDH) genes encode enzymes involved in cellular glucose metabolism. Mutations in IDH genes primarily involve codons R132 in IDH1 and R140 and R172 in IDH2, and lead to the neomorphic ability to generate oncometabolite R(-)-2-hydroxyglutarate, which contributes to tumorigenesis. TERT gene encodes the catalytic subunit of telomerase, an enzyme complex that regulates telomere length. Mutations in the TERT promoter primarily involve the mutational hotspot positions c.-124 (also known as C228) and c.-146 (also known as C250) and increase telomerase activity allowing tumor cells to overcome cellular senescence. IDH and TERT promoter mutations are essential diagnostic molecular biomarkers for diffuse gliomas, a group of central nervous system (CNS) tumors. Testing for both biomarkers is often diagnostically necessary. This test simultaneously assesses for somatic mutations involving the IDH and TERT promoter genes. IDH and TERT promoter mutations are also molecular biomarkers for a variety of non-CNS tumors but usually do not co-occur and would be best evaluated by stand-alone IDH and TERT promoter tests.

Useful For: Identifying specific mutations within the IDH1 and IDH2 genes and the TERT promoter to assist in tumor diagnosis/classification

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. WHO Classification of Tumours Editorial Board: Central nervous system tumours. 5th ed. World Health Organization; 2021. WHO Classification of Tumours. Vol 6 4. Killela PJ, Reitman ZJ, Jiao Y, et al: TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. Proc Natl Acad Sci USA.

2013;110(15):6021-6026 5. Koelsche C, Sahm F, Capper D, et al: Distribution of TERT promoter mutations in pediatric and adult tumors of the nervous system. Acta Neuropathol. 2013;126(6):907-915 6. Eckel-Passow JE, Lachance DH, Molinaro AM, et al: Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med. 2015;372(26):2499-2508 7. Cancer Genome Atlas Research Network, Brat DJ, Verhaak RGW, et al: Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med. 2015;372(26):2481-2498 8. Yan H, Parsons DW, Jin G, et al: IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360(8):765-773

IPFGP
621589

Idiopathic Pulmonary Fibrosis Gene Panel, Varies

Clinical Information: Pulmonary fibrosis is characterized by irreversible, progressive damage and scarring of tissue around and between alveoli in the lungs. Causes include certain medications, chest radiation treatment, long term exposure to toxins, pollutants or other environmental triggers, and autoimmune disease. When none of these causes is identified, pulmonary fibrosis is described as "idiopathic". The histologic pattern "usual interstitial pneumonia" is associated with the clinical diagnosis of idiopathic pulmonary fibrosis (IPF). Although IPF is considered a disease of unknown cause, some factors increase the risk for IPF, such as age and smoking. A subset of individuals with IPF may carry genetic variants that predispose them to disease. When IPF occurs at a younger age than expected (ie, before age 50 years), affects more than one individual in a family, or presents with other clinical features (eg, bone marrow failure, macrocytosis, cryptogenic cirrhosis or portal hypertension, premature graying of hair, abnormal nails, skin pigmentation, or bleeding), genetic testing may be considered. This panel assesses 27 genes associated with the following heritable causes of pulmonary fibrosis. Disorders of Surfactant Dysfunction Surfactant is a lipoprotein complex secreted by alveolar cells that reduces the surface tension of fluids coating the lung. It is essential for alveolar stability and lung function. Genes important for surfactant production and metabolism include ABCA3, SFTPA1, SFTPA2, SFTPB, and SFTPC. In neonates and infants, inborn errors of pulmonary surfactant metabolism present as severe respiratory insufficiency or failure. However, individuals with disease-causing variants in these genes can present with pulmonary fibrosis at any age, from infancy to late adulthood. While these conditions are not associated with extrapulmonary features, they can cosegregate with lung adenocarcinoma in some families. Telomere Biology Disorders Telomeres are protective DNA repeats at the ends of chromosomes that protect the chromosome from shortening and damage caused by cellular replication. Genes involved in telomere synthesis, maintenance, and elongation include ACD, CTC1, DKC1, NAF1, NHP2, NOP10, PARN, POT1, RPA1, RTEL1, STN1, TERC, TERT, TINF2, WRAP53, and ZCCHC8. Although idiopathic pulmonary fibrosis is the one of the most common manifestations of telomere biology disorders (TBDs), these conditions often cause extrapulmonary features and are highly pleiotropic. Dyskeratosis congenita, for example, is characterized by reticular skin pigmentation, nail dystrophy, and oral mucosal leukoplakia, and often causes bone marrow failure. Cerebroretinal microangiopathy with calcifications and cysts (aka Coats plus syndrome), which is associated with CTC1 and STN1, is characterized by retinal telangiectasia exudates, leukodystrophy, intracranial calcifications and cysts. Of note, TBDs characterized by short telomeres show genetic anticipation with each generation potentially presenting with earlier and/or more severe disease phenotype. Hemansky-Pudlak syndrome, types 1, 2, and 4 Hermansky-Pudlak syndrome (HPS) is a multisystem disorder with 10 different subtypes that is primarily characterized by skin, hair, and eye hypopigmentation and bleeding diathesis caused by platelet dysfunction. Some individuals with HPS types 1 and 4 also have granulomatous inflammation of the bowel. HPS types 1, 2, and 4, which are caused by disease-causing variants in HPS1, AP3B1, and HPS4 respectively, are associated with pulmonary fibrosis that typically presents at 30 to 40 years of age. Almost all individuals with HPS1 develop pulmonary fibrosis. This panel also includes genes associated with 3 rare syndromic monogenic disorders for which pulmonary fibrosis have been reported: RIDDLE syndrome (RNF168) (increased radiosensitivity, mild immunodeficiency, dysmorphic features, and learning difficulties); STING-associated vasculopathy with onset in infancy (STING1) (SAVI; systemic inflammation, small vessel vasculopathy, progressive lung disease); and poikiloderma with neutropenia (USB1).

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of familial idiopathic pulmonary fibrosis Establishing a diagnosis of familial idiopathic pulmonary fibrosis associated with known causal genes Identifying variants within genes known to be associated with inherited risk for idiopathic pulmonary fibrosis, allowing for predictive testing of at-risk family members and/or determination of targeted management (anticipatory guidance, management changes, specific therapies)

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-424. 2. Alder JK, Armanios M. Telomere-mediated lung disease. Physiol Rev. 2022;102(4):1703-1720. doi:10.1152/physrev.00046.2021 3. Magnani JE, Donn SM. Persistent respiratory distress in the term neonate: Genetic surfactant deficiency diseases. Curr Pediatr Rev. 2020;16(1):17-25. doi:10.2174/1573396315666190723112916 4. van Moorsel CHM, van der Vis JJ, Grutters JC. Genetic disorders of the surfactant system: focus on adult disease. Eur Respir Rev. 2021 Feb 16;30(159):200085. doi:10.1183/16000617.0085-2020 5. Velazquez-Diaz P, Nakajima E, et al. Hermansky-Pudlak Syndrome and Lung Disease: Pathogenesis and Therapeutics. Front Pharmacol. 2021;12:644671. doi:10.3389/fphar.2021.644671. PMID: 33841163; PMCID: PMC8028140. 6. Zhang D, Newton CA. Familial pulmonary fibrosis: Genetic features and clinical implications. Chest. 2021;160(5):1764-1773. doi:10.1016/j.chest.2021.06.037

I2SB
618290

Iduronate-2-Sulfatase, Blood Spot

Clinical Information: Mucopolysaccharidosis II (MPS II; Hunter syndrome) is an X-linked lysosomal disorder caused by the deficiency of iduronate sulfatase enzyme due to variants in the IDS gene. Clinical features and severity of symptoms are widely variable ranging from severe infantile onset disease to an attenuated form, which generally has a later onset with a milder clinical presentation. Symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. As an X-linked disorder, MPS II occurs primarily in male patients with an estimated incidence of 1 in 120,000 male births, although symptomatic carrier females have been reported. Treatment availability, including hematopoietic stem cell transplantation and enzyme replacement therapy, makes early diagnosis desirable, as early initiation of treatment has been shown to improve clinical outcomes. Newborn screening for MPS II has been implemented in some states. A diagnostic workup in an individual with MPS II includes urine or blood glycosaminoglycans levels showing increased amounts of both dermatan and heparan sulfate (see MPSQU / Mucopolysaccharides Quantitative, Random, Urine and MPSBS / Mucopolysaccharidosis, Blood Spot). Reduced or absent activity of iduronate sulfatase can confirm a diagnosis of MPS II but may also be deficient in unaffected individuals with pseudodeficiency as well as individuals with multiple sulfatase deficiency. Enzymatic testing is not reliable to detect carriers. Molecular genetic testing of the IDS gene allows for detection of the disease-causing variant in affected patients and subsequent carrier detection in female relatives (see MPS2Z / Hunter Syndrome, Full Gene Analysis, Varies).

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidosis II (MPS II; Hunter

syndrome) This test is not useful for determining carrier status for MPS II.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular genetic analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
>4.30 nmol/mL/hour

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed May 24, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ, Ballabio A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed May 24, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546905

I2SWB
618291

Iduronate-2-Sulfatase, Leukocytes

Clinical Information: Mucopolysaccharidosis II (MPS II; Hunter syndrome) is an X-linked lysosomal disorder caused by the deficiency of iduronate sulfatase enzyme due to variants in the IDS gene. Clinical features and severity of symptoms are widely variable ranging from severe infantile onset disease to an attenuated form, which generally has a later onset with a milder clinical presentation. Symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. As an X-linked disorder, MPS II occurs primarily in male patients with an estimated incidence of 1 in 120,000 male births, although symptomatic carrier females have been reported. Treatment availability, including hematopoietic stem cell transplantation and enzyme replacement therapy, makes early diagnosis desirable, as early initiation of treatment has been shown to improve clinical outcomes. Newborn screening for MPS II has been implemented in some states. A diagnostic workup in an individual with MPS II includes urine or blood glycosaminoglycans levels showing increased amounts of both dermatan and heparan sulfate (see MPSQU / Mucopolysaccharides Quantitative, Random, Urine and MPSBS / Mucopolysaccharidosis, Blood Spot). Reduced or absent activity of iduronate sulfatase can confirm a diagnosis of MPS II but may also be deficient in unaffected individuals with pseudodeficiency as well as individuals with multiple sulfatase deficiency. Enzymatic testing is not reliable to detect carriers. Molecular genetic testing of the IDS gene allows for detection of the disease-causing variant in affected patients and subsequent carrier detection in female relatives (see MPS2Z / Hunter Syndrome, Full Gene Analysis, Varies).

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidosis II (MPS II; Hunter syndrome) in whole blood specimens This test is not useful for carrier detection for MPS II.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview

of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
>2.20 nmol/hour/mg protein

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed May 24, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ, Ballabio A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed May 24, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546905

IFPCA
113304

IF Additional (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IFA26
603534

IF Additional, Professional Only (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IFTOA
603532

IF Additional, Technical Only (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IFPCI
113303

IF Initial (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IFI26
603533

IF Initial, Professional Only (Bill Only)

Reference Values:
This test is for billing purposes only.

This is not an orderable test.

IFTOI
603531

IF Initial, Technical Only (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IGAI
70470

IgA Immunostain, Technical Component Only

Clinical Information: The immunoglobulin molecules (antibodies) function as surface receptors for antigens for B lymphocytes and as secretory products of plasma cells forming the humoral arm of the immune system. IgA represents one of the immunoglobulin heavy chain types and is the major immunoglobulin class secreted at mucosal surfaces. Diagnostically, staining for immunoglobulin heavy chains can aid in the diagnosis and classification of small B-cell malignant lymphomas and multiple myeloma.

Useful For: Aiding in the classification of lymphomas and multiple myeloma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Cox SN, Chiurlia S, Divella C, et al. Formalin-fixed paraffin-embedded renal biopsy tissues: an underexploited biospecimen resource for gene expression profiling in IgA nephropathy. Sci Rep. 2020;10(1):15164. doi:10.1038/s41598-020-72026-2 2. Yu L, Lin X, Zhang L, et al. The combination of IgA and IgG autoantibodies against transcriptional intermediary factor-1 gamma contributes to the early diagnosis of lung cancer. Int J Med Sci. 2020;17(11):1561-1568. doi:10.7150/ijms.47463 3. Zbesko JC, Frye JB, Becktel DA, et al. IgA natural antibodies are produced following T-cell independent B-cell activation following stroke. Brain Behav Immun. 2021;91:578-586. doi:10.1016/j.bbi.2020.09.014 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

IGAS
87938

IgA Subclasses, Serum

Clinical Information: Immunoglobulin A (IgA), the predominant immunoglobulin secreted at mucosal surfaces and the second most abundant immunoglobulin in serum, consists of 2 subclasses, IgA1 and IgA2. These subclasses differ in their molecular structure and tissue distribution. IgA1 is the major (approximately 80%) subclass in serum. It has a longer hinge region making it more susceptible to proteolytic cleavage. IgA2 is the major subclass in secretions such as milk, tears, sweat, and saliva. Although IgA deficiency is a common defect (1 in 700), it is usually asymptomatic. IgA deficiency with or without IgG subclass deficiency, however, can lead to recurrent pulmonary and gastrointestinal infections. In selective IgA deficiency, both IgA1 and IgA2 are deficient. It is also possible that only one of the subclasses is deficient. Some infections (eg, recurrent sinopulmonary infections with Haemophilus influenzae) may be related to a deficiency of IgA2, even in the presence of normal total IgA concentrations. Paradoxically, bacterial infections may also cause IgA deficiency. IgA2 is more resistant

to bacterial destruction than IgA1. Certain bacteria can cleave and inactivate IgA1, but not IgA2, thus depleting most of the IgA. In the presence of a concurrent IgA2 deficiency, infection by these organisms results in an apparent IgA deficiency. IgA deficiency is a cause of anaphylactic transfusion reactions. In these situations, patients who are IgA deficient produce anti-IgA antibodies that react with IgA present in the transfusion product. While transfusion reactions typically occur in patients who have no detectable concentrations of IgA, they can also occur in patients with measurable IgA. In these situations, the complete deficiency of 1 of the IgA subclasses may be the cause of the transfusion reactions.

Useful For: Investigation of immune deficiency due to IgA2 deficiency Evaluating patients with anaphylactic transfusion reactions

Interpretation: Low concentrations of IgA2 with normal amounts of IgA1 suggest an IgA2 deficiency. Elevated concentrations of IgA2 with normal or low amounts of IgA1 suggest a clonal plasma cell proliferative disorder secreting a monoclonal IgA2. Increased total IgA concentrations may also be seen in benign disorders (eg, infection, inflammation, allergy), hyper IgD syndrome with periodic fever, and monoclonal gammopathies (eg, myeloma, monoclonal gammopathies of undetermined significance [MGUS]).

Reference Values:

IgA
1-3.9 years: 5-194 mg/dL
4-6.9 years: 16-210 mg/dL
7-9.9 years: 27-227 mg/dL
10-11.9 years: 35-241 mg/dL
12-13.9 years: 43-252 mg/dL
14-15.9 years: 50-263 mg/dL
16-17.9 years: 57-274 mg/dL
>18 years: 85-499 mg/dL

IgA1
1-3.9 years: 6-163 mg/dL
4-6.9 years: 16-186 mg/dL
7-9.9 years: 26-209 mg/dL
10-11.9 years: 34-228 mg/dL
12-13.9 years: 40-243 mg/dL
14-15.9 years: 46-259 mg/dL
16-17.9 years: 53-274 mg/dL
>18 years: 76-328 mg/dL

IgA2
1-3.9 years: <0.5-12.4 mg/dL
4-6.9 years: <0.5-25.7 mg/dL
7-9.9 years: 1.5-38.9 mg/dL
10-11.9 years: 2.9-49.9 mg/dL
12-13.9 years: 4.0-58.7 mg/dL
14-15.9 years: 5.2-67.5 mg/dL
16-17.9 years: 6.3-76.3 mg/dL
>18 years: 6.9-114.3 mg/dL

Clinical References: 1. Schauer U, Stemberg F, Rieger CHL, et al. Establishment of age-dependent reference values for IgA subclasses. Clin Chim Acta. 2003;328(1-2):129-133 2. Saulsbury FT. Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) in a child with normal serum IgD, but increased serum IgA concentration. J Pediatrics. 2003;143(1):127-129 3. Popovsky MA.

Transfusion Reactions. American Association of Blood Banks, 3rd ed, 2007 4. Derksen VFAM, Allaart CF, Van der Helm-Van Mil AHM, Huizinga TWJ, Toes REM, van der Woude D. In rheumatoid arthritis patients, total IgA1 and IgA2 levels are elevated: implications for the mucosal origin hypothesis. Rheumatology (Oxford). 2022;62(1):407-416. doi:10.1093/rheumatology/keac237 5. Dietzen DJ, Willrich MAV. Amino acids, peptides, and proteins. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. 2023:chap 31 6. Steffen U, Koeleman CA, Sokolova MV, et al. IgA subclasses have different effector functions associated with distinct glycosylation profiles. Nat Commun. 2020;11(1):120. Published 2020 Jan 8. doi:10.1038/s41467-019-13992-8

IGDI
70471

IgD Immunostain, Technical Component Only

Clinical Information: The immunoglobulin molecules (antibodies) function as surface receptors for antigens for B lymphocytes and as secretory products of plasma cells forming the humoral arm of the immune system. IgD represents one of the immunoglobulin heavy chain types. Immunoreactivity is a specific marker for B lymphocytes and plasma cells; it is expressed normally on mantle zone lymphocytes. Diagnostically, staining for immunoglobulin heavy chains can aid in the diagnosis and classification of small B cell malignant lymphomas and multiple myeloma.

Useful For: Aids in the classification of lymphomas and multiple myeloma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Dai X, Wu YJ, Jia XY, et al. Immunoglobulin D (IgD) and IgD receptor expression in diffuse large B-cell lymphoma. Hematology. 2019;24(1):544-551. doi:10.1080/16078454.2019.1642553 2. Royal V, Quint P, Leblanc M, et al. IgD heavy-chain deposition disease: detection by laser microdissection and mass spectrometry. J Am Soc Nephrol. 2015;26(4):784-90. doi:10.1681/ASN.2014050481 3. Sorigue M, Junca J, Gassiot S, Milla F, Mate JL, Navarro JT. A case of CD138-/CD19+/CD4+ IgD plasma cell leukemia. Cytometry B Clin Cytom. 2014. doi:10.1002/cytob.21173 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FIERA
75754

IgE Receptor Antibody

Useful For: The test detects functional autoantibodies to the Fc-epsilon receptor (high affinity IgE receptor) or to IgE and is useful in the evaluation of chronic urticaria.

Interpretation: Chronic autoimmune urticaria (CIU) may be associated with autoantibodies to the high affinity IgE receptor (Fc-epsilon R1) or to IgE. In the presence of the autoantibodies, cross-linking of the Fc-epsilon-R1 receptor occurs, leading to basophil activation. The laboratory tests for the activation of donor basophils by CIU serum by analyzing the expression of the basophil specific ectoenzyme, CD203c. CD203c is upregulated on the surface of basophils following activation. A positive result is indicative of the presence of autoantibodies associated with CUI, but may also be due to other basophil-activating serum factors. Results must be correlated with clinical findings. The reference range was developed by the National Jewish Health Advanced Diagnostic Laboratories by analyzing 80 healthy control serum samples.

Reference Values:
0-12

Clinical References: Chronic urticaria sera increase basophil CD203c expression. Yasnowsky KM1, Drekin SC, Efaw B, Shoen D, Vedanthan PL, Alam R, Harbek RJ, J Allergy Clin Immunol 2006 Jun; 117(6): 1430-4.

FIGF1
75932

IGF-1, LC/MS

Reference Values:

Pediatric	Male (ng/mL)	Female (ng/mL)
	14-142	17-185
1-1.9 Years	12-134	15-175
2-2.9 Years	12-135	16-179
3-3.9 Years	30-155	38-214
4-4.9 Years	28-181	34-238
5-5.9 Years	31-214	37-272
6-6.9 Years	38-253	45-316
7-7.9 Years	48-298	58-367
8-8.9 Years	62-347	76-424
9-9.9 Years	80-398	99-483
10-10.9 Years	100-449	125-541
11-11.9 Years	123-497	152-593
12-12.9 Years	146-541	178-636
13-13.9 Years	168-576	200-664
14-14.9 Years	187-599	214-673
15-15.9 Years	201-609	218-659
16-16.9 Years	209-602	208-619
17-17.9 Years	207-576	185-551
Adult	(ng/mL)	
18-19.9 Years	108-548	
20-24.9 Years	83-456	
25-29.9 Years	63-373	
30-39.9 Years	53-331	
40-49.9 Years	52-328	
50-59.9 Years	50-317	
60-69.9 Years	41-279	
70-79.9 Years	34-245	

>80 Years	34-246

FFIG2
75924

IGF-2

Reference Values:
Prepubertal: 258-882 ng/mL
Pubertal: 273-892 ng/mL
Adults: 333-967 ng/mL

IGGI
70473

IgG Immunostain, Technical Component Only

Clinical Information: The immunoglobulin molecules (antibodies) function as surface receptors for antigens for B lymphocytes and as secretory products of plasma cells forming the humoral arm of the immune system. IgG represents one of the immunoglobulin heavy chain types. Immunoreactivity is a specific marker for B lymphocytes and plasma cells. Diagnostically, staining for immunoglobulin heavy chains can aid in the diagnosis and classification of small B-cell malignant lymphomas and multiple myeloma.

Useful For: Classification of lymphomas and multiple myeloma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Yu L, Lin X, Zhang L, et al. The combination of IgA and IgG autoantibodies against transcriptional intermediary factor-1 gamma contributes to the early diagnosis of lung cancer. Int J Med Sci. 2020;17(11):1561-1568. doi:10.7150/ijms.47463 2. Arora K, Rivera M, Ting DT, Deshpande V. The histological diagnosis of IgG4-related disease on small biopsies: challenges and pitfalls. Histopathology. 2019;74(5):688-698. doi:10.1111/his.13787. 3. Moreira RK, Revetta F, Koehler E, Washington MK. Diagnostic utility of IgG and IgM immunohistochemistry in autoimmune liver disease. World J Gastroenterol. 2010;16(4):453-457. doi:10.3748/wjg.v16.i4.453 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

IGGS
9259

IgG Subclasses, Serum

Clinical Information: The most abundant immunoglobulin isotype in human serum is IgG. IgG immunoglobulins are comprised of 4 subclasses designated IgG1 through IgG4. Of total IgG, approximately 65% is IgG1, 25% is IgG2, 6% is IgG3, and 4% is IgG4. Each IgG subclass contains structurally unique portions of the constant region of the gamma heavy chain. The half-life of IgG1, IgG2, and IgG4 is around 22 days, while IgG3 has a half-life of approximately 7 days. The complement classical pathway is activated most strongly by IgG1 and IgG3 followed by weak strength in activation by IgG2. IgG4 does not activate complement. Clustering of multiple IgG molecules is required to activate complement. Both IgG1 and IgG3 bind Fc receptors on phagocytic cells, activate killer monocytes, and

cross the placenta via receptor-mediated active transport. IgG1 is the principal IgG to cross the placenta, and neonatal concentrations are similar to maternal concentrations. Neonates have low production of IgG as the result of immaturity of their immune systems, and IgG concentrations fall through infancy, as the maternally-acquired antibody repertoire is cleared. Measurement of the concentrations of IgG subclass proteins in serum is useful in evaluating patients with clinical signs and symptoms of humoral immunodeficiency or combined immunodeficiency (cellular and humoral). Diminished concentrations of one or more IgG subclass protein may occur in the context of hypogammaglobulinemia, eg, common variable immunodeficiency or deficiencies may be selective, usually involving IgG subclass 2. Deficiency of IgG subclass 1 usually occurs in patients with severe immunoglobulin deficiency involving other IgG subclasses. Deficiency of IgG subclass 2 is more heterogeneous and can occur as an isolated deficiency or in combination with deficiency of IgA or IgA and other IgG subclasses. Most patients with IgG2 deficiency present with recurrent infections, usually sinusitis, otitis, or pulmonary infections. Children with deficiency of IgG subclass 2 often have deficient antibody responses to polysaccharide antigens, including bacterial antigens associated with Haemophilus influenzae type B and Streptococcus pneumoniae. Isolated deficiencies of IgG subclass 3 or 4 occur rarely, and the clinical significance of these findings is not clear.

Useful For: Second-order testing for evaluation of patients with clinical signs and symptoms of humoral immunodeficiency or combined immunodeficiency (cellular and humoral)

Interpretation: Diminished concentrations of all IgG subclasses are found in common variable immunodeficiency, combined immunodeficiency, ataxia telangiectasia, and other primary and acquired immunodeficiency diseases. A diminished concentration of IgG2 protein may be clinically significant in the context of recurrent sinopulmonary infection and may occur with or without concomitant IgA deficiency. Elevated concentration of IgG4 is consistent with, but not diagnostic of, IgG4-related disease. Slightly diminished concentrations of 1 or more IgG subclass proteins are not uncommon, and usually have little clinical significance. Conversely, some individuals with deficient specific antibody responses to polysaccharide antigens may have normal serum concentrations of IgG subclasses.

Reference Values:

TOTAL IgG
0-<5 months: 100-334 mg/dL
5-<9 months: 164-588 mg/dL
9-<15 months: 246-904 mg/dL
15-<24 months: 313-1,170 mg/dL
2-<4 years: 295-1,156 mg/dL
4-<7 years: 386-1,470 mg/dL
7-<10 years: 462-1,682 mg/dL
10-<13 years: 503-1,719 mg/dL
13-<16 years: 509-1,580 mg/dL
16-<18 years: 487-1,327 mg/dL
> or =18 years: 767-1,590 mg/dL

IgG1
0-<5 months: 56-215 mg/dL
5-<9 months: 102-369 mg/dL
9-<15 months: 160-562 mg/dL
15-<24 months: 209-724 mg/dL
2-<4 years: 158-721 mg/dL
4-<7 years: 209-902 mg/dL
7-<10 years: 253-1,019 mg/dL
10-<13 years: 280-1,030 mg/dL
13-<16 years: 289-934 mg/dL
16-<18 years: 283-772 mg/dL

> or =18 years: 341-894 mg/dL

IgG2
0-<5 months: < or =82 mg/dL
5-<9 months: < or =89 mg/dL
9-<15 months: 24-98 mg/dL
15-<24 months: 35-105 mg/dL
2-<4 years: 39-176 mg/dL
4-<7 years: 44-316 mg/dL
7-<10 years: 54-435 mg/dL
10-<13 years: 66-502 mg/dL
13-<16 years: 82-516 mg/dL
16-<18 years: 98-486 mg/dL
> or =18 years: 171-632 mg/dL

IgG3
0-<5 months: 7.6-82.3 mg/dL
5-<9 months: 11.9-74.0 mg/dL
9-<15 months: 17.3-63.7 mg/dL
15-<24 months: 21.9-55.0 mg/dL
2-<4 years: 17.0-84.7 mg/dL
4-<7 years: 10.8-94.9 mg/dL
7-<10 years: 8.5-102.6 mg/dL
10-<13 years: 11.5-105.3 mg/dL
13-<16 years: 20.0-103.2 mg/dL
16-<18 years: 31.3-97.6 mg/dL
> or =18 years: 18.4-106.0 mg/dL

IgG4
0-<5 months: < or =19.8 mg/dL
5-<9 months: < or =20.8 mg/dL
9-<15 months: < or =22.0 mg/dL
15-<24 months: < or =23.0 mg/dL
2-<4 years: < or =49.1 mg/dL
4-<7 years: < or =81.9 mg/dL
7-<10 years: 1.0-108.7 mg/dL
10-<13 years: 1.0-121.9 mg/dL
13-<16 years: < or =121.7 mg/dL
16-<18 years: < or=111.0 mg/dL
> or =18 years: 2.4-121.0 mg/dL

Clinical References: 1. Schauer U, Stemberg F, Rieger CHL, et al. IgG subclass concentration in certified reference material 470 and reference values for children and adults determined with the binding site reagents. Clin Chem. 2003;49(11):1924-1929 2. Dietzen DJ. Amino acids, peptides, and proteins. In: Rifai N, Horvath AR, Wittwer C, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:393-394 3. Vidarsson G, Dekkers G, Rispens T. IgG subclasses and allotypes: From structure to effector functions. Front Immunol. 2014;5:520 4. Napodano C, Marino M, Stefanile A, et al. Immunological role of IgG subclasses. Immunol Invest. 2021;50(4):427-444 5. Barton JC, Barton JC, Bertoli LF, Acton RT. Factors associated with IgG levels in adults with IgG subclass deficiency. BMC Immunol. 2021;22(1):53

SFIGS
610784

IgG, Serum

Clinical Information: Elevation of IgG in the cerebrospinal fluid (CSF) of patients with inflammatory diseases of the central nervous system (CNS), such as multiple sclerosis, neurosyphilis, acute inflammatory polyradiculoneuropathy, and subacute sclerosing panencephalitis may be due to local (intrathecal) synthesis of IgG. Elevations of CSF IgG or the CSF/serum IgG ratio may also occur because of permeability of the blood brain barrier, and hence, a correction using albumin measurements in CSF and serum is appropriate. The CSF index is the CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The CSF index is, therefore, an indicator of the relative amount of CSF IgG compared to serum. Any increase in the index reflects IgG production in the CNS. The IgG synthesis rate is a mathematical manipulation of the CSF index data and can also be used as a marker for CNS inflammatory diseases. The test is commonly ordered with oligoclonal banding or immunoglobulin kappa free light chains in CSF to aid in the diagnosis of demyelinating conditions.

Useful For: Aiding in the diagnosis of multiple sclerosis and other central nervous system inflammatory conditions as a part of a profile

Interpretation: Cerebrospinal fluid (CSF) IgG synthesis rate indicates the rate of increase in the daily CSF production of IgG in milligrams per day. A result greater than 12 mg/24 h is elevated. A CSF IgG index greater than 0.70 is elevated and indicative of increased synthesis of IgG.

Reference Values:
Only orderable as part of a profile. For more information see SFIG / Cerebrospinal Fluid IgG Index Profile, Serum and Spinal Fluid.

0-4 months: 100-334 mg/dL
5-8 months: 164-588 mg/dL
9-14 months: 246-904 mg/dL
15-23 months: 313-1,170 mg/dL
2-3 years: 295-1,156 mg/dL
4-6 years: 386-1,470 mg/dL
7-9 years: 462-1,682 mg/dL
10-12 years: 503-1,719 mg/dL
13-15 years: 509-1,580 mg/dL
16-17 years: 487-1,327 mg/dL
> or =18 years: 767-1,590 mg/dL

Clinical References:

CASF
8271

IgG/Albumin Ratio, Spinal Fluid

Clinical Information: Elevation of IgG levels in the cerebrospinal fluid (CSF) of patients with inflammatory diseases of the central nervous system (CNS) (multiple sclerosis [MS], neurosyphilis, acute inflammatory polyradiculoneuropathy, subacute sclerosing panencephalitis) is due to local (intrathecal) CNS synthesis of IgG. The 2 most commonly used diagnostic laboratory tests for MS are CSF index and oligoclonal banding. The CSF index is the CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The CSF index is therefore an indicator of the relative amount of CSF IgG compared to serum, and any increase in the index is a reflection of IgG production in the CNS. The IgG synthesis rate is a mathematical manipulation of the CSF index data and can also be used as a marker for CNS inflammatory diseases.

Useful For: Assessment of cerebrospinal fluid (CSF) IgG/albumin ratio in the absence of a paired CSF and serum specimen

Interpretation: Cerebrospinal fluid IgG index is positive (elevated) in approximately 80% of patients with multiple sclerosis.

Reference Values:
CSF IgG: 0.0-8.1 mg/dL
CSF albumin: 0.0-27.0 mg/dL
CSF IgG/albumin: 0.00-0.21

Clinical References: 1. Tourtellotte WW, Walsh MJ, Baumhefner RW, Staugaitis SM, Shapshak P. The current status of multiple sclerosis intra-blood-brain-barrier IgG synthesis. Ann NY Acad Sci. 1984;436:52-67 2. Bloomer LC, Bray PF. Relative value of three laboratory methods in the diagnosis of multiple sclerosis. Clin Chem. 1981;27(12):2011-2013 3. Hische EA, van der Helm HJ. Rate of synthesis of IgG within the blood-brain barrier and the IgG index compared in the diagnosis of multiple sclerosis. Clin Chem. 1987;33(1):113-114 4. Swanson JW. Multiple sclerosis: update in diagnosis and review of prognostic factors. Mayo Clin Proc. 1989;64(5):577-586 5. Markowitz H, Kokmen E. Neurologic diseases and the cerebrospinal fluid immunoglobulin profile. Mayo Clin Proc. 1983;58(4):273-274 6. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-73. doi:10.1016/S1474-4422(17)30470-2 7. Gurtner KM, Shosha E, Bryant SC, et al. CSF free light chain identification of demyelinating disease: comparison with oligoclonal banding and other CSF indexes. Clin Chem Lab Med. 2018;56(7):1071-1080. doi:10.1515/cclm-2017-0901 8. Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

FG4FI
57851

IgG4 Food Panel I

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

FGFP2
57904

IgG4 Food Panel II

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

FG4FP
57591

IgG4 Food Panel VIII

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-

specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

IGG4I
70472

IgG4 Immunostain, Technical Component Only

Clinical Information: Immunoglobulin G4 is the least abundant of IgG subclasses, normally comprising 6% of total IgG. Elevated serum IgG4 levels may be associated with localized or systemic allergic and autoimmune manifestations, such as inflammatory pseudotumor in liver, breast, and lung, sclerosing pancreatitis, and pemphigus vulgaris. In these disease states, increased numbers of IgG4-positive plasma cells are present in the tissue.

Useful For: Identification of IgG4-positive plasma cells in the tissue of patients with systemic autoimmune or allergic manifestations

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Heidarpour M, Rajabi P, Pour EB, Fayyazi E. Immunohistochemistry for immunoglobulin G4 in the diagnosis of pemphigus. Indian J Dermatol. 2019;64(4):338. doi:10.4103/ijd.IJD_87_18 2. Chen LYC, Mattman A, Seidman MA, Carruthers MN. IgG4-related disease: what a hematologist needs to know. Haematologica. 2019;104(3):444-455. doi:10.3324/haematol.2018.205526 3. Miyabe K, Zen Y, Cornell LD, et al. Gastrointestinal and extra-intestinal manifestations of IgG4-related disease. Gastroenterology. 2018;155(4):990-1003.e1. doi:10.1053/j.gastro.2018.06.082 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

IGGS4
84250

IgG4, Immunoglobulin Subclasses, Serum

Clinical Information:

Useful For: Supporting the diagnosis of IgG4-related disease

Interpretation: Elevated concentration of IgG4 is consistent with, but not diagnostic of, IgG4-related disease.

Reference Values:
0-<5 months: < or =19.8 mg/dL
5-<9 months: < or =20.8 mg/dL
9-<15 months: < or =22.0 mg/dL
15-<24 months: < or =23.0 mg/dL
2-<4 years: < or =49.1 mg/dL
4-<7 years: < or =81.9 mg/dL
7-<10 years: 1.0-108.7 mg/dL

10-<13 years: 1.0-121.9 mg/dL
13-<16 years: < or =121.7 mg/dL
16-<18 years: < or =111.0 mg/dL
> or =18 years: 2.4-121.0 mg/dL

Clinical References: 1. Cheuk W, Chan JKC. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. Adv Anat Pathol. 2010;17(5):303-332 2. Zen Y, Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. Am J Surg Pathol. 2010;34(12):1812-1819 3. Bateman AC, Deheragoda MG. IgG4-related systemic sclerosing disease-an emerging and under-diagnosed condition. Histopathology. 2009;55(4):373-383 4. Vidarsson G, Dekkers G, Rispens T. IgG subclasses and allotypes: from structure to effector functions. Front Immunol. 2014;5:520 5. Maslinska M, Dmowska-Chalaba J, Jakubaszek M. The role of IgG4 in autoimmunity and rheumatic diseases. Front Immunol. 2022;12:787422 6. Wallace ZS, Naden RP, Chari S, et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. Ann Rheum Dis. 2020;79(1):77-87. doi:10.1136/annrheumdis-2019-216561

BCLL
89008

IGH Somatic Hypermutation Analysis, B-Cell Chronic Lymphocytic Leukemia (B-CLL), Varies

Clinical Information: During early B-cell development, IGH genes are assembled from multiple polymorphic gene segments that undergo rearrangements and selection, generating variable diversity joining (VDJ) combinations that are unique in both length and sequence for each B cell. In addition, newly acquired (somatic) point variations are introduced into the variable (V) regions of mature B cells during the germinal center reaction in lymph nodes in a process called somatic hypermutation (SHM). Since chronic lymphocytic leukemia (CLL) originates from the malignant transformation of single lymphoid cells, each daughter cell shares one or, sometimes, more unique "clonal" antigen receptor gene rearrangements, which are cell and tumor specific (ie, a tumor cell "fingerprint"). Clonal IGHV gene hypermutation status provides important prognostic information for patients with CLL and small lymphocytic lymphoma (SLL). The presence of IGH SHM is defined as greater than 2% difference from the germline VH gene sequence identity (mutated), whereas less than or equal to 2% difference is considered no SHM (unmutated). The status of SHM has clear influence on the median survival of CLL patients. Hypermutation of the IGH variable region is strongly predictive of a good prognosis, while lack of variants predicts a poorer prognosis.

Useful For: Providing prognostic information in patients with newly diagnosed B-cell chronic lymphocytic leukemia This test is not intended for use in providing prognostic information for patient with other B-cell neoplasms or hematopoietic tumors.

Interpretation: The presence or absence of somatic hypermutation (SHM) in the immunoglobulin heavy chain gene (IGH) variable (V) region DNA will be reported. A variation frequency of greater than 2% will be reported as mutated. Both the percent mutation and the V region allele identified in the rearrangement will be included in the report. B-cell chronic lymphocytic leukemia (B-CLL) lacking SHM of the IGH V region (unmutated) is associated with a significantly worse prognosis than B-CLL containing SHM of the IGH V region (mutated).

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Davi F, Langerak AW, de Septenville AL, et al. Immunoglobulin gene analysis in chronic lymphocytic leukemia in the era of next generation sequencing. Leukemia. 2020;34(10):2545-2551. doi:10.1038/s41375-020-0923-9 2. Agathangelidis A, Sutton LA, Hadzidimitriou A, et al. Immunoglobulin gene sequence analysis in chronic lymphocytic leukemia: From patient material

to sequence interpretation. J Vis Exp. 2018;(141):10.3791/57787. Published 2018 Nov 26. doi:10.3791/57787 3. Rosenquist R, Ghia P, Hadzidimitriou A, et al. Immunoglobulin gene sequence analysis in chronic lymphocytic leukemia: updated ERIC recommendations. Leukemia. 2017;31(7):1477-1481. doi:10.1038/leu.2017.125

IGMI
70474

IgM Immunostain, Technical Component Only

Clinical Information: The immunoglobulin molecules (antibodies) function as surface receptors for antigens for B lymphocytes and as secretory products of plasma cells forming the humoral arm of the immune system. IgM represents one of the immunoglobulin heavy chain types. IgM positive-B lymphocytes are normally present in the follicular mantle zones and germinal centers. Immunoreactivity is a specific marker for B lymphocytes and plasma cells. Diagnostically, staining for immunoglobulin heavy chains can aid in the diagnosis and classification of small B cell malignant lymphomas and multiple myeloma.

Useful For: Classification of lymphomas and multiple myeloma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Moreira RK, Revetta F, Koehler E, Washington MK. Diagnostic utility of IgG and IgM immunohistochemistry in autoimmune liver disease. World J Gastroenterol. 2010;16(4):453-457. doi:10.3748/wjg.v16.i4.453 2. Shubham S, Bhardwaj M, Mahapatra HS. Comparative evaluation of immunoperoxidase versus immunofluorescent techniques in interpretation of kidney biopsies. Indian J Pathol Microbiol. 2016;59(3):305-309. doi:10.4103/0377-4929.188105 3. Zhu Z, Zhang M, Shao W, et al. Immunoglobulin M, a novel molecule of myocardial cells of mice. Int J Biochem Cell Biol. 2017;88:172-180. doi:10.1016/j.biocel.2017.04.003 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

IHPCA
113298

IHC Additional (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IHA26
113300

IHC Additional, Professional Only (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IHPCI
113297

IHC Initial (Bill Only)

Reference Values:

This test is for billing purposes only.
This is not an orderable test.

IHC26
113299

IHC Initial, Professional Only (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IHMPC
113301

IHC Multiplex (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IHM26
113302

IHC Multiplex, Professional Only (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IHMTO
113211

IHC Multiplex, Tech Only (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IDH2
616903

IHD2, R172K Mutation, Immunostain, Technical Component Only

Clinical Information: The IDH2 R172K mutation is present in a subset of cases of angioimmunoblastic T-cell lymphoma (AITL). Detection of the mutant protein using a mutation-specific antibody is useful in the diagnosis of AITL. This mutation may also be found in cases of acute myeloid leukemia.

Useful For: Identification of IDH2 R172K mutant protein in angioimmunoblastic T-cell lymphoma or acute myeloid leukemia

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Wang C, McKeithan TW, Gong Q, et al. IDH2R172 mutations define a

unique subgroup of patients with angioimmunoblastic T-cell lymphoma. Blood. 2015;126(15):1741-1752 2. Dupuy A, Lemonnier F, Fataccioli V, et al. Multiple ways to detect IDH2 mutations in angioimmunoblastic T-cell lymphoma from immunohistochemistry to next-generation sequencing. J Mol Diagn. 2018;20(5):677-685 3. Steinhilber J, Mederake M, Bonzheim I, et al. The pathological features of angioimmunoblastic T-cell lymphomas with IDH2 R172 mutations. Mod Pathol. 2019;32(8):1123-1134 4. Dogan S, Frosina DF, Geronima JA, et al. Molecular epidemiology of IDH2 hotspot mutations in cancer and immunohistochemical detection of R172K, R172G, and R172M variants. Human Pathology. 2020;106:45-53 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

IMIPR 63508 Imipramine and Desipramine, Serum

Clinical Information: Imipramine and its metabolite desipramine are tricyclic antidepressants used to treat endogenous depression requiring 1 to 3 weeks of treatment before therapeutic effectiveness becomes apparent. Desipramine is used for treatment of endogenous depression when the patient needs a drug with significant stimulatory side effects. These drugs have also been employed in the treatment of enuresis (involuntary urination) in childhood and severe obsessive-compulsive neurosis. Imipramine: The optimal dosage of imipramine yields trough (just before the next dose) blood levels of imipramine and desipramine combined from 175 to 300 ng/mL. If desipramine is given, no imipramine should be detected, and the therapeutic concentration for desipramine alone is 100 to 300 ng/mL. Toxicity associated with imipramine is characterized by QRS widening (intraventricular conduction delay) leading to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations or at therapeutic concentrations in the early state of therapy. Cardiac toxicity (first-degree heart block) is usually associated with blood concentrations more than 400 ng/mL. Desipramine: Desipramine is the antidepressant of choice in patients where maximal stimulation is indicated. The therapeutic concentration of desipramine is 100 to 300 ng/mL. About 1 to 3 weeks of treatment are required before therapeutic effectiveness becomes apparent. The most frequent side effects are those attributable to anticholinergic effects, such as dry mouth, constipation, dizziness, tachycardia, palpitations, blurred vision, and urinary retention. These occur at blood concentrations more than 400 ng/mL, although they may occur at therapeutic concentrations in the early stage of therapy. Cardiac toxicity (first-degree heart block) is usually associated with blood concentrations more than 400 ng/mL.

IFXED 606458 Immunofixation Heavy Chain Type Delta and Epsilon, Serum

Clinical Information: Monoclonal gammopathies indicate a clonal expansion of plasma cells or mature B lymphocytes that commonly consist of IgG, IgA, and IgM heavy chains. However, these monoclonal proteins may rarely consist of IgD or IgE immunoglobulin heavy chains. Diseases that are associated with monoclonal gammopathies include multiple myeloma, primary systemic amyloidosis, and light-chain deposition disease, as well as premalignant disorders such as smoldering multiple myeloma and monoclonal gammopathy of undetermined significance. Initial Isotyping or immunofixation identifies the monoclonal immunoglobulin heavy-chain (gamma, alpha, or mu) and/or light-chain type (kappa or lambda). Since IgD and IgE monoclonal gammopathies are rare, they are not part of the initial screening/isotyping. Since the anti-sera against IgD and IgE are excluded from initial screening methods, this testing should only be ordered on patients with confirmed IgD or IgE monoclonal gammopathy or patients with only free monoclonal kappa or lambda light chains upon initial isotyping. Once the presence of an IgD or IgE heavy chain is excluded, there is no need to continue monitoring with this specialized isotyping assay; rather, continued monitoring via serum protein electrophoresis and traditional isotyping is more appropriate.

Useful For: Identification and isotyping of IgD or IgE monoclonal gammopathy Documentation of

complete response to therapy with established monoclonal gammopathy consisting of an IgD or IgE heavy chain

IMFXO
800316

Immunofixation Only, Serum

Interpretive and immunofixation impression comments are made based on visual interpretation of gels.

Clinical Information: Monoclonal gammopathies indicate a clonal expansion of plasma cells or mature B lymphocytes. The monoclonal gammopathies include diseases such as multiple myeloma, Waldenstrom macroglobulinemia, lymphoproliferative disease, primary systemic amyloidosis, light-chain deposition disease, as well as the premalignant disorders of smoldering myeloma and monoclonal gammopathy of undetermined significance (MGUS). Monoclonal gammopathy patients may have a relatively small monoclonal protein abnormality or a large quantifiable peak (M-spike) on serum or urine protein electrophoresis. Abnormalities detected on serum protein electrophoresis (SPE) should have immunotyping performed to confirm and characterize the monoclonal protein. Immunotyping of monoclonal proteins is usually done by immunofixation electrophoresis (IFE) and identifies the monoclonal immunoglobulin heavy-chain (gamma, alpha, mu, delta, or epsilon) and/or light-chain type (kappa or lambda). It is generally recommended that both SPE and IFE be used as a screening panel. Because IFE is more sensitive than SPE, IFE is not only recommended as part of the initial screening process but also for confirmation of complete response to therapy.

Useful For: Identification of monoclonal immunoglobulin heavy and light chains Documentation of complete response to therapy

Interpretation:

Reference Values:
Immunofixation: No monoclonal protein detected
Immunofixation Flag: Negative

Clinical References:

FIFLC
75678

Immunofixation with Free Light Chains, Quantitative, Urine

Interpretation: Results of urine free light chain testing can be used to monitor disease progression or response to therapy in patients for whom urine electrophoresis is unable to provide reliable Bence Jones Protein quantification. The results of urine kappa and lambda free light chain quantitative values may be misleading in specimens with high levels of urinary polyclonal free light chains, and absent Bence Jones protein by immunofixation; therefore correlation with urine immunofixation is required to identify inconsistent results. Total urinary protein is determined turbidmetrically by adding the albumin and kappa and/or lambda light chains. This value may not agree with the total protein as determined by chemical methods, which characteristically underestimates urinary light chains.

Reference Values:

Total Protein	Less than 150 mg/d
Free Urinary Kappa Light Chains	0.00-32.90 mg/L
Free Urinary Kappa Excretion/Day	By report
Free Urinary Lambda Light Chain	0.00-3.79 mg/L

Free Urinary Lambda Excretion/Day	By report
IFE Interpretation	By report

FIXCF
75749

Immunofixation, CSF

Reference Values:
No abnormal bands are present on immunofixation.

IMFX
800306

Immunofixation, Serum

Clinical Information: Immunotyping of monoclonal (M-) proteins identifies the monoclonal immunoglobulin heavy chain type (gamma, alpha, mu, delta, or epsilon) and light chain type (kappa or lambda) in serum.

Useful For: Aids in diagnosis of monoclonal gammopathies when used in conjunction with urine monoclonal studies Identification and isotyping of monoclonal immunoglobulin heavy and light chains Documentation of complete response to therapy

Interpretation: If present, a characteristic monoclonal band (M-spike) is most often found in the gamma region on serum protein electrophoresis (PEL) and, occasionally, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic PEL pattern is suggestive of a possible monoclonal protein. Immunofixation electrophoresis is primarily performed to identify and characterize the presence of any monoclonal immunoglobulin heavy or light chains. Immunofixation impression comments are made based on visual interpretation of gels.

Reference Values:
Only orderable as part of a profile. For more information see MPSS / Monoclonal Protein Study, Serum.

Immunofixation: No monoclonal protein detected
Flag, Immunofixation: Negative

Clinical References: 1. Keren DF, Humphrey RL. Clinical indications and applications of serum and urine protein electrophoresis. In: Detrick B, Schmitz JL, Hamilton RG, eds. Manual of Molecular and Clinical Laboratory Immunology. 8th ed. ASM Press; 2016:74-88 2. Katzmann JA, Keren DF. Strategy for detecting and following monoclonal gammopathies. In: Detrick B, Schmitz JL, Hamilton RG, eds. Manual of Molecular and Clinical Laboratory Immunology. 8th ed. ASM Press; 2016:112-124 3. Kyle RA, Katzmann JA, Lust, JA, Dispenzieri A: Clinical indications and applications of electrophoresis and immunofixation. In: Rose NR, Hamilton RG, Detrick B, eds. Manual of Clinical Laboratory Immunology. 6th ed. ASM Press; 2002:66-70

FHLCA
75550

Immunoglobulin A (IgA) Heavy and Light Chain (HLC) Pairs, Kappa and Lambda with Ratio

Clinical Information: Elevated serum concentrations of monoclonal protein are indicative of an

underlying abnormality, such as monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, and other lymphoproliferative disorders. International guidelines recommend serum protein electrophoresis (SPE) densitometry to be performed to quantify monoclonal proteins. However, monoclonal IgA proteins can often be obscured by other proteins in the Beta region of a SPE gel, making quantification inaccurate. Nephelometry can be used in these instances to measure total IgA, but this will include nontumor immunoglobulin, and measurement of either IgA Kappa or IgA Lambda may give a more accurate representation of tumor production. Furthermore, measurement of both IgA Kappa and IgA Lambda, calculation of the IgA Kappa:IgA Lambda ratio and comparison with values found in normal subjects can give a more sensitive indication of clonality. Use of the IgA Kappa:IgA Lambda ratio will also compensate for any changes in plasma volume.

Useful For: For the quantitative measurement of human IgA heavy chain and light chain intact immunoglobulin in serum. The result can be used when monitoring previously diagnosed IgA multiple myeloma patients and is used in conjunction with other clinical and laboratory findings. Heavy and light chain pair quantitation may be useful for: 1. Distinguishing between broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin patterns on serum protein electrophoresis. 2. Quantitating monoclonal IgA proteins that are difficult to quantitate using serum protein electrophoresis alone. 3. Providing a more specific quantitation of the monoclonal protein than total IgA measurements alone.

Interpretation: An elevated IgA heavy and light chain (HLC) pair ratio suggests a clonal proliferation of an IgA Kappa clone of plasma cells. A low IgA HLC pair ratio suggests a clonal proliferation of an IgA Lambda clone of plasma cells.

Reference Values:
IgA Kappa (g/L): 0.48-2.82
IgA Lambda (g/L): 0.36-1.98
IgA Kappa:IgA Lambda ratio: 0.80-2.04

Clinical References: 1. Smith A, Wisloff F, Samson D; UK Myeloma Forum; Nordic Myeloma Study Group; British Committee for Standards in Haematology. (2005) Guidelines on the diagnosis and management of multiple myeloma 2005. Br J Haematol. 2006 Feb; 132(4):410-451. PubMed 16412016 2. Bradwell AR, Harding S, Drayson M, Mead G. Novel nephelometric assays give a sensitive measure of residual disease in multiple myeloma (MM). Br J Haematol. 2008; 141(s1):39. Abstract 107.

IGA
8157

Immunoglobulin A (IgA), Serum

Clinical Information: Immunoglobulins are produced by plasma cells as a humoral immune response to contact of the immune system by antigens. The primary reaction after the initial contact is the formation of antibodies of the IgM class, followed later by IgG and IgA antibodies. Quantitative determination of the immunoglobulins can provide important information on the humoral immune status. Decreased serum immunoglobulin concentrations occur in primary immunodeficiency conditions as well as in secondary immune insufficiencies (eg, in advanced malignant tumors, lymphatic leukemia, multiple myeloma, and Waldenstrom disease). Monoclonal immunoglobulin proliferations in the serum are found in plasmacytomas, Waldenstrom disease, and heavy-chain disease. Monoclonal immunoglobulinemia requires detailed differential diagnostic investigations in addition to the quantitative determination. Local immune reactions result in elevated immunoglobulin levels, particularly IgG, in the cerebrospinal fluid. IgA increases with asparaginase treatment, during pregnancy, with exercise, and in people with alcohol use disorder. It falls with prolonged exposure to benzene and after 1 year's abstinence from drinking alcohol. Diphenylhydantoin, dextran, methyl prednisolone, toluene, xylol, and oral contraceptives may also lower IgA levels. IgM may rise in people with narcotic addiction and after various drug use, as with IgA and IgG. The gamma globulin band as seen in conventional serum protein electrophoresis consists of

5 immunoglobulins. In normal serum, about 15% is IgA. Monoclonal gammopathies of all types may lead to a spike in the gamma globulin zone seen on serum protein electrophoresis. Monoclonal elevations of IgA characterize multiple myeloma. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

Useful For: Detection or monitoring of IgA monoclonal gammopathies and IgA-related immune deficiencies

Interpretation: Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevation of IgA may occur in monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

Reference Values:
0-<5 months: 7-37 mg/dL
5-<9 months: 16-50 mg/dL
9-<15 months: 27-66 mg/dL
15-<24 months: 36-79 mg/dL
2-<4 years: 27-246 mg/dL
4-<7 years: 29-256 mg/dL
7-<10 years: 34-274 mg/dL
10-<13 years: 42-295 mg/dL
13-<16 years: 52-319 mg/dL
16-<18 years: 60-337 mg/dL
> or =18 years: 61-356 mg/dL

Clinical References: 1. Webster ADB. Laboratory investigation of primary deficiency of the lymphoid system. In: Clinics in Immunology and Allergy. Vol 5. 3rd ed. WB Saunders Company; 1985:447-468 2. Pinching AJ. Laboratory investigation of secondary immunodeficiency. In: Clinics in Immunology and Allergy. Vol 5. 3rd ed. WB Saunders Company; 1985:469-490 3. Dispenzieri A, Gertz MA, Kyle RA. Distribution of diseases associated with moderate polyclonal gammopathy in patients seen at Mayo Clinic during 1991. Blood. 1997;90:353A 4. Kyle RA, Greipp PR. The laboratory investigation of monoclonal gammopathies. Mayo Clin Proc. 1978;53(11):719-739 5. Ballow M, O'Neil KM. Approach to the patient with recurrent infections. In: Middleton Jr E, Reed CE, Ellis, et al. Allergy: Principles and Practice. Vol 2. 4th ed. Mosby-Year Book, Inc; 1993:1027-1058 6. Kyle RA. Detection of quantitation of monoclonal proteins. Clin Immunol Newsletter. 1990;10(6):84-86 7. Dietzen DJ, Willrich MAV. Amino acids, peptides, and proteins. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 31

IGD
9272

Immunoglobulin D (IgD), Serum

Clinical Information: Antibodies or immunoglobulins are formed by plasma cells as a humoral immune response to antigens. The first antibodies formed after antigen stimulation are of the IgM class, followed later by IgG and IgA antibodies. IgD normally occurs in serum in trace amounts. Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic diseases (chronic hepatitis, liver cirrhosis), acute and chronic infections, autoimmune diseases, as well as in the cord blood of neonates with intrauterine and perinatal infections. Increases in serum immunoglobulin concentration are seen in monoclonal gammopathies such as

multiple myeloma, Waldenstrom macroglobulinemia, primary amyloidosis, and monoclonal gammopathy of undetermined significance. Decreased serum immunoglobulin concentrations occur in primary immunodeficiency conditions as well as in secondary immune insufficiencies including advanced monoclonal gammopathies, lymphatic leukemia, and advanced malignant tumors. Changes in IgD concentration are used as a marker of changes in the size of the clone of monoclonal IgD plasma cells.

Useful For: Providing information on the humoral immune status Identifying an IgD monoclonal gammopathy

Interpretation: The physiologic significance of serum IgD concentration is unclear and in many normal persons serum IgD is undetectable. Increased concentrations may be due to polyclonal (reactive) or monoclonal plasma cell proliferative processes. A monoclonal IgD protein is present in 1% of patients with myeloma. Monoclonal IgD proteins are often in low concentrations and do not have a quantifiable monoclonal protein on serum protein electrophoresis. However, the presence of an IgD monoclonal protein is almost always indicative of a malignant plasma cell disorder such as multiple myeloma or primary amyloidosis.

Reference Values:
< or =10 mg/dL

Clinical References: 1. Blade J, Lust JA, Kyle RA: Immunoglobulin D multiple myeloma: Presenting features, response to therapy, and survival in a series of 53 cases. J Clin Oncol. 1994;12(11):2398-2404. doi: 10.1200/JCO.1994.12.11.2398 2. Kyle RA, Katzmann JA: Immunochemical characterization of immunoglobulins. In: Rose NR, de Macario EC, Folds JD, et al: eds. Manual of Clinical Laboratory Immunology. 5th ed. ASM Press; 1997:156-176 3. Rifai N, Horvath AR, Wittwer C. eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1888

IGE
8159

Immunoglobulin E (IgE), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE that is present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE are generally thought of in the context of allergic disease. However, increases in the amount of circulating total serum IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease, except for allergic bronchopulmonary aspergillosis (ABPA). ABPA is a hypersensitivity reaction against the fungi Aspergillus that occurs most frequently in patients with asthma or cystic fibrosis. An elevation of total IgE is part of the diagnostic criteria for ABPA, although the specific diagnostic concentration is dependent on certain patient characteristics. For patients with an established diagnosis of allergic disease, measurement of total IgE is necessary for identification of candidates for omalizumab (anti-IgE) therapy and for determination of proper dosing. In addition to specific patient demographics and clinical presentations, candidates for omalizumab must have total IgE

concentrations between 30 and 700 KU/L.

Useful For: Evaluating patients with suspected diseases associated with elevations in total immunoglobulin E (IgE), including allergic disease, primary immunodeficiencies, infections, malignancies, or other inflammatory diseases Diagnostic evaluation of patients with suspected allergic bronchopulmonary aspergillosis Identifying candidates for omalizumab (anti-IgE) therapy

Interpretation: Elevated concentrations of total immunoglobulin E (IgE) may be found in a variety of clinical diseases including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Elevated total IgE concentrations may be consistent with a diagnosis of allergic bronchopulmonary aspergillosis, provided other laboratory and clinical criteria are fulfilled. Total IgE concentrations between 30 to 700 KU/L may identify candidates for omalizumab therapy and may help to determine proper therapeutic dosing.

Reference Values:

Results reported in kU/L
Age
0-5 months
6-11 months
1 and 2 years
3 years
4-6 years
7 and 8 years
9-12 years
13-15 years
16 and 17 years
18 years and older

Clinical References: 1. Homburger HA: Allergic diseases. In: Clinical Diagnosis and Management by Laboratory Methods. 21st ed. WB Saunders Company. 2007;961-971 2. Martins TB, Bandhauer ME, Bunker AM, Roberts WL, Hill HR: New childhood and adult reference intervals for total IgE. J Allergy Clin Immunol. 2014 Feb;133(2):589-591 3. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: An updated practice parameter. Ann Allergy Asthma Immunol. 2008 Mar;100(3 Suppl 3):S1-148 4. Ansotegui IJ, Melioli G, Canonica GW, et al: IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. World Allergy Organ J. 2020 Feb;13(2):100080. doi: 10.1016/j.waojou.2019.100080

FLCS
608250

Immunoglobulin Free Light Chains, Serum

Clinical Information: The monoclonal gammopathies are characterized by a clonal expansion of plasma cells that secrete a monoclonal immunoglobulin. The monoclonal immunoglobulin secreted by these cells serves as a marker of the clonal proliferation, and the quantitation of monoclonal protein can

be used to monitor the disease course. The monoclonal gammopathies include multiple myeloma (MM), light chain MM (LCMM), Waldenstrom macroglobulinemia (WM), nonsecretory MM (NSMM), smoldering MM (SMM), monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis (AL), and light chain deposition disease (LCDD). The monoclonal light chain diseases (LCMM, AL, LCDD, and NSMM) often do not have serum monoclonal proteins in high enough concentration to be detected and quantitated by serum protein electrophoresis. An elevated ratio of kappa to lambda free light chains (FLC K/L) indicates a monoclonal kappa FLC, and an abnormally low FLC K/L indicates a monoclonal lambda FLC. The kappa and lambda FLC may both be elevated in the sera of patients with polyclonal hypergammaglobulinemia, but the FLC K/L is normal. If a patient has an abnormal serum FLC K/L ratio but has no serum monoclonal protein detected by immunofixation, a urine monoclonal protein study (eg, immunofixation) should be performed and the serum immunofixation should be repeated. The FLC K/L ratio may be useful as a diagnostic test for patients in whom immunofixation for serum monoclonal light chains is negative and in whom there is a suspicion of primary systemic amyloidosis, light chain deposition disease, or non-secretory myeloma. The quantitation of kappa or lambda immunoglobulin free light chains may be used to monitor disease activity in patients with monoclonal light chain diseases without a serum M-spike. The following algorithms are available: -Amyloidosis: Laboratory Approach to Diagnosis -Multiple Myeloma: Laboratory Screening

Useful For: Monitoring serum from patients with monoclonal light chain diseases without a M-spike on protein electrophoresis May be useful as a diagnostic test in patients in whom there is a suspicion of primary systemic amyloidosis, light chain deposition disease, or non-secretory myeloma

Interpretation: The specificity of this assay for detection of monoclonal light chains relies on the ratio of free kappa and lambda (K/L) light chains. Once an abnormal free light chain (FLC) K/L ratio has been demonstrated and a diagnosis has been made, the quantitation of the monoclonal light chain is useful for monitoring disease activity. Changes in FLC quantitation reflect changes in the size of the monoclonal plasma cell population. Our experience to date is limited, but changes of more than 25% or trending of multiple specimens are needed to conclude biological significance.

Reference Values:

KAPPA-FREE LIGHT CHAIN
0.33-1.94 mg/dL

LAMBDA-FREE LIGHT CHAIN
0.57-2.63 mg/dL

KAPPA/LAMBDA FLC RATIO
0.26-1.65

Clinical References: 1. Kaleta E, Kyle R, Clark R, Katzmann J: Analysis of patients with gamma-heavy chain disease by the heavy/light chain and free light chain assays. Clin Chem Lab Med. 2014 May;52(5):665-669. doi: 10.1515/cclm-2013-0714 2. Palladini G, Russo P, Bosoni T, et al: Identification of amyloidogenic light chains requires the combination of serum-free light chain assay with immunofixation of serum and urine. Clin Chem. 2009 Mar;55(3):499-504. doi: 10.1373/clinchem.2008.117143 3. Dispenzieri A, Kyle R, Merlini G, et al: International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia. 2009 Feb;23(2):215-224. doi: 10.1038/leu.2008.307 4. Drayson M, Tang LX, Drew R, Mead GP, Carr-Smith H, Bradwell AR: Serum free light chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. Blood. 2001 May 1;97(9):2900-2902

FHLCG
75551

Immunoglobulin G (IgG) Heavy and Light Chain (HLC) Pairs, Kappa and Lambda with Ratio

Clinical Information: Elevated serum concentrations of monoclonal protein are indicative of an underlying abnormality, such as monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, and other lymphoproliferative disorders. International guidelines recommend serum protein electrophoresis or nephelometric immunoglobulin quantification as tools to monitor patients' disease (alongside other tests including flow cytometry and serum free light chain analysis). Total IgG nephelometric assays will include nontumor immunoglobulin, and measurement of either IgG Kappa or IgG Lambda may give a more accurate representation of tumor production. Furthermore, measurement of both IgG Kappa and IgG Lambda, calculation of the IgG Kappa:IgG Lambda ratio, and comparison with values found in normal subjects can give a more sensitive indication of clonality. Additionally, changes in the IgG Kappa:IgG Lambda ratio and its normalization when compared to a normal ratio range should assist in monitoring patients' disease. Use of the IgG Kappa:IgG Lambda ratio will also compensate for any changes in plasma volume and correct for half life variations due to receptor saturation.

Useful For: Heavy and light chain pair quantitation may be useful for: 1. Distinguishing between broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin patterns on serum electrophoresis. 2. Quantitating monoclonal IgG proteins that are difficult to quantitate using serum protein electrophoresis alone. 3. Providing a more specific quantitation of the monoclonal protein than total IgG measurements alone.

Interpretation: An elevated IgG heavy and light chain (HLC) pair ratio suggests a clonal proliferation of an IgG Kappa clone of plasma cells. A low IgG HLC pair ratio suggests a clonal proliferation of an IgG Lambda clone of plasma cells.

Reference Values:
IgG Kappa (g/L): 4.03 - 9.78
IgG Lambda (g/L): 1.97 - 5.71
IgG Kappa:IgG Lambda ratio: 0.98 - 2.75

Clinical References: 1. Dimopoulos M, Kyle R, Fermand JP, et al. Consensus recommendations for standard investigative workup: Report of the International Myeloma Workshop Consensus Panel 3. Blood. 2011 May 5; 117(18):4701-4705. PubMed 21292778 2. Rajkumar SV, Harousseau JL, Durie B, et al. Concensus recommendations for the uniform reporting of clinical trials: Report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011 May 5; 117(18):4691-4695. PubMed 21292775 3. Bradwell AR, Harding SJ, Fourrier NJ, et al. Assessment of monoclonal gammopathies by nephelometric measurement of individual immunoglobulin kappa/lambda ratios. Clin. Chem. 2009 Sep; 55(9):1646-1655. PubMed 19617289 4. Ludwig H, Milosavljevic D, Zojer N, et al. Immunoglobulin heavy/light chain ratios improve paraprotein detection and monitoring, identify residual disease and correlate with survival in multiple myeloma patients. Leukemia. 2013 Jan; 27(1):213-219. PubMed 22955329 5. Bradwell A, Harding S, Fourrier N, et al. Prognostic utility of intact immunoglobulin Ig'?/Ig'? ratios in multiple myeloma patients. Leukemia. 2013 Jan; 27(1):202-207. PubMed 22699454

SUBIF 70620 Immunoglobulin G (IgG) Subtypes Immunofluorescence, Tissue

Clinical Information: IgG subtypes are helpful in confirming some disease processes affecting the kidney.

Useful For: Determining the subclass of IgG antibody found in renal immunofluorescent panel and determining if the deposits are monoclonal or monotypic

Interpretation: Staining intensity is graded as negative (0), weak (trace, 1+), moderate (2+) and strong (3+) and will be reported as such when not accompanied by a pathology consultation request. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test and provide the corresponding renal pathology light

Reference Values:
An interpretive report will be provided.

Clinical References: Hemminger J, Nadasdy G, Satoskar A, Brodsky SV, Nadasdy T. IgG subclass staining in routine renal biopsy material. Am J Surg Pathol. 2016;40(5):617-626

IGG
8160

Immunoglobulin G (IgG), Serum

Clinical Information: Immunoglobulins are produced by plasma cells as a humoral immune response to contact of the immune system by antigens. The primary reaction after the initial contact is the formation of antibodies of the IgM class, followed later by IgG and IgA antibodies. Quantitative determination of the immunoglobulins can provide important information on the humoral immune status. Decreased serum immunoglobulin concentrations occur in primary immunodeficiency conditions as well as in secondary immune insufficiencies (eg, in advanced malignant tumors, lymphatic leukemia, multiple myeloma, and Waldenstrom disease). Monoclonal immunoglobulin proliferations in the serum are found in plasmacytomas, Waldenstrom disease, and heavy-chain disease. Monoclonal immunoglobulinemia requires detailed differential diagnostic investigations in addition to the quantitative determination. Local immune reactions result in elevated immunoglobulin levels, particularly IgG, in the cerebrospinal fluid. IgA increases with asparaginase treatment, during pregnancy, with exercise, and in people with alcohol use disorder. It falls with prolonged exposure to benzene and after 1 year's abstinence from drinking alcohol. Diphenylhydantoin, dextran, methyl prednisolone, toluene, xylol, and oral contraceptives may also lower IgA levels. IgM may rise in people with narcotic addiction and after various drug use, as with IgA and IgG. The gamma globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 80% is IgG. Elevations of IgG may be due to polyclonal immunoglobulin production. Monoclonal elevations of IgG characterize multiple myeloma. Monoclonal gammopathies of all types may lead to a spike in the gamma globulin zone seen on serum protein electrophoresis. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

Useful For: Detecting or monitoring of IgG monoclonal gammopathies and immune deficiencies

Interpretation: Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevation of IgG may occur in monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

Reference Values:
0-<5 months: 100-334 mg/dL
5-<9 months: 164-588 mg/dL
9-<15 months: 246-904 mg/dL
15-<24 months: 313-1,170 mg/dL
2-<4 years: 295-1,156 mg/dL
4-<7 years: 386-1,470 mg/dL
7-<10 years: 462-1,682 mg/dL
10-<13 years: 503-1,719 mg/dL
13-<16 years: 509-1,580 mg/dL

16-<18 years: 487-1,327 mg/dL
> or =18 years: 767-1,590 mg/dL

Clinical References: 1. Webster ADB: Laboratory investigation of primary deficiency of the lymphoid system. In: Clinics in Immunology and Allergy. Vol 5. 3rd ed. 1985:447-468 2. Pinching AJ: Laboratory investigation of secondary immunodeficiency. In: Clinics in Immunology and Allergy. Vol 5. 3rd ed. WB Saunders Company; 1985:469-490 3. Dispenzieri A, Gertz MA, Kyle RA. Distribution of diseases associated with moderate polyclonal gammopathy in patients seen at Mayo Clinic during 1991. Blood. 1997;90:353 4. Kyle RA, Greipp PR. The laboratory investigation of monoclonal gammopathies. Mayo Clin Proc. 1978;53:719-739 5. Ballow M, O'Neil KM: Approach to the patient with recurrent infections. In: Middleton Jr E, Reed CE, Ellis EF, et al, eds. Allergy: Principles and Practice. Vol 2. 4th ed. Mosby-Year Book, Inc.; 1993:1027-1058 6. Kyle RA. Detection of quantitation of monoclonal proteins. Clin Immunol Newsletter. 1990;10:84-86 7. Dietzen DJ, Willrich MAV: Amino acids, peptides, and proteins. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 31

BCGR
83123

Immunoglobulin Gene Rearrangement, Blood

Clinical Information: The immunoglobulin genes (heavy, kappa, and lambda) are comprised of numerous, discontinuous coding segments. As B cells develop, the segments are rearranged such that each mature B cell and plasma cell has a unique rearrangement profile. Other cell types usually retain the unrearranged gene structures. Clonal expansion of any B cell or plasma cell will result in a population of cells that all contain an identical immunoglobulin gene rearrangement profile. Reactive B-cell or plasma cell expansions are polyclonal, with each clone containing relatively few cells and no one clone predominating. Conversely, neoplastic clones are generally large such that the clonal cells are the predominant B cells or plasma cells present. In the appropriate clinical and pathologic setting, detection of a prominent immunoglobulin gene rearrangement profile may be equated to the presence of a neoplastic B-cell or plasma cell clone.

Useful For: Determining whether a B-cell or plasma cell population is polyclonal or monoclonal using whole blood specimens Identifying neoplastic cells as having B-cell or plasma cell differentiation Monitoring for a persistent neoplasm by detecting an immunoglobulin gene rearrangement profile similar to one from a previous neoplastic specimen

Interpretation: An interpretive report will be provided. The interpretation of the presence or absence of a predominant immunoglobulin gene rearrangement profile is sometimes subjective. These results must always be interpreted in the context of other clinicopathologic information to determine the significance of the result. The detection of a clonal immunoglobulin gene rearrangement by this test is not synonymous with the presence of a B-cell or plasma cell neoplasm.

Reference Values:
An interpretive report will be provided.

Clinical References:

BCGBM
31141

Immunoglobulin Gene Rearrangement, PCR, Bone Marrow

Clinical Information: The immunoglobulin genes (heavy, kappa, and lambda) are comprised of numerous, discontinuous coding segments. As B cells develop, the segments are rearranged such that each mature B cell or plasma cell has a unique rearrangement profile. Other cell types usually retain the unrearranged gene structures. Clonal expansion of any B cell or plasma cell will result in a population

of cells that all contain identical immunoglobulin gene rearrangement profiles. Reactive B-cell or plasma cell expansions are polyclonal, with each clone containing relatively few cells and no single clone predominating. Conversely, neoplastic clones are generally large such that the clonal cells are the predominant B cells or plasma cells present. In the appropriate clinical and pathologic setting, detection of a prominent immunoglobulin gene rearrangement profile may be equated to the presence of a neoplastic B-cell or plasma cell clone.

Useful For: Determining whether a B-cell or plasma cell population is polyclonal or monoclonal using bone marrow specimens Identifying neoplastic cells as having B-cell or plasma cell differentiation Monitoring for a persistent neoplasm by detecting an immunoglobulin gene rearrangement profile similar to a previous neoplastic specimen

Interpretation: An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal B-cell population. The interpretation of the presence or absence of a predominant immunoglobulin gene rearrangement profile is sometimes subjective. These results must always be interpreted in the context of other clinicopathologic information to determine the significance of the result. The detection of a clonal immunoglobulin gene rearrangement by this test is not synonymous with the presence of a B-cell or plasma cell neoplasm.

Reference Values:
An interpretive report will be provided.

Clinical References:

BCGRV 31142 Immunoglobulin Gene Rearrangement, PCR, Varies

Clinical Information: The immunoglobulin genes (heavy, kappa, and lambda) are comprised of numerous, discontinuous coding segments. As B cells develop, the segments are rearranged such that each mature B cell and plasma cell has a unique rearrangement profile. Other cell types usually retain the unrearranged gene structures. Clonal expansion of any B cell or plasma cell will result in a population of cells that all contain identical immunoglobulin gene rearrangement profiles. Reactive B-cell or plasma cell expansions are polyclonal, with each clone containing relatively few cells and no single clone predominating. Conversely, neoplastic clones are generally large such that the clonal cells are the predominant B cells or plasma cells present. In the appropriate clinical and pathologic setting, detection of a prominent immunoglobulin gene rearrangement profile may be equated to the presence of a neoplastic B-cell or plasma cell clone.

Useful For: Determining whether a B-cell or plasma cell population is polyclonal or monoclonal in specimens other than blood or bone marrow Identifying neoplastic cells as having B-cell or plasma cell differentiation Monitoring for a persistent neoplasm by detecting an immunoglobulin gene rearrangement profile similar to that from a previous neoplastic specimen

Interpretation: An interpretive report will be provided. The interpretation of the presence or absence of a predominant immunoglobulin gene rearrangement profile is sometimes subjective. These results must always be interpreted in the context of other clinicopathologic information to determine the significance of the result. The detection of a clonal immunoglobulin gene rearrangement by this test is not synonymous with the presence of a B-cell or plasma cell neoplasm.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. van Dongen JJ, Wolvers-Tettero IL: Analysis of immunoglobulin and T-cell receptor genes. Part II: Possibilities and limitations in the diagnosis and management of lymphoproliferative diseases and related disorders. Clin Chim Acta. 1991 Apr;198(1-2):93-174 2. Coad JE, Olson DJ, Lander TA, McGlennen RC: Molecular assessment of clonality in lymphoproliferative disorders: I. Immunoglobulin gene rearrangements. Mol Diagn. 1996 Dec;1(4):335-355 3. Kokovic I, Novakovic BJ, Novakovic S: Diagnostic value of immunoglobulin k light chain gene rearrangement analysis in B-cell lymphomas. Int J Oncol. 2015 Mar;46(3):953-962. doi: 10.3892/ijo.2014.2790

BCGET
802123

Immunoglobulin Gene Rearrangement, Tissue

Clinical Information: The immunoglobulin genes (heavy, kappa, and lambda) are comprised of numerous discontinuous coding segments. As B cells develop, the segments are rearranged such that each mature B cell or plasma cell has a unique rearrangement profile. Other cell types usually retain the unrearranged gene structures. Clonal expansion of any B cell or plasma cell will result in a population of cells that all contain an identical immunoglobulin gene rearrangement profile. Reactive B cell or plasma cell expansions are polyclonal, with each clone containing relatively few cells and no single clone predominating. Conversely, neoplastic clones are generally large such that the clonal cells are the predominant B cells or plasma cells present. In the appropriate clinical and pathologic setting, detection of a prominent immunoglobulin gene rearrangement profile may be equated to the presence of a neoplastic B-cell or plasma cell clone.

Useful For: Determining whether a B cell or plasma cell population is polyclonal or monoclonal using paraffin-embedded specimens Identifying neoplastic cells as having B-cell or plasma cell differentiation Monitoring for a persistent neoplasm by detecting an immunoglobulin gene rearrangement profile similar to that from a previous neoplastic specimen

Interpretation: An interpretive report will be provided. The interpretation of the presence or absence of a predominant immunoglobulin gene rearrangement profile is sometimes subjective. These results must always be interpreted in the context of other clinicopathologic information to determine the significance of the result. The detection of a clonal Ig gene rearrangement by this test is not synonymous with the presence of a B-cell or plasma cell neoplasm.

Reference Values:

An interpretive report will be provided and include whether the specimen was positive, negative, or indeterminate for a clonal B-cell population.

Clinical References: 1. Liu H, Bench AJ, Bacon CM, et al. A practical strategy for the routine use of BIOMED-2 PCR assays for detection of B- and T-cell clonality in diagnostic haematopathology. Br J Haematol. 2007;138(1):31-43 2. Van Krieken JH, Langerak AW, Macintyre EA, et al. Improved reliability of lymphoma diagnostics via PCR-based clonality testing: report of the BIOMED-2 Concerted Action BHM4-CT98-3936. Leukemia. 2007;21(2):201-206 3. Bruggemann M, White H, Gaulard P, et al. Powerful strategy for polymerase chain reaction-based clonality assessment in T-cell malignancies Report of the BIOMED-2 Concerted Action BHM4 CT98-3936. Leukemia. 2007;21(2):215-221 4. van Dongen JJ, Wolvers-Tettero IL. Analysis of immunoglobulin and T-cell receptor genes. Part II: Possibilities and limitations in the diagnosis and management of lymphoproliferative diseases and related disorders. Clin Chim Acta. 1991;198(1-2):93-174 5. Coad JE, Olson DJ, Lander TA, et al. Molecular assessment of clonality in lymphoproliferative disorders: I. Immunoglobulin gene rearrangements. Mol Diagn. 1996;1(4):335-355 6. Kokovic I, Novakovic BJ, Novakovic S. Diagnostic value of immunoglobulin k light chain gene rearrangement analysis in B-cell lymphomas. Int J Oncol. 2015;46(3):953-962. doi:10.3892/ijo.2014.2790

KCSFP
607839

Immunoglobulin Kappa Free Light Chain, Spinal Fluid

Clinical Information: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS). The clinical diagnosis of MS is centered on each individual patient while applying diagnostic guidelines. Immunoglobulin free light chain (FLC) presence in cerebrospinal fluid (CSF) is an alternative for diagnosis of MS using nephelometry. Light chains are produced in excess during antibody formation and secreted from the plasma cells or plasma blasts. Quantitative FLC assays use antisera directed against epitopes that are exposed only when the light chains are free (unbound to heavy chain) in solution. FLC immunoassays can be used to specifically quantitate FLC even in the presence of large concentrations of polyclonal immunoglobulins. Routine use of isoelectric focusing electrophoresis coupled with IgG-specific immunoblotting identifies immunoglobulins specific to the CNS. This method is part of the diagnostic criteria used in cases of MS, ie, oligoclonal banding (OLIG). However, OLIG / Oligoclonal Banding, Serum and Spinal Fluid is a labor-intensive technique that includes subjective interpretation of IgG bands from paired CSF and serum. This test, when considered positive at a concentration greater than or equal to 0.1000 mg/dL as a medical decision point, has a sensitivity of 70% with a specificity of 87%, which is comparable in terms of sensitivity and specificity to oligoclonal banding. The differences between this FLC test and the OLIG analysis are not statistically significant. This profile combines the ease of use and interpretation of the quantitative measurement of kappa-free light chains in CSF and allies it to the traditional interpretation of oligoclonal bands for optimized efficiency in laboratory testing for demyelinating diseases and improved test utilization.

Useful For: Diagnosis of multiple sclerosis and other demyelinating conditions

Interpretation: When result is less than 0.0600 mg/dL, the kappa free light chain concentration measured in cerebrospinal fluid (CSF) is lower than the threshold associated with demyelinating disease. This is a negative result. Testing for oligoclonal banding is not performed. Clinical correlation is recommended. When result is from 0.0600 to 0.0999 mg/dL, the kappa free light chain concentration measured in CSF is slightly elevated but not above the medical decision point of 0.1000 mg/dL associated with demyelinating disease. This is a borderline result. Reflexing to oligoclonal bands will be automatically performed and clinical correlation is recommended. When result is greater than or equal to 0.1000 mg/dL, the kappa free light chain concentration measured in CSF is at or greater than the threshold associated with demyelinating disease. This is a positive result. These findings, however, are not specific for multiple sclerosis (MS) because CSF-specific immunoglobulin synthesis may also be detected in patients with other neurologic diseases (infectious, inflammatory, cerebrovascular, autoimmune, and paraneoplastic). Clinical correlation is recommended. Automatic reflexing to oligoclonal bands will occur.

Reference Values:
Only orderable as part of a profile. For more information see MSP3 / Multiple Sclerosis (MS) Cascade, Serum and Spinal Fluid.

Medical decision point: 0.1000 mg/dL
Positive: > or =0.1000 mg/dL
Borderline: 0.0600 mg/dL-0.0999 mg/dL
Negative: <0.0600 mg/dL

Clinical References: 1. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-173 2. Gurtner KM, Shosha E, Bryant SC, et al. CSF free light chain identification of demyelinating disease: comparison with oligoclonal banding and other CSF indexes. Clin Chem Lab Med. 2018;56(7):1071-1080 3. Saadeh R, Pittock S, Bryant S, et al. CSF kappa Free Light Chains as a Potential Quantitative Alternative to Oligoclonal Bands in Multiple Sclerosis. American Academy of Neurology Annual Meeting. Philadelphia, PA. 2019 4. Fortini AS, Sanders EL, Weinshenker BG, Katzmann JA. Cerebrospinal fluid oligoclonal bands in the diagnosis of multiple sclerosis. Isoelectric focusing with IgG immunoblotting

compared with high-resolution agarose gel electrophoresis and cerebrospinal fluid IgG index. Am J Clin Pathol. 2003;120(5):672-675 5. Awad A, Hemmer B, Hartung HP, Kieseier B, Bennett JL, Stuve O. Analyses of cerebrospinal fluid in the diagnosis and monitoring of multiple sclerosis. J Neuroimmunol. 2010;219(1-2):1-7 6. Hassan-Smith G, Durant L, Tsentemeidou A, et al. High sensitivity and specificity of elevated cerebrospinal fluid kappa free light chains in suspected multiple sclerosis. J Neuroimmunol. 2014;276(1-2):175-179 7. Presslauer S, Milosavljevic D, Brucke T, Bayer P, Huebl W. Elevated levels of kappa free light chains in CSF support the diagnosis of multiple sclerosis. J Neurol. 2008;255(10):1508-1514 8. Presslauer S, Milosavljevic D, Huebl W, et al. Validation of kappa free light chains as a diagnostic biomarker in multiple sclerosis and clinically isolated syndrome: A multicenter study. Mult Scler. 2016;22(4):502-510 9. Presslauer S, Milosavljevic D, Huebl W, Parigger S, Schneider-Koch G, Bruecke T. Kappa free light chains: Diagnostic and prognostic relevance in MS and CIS. PLoS ONE. 2014;9(2):e89945 10. Makshakov G, Nazarov V, Kochetova O, Surkova E, Lapin S, Evdoshenko E. Diagnostic and prognostic value of the cerebrospinal fluid concentration of immunoglobulin free light chains in clinically isolated syndrome with conversion to multiple sclerosis. PLoS One. 2015;10(11):e0143375

KCSF
65572

Immunoglobulin Kappa Free Light Chain, Spinal Fluid

Clinical Information: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS). The clinical diagnosis of MS is centered on each patient while applying diagnostic guidelines. Immunoglobulin free light chain (FLC) presence in cerebrospinal fluid (CSF) is an alternative for diagnosing MS using nephelometry. Light chains are produced in excess during antibody formation and secreted from plasma cells or plasmablasts. Quantitative FLC assays use antisera directed against epitopes that are exposed only when the light chains are free (unbound to heavy chain) in solution. FLC immunoassays can be used to specifically quantitate FLC even in the presence of large concentrations of polyclonal immunoglobulins. Routine use of isoelectric focusing electrophoresis coupled with IgG-specific immunoblotting (IgG-IEF) identifies immunoglobulins specific to the CNS. This method is part of the diagnostic criteria used for MS, ie, oligoclonal banding (OLIG / Oligoclonal Banding, Serum and Spinal Fluid). However, oligoclonal banding is a labor-intensive technique that includes subjective interpretation of IgG bands from paired CSF and serum. This test, when considered positive at a concentration greater than or equal to 0.1000 mg/dL as a medical decision point, has a sensitivity of 70.4% with a specificity of 86.8%. The differences between this test and the oligoclonal banding analysis are not statistically significant (p=0.20), and the 2 tests show comparable performance. However, this test does not require a paired serum specimen, offers a shorter turnaround-time for results, and an objective quantitative result. This testing is most useful in patients presenting with a clinically isolated syndrome, which is a clinical episode where patient reports symptoms (headaches, optic neuritis, fatigue, and many others, depending on the disease location) characteristic of inflammation and demyelination of the CNS, and needs to be checked by a neurologist. This is when the likelihood of a diagnosis of MS is greater or most likely but not yet known or confirmed. CSF laboratory testing is also strongly recommended in cases where the imaging findings are atypical and in populations in which MS is less common (eg, children, older individuals, or non-White populations).

Useful For: Diagnosing multiple sclerosis and other demyelinating conditions Evaluating patients who present with a clinically isolated syndrome in which the patient reports symptoms (headaches, optic neuritis, fatigue, and many others, depending on the disease location) characteristic of inflammation and demyelination of the central nervous system Recommended in cases where the imaging findings are atypical and in populations in which multiple sclerosis is less common (eg, children, older individuals, or non-White populations) The test is not useful when a clear diagnosis is already known because a positive result does not correlate with severity of the disease or disease outcomes.

Interpretation: When a result is less than 0.0600 mg/dL, the kappa free light-chain concentration

measured in cerebrospinal fluid (CSF) is lower than the threshold associated with demyelinating disease. This is a negative result. Clinical correlation is recommended. When result is between 0.0600 and 0.0999 mg/dL, this is a borderline result. These findings are not specific for multiple sclerosis (MS) because CSF-specific immunoglobulin synthesis may also be detected in patients with other neurologic diseases (infectious, inflammatory, cerebrovascular, autoimmune, and paraneoplastic). If clinically indicated, consider additional CSF testing such as oligoclonal banding by isoelectric focusing and CSF IgG index. When result is greater than or equal to 0.1000 mg/dL, the kappa free light chain concentration measured in CSF is at or greater than the threshold associated with demyelinating disease. This is a positive result. These findings, however, are not specific for MS because CSF-specific immunoglobulin synthesis may also be detected in patients with other neurologic diseases (infectious, inflammatory, cerebrovascular, autoimmune, and paraneoplastic). If clinically indicated, consider additional CSF testing such as oligoclonal banding by isoelectric focusing and CSF IgG index. A Mayo Clinic study published in 2018 with 325 patients suggested that a kappa free light-chain concentration in CSF greater than or equal to 0.06 mg/dL has 92.5% clinical sensitivity in the diagnosis of multiple sclerosis.(1) A second, larger Mayo Clinic study with 1355 patients published in 2021 showed that a kappa CSF concentration greater than or equal to 0.06 mg/dL had approximately 89% sensitivity. When the kappa level was greater than or equal to 0.1 mg/dL, it had similar sensitivity (87%) to the finding of two unique CSF oligoclonal bands (89%).(2)

Reference Values:

Medical Decision Point: 0.1000 mg/dL
Positive: > or =0.1000 mg/dL
Borderline: 0.0600 mg/dL-0.0999 mg/dL
Negative <0.0600 mg/dL

Clinical References: 1. Gurtner KM, Shosha E, Bryant SC, et al. CSF free light chain identification of demyelinating disease: comparison with oligoclonal banding and other CSF indexes. Clin Chem Lab Med. 2018;56(7):1071-1080 2. Saadeh RS, Bryant SC, McKeon A, et al. CSF kappa free light chains: Cutoff validation for diagnosing multiple sclerosis. Mayo Clin Proc. 2022;97(4):738-751. doi:10.1016/j.mayocp.2021.09.014 3. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology. 2018;17(2):162-173 4. Saadeh R, Pittock S, Bryant S, et al. CSF kappa free light chains as a potential quantitative alternative to oligoclonal bands in multiple sclerosis. American Academy of Neurology Annual Meeting. Philadelphia, PA. 2019 5. Awad A, Hemmer B, Hartung HP, Kieseier B, Bennett JL, Stuve O. Analyses of cerebrospinal fluid in the diagnosis and monitoring of multiple sclerosis. J Neuroimmunol. 2010;219(1-2):1-7 6. Hassan-Smith G, Durant L, Tsentemeidou A, et al. High sensitivity and specificity of elevated cerebrospinal fluid kappa free light chains in suspected multiple sclerosis. J Neuroimmunol. 2014;276(1-2):175-179 7. Presslauer S, Milosavljevic D, Brucke T, et al. Elevated levels of kappa free light chains in CSF support the diagnosis of multiple sclerosis. J Neurol. 2008;255(10):1508-1514 8. Presslauer S, Milosavljevic D, Brucke T, et al. Validation of kappa free light chains as a diagnostic biomarker in multiple sclerosis and clinically isolated syndrome: a multicenter study. Mult Scler. 2016;22(4):502-10 9. Presslauer S, Milosavljevic D, Hubl W, Parigger S, Schneider-Koch G, Bruecke T. Kappa free light chains: Diagnostic and prognostic relevance in MS and CIS. PLoS One. 2014;9(2):e89945 10. Makshakov G, Nazarov V, Kochetova O, Surkova E, Lapin S, Evdoshenko E. Diagnostic and prognostic value of the cerebrospinal fluid concentration of immunoglobulin free light chains in clinically isolated syndrome with conversion to multiple sclerosis. PLoS One. 2015;10(11):e0143375

IGM
8158

Immunoglobulin M (IgM), Serum

Clinical Information: Immunoglobulins are produced by plasma cells as a humoral immune response to contact of the immune system by antigens. The primary reaction after the initial contact is the formation of antibodies of the IgM class, followed later by IgG and IgA antibodies. Quantitative

determination of the immunoglobulins can provide important information on the humoral immune status. Decreased serum immunoglobulin concentrations occur in primary immunodeficiency conditions as well as in secondary immune insufficiencies (eg, in advanced malignant tumors, lymphatic leukemia, multiple myeloma, and Waldenstrom disease). Monoclonal immunoglobulin proliferations in the serum are found in plasmacytomas, Waldenstrom disease, and heavy-chain disease. Monoclonal immunoglobulinemia requires detailed differential diagnostic investigations in addition to the quantitative determination. Local immune reactions result in elevated immunoglobulin levels, particularly IgG, in the cerebrospinal fluid. IgA increases with asparaginase treatment, during pregnancy, with exercise, and in people with alcohol use disorder. It falls with prolonged exposure to benzene and after 1 year's abstinence from drinking alcohol. Diphenylhydantoin, dextran, methyl prednisolone, toluene, xylol, and oral contraceptives may also lower IgA levels. IgM may rise in people with narcotic addiction and after various drug use, as with IgA and IgG. The gamma globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 5% is IgM. Elevations of IgM may be due to polyclonal immunoglobulin production. Monoclonal elevations of IgM occur in macroglobulinemia. Monoclonal gammopathies of all types may lead to a spike in the gamma globulin zone seen on serum protein electrophoresis. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

Useful For: Detecting or monitoring of IgM monoclonal gammopathies and IgM-related immune deficiencies

Interpretation: Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (eg, hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevation of IgM may occur in monoclonal gammopathies such as macroglobulinemia, primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

Reference Values:

0-<5 months: 26-122 mg/dL
5-<9 months: 32-132 mg/dL
9-<15 months: 40-143 mg/dL
15-<24 months: 46-152 mg/dL
2-<4 years: 37-184 mg/dL
4-<7 years: 37-224 mg/dL
7-<10 years: 38-251 mg/dL
10-<13 years: 41-255 mg/dL
13-<16 years: 45-244 mg/dL
16-<18 years: 49-201 mg/dL
> or =18 years: 37-286 mg/dL

Clinical References: 1. Webster ADB. Laboratory Investigation of primary deficiency of the lymphoid system. In: Clinics in Immunology and Allergy. Vol 5. 3rd ed. WB Saunders Company; 1985:447-468 2. Pinching AJ. Laboratory investigation of secondary immunodeficiency. In: Clinics in Immunology and Allergy. Vol 5. 3rd ed. WB Saunders Company; 1985:469-490 3. Dispenzieri A, Gertz MA, Kyle RA. Distribution of diseases associated with moderate polyclonal gammopathy in patients seen at Mayo Clinic during 1991. Blood. 1997;90:353 4. Kyle RA, Greipp PR. The laboratory investigation of monoclonal gammopathies. Mayo Clin Proc. 1978;53(11):719-739 5. Ballow M, O'Neil KM. Approach to the patient with recurrent infections. In: Middleton Jr E, Reed CE, Ellis EF, et al, eds. Allergy: Principles and Practice. Vol 2. 4th ed. Mosby-Year Book, Inc.; 1993:1027-1058 6. Kyle RA. Detection of quantitation of monoclonal proteins. Clin Immunol Newsletter. 1990;10:84-86 7. Dietzen DJ, Willrich MAV. Amino acids, peptides, and proteins. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 31

TLCU
87934

Immunoglobulin Total Light Chains, Urine

Clinical Information: Immunoglobulin light chains are usually cleared from blood through the renal glomeruli and reabsorbed in the proximal tubules so that urine light-chain concentrations are very low or undetectable. The production of large amounts of monoclonal light chains, however, can overwhelm this reabsorption mechanism. The detection of monoclonal light chains in the urine (Bence Jones proteinuria) has been used as a diagnostic marker for multiple myeloma since the report by Dr. H. Bence Jones in 1847. Current laboratory procedures employ protein electrophoresis and isotype testing for the identification and characterization of urine monoclonal light chains, which may be present in large enough amounts to also be quantitated as an M-spike on protein electrophoresis. The electrophoretic M-spike is the recommended method of monitoring monoclonal gammopathies, such as multiple myeloma. Monitoring the urine M-spike is especially useful in patients with light-chain multiple myeloma in whom the serum M-spike is very small or absent, but the urine M-spike is large. Just as quantitative serum immunoglobulins by immunonephelometry are a complement to M-spike quantitation by serum electrophoresis, this quantitative urine light-chain assay may be used to complement urine M-spike quantitation by electrophoresis.

Useful For: Monitoring patients whose urine demonstrates large M-spikes Confirming the quantitation of specimens that show M-spikes by electrophoresis Detecting urine monoclonal proteins and identification of specimens that need urine protein electrophoresis

Interpretation: A kappa/lambda (K/L) ratio greater than 6.2 suggests the presence of monoclonal kappa light chains. A K/L ratio less than 0.7 suggests the presence of monoclonal lambda light chains. In 24-hour specimens, a greater than 90% increase in concentration suggests progression or relapse; a greater than 90% decrease suggests treatment response. Increased kappa and/or lambda light chains may be seen in benign (polyclonal) and neoplastic (monoclonal) disorders.

Reference Values:
KAPPA TOTAL LIGHT CHAIN
<0.9 mg/dL

LAMBDA TOTAL LIGHT CHAIN
<0.7 mg/dL

KAPPA/LAMBDA RATIO
0.7-6.2

Clinical References: 1. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346 2. Leung N, Barnidge DR, Hutchison CA. Laboratory testing in monoclonal gammopathy of renal significance (MGRS). Clin Chem Lab Med. 2016;54(6):929-937 3. Willrich MA, Katzmann JA. Laboratory testing requirements for diagnosis and follow-up of multiple myeloma and related plasma cell dyscrasias. Clin Chem Lab Med. 2016;54(6):907-919 4. Rajkumar SV, Kyle RA. Multiple myeloma: diagnosis and treatment. Mayo Clin Proc. 2005;80(10):1371-1382

IMMG
8156

Immunoglobulins (IgG, IgA, and IgM), Serum

Clinical Information: Immunoglobulins are formed by plasma cells as a humoral immune response to contact of the immune system with antigens. The primary reaction after initial contact is formation of antibodies of the IgM class, followed later by IgG and IgA antibodies. Quantitative determination of immunoglobulins can provide important information on humoral immune status. Decreased serum immunoglobulin concentrations occur in primary immunodeficiency conditions as well as in secondary

immune insufficiencies (eg, in advanced malignant tumors, lymphatic leukemia, multiple myeloma, and Waldenstrom disease). Monoclonal immunoglobulin proliferations in the serum are found in plasmacytomas, Waldenstrom disease, and heavy-chain disease. Monoclonal immunoglobulinemia requires detailed differential diagnostic investigations in addition to the quantitative determination. Local immune reactions result in elevated immunoglobulin levels, particularly IgG, in the cerebrospinal fluid. IgA increases with asparaginase treatment, during pregnancy, with exercise, and in people with alcohol use disorder. It falls with prolonged exposure to benzene and after a 1 year abstinence from drinking alcohol. Diphenylhydantoin, dextran, methyl prednisolone, toluene, xylol, and oral contraceptives may also lower IgA levels. IgM may rise in those with narcotic addiction and after various drug use, as with IgA and IgG. The gamma globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 80% is IgG, 15% is IgA, 5% is IgM, 0.2% is IgD, and a trace is IgE. Elevations of IgG, IgA, and IgM may be due to polyclonal immunoglobulin production. Monoclonal gammopathies of all types may lead to a spike in the gamma globulin zone seen on serum protein electrophoresis. Monoclonal elevations of IgG, IgA, IgD, and IgE characterize multiple myeloma. Monoclonal elevations of IgM occur in macroglobulinemia. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

Useful For: Detecting or monitoring of monoclonal gammopathies and immune deficiencies

Interpretation: Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (eg, hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevations of IgG, IgA, or IgM may occur in monoclonal gammopathies such as multiple myeloma (IgG, IgA), macroglobulinemia (IgM), primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

Reference Values:

IgG
0-<5 months: 100-334 mg/dL
5-<9 months: 164-588 mg/dL
9-<15 months: 246-904 mg/dL
15-<24 months: 313-1,170 mg/dL
2-<4 years: 295-1,156 mg/dL
4-<7 years: 386-1,470 mg/dL
7-<10 years: 462-1,682 mg/dL
10-<13 years: 503-1,719 mg/dL
13-<16 years: 509-1,580 mg/dL
16-<18 years: 487-1,327 mg/dL
> or =18 years: 767-1,590 mg/dL

IgA
0-<5 months: 7-37 mg/dL
5-<9 months: 16-50 mg/dL
9-<15 months: 27-66 mg/dL
15-<24 months: 36-79 mg/dL
2-<4 years: 27-246 mg/dL
4-<7 years: 29-256 mg/dL
7-<10 years: 34-274 mg/dL
10-<13 years: 42-295 mg/dL
13-<16 years: 52-319 mg/dL
16-<18 years: 60-337 mg/dL
> or =18 years: 61-356 mg/dL

IgM
0-<5 months: 26-122 mg/dL
5-<9 months: 32-132 mg/dL
9-<15 months: 40-143 mg/dL
15-<24 months: 46-152 mg/dL
2-<4 years: 37-184 mg/dL
4-<7 years: 37-224 mg/dL
7-<10 years: 38-251 mg/dL
10-<13 years: 41-255 mg/dL
13-<16 years: 45-244 mg/dL
16-<18 years: 49-201 mg/dL
> or =18 years: 37-286 mg/dL

Clinical References: 1. Webster ADB. Laboratory Investigation of primary deficiency of the lymphoid system. In: Clinics in Immunology and Allergy. Vol 5. 3rd ed. WB Saunders Company; 1985:447-468 2. Pinching AJ. Laboratory investigation of secondary immunodeficiency. In: Clinics in Immunology and Allergy. Vol.5. 3rd ed. WB Saunders Company; 1985:469-490 3. Dispenzieri A, Gertz MA, Kyle RA. Distribution of diseases associated with moderate polyclonal gammopathy in patients seen at Mayo Clinic during 1991. Blood. 1997;90:353 4. Kyle RA, Greipp PR. 3. The laboratory investigation of monoclonal gammopathies. Mayo Clin Proc. 1978;53(11):719-739 5. Ballow M, O'Neil KM. Approach to the patient with recurrent infections. In: Middleton Jr E, Reed CE, Ellis EF, et al, eds. Allergy: Principles and Practice. Vol 2. 4th ed. Mosby-Year Book, Inc; 1993:1027-1058 6. Kyle RA. Detection of quantitation of monoclonal proteins. Clin Immunol Newsletter. 1990;10:84-86 7. Dietzen DJ, Willrich MAV. Amino acids, peptides, and proteins. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 31

FIMMC
57370

Immunoglobulins, CSF Quantitative

Reference Values:

Immunoglobulin M CSF	(0.0 - 0.7)	mg/dL
Immunoglobulin G CSF	(0.0 - 6.0)	mg/dL
Immunoglobulin A CSF	(0.0 - 0.7)	mg/dL

IMMAU
619858

Inborn Errors of Immunity with Immune Dysregulation and Autoimmunity Gene Panel, Varies

Clinical Information:

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an inborn error of immunity (IEI) associated with immune dysregulation or autoimmunity Establishing a diagnosis of an IEI, allowing for appropriate management and surveillance for disease features based on the gene and/or variant involved Identifying variants within genes known to be associated with immune dysregulation or autoimmunity, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 2. Tangye SG, Al-Herz W, Bousfiha A, et al: Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022 Oct;42(7):1473-1507. doi: 10.1007/s10875-022-01289-3 3. Azizi G, Yazdani R, Rae W, et al: Monogenic polyautoimmunity in primary immunodeficiency diseases. Autoimmun Rev. 2018 Oct;17(10):1028-1039. doi: 10.1016/j.autrev.2018.05.001 4. Baxter SK, Walsh T, Casadei S, et al: Molecular diagnosis of childhood immune dysregulation, polyendocrinopathy, and enteropathy, and implications for clinical management. J Allergy Clin Immunol. 2022 Jan;149(1):327-339. doi: 10.1016/j.jaci.2021.04.005 5. Cepika AM, Sato Y, Liu JM, Uyeda MJ, Bacchetta R, Roncarolo MG: Tregopathies: Monogenic diseases resulting in regulatory T-cell deficiency. J Allergy Clin Immunol. 2018 Dec;142(6):1679-1695. doi: 10.1016/j.jaci.2018.10.026 6. Consonni F, Favre C, Gambineri E: IL-2 signaling axis defects: How many faces? Front Pediatr. 2021 Jul 2;9:669298. doi: 10.3389/fped.2021.669298 7. Bjorklund G, Pivin M, Hangan T, Yurkovskaya O, Pivina L: Autoimmune polyendocrine syndrome type 1: Clinical manifestations, pathogenetic features, and management approach. Autoimmun Rev. 2022 Aug;21(8):103135. doi: 10.1016/j.autrev.2022.103135

MONOS
9081

Infectious Mononucleosis, Rapid Test, Serum

Clinical Information: Infectious mononucleosis (IM) is a viral illness that involves reticuloendothelial tissue and is generally limited to children and young adults. IM is most frequently caused by Epstein-Barr virus. The disease is characterized by fever, sore throat, lymphadenopathy, headache, and fatigue and, on a symptomatic basis, may be confused with other diseases. Detectable levels of unique heterophile antibodies are produced in patients with IM.

Useful For: Diagnosis of Epstein-Barr virus mononucleosis

Interpretation: Detectable levels of the infectious mononucleosis heterophile antibody can usually be expected to occur between the sixth and tenth day following the onset of symptoms. The level usually increases through the second or third week of illness and, thereafter, can be expected to persist, gradually declining over a 12-month period.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: Johannsen EC, Kaye KM. Epstein-Barr virus (infectious mononucleosis, Epstein-Barr virus-associated malignant diseases, and other diseases). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:1872-1890

IBDP2
610004

Inflammatory Bowel Disease Serology Panel, Serum

Clinical Information: Inflammatory bowel disease (IBD) refers to 2 diseases - ulcerative colitis (UC) and Crohn disease (CD), both of which result from chronic inflammation in the gastrointestinal (GI) tract.(1) CD is characterized by chronic diarrhea, abdominal pain, and fatigue.(2) In comparison,

UC frequently presents with bloody diarrhea that is of an urgent nature.(3) Inflammation in UC most frequently affects the rectum and proximal colon, and presents with continue mucosal involvement. In CD, inflammation can affect almost any area of the GI tract and is usually evidenced as patchy, transmural lesions. Diagnosis of IBD is primarily based on clinical evaluation, endoscopy with biopsy, and imaging studies.(4) Because CD and UC are characterized by GI inflammation, fecal calprotectin can be used to differentiate IBD from noninflammatory conditions such as irritable bowel syndrome (IBS). Fecal calprotectin is useful in excluding IBD as a diagnosis and avoiding unnecessary endoscopic or imaging procedures. CD and UC are associated with the presence of various antimicrobial and autoantibodies.(5) Patients with UC often have measurable antineutrophil cytoplasmic antibodies (ANCA), which react with as yet uncharacterized target antigens in human neutrophils; in contrast, patients with CD often have measurable IgA and/or IgG antibodies, which react with cell wall mannan of Saccharomyces cerevisiae. Despite these associations, current guidelines indicate that testing for these antibodies is not sufficiently sensitive for use in the diagnosis of IBD.(2,3) Rather, these antibodies should be limited to distinguishing between CD and UC in cases where the specific diagnosis is unclear based on pathologic and imaging studies.

Useful For: Distinguishing between ulcerative colitis and Crohn disease in patients for whom the specific diagnosis is unclear based on endoscopic, pathologic, and imaging evaluations This test is not useful for determining the extent of disease in patients with inflammatory bowel disease or determining the response to disease-specific therapy including surgical resection of diseased intestine.

Interpretation: The presence of antineutrophil cytoplasmic antibodies in the absence of IgA and IgG anti-Saccharomyces cerevisiae antibodies is consistent with the diagnosis of ulcerative colitis; the presence of IgA and IgG ASCA in the absence of ANCA is consistent with Crohn disease.

Reference Values:

Saccharomyces cerevisiae ANTIBODY, IgA
Negative: <20.0 RU/mL
Positive: > or =20.0 RU/mL

Saccharomyces cerevisiae ANTIBODY, IgG
Negative: <20.0 RU/mL
Positive: > or =20.0 RU/mL

CYTOPLASMIC NEUTROPHIL ANTIBODIES, INFLAMMATORY BOWEL DISEASE PANEL, SERUM
Negative (not detectable)

Clinical References: 1. Rose NR, Mackay IR, eds: Inflammatory bowel diseases. In: The Autoimmune Diseases. Elsevier; 2008 2. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG clinical guideline: Management of crohn's disease in adults. Am J Gastroenterol. 2018;113(4):481-517 3. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: Ulcerative colitis in adults. Am J Gastroenterol. 2019;114(3):384-413 4. Clark C, Turner J. Diagnostic modalities for inflammatory bowel disease: Serologic markers and endoscopy. Surg Clin North Am. 2015;95(6):1123-1141 5. Zhou G, Song Y, Yang W, et al. ASCA, ANCA, ALCA and many more: Are they useful in the diagnosis of inflammatory bowel disease? Dig Dis. 2016;34:90-97

IMTF 35277 Inflammatory Myofibroblastic Tumors (IMT), 2p23 (ALK) Rearrangement, FISH, Tissue

Clinical Information: Inflammatory myofibroblastic tumor (IMT) is a distinctive lesion composed of myofibroblastic spindle cells accompanied by an inflammatory infiltrate which occur primarily in the soft

tissue but may arise in any anatomical site including lung, soft tissue, retroperitoneum, and bladder. A subset of IMT are characterized by rearrangements involving the ALK gene at 2p23. Studies support that identification of ALK gene rearrangement is useful to differentiate IMTs from other spindle cell neoplasms of soft tissue and viscera.

Useful For: Supporting the diagnosis of inflammatory myofibroblastic tumors when used conjunction with an anatomic pathology consultation

Interpretation: ALK will be clinically interpreted as positive or negative. A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the ALK probe set. A positive result is consistent with rearrangement of the ALK gene and likely reflects ALK fusion with a partner gene. The significance of this finding is dependent on the clinical and pathologic features. A negative result suggests an ALK gene rearrangement is not present but does not completely exclude the presence of an ALK gene rearrangement and does not exclude the diagnosis of inflammatory myofibroblastic tumors.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Sukov WR, Cheville JC, Carlson AW, et al. Utility of ALK-1 protein expression and ALK rearrangements in distinguishing inflammatory myofibroblastic tumor from malignant spindle cell lesions of the urinary bladder. Mod Pathol. 2007;20(5):592-603 2. Tsuzuki T, Magi-Galluzzi C, Epstein JI. ALK-1 expression in inflammatory myofibroblastic tumor of the urinary bladder. Am J Surg Pathol. 2004;28(12):1609-1614 3. WHO Classification of Tumours Editorial Board. Soft Tissue and Bone Tumours. 5th ed. IARC; 2020. WHO Classification of Tumours Series. Vol. 3, 109-111

INFXP 620151 Infliximab Quantitation with Antibodies to Infliximab, Serum

Clinical Information: Infliximab is a chimeric immunoglobulin (IgG1 kappa) targeting tumor necrosis factor-alpha (TNF-a) and it is currently US Food and Drug Administration (FDA)-approved for the treatment of multiple inflammatory conditions. Infliximab binds to soluble TNF-a and transmembrane homotrimers, which are found on the surface of macrophages and T cells, with similar affinity. Infliximab has the ability to mediate complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity, which leads to the lysis of target cells. The reference product for infliximab is Remicade (Janssen Pharmaceuticals) and several biosimilar products are FDA-approved, including but not limited to: Renflexis (infliximab-abda, Organon), Inflectra (infliximab-dyyb, Pfizer inc), Ixifi (infliximab-qbtx, Pfizer Inc), and Avsola (infliximab-axxq, Amgen). Inflectra, Renflexis, and Avsola have the same primary amino acid sequence as Remicade. Therefore, "infliximab" will be used to refer to both the reference product and the biosimilar products interchangeably. This test cannot distinguish between Remicade and the infliximab biosimilar products. A biosimilar product is a biological product that is highly similar to an FDA-approved biological product, known as the reference product, but manufactured by a different company. No clinically meaningful differences in terms of safety and effectiveness from the reference product are present. Only minor differences in clinically inactive components are allowable in biosimilar products. In contrast to generic medications, a prescription of biosimilars needs to come from the ordering physician and not the dispensing pharmacy (pharmacies cannot substitute a biosimilar for another medication; a separate prescription is required). This assay has been verified to measure antibodies to infliximab (ATI) (Remicade and the biosimilars infliximab-dyyb, infliximab-abda, and infliximab-axxq) with no analytical differences between the detection of ATI for the four drugs. It is expected that antibodies developed against other biosimilars would also demonstrate no significant analytical differences. Infliximab pharmacokinetic properties may vary with disease and clearance is affected by concomitant use of immunosuppressants, high

concentrations of TNF-a and C-reactive proteins,(1,2) low albumin concentrations, high body mass index, and presence of ATI, also known as human antichimeric antibodies (HACA).(3) Male patients seem to clear infliximab faster than female patients.(3) Several studies have demonstrated that infliximab quantitation in the setting of loss of response to therapy can aid in patient management, as trough concentrations defined as therapeutic have been associated with superior clinical response and improved prognosis.(4-6) Other studies have shown that proactive monitoring of infliximab concentrations in the maintenance stage, even when there is clinical response was more effective in sustaining disease control than standard therapy without any therapeutic drug monitoring in preventing disease worsening during a 52-week period.(7) Evaluation of infliximab concentrations may be of value for all inflammatory diseases for which it is prescribed. Primary indications for testing of infliximab include loss of response, partial response on initiation of therapy, autoimmune or hypersensitivity reactions, primary nonresponse, reintroduction after drug holiday, endoscopic/computed tomography enterography recurrence (in inflammatory bowel disease), acute infusion reactions, and proactive monitoring. Measurement of infliximab concentrations is indicated at trough, immediately prior to the next scheduled infusion. Infliximab concentrations tend to reach steady state and stabilize after 14 weeks (approximately 100 days). Quantitation of peak infliximab concentrations is strongly discouraged. Low trough concentrations may be correlated with loss of response to infliximab. For evaluation of loss of response to therapy, a reflex approach starting with the drug quantitation first, and then assessing for ATI when drug level is subtherapeutic is indicated for adults experiencing active inflammatory bowel disease. For other situations, like evaluation of pediatric patients or proactive monitoring, a panel where both drug quantitation of infliximab and ATI are performed simultaneously may be appropriate.

Useful For: Trough level quantitation for evaluation of patients undergoing therapy with infliximab for proactive or reactive therapeutic drug monitoring.

Interpretation: Results above 35 mcg/mL are suggestive of a blood draw at a time-point in treatment other than trough. Interpretation and patient management will be different according to disease state, clinical presentation (symptomatic versus appropriate response to therapy), several other laboratory tests and a combination of the drug concentration and presence of antibodies to infliximab. IFX quant, mcg/mL ATI, U/mL Comment <5 Negative Absence of detectable antibody-to-infliximab (ATI). Low concentration of infliximab (IFX) may be attributable to other parameters related to infliximab clearance. <5 Positive Presence of ATI detected, which correlates with low concentration of infliximab. ATIs may be associated with increased clearance and lower circulating concentrations of IFX. 5-10 Negative Absence of detectable ATI. At this concentration of IFX, a low-titer ATI (50-499 U/mL) cannot be completely excluded. However, the presence of a high-titer ATI (> or =500 U/mL) is unlikely. If there is clinical suspicion for a low-titer ATI, suggest submission of a new sample obtained at trough. This test has demonstrated drug tolerance of up to 100 mcg/mL IFX for ATI > or =500 U/mL and up to 10 mcg/mL IFX for ATI <500 U/mL Low positive (50-499 U/mL) Presence of ATI detected. At this concentration of IFX, the detected titer of the ATI may be modestly underestimated. This test has demonstrated drug tolerance of up to 100 mcg/mL IFX for ATI > or =500 U/mL and up to 10 mcg/mL IFX for ATI <500 U/mL High positive (> or =500 U/mL) Presence of ATI detected. This test has demonstrated drug tolerance of up to 100 mcg/mL IFX for ATI > or =500 U/mL and up to 10 mcg/mL IFX for ATI <500 U/mL >10 Negative Absence of detectable ATI. At this concentration of IFX, a low-titer ATI (50-499 U/mL) cannot be completely excluded. The presence of a high-titer ATI (> or =500 U/mL) is unlikely, but also cannot be completely excluded. If there is clinical suspicion for an ATI, suggest submission of a new sample at trough, preferably during maintenance phase. This test has demonstrated drug tolerance of up to 100 mcg/mL IFX for ATI > or =500 U/mL and up to 10 mcg/mL IFX for ATI <500 U/mL Low positive (50-499 U/mL) Presence of ATI detected. At this concentration of IFX, the detected titer of the ATI may be underestimated. Suggest submission of a new sample obtained at trough, preferably during maintenance phase. This test has demonstrated drug tolerance of up to 100 mcg/mL IFX for ATI > or =500 U/mL and up to 10 mcg/mL IFX for ATI <500 U/mL High positive (> or =500 U/mL) Presence of ATI detected. This test has demonstrated drug tolerance of up to 100 mcg/mL IFX for ATI > or =500 U/mL and up to 10 mcg/mL IFX for ATI <500 U/mL

Reference Values:

INFLIXIMAB QUANTITATION:
Limit of quantitation is 1.0 mcg/mL. Therapeutic ranges are disease specific.

Pediatric reference ranges are not established.

INFLIXIMAB ANTIBODIES
Absence of antibodies to infliximab (ATI) is defined as <50 U/mL
Presence of ATI is reported as positive when concentrations are > or =50 U/mL

Clinical References: 1. Colombel JF, Sandborn WJ, Reinisch W, et al: Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010 Apr;362(15):1383-1395. doi: 10.1056/NEJMoa0904492 2. Jurgens M, Mahachie John JM, Cleynen I, et al: Levels of C-reactive protein are associated with response to infliximab therapy in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2011 May;9(5):421-427.e1. doi: 10.1016/j.cgh.2011.02.008 3. Ordas I, Mould DR, Feagan BG, Sandborn WJ: Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther. 2012 Apr;91(4):635-646. doi: 10.1038/clpt.2011.328 4. Afif W, Loftus EV Jr, Faubion WA, et al: Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol. 2010 May;105(5):1133-1139. doi: 10.1038/ajg.2010.9 5. Imaeda H, Bamba S, Takahashi K, et al: Relationship between serum infliximab trough levels and endoscopic activities in patients with Crohn's disease under scheduled maintenance treatment. J Gastroenterol. 2014 Apr;49(4):674-682. doi: 10.1007/s00535-013-0829-7 6. Steenholdt C, Bendtzen K, Brynskov J, et al: Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. Scand J Gastroenterol. 2011 Mar;46(3):310-318. doi: 10.3109/00365521.2010.536254 7. Syversen SW, Jorgensen KK, Goll GL, et al. Effect of Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy on Disease Control in Patients With Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. JAMA. 2021;326(23):2375-2384. doi:10.1001/jama.2021.21316 8. Feuerstein JD, Nguyen GC, Kupfer SS, et al: American Gastroenterological Association Institute guideline on therapeutic drug monitoring in inflammatory bowel disease. Gastroenterology. 2017 Sep;153(3):827-834. doi: 10.1053/j.gastro.2017.07.032 9. Silva-Ferreira F, Afonso J, Pinto-Lopes P, Magro F: A systematic review on infliximab and adalimumab drug monitoring: Levels, clinical outcomes and assays. Inflamm Bowel Dis. 2016 Sep;22(9):2289-2301. doi: 10.1097/MIB.0000000000000855 10. Willrich MA, Murray DL, Barnidge DR, Ladwig PM, Snyder MR. Quantitation of infliximab using clonotypic peptides and selective reaction monitoring by LC-MS/MS. Int Immunopharmacol. Sep 2015;28(1):513-20. doi:10.1016/j.intimp.2015.07.007 11. Willrich MAV, Lazar-Molnar E, Snyder MR, Delgado JC. Comparison of Clinical Laboratory Assays for Measuring Serum Infliximab and Antibodies to Infliximab. J Appl Lab Med. 2018;2(6):893-903. doi:10.1373/jalm.2017.024869

INFXR 63437 Infliximab Quantitation with Reflex to Antibodies to Infliximab, Serum

Clinical Information:

Useful For: Trough level quantitation for evaluation of patients undergoing therapy with infliximab, with signs and symptoms of loss of response to therapy.

Interpretation: Low trough concentrations may be correlated with loss of response to infliximab. For infliximab trough concentrations 5.0 mcg/mL or less, testing for antibodies to infliximab (ATI) is suggested. For infliximab trough concentrations above 5.0 mcg/mL measured in the setting of loss of response to therapy, patients may benefit from treatment with a different pharmaceutical agent. Results

above 35 mcg/mL are suggestive of a blood draw at a time-point in treatment other than trough. Interpretation and patient management will be different according to disease state, clinical presentation (symptomatic versus appropriate response to therapy), several other laboratory tests and a combination of the drug concentration and/or presence of ATI. A low titer ATI is reported with a quantitative value of 50 to 499 U/mL. A high-titer ATI is reported with a quantitative value greater than or equal to 500 U/mL, using the Mayo Clinic assay.

Reference Values:

INFLIXIMAB QUANTITATION:
Limit of quantitation is 1.0 mcg/mL. Therapeutic ranges are disease specific.

Pediatric reference ranges are not established.

INFLIXIMAB ANTIBODIES
Absence of antibodies to infliximab (ATI) is defined as <50 U/mL
Presence of ATI is reported as positive when concentrations are > or =50 U/mL

Clinical References: 1. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362(15):1383-1395. doi:10.1056/NEJMoa0904492 2. Jurgens M, Mahachie John JM, Cleynen I, et al. Levels of C-reactive protein are associated with response to infliximab therapy in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2011;9(5):421-427.e1. doi:10.1016/j.cgh.2011.02.008 3. Ordas I, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther. 2012;91(4):635-646. doi:10.1038/clpt.2011.328 4. Afif W, Loftus EV Jr, Faubion WA, et al: Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol. 2010;105(5):1133-1139. doi:10.1038/ajg.2010.9 5. Imaeda H, Bamba S, Takahashi K, et al. Relationship between serum infliximab trough levels and endoscopic activities in patients with Crohn's disease under scheduled maintenance treatment. J Gastroenterol. 2014;49(4):674-682. doi:10.1007/s00535-013-0829-7 6. Steenholdt C, Bendtzen K, Brynskov J, Thomsen OO, Ainsworth MA.: Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. Scand J Gastroenterol. 2011;46(3):310-318. doi:10.3109/00365521.2010.536254 7. Syversen SW, Jorgensen KK, Goll GL, et al. Effect of Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy on Disease Control in Patients With Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. JAMA. 2021;326(23):2375-2384. doi:10.1001/jama.2021.21316 8. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on therapeutic drug monitoring in inflammatory bowel disease. Gastroenterology. 2017;153(3):827-834. doi:10.1053/j.gastro.2017.07.032 9. Silva-Ferreira F, Afonso J, Pinto-Lopes P, Magro F. A systematic review on infliximab and adalimumab drug monitoring: Levels, clinical outcomes and assays. Inflamm Bowel Dis. 2016;22(9):2289-2301. doi:10.1097/MIB.0000000000000855 10. Willrich MA, Murray DL, Barnidge DR, Ladwig PM, Snyder MR. Quantitation of infliximab using clonotypic peptides and selective reaction monitoring by LC-MS/MS. Int Immunopharmacol. Sep 2015;28(1):513-20. doi:10.1016/j.intimp.2015.07.007 11. Willrich MAV, Lazar-Molnar E, Snyder MR, Delgado JC. Comparison of Clinical Laboratory Assays for Measuring Serum Infliximab and Antibodies to Infliximab. J Appl Lab Med. 2018;2(6):893-903. doi:10.1373/jalm.2017.024869

HPFLU
610411

Influenza Virus Type A and Type B and Respiratory Syncytial Virus (RSV) RNA, Molecular Detection, PCR, Varies

Clinical Information: Influenza, otherwise known as the "flu," is an acute, contagious respiratory

illness caused by influenza A, B, and C viruses. Of these, only influenza A and B are thought to cause significant disease, with infections due to influenza B usually being milder than infections with influenza A. Influenza A viruses are further categorized into subtypes based on the 2 major surface protein antigens: hemagglutinin (H) and neuraminidase (N). Common symptoms of influenza infection include fever, chills, sore throat, muscle pains, severe headache, weakness, fatigue, and a nonproductive cough. Certain patients, including infants, older individuals, patients who are immunocompromised, and those with impaired lung function, are at risk for serious complications. In the United States, influenza results in 10,000 to 30,000 deaths and more than 200,000 hospitalizations each year.(1) In the northern hemisphere, annual epidemics of influenza typically occur during the fall or winter months. However, the peak of influenza activity can occur as late as April or May, and the timing and duration of flu seasons vary. Influenza infection may be treated with supportive therapy as well as antiviral drugs, such as the neuraminidase inhibitors, oseltamivir (Tamiflu) and zanamivir (Relenza). These drugs are most effective when given within the first 48 hours of infection, so prompt diagnosis and treatment are essential for proper management. Respiratory syncytial virus (RSV) is a respiratory virus that also infects the human respiratory tract, causing an influenza-like illness. Most otherwise healthy people recover from RSV infection in 1 to 2 weeks, but infection can be severe in infants, young children, and older adults. RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children younger than 1 year in the United States. It is increasingly recognized as a frequent cause of respiratory illness in older adults.(2) RSV and influenza viruses can be detected in respiratory secretions, including upper and lower respiratory tract specimens, by molecular test methods. Nasopharyngeal swabs or aspirates are the preferred specimen types for detection of influenza A virus, influenza B virus, and RSV. Nasal swabs have been shown to provide comparable yield to nasopharyngeal specimens for molecular detection of influenza A and B viral RNA but not RSV RNA.(3-4)

Useful For: Simultaneous detection of influenza A virus, influenza B virus, and respiratory syncytial virus in upper or lower respiratory tract specimens from individuals with flu-like illnesses

Interpretation:

Reference Values:
Undetected

Clinical References: 1. Centers for Disease Control and Prevention. Information for clinicians on influenza virus testing. Updated December 11. 2023. Accessed August 22, 2024. Available at www.cdc.gov/flu/professionals/diagnosis/index.htm 2. Centers for Disease Control and Prevention. Respiratory syncytial virus infection (RSV). Updated July 3, 2024. Accessed August 22, 2024. Available at https://www.cdc.gov/rsv/older-adults/index.html 3. Anderson NW, Binnicker MJ, Harris DM, et al. Morbidity and mortality among patients with respiratory syncytial virus infection: a 2-year retrospective review. Diagn Microbiol Infect Dis. 2016; 85(3):367-371 4. Boerger AC, Binnicker MJ. Comparison of the panther fusion respiratory panels to routine methods for detection of viruses in upper and lower respiratory tract specimens. Diagn Microbiol Infect Dis. 2020;97(2):115014

FLUNP 802208 Influenza Virus Type A and Type B, and Respiratory Syncytial Virus (RSV), Molecular Detection, PCR, Nasopharyngeal Swab

Clinical Information: Influenza, otherwise known as the "flu," is an acute, contagious respiratory illness caused by influenza A, B, and C viruses. Of these, only influenza A and B are thought to cause significant disease, with infections due to influenza B usually being milder than infections with influenza A. Influenza A viruses are further categorized into subtypes based on the 2 major surface protein antigens: hemagglutinin (H) and neuraminidase (N). Common symptoms of influenza infection include fever, chills, sore throat, muscle pains, severe headache, weakness, fatigue, and a nonproductive

cough. Certain patients, including infants, the elderly, the immunocompromised, and those with impaired lung function, are at risk for serious complications. In the United States, influenza results in approximately 36,000 deaths and more than 200,000 hospitalizations each year.(1) In the northern hemisphere, annual epidemics of influenza typically occur during the fall or winter months. However, the peak of influenza activity can occur as late as April or May, and the timing and duration of flu seasons vary. In 2009 to 2010, a novel influenza virus (called 2009 H1N1, previously "swine" flu) appeared in Mexico and quickly spread worldwide, causing the first influenza pandemic in more than 40 years. The resultant influenza season had an atypical distribution, with illness occurring during normally low-incidence months. Following a pandemic, disease incidence usually returns to the typical seasonal distribution within 1 to 2 years.(1) Influenza infection may be treated with supportive therapy, as well as antiviral drugs such as the neuraminidase inhibitors, oseltamivir (TAMIFLU) and zanamivir (RELENZA). These drugs are most effective when given within the first 48 hours of infection, so prompt diagnosis and treatment are essential for proper management. Respiratory syncytial virus (RSV) is a respiratory virus that also infects the respiratory system and can cause an influenza-like illness. Most otherwise healthy people recover from RSV infection in 1 to 2 weeks. However, infection can be severe in infants, young children, and older adults. RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children under 1 year of age in the United States, and is more frequently being recognized as an important cause of respiratory illness in older adults.(2) RSV and influenza virus RNA can be detected by PCR in respiratory secretions, including upper and lower respiratory specimens. Nasopharyngeal swabs or aspirates are the preferred specimen types for detection of RNA from influenza A, influenza B, and RSV. Nasal swabs have also been shown to provide equivalent yield to nasopharyngeal specimens for molecular detection of influenza A and B RNA, but not RSV RNA.(3-4) Tracheal aspirates are generally not acceptable for testing due to the viscous nature of these specimens.

Useful For: Rapid and accurate detection of influenza A, influenza B, and respiratory syncytial virus in a single test for nasopharyngeal swab specimens

Interpretation: A positive test result indicates that the patient is presumptively infected with the indicated virus. The test does not indicate the stage of infection. Rarely, more than 1 virus may be detected from the same patient specimen. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis. A negative test result suggests that the patient is not infected with influenza A, influenza B, or respiratory syncytial virus (RSV).

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention. Influenza Accessed April 2020. Available at: www.cdc.gov/flu/index.htm 2. Lee N, Lui GC, Wong KT, et al: High morbidity and mortality of adults hospitalized for respiratory syncytial virus infections. Clin Infect Dis 2013;57(8):1069-1077 3. Meerhoff TJ, Houben ML, Coenjaerts FE, et al: Detection of multiple respiratory pathogens during primary respiratory infection: nasal swab versus nasopharyngeal aspirate using real-time polymerase chain reaction. Eur J Clin Microbiol Infect Dis 2010;29:365-371 4. Heikkinen T, Marttila J, Salmi AA, Ruuskanen O: Nasal swab versus nasopharyngeal aspirate for isolation of respiratory viruses. J Clin Microbiol 2002;40(11):4337-4339

ATAXP
617506

Inherited Ataxia Gene Panel, Varies

Clinical Information: Ataxia involves impaired coordination of voluntary muscle movement and can present in isolation or as part of a more complex disease. Additionally, ataxia may present as an abnormality in gait, changes in speech, and abnormal eye movements. The age of onset of symptoms can

vary dramatically both within and across different ataxias. While there are acquired causes of ataxia, many have an underlying genetic cause. The hereditary ataxias can be subdivided by inheritance, including autosomal dominant, autosomal recessive, X-linked, and mitochondrial. The hereditary ataxias are a heterogeneous group of disorders in which a diagnosis can be made based on a neurologic exam, family history, and molecular analysis. Given the clinical overlap of hereditary ataxia disorders, multigene panels can be an efficient and cost-effective way to establish a molecular diagnosis for individuals with ataxia.

Useful For: Establishing a molecular diagnosis for patients with ataxia Identifying variants within genes known to be associated with ataxia, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-424. 2. Sandford E, Burmeister M. Genes and genetic testing in hereditary ataxias. Genes (Basel). 2014;5(3):586-603 3. Jayadev S, Bird TD. Hereditary ataxias: overview. Genet Med. 2013;15(9):673-83

BMFGP
621561

Inherited Bone Marrow Failure Gene Panel, Varies

Clinical Information: Bone marrow failure (BMF) is characterized by the inadequate production of peripheral blood cells, resulting in single cytopenias or pancytopenia. BMF is associated with a loss, or deficient function, of hematopoietic stem or progenitor cells that may occur from a variety of acquired causes including aplastic anemia, myelodysplasia, environmental factors, drugs, and infections. BMF may also be caused by inherited or de novo genetic variants in one or more genes involved in hematopoiesis or bone marrow function. The genetic landscape of inherited BMF is broad. For instance, some of the commonly recognized forms of inherited BMF include Fanconi anemia (caused by germline variants in one of several genes, such as FANCA and FANCC), Schwachman-Diamond syndrome (caused by variants in SBDS, DNAJC21, EFL1, SRP54), dyskeratosis congenita (caused by variants in one of multiple genes related to telomere biology, such as DKC1 and TINF2), and Diamond-Blackfan anemia (caused by variants in one of multiple genes encoding ribosomal subunits, such as RPS19). Other BMF disorders also include GATA2 deficiency (GATA2), MIRAGE (myelodysplasia, infection, growth restriction, adrenal hypoplasia, genital phenotypes, and enteropathy) syndrome (SAMD9), ataxia-pancytopenia syndrome (SAMD9L), severe congenital neutropenia (ELANE, HAX1, G6PC3, GFI1, and others) and congenital amegakaryocytic thrombocytopenia (MPL). In addition to these classically recognized BMF syndromes, variants in a broad spectrum of other genes are associated with inherited forms of cytopenias and BMF. A suspicion for BMF should be raised by the identification of cytopenias with or without related clinical features such as infections, bleeding diathesis, fatigue, pallor, or dyspnea. In addition to hematologic findings, certain inherited BMF syndromes present with additional phenotypic and syndromic features. Importantly, several inherited BMF disorders also confer a predisposition to myeloid malignancies, such as myelodysplastic syndrome and acute myeloid leukemia, as well as other malignancies. The diagnostic investigation of suspected BMF should include a bone marrow study. Bone marrow findings may be variable yet may include abnormalities in cellularity and dysplastic features. In patients with severely reduced cellularity and apparent aplastic

anemia, a genetic etiology should also be considered. The investigation of suspected inherited BMF may also include functional screens, such as assessment of chromosomal breakage and telomere length analysis. Other tests, including viral studies and evaluation for autoimmune conditions or toxins, may also be performed to identify alternate causal factors. Nonetheless, the differential diagnosis of unilineage and multilineage cytopenias is broad, and distinguishing inherited forms of BMF from other underlying etiologies may be challenging. Next-generation sequencing-based genetic panels may be useful in the diagnostic investigation of suspected BMF in concert with the testing and screens described above. Genetic testing for a possible inherited BMF syndrome may be considered in the setting of unexplained peripheral blood cytopenias and bone marrow abnormalities, especially when present during infancy or childhood, although contributory germline variants may be present in adults with BMF as well. The presence of extra hematopoietic features associated with syndromic forms of inherited BMF, such as skeletal abnormalities, leukoplakia, or pancreatic exocrine insufficiency, may also warrant testing. Furthermore, a myeloid malignancy arising at a young age also suggests an underlying genetic etiology, and there is increasing recognition that germline variants in genes associated with inherited forms of BMF also result in predisposition to hematological malignancies in adults. Alternatively, a family history of the clinical features or conditions described above may also suggest an underlying genetic basis for BMF. In addition to diagnostic considerations, the identification of underlying hereditary variants in BMF carries important management implications. For instance, it may inform surveillance for malignancies and organ dysfunction in the setting of variants in genes associated with a risk for other clinical features and complications. Additionally, several forms of inherited BMF may confer a predisposition to myeloid malignancies that exhibit distinct sensitivity to cytotoxic therapy. Accordingly, the detection of certain germline variants may also guide treatment approaches including the selection of systemic therapy and conditioning regimens for hematopoietic stem cell transplantation. The identification of underlying inherited variants is also important for the optimal choice of donors for transplantation as related donors may share deleterious variants. Finally, detection of germline genetic variants associated with disease allows for familial testing to identify other individuals at risk of developing disease. Note that testing of peripheral blood in patients with bone marrow failure, particularly in the setting of hematopoietic malignancy, may identify germline genetic variants and/or somatic mutations. This test is unable to definitively differentiate between germline variants and somatic mutations when performed on blood, bone marrow, or saliva specimens; however, testing may be performed on fibroblasts derived from a skin biopsy to aid in this differentiation.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of a hereditary bone marrow failure syndrome Establishing a diagnosis of a hereditary bone marrow failure syndrome associated with known causal genes Identifying variants within genes known to be associated with heritable bone marrow syndromes, allowing for predictive testing of at-risk family members and/or determination of targeted management (anticipatory guidance, management changes, specific therapies)

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. 2. Dokal I, Tummala H, Vulliamy T. Inherited bone marrow failure in the pediatric patient. Blood. 2022;140(6):556-570. doi:10.1182/blood.2020006481 3. DeZern AE, Churpek JE. Approach to the diagnosis of aplastic anemia. Blood Adv. 2021;5(12):2660-2671. doi:10.1182/bloodadvances.2021004345 4. Duncavage EJ, Bagg A, Hasserjian RP, et al. Genomic

profiling for clinical decision making in myeloid neoplasms and acute leukemia. Blood. 2022;140(21):2228-2247. doi:10.1182/blood.2022015853 5. Feurstein S, Trottier AM, Estrada-Merly N, et al. Germ line predisposition variants occur in myelodysplastic syndrome patients of all ages. Blood. 2022;140(24):2533-2548. doi:10.1182/blood.2022015790 6. Keel S, Geddis A. The clinical and laboratory evaluation of patients with suspected hypocellular marrow failure. Hematology Am Soc Hematol Educ Program. 2021;2021(1):134-142. doi:10.1182/hematology.2021000244 7. Weinzierl EP, Arber DA. The differential diagnosis and bone marrow evaluation of new-onset pancytopenia. Am J Clin Pathol. 2013;139(1):9-29. doi:10.1309/AJCP50AEEYGREWUZ

CMSP
617519

Inherited Congenital Myasthenic Syndrome Gene Panel, Varies

EDMDP
617558

Inherited Emery-Dreifuss Gene Panel, Varies

Clinical Information: Emery-Dreifuss muscular dystrophy typically presents in early childhood and is characterized by a triad of early contractures, slowly progressive muscle weakness and atrophy, and cardiac abnormalities. Joint contractures usually being in early childhood and predominate in the elbows, ankles, and posterior cervical muscles. Muscle wasting and atrophy typically become evident by the second or third decade and initially follows a humeroperoneal distribution. Later in the course of disease the scapular and pelvic girdle muscles become affected. The most common cardiac manifestations include atrial tachyarrhythmias, atrial standstill, ventricular tachyarrhythmias, and cardiomyopathy. Age of onset and disease severity demonstrate inter- and intrafamilial variability.

Useful For: Establishing a molecular diagnosis for patients with Emery-Dreifuss muscular dystrophy Identifying variants within genes known to be associated with Emery-Dreifuss muscular dystrophy, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-424. 2. Heller SA, Shih R, Kalra R, Kang PB: Emery-Dreifuss muscular dystrophy. Muscle Nerve. 2020;61(4):436-448

AFTDP
617493

Inherited Frontotemporal Dementia and Amyotrophic Lateral Sclerosis Gene Panel, Varies

Clinical Information: Frontotemporal dementia (FTD) is a progressive neurodegenerative syndrome that affects the frontal and temporal cerebral cortices. Clinical presentation is variable and includes changes in behavior, difficulties with language, rigidity, palsy, and saccadic (rapid) eye movement. Symptoms generally begin between 40 and 60 years of age, with a mean age of onset at approximately 45 years. They typically last between 5 and 10 years, progressing to severe dementia and mutism. The presentation of frontotemporal dementia may be confused with other dementias, including

Alzheimer disease. It is important to distinguish between these different dementias because progression and patient management are different for the various dementias. Amyotrophic lateral sclerosis (ALS) is a motor neuron disease with progressive loss of upper and lower motor neurons. ALS typically presents with progressive muscle wasting, hyperreflexia, and spasticity. Death from respiratory failure usually occurs within 3 to 5 years of disease onset. Frontotemporal dementia and ALS are thought to represent a continuous disease spectrum. However, the molecular mechanism underlying the co-occurrence of FTD and ALS remains unclear. In some individuals ALS occurs first, while in others FTD precedes ALS by several years. Between 40% and 50% of individuals with ALS present with an FTD-associated clinical phenotype. Given the clinical overlap of FTD and ALS, this multigene panel includes genes associated with FTD and ALS.

Useful For: Establishing a molecular diagnosis for patients with frontotemporal dementia (FTD) and/or amyotrophic lateral sclerosis (ALS) Identifying variants within genes known to be associated with FTD and/or ALS, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

C9orf72 Repeats:
Normal alleles (reference): <20 GGGGCC repeats
Indeterminate alleles: 20-100 GGGGCC repeats
Pathogenic alleles:* >100 GGGGCC repeats

*The exact cutoff for pathogenicity is currently undefined. Although additional studies are needed to confirm if the cutoff for pathogenicity is 100 repeats, most individuals affected with a C9orf72-related disorder have C9orf72 hexanucleotide repeat expansions with hundreds to thousands of repeats.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Graff-Radford NR, Woodruff BK. Frontotemporal dementia. Semin Neurol. 2007;27(1):48-57 3. Karch CM, Wen N, Fan CC, et al. Selective genetic overlap between amyotrophic lateral sclerosis and diseases of the frontotemporal dementia spectrum. JAMA Neurol. 2018;75(7):860-875 4. Benatar M, Heiman-Patterson TD, Cooper-Knock J, et al. Guidance for clinical management of pathogenic variant carriers at elevated genetic risk for ALS/FTD. J Neurol Neurosurg Psychiatry. Published online January 31, 2025 5. Chambers C, Lichten L, Crook A, Uhlmann WR, Dratch L. Incorporating genetic testing into the care of patients with amyotrophic lateral sclerosis/frontotemporal degeneration spectrum disorders. Neurol Clin Pract. 2023;13(5):e200201

LGCMP
617623

Inherited Limb-Girdle Muscular Dystrophy and Congenital Myasthenic Syndrome Gene Panel, Varies

Clinical Information: The limb-girdle muscular dystrophies (LGMD) are a heterogeneous group of muscular dystrophies that show progressive weakness and muscle atrophy, predominantly affecting the hips, shoulders, and proximal extremity muscles. There is wide variability in age of onset, severity, and clinical presentation within the LGMD spectrum. Congenital myasthenic syndromes occur as a result of compromised neuromuscular transmission. Clinical manifestations include fatigable weakness involving

ocular, bulbar, and limb muscles. The severity and disease course are highly variable, but individuals usually present in infancy or early childhood. The clinical phenotype associated with a neonatal onset can include feeding difficulties, poor suck and cry, choking spells, eyelid ptosis, and muscle weakness. The clinical phenotype associated with a later childhood onset can include abnormal muscle fatigue, delayed motor milestones, ptosis, and extraocular muscle weakness. The clinical overlap of limb-girdle muscular dystrophy and limb-girdle congenital myasthenic syndromes can make these conditions difficult to distinguish clinically. Misdiagnoses can lead to diagnostic delays of several decades, impacting prognostic predictions and appropriate management. This multigene panel can be an efficient and cost-effective way to establish a molecular diagnosis.

Useful For: Establishing a molecular diagnosis for patients with limb-girdle muscular dystrophy or congenital myasthenic syndrome Identifying variants within genes known to be associated with limb-girdle muscular dystrophy or congenital myasthenic syndrome, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Nicolau S, Milone M, Liewluck T. Guidelines for genetic testing of muscle and neuromuscular junction disorders. Muscle Nerve. 2021;64(3):255-269 3. Mitsuhashi S, Kang PB. Update on the genetics of limb girdle muscular dystrophy. Semin Pediatr Neurol. 2012;19(4):211-218. 4. Iyadurai SJP. Congenital myasthenic syndromes. Neurol Clin. 2020;38(3):541-552

IMSNP
617584

Inherited Motor and Sensory Neuropathy Gene Panel, Varies

Clinical Information: Hereditary motor and sensory neuropathy, or Charcot-Marie-Tooth (CMT) disease, is a major category of inherited peripheral neuropathies and is the most frequently inherited neuromuscular disorder. Individuals with CMT typically present with slowly progressive muscle weakness and atrophy primarily affecting the distal extremities. Traditionally, the classification of CMT was based on nerve conduction velocity (NCV) and inheritance. The three neuropathy types based on NCV include demyelinating, axonal (non-demyelinating), and dominant intermediate CMT. Demyelinating CMT has a NCV less than 35 m/s and involves slowly progressive muscle weakness and atrophy and sensory loss. Often it can include pes cavus foot deformity and bilateral foot drop. Axonal CMT has a NCV greater than 45 m/s and includes distal muscle weakness and atrophy. Individuals tend to be less disabled and have less sensory loss than those with demyelinating neuropathy. Dominant-intermediate CMT has a NCV of 35 to 45 m/s and is consistent with a typical CMT phenotype. If a tiered testing approach is preferred, healthcare professionals for individuals with demyelinating polyneuropathy and an autosomal dominant family history of similar features can consider ordering testing for large deletions and duplications in the PMP22 gene (PMPDD / PMP22 Gene, Large Deletion/Duplication Analysis, Varies) as a first-tier test. However, copy number variants involving PMP22 would also be identified by this assay. Duplications in the PMP22 gene account for as much as 50% of all CMT.

Useful For: Establishing a molecular diagnosis for patients with hereditary motor and sensory

neuropathy (HMSN) or Charcot-Marie-Tooth (CMT) disease Identifying variants within genes known to be associated with HMSN or CMT disease, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Klein CJ. Charcot-Marie-Tooth disease and other hereditary neuropathies. Continuum (Minneap Minn). 2020;26(5):1224-1256 3. Bird TD. Charcot-Marie-Tooth hereditary neuropathy In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated January 23, 2025. Accessed March 24, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1358/ 4. Pisciotta C, Bertini A, Tramacere I, et al. Clinical spectrum and frequency of Charcot-Marie-Tooth disease in Italy: Data from the National CMT Registry. Eur J Neurol. 2023;30(8):2461-2470. doi:10.1111/ene.15860

MNDP
617649

Inherited Motor Neuron Disease Gene Panel, Varies

Clinical Information: Motor neuron diseases (MND) selectively affect the motor neurons with degeneration. MND include primary lateral sclerosis (PLS), primary muscular atrophy (PMA), and amyotrophic lateral sclerosis (ALS). In PLS and PMA, the motor neuron degeneration is limited to the upper motor neuron and lower motor neuron, respectively. The clinical phenotype of PLS can include gradual progressive leg weakness and spasticity and spastic bulbar weakness. In ALS, the most frequent form of MND, degeneration involves both upper and lower motor neurons and results in progressive muscle weakness, paralysis, and death from respiratory failure. Onset typically occurs in late middle life, with death occurring usually within 3 to 5 years of disease onset. A hexanucleotide repeat expansion in a noncoding region of the C9orf72 gene is the most common cause of inherited ALS, which is assessed for by this test.

Useful For: Establishing a molecular diagnosis for patients with motor neuron disease Identifying variants within genes known to be associated with motor neuron disease, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

C9orf72 Repeats:
Normal alleles (reference):<20 GGGGCC repeats
Indeterminate alleles: 20-100 GGGGCC repeats
Pathogenic alleles:* >100 GGGGCC repeats

*The exact cutoff for pathogenicity is currently undefined. Although additional studies are needed to confirm if the cutoff for pathogenicity is 100 repeats, most individuals affected with a C9orf72-related disorder have C9orf72 hexanucleotide repeat expansions with hundreds to thousands of repeats.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Hardiman O, Al-Chalabi A, Chio A, et al. Amyotrophic lateral sclerosis. Nat Rev Dis Primers. 2017;3:17071 3. Mejzini R, Flynn LL, Pitout IL, Fletcher S, Wilton SD, Akkari PA. ALS Genetics, mechanisms, and therapeutics: Where are we now?. Front Neurosci. 2019;13:1310

IMNP
617571

Inherited Motor Neuropathy Gene Panel, Varies

Clinical Information: Distal hereditary motor neuropathies (dHMN) are one of the major categories of peripheral inherited neuropathies and are characterized by length-dependent lower motor neuron dysfunction. The clinical phenotype is variable but includes progressive weakness and atrophy of the distal muscles, foot deformities, and decreased reflexes. While there is significant phenotypic overlap with hereditary motor and sensory neuropathy/Charcot-Marie-Tooth disease, sensory loss is usually mild or absent in dHMN. Most individuals develop symptoms in childhood or adolescence.

Useful For: Establishing a molecular diagnosis for patients with distal hereditary motor neuropathy (dHMN) Identifying variants within genes known to be associated with dHMN, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Klein CJ. Charcot-Marie-Tooth disease and other hereditary neuropathies. Continuum (Minneap Minn). 2020;26(5):1224-1256 3. Beijer D, Baets J. The expanding genetic landscape of hereditary motor neuropathies. Brain. 2020;143(12):3540-3563 4. Rossor AM, Kalmar B, Greensmith L, Reilly MM. The distal hereditary motor neuropathies. J Neurol Neurosurg Psychiatry. 2012;83(1):6-14

MDYSP
617636

Inherited Muscular Dystrophy Gene Panel, Varies

Clinical Information: Muscular dystrophies are a heterogeneous group of neuromuscular conditions characterized by skeletal muscle wasting due to muscle dysfunction. The muscular dystrophies can be subdivided into the dystrophinopathies: Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophies, distal myopathies, and congenital muscular dystrophies. A clinical diagnosis is typically based on distribution and severity of muscular involvement, mode of inheritance, and other associated symptoms. The dystrophinopathies include Duchenne muscular dystrophy and Becker muscular dystrophy. These 2 forms are inherited in an X-linked manner and typically present with variable degrees of a limb-girdle pattern of weakness and can develop dilated cardiomyopathy. Emery-Dreifuss muscular dystrophy is characterized by the triad of joint contractures, slowly progressive muscle weakness and wasting, and cardiac involvement. Limb-girdle muscular dystrophy is characterized by weakness and wasting predominately of the hips, shoulders, and proximal extremity muscles. Distal myopathies are disorders with weakness and atrophy predominantly in the distal

muscles. Congenital muscular dystrophies are progressive early-onset muscle disorders that often have brain and other organ involvement. They are characterized by hypotonia, delayed motor development, and progressive weakness. Given the clinical overlap of muscular dystrophies, multigene panels can be an efficient and cost-effective way to establish a molecular diagnosis for individuals who are symptomatic.

Useful For: Establishing a molecular diagnosis for patients with muscular dystrophy Identifying variants within genes known to be associated with muscular dystrophy, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Hermans MC, Pinto YM, Merkies IS, et al. Hereditary muscular dystrophies of the heart. Neuromuscul Disord. 2010;20(8):479-492 3. Wicklund MP, Kissel JT. The limb-girdle muscular dystrophies. Neurol Clin. 2014;32(3):729-749 4. Flanigan KM. The muscular dystrophies. Semin Neurol. 2012;32(3):255-263 5. Iannaccone ST, Castro D. Congenital muscular dystrophies and congenital myopathies. Continuum (Minneap Minn). 2013;19(6 Muscle Disease):1509-1534

PARDP
617675

Inherited Parkinson Disease Gene Panel, Varies

Clinical Information: Parkinson disease is the second most common neurodegenerative movement disorder, and is characterized by rest tremor, muscle rigidity, bradykinesia, and postural instability. The most common nonmotor features include olfactory dysfunction, cognitive impairment, psychiatric symptoms, and autonomic dysfunction. Onset of disease is commonly around 60 years, but the juvenile form can have onset prior to age 20 years. Early-Parkinson disease has an onset between 20 to 50 years, and late-onset Parkinson disease occurs after age 50 years. The clinical diagnosis is based on parkinsonian motor features, namely bradykinesia plus rigidity and resting tremor. Parkinson disease results from interplay between nongenetic and genetic factors. Risk factors for Parkinson disease include sex, ethnicity, age, and environmental exposures. However, genetic factors are increasingly recognized as causative, with both known monogenic causes and susceptibility genes known.

Useful For: Establishing a molecular diagnosis for patients with Parkinson disease Identifying variants within genes known to be associated with Parkinson disease, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-424. 2. Deng H, Wang P, Jankovic J. The genetics of Parkinson disease. Ageing Res Rev. 2018;42:72-85 3. Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015;386(9996):896-912

RABMP 617701 Inherited Rhabdomyolysis and Metabolic Myopathy Panel, Varies

Clinical Information: Rhabdomyolysis results from the rapid breakdown of skeletal muscle fibers, which leads to leakage of potentially toxic cellular contents into the blood stream. The clinical severity can range from asymptomatic creatine kinase elevation to a life-threatening disease. The clinical features include acute-onset myalgia, transient muscle weakness, and pigmenturia. Genetic causes of rhabdomyolysis include metabolic myopathy, mitochondrial disorders, disorders of intramuscular calcium release, and muscular dystrophies. Metabolic myopathies are a diverse group of inherited biochemical diseases involving limitation of the use of fuels by skeletal muscle to generate energy. Metabolic myopathies include disorders of fatty acid oxidation, disorders of glycogen and glucase metabolism, and mitochondrial respiratory chain disease. Biochemical testing in multiple tissue types, including blood, urine, and muscle, can help to determine which category of muscle disease is most likely. Disorders of fatty acid oxidation are one category of metabolic myopathies characterized by hypoketotic hypoglycemia, hepatic dysfunction, skeletal myopathy, dilated and hypertrophic cardiomyopathy, and sudden or unexpected death. Mitochondrial fatty acid beta-oxidation plays an important role in energy production, particularly in skeletal and heart muscle, and in hepatic ketone body formation during periods of fasting. Biochemical testing such as urine organic acids, plasma acylcarnitines, and fatty acids can aid in diagnosis. These test results are influenced by dietary factors and the clinical status of the patient, which often leads to incomplete diagnostic information or even false-negative results. Disorders of glycogen and glucose metabolism are another category of metabolic myopathies primarily affecting muscle and resulting in exercise intolerance, recurrent rhabdomyolysis, and myoglobinuria. Creatine kinase level is typically elevated during a major event. Muscle biopsy is often performed to verify absence of enzyme activity for the specific type of glycogenosis disease. Polyglucosan body disease involves progressive neurogenic bladder, spasticity and weakness causing gait difficulties from either primary muscle or nerve involvements, sensory loss mainly in the distal lower extremities, and mild cognitive difficulties such as executive dysfunction. Mitochondrial myopathies due to coenzyme Q10 deficiency are a group of heterogenous diseases. These mitochondrial diseases are characterized by muscle weakness, exercise intolerance, elevated creatine kinase, and abnormal muscle biopsy findings.

Useful For: Establishing a molecular diagnosis for patients with rhabdomyolysis and metabolic myopathy Identifying variants within genes known to be associated with rhabdomyolysis and metabolic myopathy, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med.

2015;17(5):405-424 2. Scalco RS, Gardiner AR, Pitceathly RD, et al. Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis. 2015 2;10:51

ISNP
617597

Inherited Sensory Neuropathy Gene Panel, Varies

Clinical Information: The hereditary sensory and autotomic neuropathies (HSAN), or hereditary sensory neuropathies (HSN) if autonomic dysfunction is absent, are one of the major categories of inherited peripheral neuropathies. They predominantly feature slowly progressive loss of multimodal sensation and autonomic dysfunction. The HSAN have a range of phenotypes from pure sensory involvement through phenotypes with levels of motor involvement and minor autonomic disturbances, to almost pure autonomic neuropathies. The most common features of HSAN include the loss of sensation of pain and temperature. The hereditary sensory and autotomic neuropathies are subdivided into types 1 through 5 based on age of onset, inheritance pattern, and clinical features. HSAN type 1 follows an autosomal dominant inheritance pattern with juvenile through adult onset. Clinically this group is variable but can include severe sensory loss and autonomic dysfunction. HSAN type 2 follows an autosomal recessive inheritance pattern with onset in infancy or early childhood. This group is predominantly a sensory neuropathy with distal numbness and progressive loss of pain, temperature, and touch sensation. Motor involvement is not common in patients with HSAN type II. HSAN type 3 is also called familial dysautonomia and has autosomal recessive inheritance. Patients present with prominent, widespread autonomic disturbances, as well as small-fiber sensory dysfunction. HSAN type 4 is also called congenital insensitivity to pain with anhidrosis and has autosomal recessive inheritance. HSAN type 5 strongly resembles HSAN type 4, but patients show hypohidrosis instead of anhidrosis and do not have intellectual disability.

Useful For: Establishing a molecular diagnosis for patients with hereditary sensory (HSN) and autonomic neuropathy (HSAN) Identifying variants within genes known to be associated with HSN and HSAN, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Schwartzlow C, Kazamel M. Hereditary sensory and autonomic neuropathies: Adding more to the classification. Curr Neurol Neurosci Rep. 2019;19(8):52 3. Rotthier A, Baets J, Timmerman V, Janssens K. Mechanisms of disease in hereditary sensory and autonomic neuropathies. Nat Rev Neurol. 2012;8(2):73-85 4. Klein CJ. Charcot-Marie-Tooth disease and other hereditary neuropathies. Continuum (Minneap Minn). 2020;26(5):1224-1256

SMCP
617727

Inherited Skeletal Muscle Channelopathy Gene Panel, Varies

Clinical Information: Skeletal muscle channelopathies are neuromuscular disorders with onset predominantly in childhood and are characterized by episodic symptoms of either myotonia or paralysis. Skeletal muscle channelopathies can be divided into nondystrophic myopathies and periodic paralyses. The nondystrophic myotonias include myotonia congenita, paramyotonia congenita, and sodium channel

myotonia and are characterized by muscle stiffness generated by voluntary movement. Other features include transient or prolonged weakness, pain associated with myotonia, and fatigue. The periodic paralyses include hyperkalemic periodic paralysis, hypokalemic periodic paralysis, and Andersen-Tawil syndrome and are characterized by episodic attacks of weakness, often triggered by diet or rest after exercise.

Useful For: Establishing a molecular diagnosis for patients with a skeletal muscle channelopathy
Identifying variants within genes known to be associated with a skeletal muscle channelopathy allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30 2. Vivekanandam V, Munot P, Hanna MG, Matthews E. Skeletal Muscle Channelopathies. Neurol Clin. 2020;38(3):481-491. doi:10.1016/j.ncl.2020.04.003 3. Matthews E, Holmes S, Fialho D. Skeletal muscle channelopathies: a guide to diagnosis and management. Pract Neurol. 2021;21(3):196-204. doi:10.1136/practneurol-2020-002576

ISPP
617610

Inherited Spastic Paraplegia Gene Panel, Varies

Clinical Information: Hereditary spastic paraplegias (HSP) are a group of neurodegenerative disorders characterized by progressive lower extremity weakness and spasticity, both of which can be variable. Other common neurological symptoms include ataxia, cognitive impairment, neuropathy, seizures, and dysarthria. If onset of symptoms occurs in very early childhood, symptoms may be nonprogressive and resemble spastic digenic cerebral palsy. If the onset of symptoms occurs in later childhood or after, symptoms usually progress slowly and steadily. Clinically HSP are classified in an uncomplicated or pure form and a complicated or complex form. The uncomplicated form presents with progressive lower-extremity spastic weakness, corticospinal tract signs, variable hypertonic urinary bladder disturbance, and disturbance in vibration sense and proprioception. The complicated form is characterized by the impairments present in uncomplicated HSP plus other system involvement or other neurologic findings. Additionally, the complicated form usually follows an autosomal recessive inheritance pattern, while the uncomplicated form predominantly follows an autosomal dominant inheritance pattern. Given HSP are a heterogeneous group of disorders, multigene panels can be an efficient and cost-effective way to establish a molecular diagnosis for symptomatic individuals.

Useful For: Establishing a molecular diagnosis for patients with hereditary spastic paraplegia
Identifying variants within genes known to be associated with hereditary spastic paraplegia, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Murala S, Nagarajan E, Bollu PC. Hereditary spastic paraplegia. Neurol Sci. 2021;42(3):883-894

INHAB
86336

Inhibin A and B, Tumor Marker, Serum

Clinical Information: Inhibins are heterodimeric protein hormones secreted by granulosa cells of the ovary and Sertoli cells of the testis. They selectively suppress secretion of pituitary follicle stimulating hormone (FSH) and have local paracrine actions in the gonads. The inhibins consist of a dimer of 2 homologous subunits, an alpha subunit and either a beta A or beta B subunit, to form inhibin A and inhibin B, respectively. In female individuals, inhibin A is primarily produced by the dominant follicle and corpus luteum; whereas inhibin B is predominantly produced by small developing follicles. Serum inhibin A and B levels fluctuate during the menstrual cycle. Inhibin A is low in the early follicular phase and rises at ovulation to maximum levels in the midluteal phase. In contrast, inhibin B levels increase early in the follicular phase to reach a peak coincident with the onset of the mid-follicular phase decline in FSH levels. Inhibin B levels decrease in the late follicular phase. There is a short-lived peak of the hormone 2 days after the midcycle luteinizing hormone (LH) peak. Inhibin B levels remain low during the luteal phase of the cycle. The timing of the inhibin B rise suggests that it plays a role in regulation of folliculogenesis via negative feedback on the production of FSH. At menopause, with the depletion of ovarian follicles, serum inhibin A and B decrease to very low or undetectable levels. Ovarian cancer is classified into 3 types: epithelial (80%), germ cell tumors (10%-15%), and stromal sex-cord tumors (5%-10%). Epithelial ovarian tumors are further subdivided into serous (70%), mucinous (10%-15%), and endometrioid (10%-15%) types. Granulosa cell tumors represent the majority of the stromal sex cord tumors. Elevations of serum inhibin A and B are detected in some patients with granulosa cell tumors. Inhibin A elevations have been reported in approximately 70% of granulosa cell tumors. In these patients, inhibin A levels tend to show a 6-fold to 7-fold increase over the reference range value. Inhibin B elevations have been reported in 89% to 100% of patients with granulosa cell tumors. In these patients, inhibin B levels tend to be elevated about 60-fold over the reference range value. The frequency of elevated levels varies amongst studies, likely due to the different specificities of the antibodies used in the immunoassays. Inhibin A and B also appear to be suitable serum markers for epithelial tumors of the mucinous type, with about 20% of cases having elevated inhibin A levels and 55% to 60% of cases having elevated inhibin B levels. In contrast, inhibin is not a very good marker in nonmucinous epithelial tumors. At best, total inhibin is elevated in 15% to 35% of nonmucinous epithelial ovarian cancer cases. Inhibin seems to be a complementary to cancer antigen 125 (CA 125) as an ovarian cancer marker. CA 125 is not as good of a tumor marker for mucinous and granulosa ovarian cell tumors. Inhibin shows a better performance in those 2 types of ovarian cancer. The majority of studies for inhibin A and B as ovarian cancer markers have been limited to postmenopausal women where the levels for both proteins are normally very low. Inhibin levels vary in relation to the menstrual cycle and, therefore, are difficult to interpret in premenopausal women. Inhibin B has also been used as a marker of ovarian reserve. Every female is born with a specific number of follicles containing oocytes, a number that steadily and naturally declines with age. The number of follicles remaining in the ovary at any time is called the ovarian reserve. As ovarian reserve diminishes, it is increasingly more difficult for the hormones used for in vitro fertilization (IVF) to stimulate follicle development and, thus, the likelihood of successful oocyte retrieval, fertilization, and embryo transfer decreases, all leading to a lower chance of conceiving. As part of an infertility evaluation, attempts are made to estimate a woman's ovarian reserve. Tests to assess ovarian reserve include the following: day 3 FSH, day 3 inhibin B, and anti-mullerian hormone levels. The amount of inhibin B measured in serum during the early follicular phase of the menstrual cycle (day 3) directly reflects the number of follicles in the ovary. Therefore, the higher the inhibin B, the more

ovarian follicles present. The level of inhibin B that predicts a poor response to IVF treatment has not been established with this assay. In male patients, inhibin B levels are higher in those with apparently normal fertility than in those with infertility and abnormal spermatogenesis. Serum inhibin B, when used in combination with FSH, is a more sensitive marker of spermatogenesis than FSH alone. However, the optimal level of inhibin B to assess male infertility has not been established.

Useful For: Aiding in the diagnosis of granulosa cell tumors and mucinous epithelial ovarian tumors
Monitoring of patients with granulosa cell tumors and epithelial mucinous-type tumors of the ovary known to secrete inhibin A or overexpress inhibin B

Interpretation: Inhibin A levels are elevated in approximately 70% of patients with granulosa cell tumors and in approximately 20% of patients with epithelial ovarian tumors. Inhibin B levels are elevated in approximately 89% to 100% of patients with granulosa cell tumors and in approximately 55% to 60% of patients with epithelial ovarian tumors. A normal inhibin A or B level does not rule out a mucinous or granulosa ovarian cell tumor. For monitoring of patients with known ovarian cancer, inhibin A and B levels decrease shortly after surgery. Elevations of inhibin A or B after treatment are suggestive of residual, recurrent, or progressive disease. In patients with recurrent disease, inhibin A or B elevation seems to be present earlier than clinical symptoms. Patients in remission show normal levels of inhibin A and B. For infertility evaluation, an inhibin B level in the postmenopausal range is suggestive of a diminished or depleted ovarian reserve.

Reference Values:
INHIBIN A, TUMOR MARKER
Males: <5.0 pg/mL

Females
<11 years: <5.0 pg/mL
11-17 years: <98 pg/mL
Premenopausal: <98 pg/mL
Postmenopausal: <5.0 pg/mL

INHIBIN B
Males
<15 days: 68-373 pg/mL
15-180 days: 42-516 pg/mL
6 months-7 years: 24-300 pg/mL
8-30 years: 47-383 pg/mL
31-72 years: <358 pg/mL
>72 years: Not established

Females
< or =12 years: <183 pg/mL
13-41 years regular Cycle (Follicular Phase): <224 pg/mL
42-51 years regular Cycle (Follicular Phase): <108 pg/mL
13-51 years regular Cycle (Luteal Phase): <80 pg/mL
>51 years (Postmenopausal): <12 pg/mL

Clinical References: 1. Mom CH, Engelen MJA, Willemse PHB, et al. Granulosa cell tumors of the ovary: the clinical value of serum inhibin A and B levels in a large single center cohort. Gynecol Oncol. 2007;105(2):365-372 2. Robertson DM, Pruysers E, Jobling T. Inhibin as a diagnostic marker for ovarian cancer. Cancer Lett. 2007;249(1):14-17 3. Jamieson S, Fuller PJ: Management of granulosa cell tumour of the ovary. Curr Opin Oncol. 2008;20(5):560-564 4. Sturgeon C. Tumor markers. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:436-478 5. Yarbrough ML, Stout M, Gronowski AM. Pregnancy and its disorders.

In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1655-1696 6. Makanji Y, Zhu J, Mishra R, et al. Inhibin at 90: from discovery to clinical application, a historical review. Endocr Rev. 2014;35(5):747-794. doi:10.1210/er.2014-1003 7. Walentowicz P, Krintus M, Sadlecki P, et al. Serum inhibin A and inhibin B levels in epithelial ovarian cancer patients. PLoS One. 2014;9(3):e90575. doi:10.1371/journal.pone.0090575

INHA
81049

Inhibin A, Tumor Marker, Serum

Clinical Information: Inhibins are heterodimeric protein hormones secreted by granulosa cells of the ovary and Sertoli cells of the testis. They selectively suppress secretion of pituitary follicle stimulating hormone and have local paracrine actions in the gonads. The inhibins consist of a dimer of 2 homologous subunits, an alpha subunit and either a beta A or beta B subunit, to form inhibin A and inhibin B, respectively. In female individuals, inhibin A is primarily produced by the dominant follicle and corpus luteum; whereas inhibin B is predominantly produced by small developing follicles. Serum inhibin A and B levels fluctuate during the menstrual cycle. At menopause, with the depletion of ovarian follicles, serum inhibin A and B decrease to very low or undetectable levels. Ovarian cancer is classified into 3 types: epithelial, stromal sex cord, and germ cell tumors. Epithelial ovarian tumors account for 90% of cases and are further subdivided into serous (70%), mucinous (10%-15%), and endometrioid (10%-15%) types. Granulosa cell tumors represent the majority of the stromal sex cord tumors, which account for 2% to 5% of all ovarian tumors. Elevations of serum inhibin A and B are detected in some patients with granulosa cell tumors. Inhibin A elevations have been reported in approximately 70% of granulosa cell tumors. In these patients, inhibin A levels tend to show a 6-fold to 7-fold increase over the reference range value. The frequency of elevated levels varies amongst studies, likely due to the different specificities of the antibodies used in the immunoassays. Inhibin A also appears to be a suitable marker for epithelial tumors of the mucinous type with about 20% of cases having elevated inhibin A levels. In contrast, inhibin is not a very good marker in nonmucinous epithelial tumors. At best, total inhibin is elevated in 15% to 35% of nonmucinous epithelial ovarian cancer cases. Inhibin seems to be complementary to cancer antigen 125 (CA 125) as an ovarian cancer marker. CA 125 is not as good of a tumor marker for mucinous and granulosa ovarian cell tumors. Inhibin shows a better performance in those 2 types of ovarian cancer. The majority of studies for inhibin A and B as ovarian cancer markers have been limited to postmenopausal women where the levels for both proteins are normally very low. Inhibin A has limited utility as an ovarian cancer marker in premenopausal women, where circulating levels are higher and fluctuate throughout the menstrual cycle and, therefore, are difficult to interpret.

Useful For: Aiding in the diagnosis of patients with granulosa cell tumors of the ovary when used in combination with inhibin B Monitoring of patients with granulosa cell tumors and epithelial mucinous-type tumors of the ovary known to secrete inhibin A

Interpretation: Inhibin A levels are elevated in approximately 70% of patients with granulosa cell tumors and in approximately 20% of patients with epithelial ovarian tumors. A normal inhibin A level does not rule out a mucinous or granulosa ovarian cell tumor. Testing for inhibin B in these cases might be informative as a higher proportion of mucinous or granulosa ovarian cell tumors will have an elevated inhibin B level. Consider ordering INHAB / Inhibin A and B, Tumor Marker, Serum. For monitoring of patients with known ovarian cancer, inhibin A levels decrease shortly after surgery. Elevations of inhibin A after treatment are suggestive of residual, recurrent, or progressive disease. In patients with recurrent disease, inhibin A elevation seems to be present earlier than clinical symptoms. Patients in remission show normal levels of inhibin A.

Reference Values:
Males: <5.0 pg/mL

Females
<11 years: <5.0 pg/mL
11-17 years: <98 pg/mL
Premenopausal: <98 pg/mL
Postmenopausal: <5.0 pg/mL

Clinical References: 1. Mom CH, Engelen MJA, Willemse PHB, et al. Granulosa cell tumors of the ovary: the clinical value of serum inhibin A and B levels in a large single center cohort. Gynecol Oncol. 2007;105(2):365-372 2. Robertson DM, Pruysers E, Jobling T. Inhibin as a diagnostic marker for ovarian cancer. Cancer Lett. 2007;249(1):14-17 3. Jamieson S, Fuller PJ. Management of granulosa cell tumour of the ovary. Curr Opin Oncol. 2008;20(5):560-564 4. Sturgeon C. Tumor markers. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:436-478 5. Yarbrough ML, Stout M, Gronowski AM. Pregnancy and its disorders. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1655-1696 6. Makanji Y, Zhu J, Mishra R, et al. Inhibin at 90: from discovery to clinical application, a historical review. Endocr Rev. 2014;35(5):747-794. doi:10.1210/er.2014-1003 7. Walentowicz P, Krintus M, Sadlecki P, et al. Serum inhibin A and inhibin B levels in epithelial ovarian cancer patients. PLoS One. 2014;9(3):e90575. doi:10.1371/journal.pone.0090575

INHB
88722

Inhibin B, Serum

Clinical Information: Inhibins are heterodimeric protein hormones secreted by granulosa cells of the ovary and Sertoli cells of the testis. Inhibins selectively suppress secretion of pituitary follicle-stimulating hormone (FSH) and have local paracrine actions in the gonads. The inhibins consist of a dimer of 2 homologous subunits, an alpha subunit and either a beta A or beta B subunit, to form inhibin A and inhibin B, respectively. In female individuals, inhibin A is primarily produced by the dominant follicle and corpus luteum, whereas inhibin B is primarily produced by small developing follicles. Serum inhibin A and B levels fluctuate during the menstrual cycle. Inhibin A is low in the early follicular phase and rises at ovulation to maximum levels in the mid-luteal phase. In contrast, inhibin B levels increase early in the follicular phase to reach a peak coincident with the onset of the mid-follicular phase decline in FSH levels. Inhibin B levels decrease in the late follicular phase. There is a short-lived peak of the hormone 2 days after the midcycle luteinizing hormone (LH) peak. Inhibin B levels remain low during the luteal phase of the cycle. The timing of the inhibin B rise suggests that it plays a role in regulation of folliculogenesis via negative feedback on the production of FSH. At menopause, with the depletion of ovarian follicles, serum inhibin A and B decrease to very low or undetectable levels. Ovarian cancer is classified into 3 types: epithelial (80%), germ cell tumors (10%-15%), and stromal sex-cord tumors (5%-10%). Epithelial ovarian tumors are further subdivided into serous (70%), mucinous (10%-15%), and endometrioid (10%-15%) types. Granulosa cell tumors represent the majority of stromal sex-cord tumors. Elevations of serum inhibin A and B are detected in some patients with granulosa cell tumors. Inhibin B elevations have been reported in 89% to 100% of patients with granulosa cell tumors. In these patients, inhibin B levels tend to be elevated about 60-fold over the reference range value. The frequency of elevated levels varies amongst studies, likely due to the different specificities of the antibodies used in the immunoassays. Inhibin B also appears to be a suitable serum marker for epithelial tumors of the mucinous type with about 55% to 60% having elevated inhibin B levels. In contrast, inhibin is not a very good marker in non-mucinous epithelial tumors. At best, total inhibin is elevated in 15% to 35% of non-mucinous epithelial ovarian cancer cases. Inhibin seems to be complementary to cancer antigen 125 (CA 125) as an ovarian cancer marker. CA 125 is not as good of a tumor marker for mucinous and granulosa ovarian cell tumors. Inhibin shows a better performance in those 2 types of ovarian cancer. The majority of studies for inhibin A and B as ovarian cancer markers have been limited to postmenopausal women where the levels of inhibin are normally very low. Inhibin levels vary in relation to the menstrual cycle and, therefore, are difficult to interpret in premenopausal women. Inhibin B has also been used as a marker of ovarian reserve.

Every female is born with a specific number of follicles containing oocytes, a number that steadily and naturally declines with age. The number of follicles remaining in the ovary at any time is called the ovarian reserve. As ovarian reserve diminishes, it is increasingly more difficult for the hormones used for in vitro fertilization (IVF) to stimulate follicle development and, thus, the likelihood of successful oocyte retrieval, fertilization, and embryo transfer decreases, all leading to a lower chance of conceiving. As part of an infertility evaluation, attempts are made to estimate a woman's ovarian reserve. Tests to assess ovarian reserve include the following: day 3 FSH, day 3 inhibin B, and anti-mullerian hormone levels. The amount of inhibin B measured in serum during the early follicular phase of the menstrual cycle (day 3) directly reflects the number of follicles in the ovary. Therefore, the higher the inhibin B, the more ovarian follicles present. The level of inhibin B that predicts a poor response to IVF treatment has not been established with this assay. In male patients, inhibin B levels are higher in those with apparently normal fertility than in those with infertility and abnormal spermatogenesis. Serum inhibin B, when used in combination with FSH, is a more sensitive marker of spermatogenesis than FSH alone. However, the optimal level of inhibin B to assess male infertility has not been established.

Useful For: Aiding in the diagnosis of granulosa cell tumors and mucinous epithelial ovarian tumors Monitoring of patients with granulosa cell tumors and epithelial mucinous-type tumors of the ovary known to overexpress inhibin B As an adjunct to follicle-stimulating hormone testing during infertility evaluation

Interpretation: Inhibin B levels are elevated in approximately 89% to 100% of patients with granulosa cell tumors and in approximately 55% to 60% of patients with epithelial ovarian tumors. A normal inhibin B level does not rule out a mucinous or granulosa ovarian cell tumor. Testing for inhibin A in these cases might be informative. Consider ordering INHAB / Inhibin A and B, Tumor Marker, Serum. For monitoring of patients with known ovarian cancer, inhibin B levels decrease to very low or undetectable levels shortly after surgery. Elevations of inhibin B after treatment are suggestive of residual, recurrent, or progressive disease. In patients with recurrent disease, inhibin B elevation seems to be present earlier than clinical symptoms. Patients in remission show normal levels of inhibin B. For infertility evaluation, an inhibin B level in the postmenopausal range is suggestive of a diminished or depleted ovarian reserve.

Reference Values:

Males
<15 days: 68-373 pg/mL
15-180 days: 42-516 pg/mL
6 months-7 years: 24-300 pg/mL
8-30 years: 47-383 pg/mL
31-72 years: <358 pg/mL
>72 years: Not established

Females
< or =12 years: <183 pg/mL
13-41 years Regular Cycle (Follicular Phase): <224 pg/mL
42-51 years Regular Cycle (Follicular Phase): <108 pg/mL
13-51 years Regular Cycle (Luteal Phase): <80 pg/mL
>51 years (Postmenopausal): <12 pg/mL

Clinical References: 1. Mom CH, Engelen MJA, Willemse PHB, et al. Granulosa cell tumors of the ovary: the clinical value of serum inhibin A and B levels in a large single center cohort. Gynecol Oncol. 2007;105(2):365-372 2. Robertson DM, Pruysers E, Jobling T. Inhibin as a diagnostic marker for ovarian cancer. Cancer Lett. 2007;249(1):14-17 3. Jamieson S, Fuller PJ. Management of granulosa cell tumour of the ovary. Curr Opin Oncol. 2008;20(5):560-564 4. Sturgeon C. Tumor markers. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:436-478 5. Yarbrough ML, Stout M, Gronowski AM. Pregnancy and its disorders. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed.

Elsevier; 2018:1655-1696 6. Makanji Y, Zhu J, Mishra R, et al. Inhibin at 90: from discovery to clinical application, a historical review. Endocr Rev. 2014;35(5):747-794. doi:10.1210/er.2014-1003 7. Walentowicz P, Krintus M, Sadlecki P, et al. Serum inhibin A and inhibin B levels in epithelial ovarian cancer patients. PLoS One. 2014;9(3):e90575. doi:10.1371/journal.pone.0090575

INHIB
70476

Inhibin Immunostain, Technical Component Only

Clinical Information: Inhibin is a hormone produced by ovarian granulosa and theca cells and testicular Sertoli and Leydig cells. Inhibin staining can be useful in the diagnosis of sex cord-stromal tumors.

Useful For: Identifying sex cord-stromal tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Kommoss F, Oliva E, Bhan AK, Young RH, Scully RE. Inhibin expression in ovarian tumors and tumor-like lesions: An immunohistochemcial study. Mod Pathol. 1998;11(7):656-664 2. McCluggage WG, Maxwell P, Sloan JM. Immunohistochemical staining of ovarian granulosa cell tumors with monoclonal antibody against inhibin. Hum Pathol. 1997;28(9):1034-1038. doi:10.1016/s0046-8177(97)90056-3 3. Movahedi-Lankarani S, Kurman RJ. Calretinin, a more sensitive but less specific marker than alpha -inhibin for ovarian sex cord-stromal neoplasms: an immunohistochemical study of 215 cases. Am J Surg Pathol. 2002;26(11):1477-1483. doi:10.1097/00000478-200211000-00010 4. Jiang W, Tao X, Fang F, Zhang S, Xu C. Benign and malignant ovarian steroid cell tumors, not otherwise specified: case studies, comparison, and review of the literature. J Ovarian Res. 2013;6(1):1-5. doi:10.1186/1757-2215-6-534 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

INHU
82789

Insulin (Human), IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to insulin (human) Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine

if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

INAB
8666

Insulin Antibodies, Serum

Clinical Information: The onset of autoimmune diabetes mellitus (type 1 diabetes mellitus) is preceded (and accompanied) by the appearance of autoantibodies to a variety of pancreatic islet cell antigens in serum, including insulin. The level of these autoantibodies is generally low and may even fall during follow-up. In genetically predisposed, but disease-free, individuals (first degree relatives of patients with type 1 diabetes or individuals with permissive human leukocyte antigen [HLA] alleles), detection of multiple islet cell autoantibodies is a strong predictor for subsequent development of type I diabetes. Once type 1 diabetes has fully manifested, insulin autoantibody levels usually fall to low or undetectable levels. However, after insulin therapy is initiated, autoantibody production may recur as a memory response. Insulin autoantibody production is more common when therapeutic insulin of animal origin is used (rarely used in contemporary practice). Larger therapeutic doses may be required because of antibody-induced insulin resistance. Insulin antibodies may be found in nondiabetic individuals complaining of hypoglycemic attacks. In this setting their presence can be an indicator of "factitious hypoglycemia" due to the surreptitious injection of insulin, rather than to a clinical problem (eg, insulinoma). However, insulin autoantibodies in nondiabetic subjects can occasionally develop without exposure to exogenous insulin and may rarely become a cause of episodic hypoglycemia. Anti-idiotypic autoantibodies against insulin autoantibodies have been demonstrated in some cases. Interaction of these antibodies with insulin autoantibodies could displace bound insulin from the insulin autoantibodies, resulting in hypoglycemia. In addition to IgG and IgM insulin autoantibodies, IgE antibodies (identified by the fluorescence enzyme immunoassay) may occur. IgE insulin autoantibodies result in immediate hypersensitivity reactions, such as urticaria, but do not lead to insulin resistance or hypoglycemia as can

be seen with the IgG antibodies. This test only determines the presence of IgG and IgM antibodies, not IgE antibodies. In conjunction with family history, HLA-typing and measurement of other islet cell autoantibodies (glutamic acid decarboxylase [GAD65] antibody and islet cell antigen 2 antibody [IA-2]), insulin autoantibody testing helps predict the future development of type I diabetes in asymptomatic children, adolescents, and young adults. Inclusion of a recently described fourth autoantibody (zinc transporter 8: ZnT8) further enhances the prediction of type 1 diabetes occurrence and its distinction from type 2 diabetes.

Useful For: Predicting the future development of type 1 diabetes in asymptomatic children, adolescents, and young adults, when used in conjunction with family history, human leukocyte antigen-typing, and other autoantibodies, including glutamic acid decarboxylase (GAD65) and islet cell antigen 2 (IA-2) antibodies Differential diagnosis of type 1 versus type 2 diabetes Evaluating diabetics with insulin resistance in patients with established diabetes (type 1 or type 2) Investigation of hypoglycemia in nondiabetic subjects

Interpretation: Seropositivity (> or =0.03 nmol/L) in a patient never treated with insulin is consistent with predisposition to type 1 diabetes. Seropositivity is not as informative of type 2 diabetes status as other islet cell antibodies in patients who are receiving (or have received) insulin therapy because this antibody can arise secondary to therapy. It is thought that high levels of insulin autoantibodies might contribute to insulin resistance. A family history of type 1 diabetes, other organ-specific autoimmunity and a diabetes-permissive human leukocyte antigen phenotype strengthens the prediction of type 1 diabetes development. The detection of multiple islet cell antibodies is indicative of the likely development of future type 1 diabetes. In patients presenting with hypoglycemia, the presence of insulin autoantibodies may indicate surreptitious insulin administration or, rarely, insulin autoantibody-related hypoglycemia. The differential diagnosis cannot be made on the basis of insulin autoantibody detection alone. C-peptide and insulin measurements are always required in addition to insulin autoantibody measurements in the diagnosis of hypoglycemia.

Reference Values:
< or =0.02 nmol/L
Reference values apply to all ages.

Clinical References: 1. Schernthaner G. Immunogenicity and allergenic potential of animal and human insulins. Diabetes Care. 1993;16 Suppl3:155-165 2. Lernmark A. Type 1 diabetes. Clin Chem. 1999;45(8 Pt 2):1331-1338 3. Eisenbarth GS, Jeffery J. The natural history of type 1A diabetes. Arq Bras Endocrinol Metabol. 2008;52(2):146-155 4. Thomas NJ, Jones AG. The challenges of identifying and studying type 1 diabetes in adults [published online ahead of print, 2023 Sep 20]. Diabetologia. 2023;10.1007/s00125-023-06004-4. doi:10.1007/s00125-023-06004-4

INSUL
70478

Insulin Immunostain, Technical Component Only

Clinical Information: Insulin is a polypeptide hormone secreted by the beta cells of the islets of Langerhans in the pancreas. It promotes glycogen storage, formation of triglycerides, and synthesis of protein and nucleic acids. Cytoplasmic staining is seen in normal pancreatic islet beta cells and insulin secreting islet cell tumors.

Useful For: Identification of normal pancreatic islet beta cells and insulin secreting islet cell tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the

patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Heitz PU, Kasper M, Polak JM, Kloppel G. Pancreatic endocrine tumors. Hum Pathol. 1982;13(3):263-271. doi:10.1016/s0046-8177(82)80183-4 2. Govindaraian M, Mohan V, Deepa R, Ashok S, Pitchumoni CS. Histopathology and immunohistochemistry of pancreatic islets in fibrocalculous pancreatic diabetes. Diabetes Res Clin Pract. 2001;51(1):29-38. doi:10.1016/s0168-8227(00)00204-7 3. Mukai K, Grotting JC, Greider MH, Rosai J. Retrospective study of 77 pancreatic endocrine tumors using the immunoperoxidase method. Am J Surg Pathol. 1982;6(5):387-399. doi:10.1097/00000478-198207000-00001 4. Kikuta K, Masamune A, Hamada S, Takikawa T, Nakano E, Shimosegawa T. Pancreatic stellate cells reduce insulin expression and induce apoptosis in pancreatic beta-cells. Biochem Biophys Res Commun. 2013;433(3):292-297. doi:10.1016/j.bbrc.2013.02.095 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

INSFT
62990

Insulin, Free and Total, Serum

Clinical Information: Insulin is produced by the beta cells of the pancreas. It regulates the uptake and utilization of glucose and is also involved in protein synthesis and triglyceride storage. Some patients receiving insulin may develop antibodies that bind insulin. These antibodies may or may not affect the activity and metabolism of insulin. The presence of insulin antibodies has 2 main consequences: 1. Insulin antibodies will directly bind to insulin, making it unavailable for metabolic activity. 2. Insulin antibodies may adversely affect the binding characteristics of insulin in immunoassays, making reliable quantitation difficult. Free (bioactive) insulin could be measured after ultrafiltration to remove anti-insulin antibodies and their bound insulin. If insulin antibodies are not present, the free and total insulin concentrations should be equivalent. The laboratory will report results of the total insulin (without ultrafiltration) and the free insulin (after ultrafiltration).

Useful For: Assessing free (bioactive) insulin concentrations in patients with known or suspected anti-insulin antibodies

Interpretation: Free insulin represents the portion of total insulin unbound by anti-insulin antibodies in the circulation. This fraction serves as a measure of biologically active insulin and provides an indication of the true relationship between insulin and blood glucose. Most individuals do not have anti-insulin antibodies in circulation and therefore the free and total insulin concentrations would be equivalent. When a significant difference between total and free insulin Concentrations is observed following ultrafiltration, the result is suggestive of the presence of insulin antibodies. In these cases, confirmation of the presence of anti-insulin antibodies (Mayo Test ID: INAB) may be helpful.

Reference Values:
FREE INSULIN:
3-25 mcIU/mL

TOTAL INSULIN:
3-25 mcIU/mL

Clinical References: 1. Lupsa BC, Chong AY, Cochran EK, Soos MA, Semple RK, Gorden P. Autoimmune forms of hypoglycemia. Medicine (Baltimore). 2009;88(3):141-153 2. Sapin R, Le Galudec V, Gasser F, Pinget M, Grucker D. Elecsys insulin assay: free insulin determination and the absence of cross-reactivity with insulin lispro. Clin Chem. 2001;47(3):602-605 3. Sacks DB: Diabetes mellitus. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 6th ed. Elsevier; 2018:1160-1200

INS
8664

Insulin, Serum

Clinical Information: Insulin is a hormone produced by the beta cells of the pancreas. It regulates the uptake and utilization of glucose and is also involved in protein synthesis and triglyceride storage. Type 1 diabetes (insulin-dependent diabetes) is caused by insulin deficiency due to destruction of insulin-producing pancreatic islet (beta) cells. Type 2 diabetes (noninsulin-dependent diabetes) is characterized by resistance to the action of insulin (insulin resistance). Insulin levels may be increased in patients with pancreatic beta cell tumors (insulinoma).

Useful For: Diagnosing insulinoma, when used in conjunction with proinsulin and C-peptide measurements Management of diabetes mellitus

Interpretation: During prolonged fasting, when the patient's glucose level is reduced to less than 40 mg/dL, an elevated insulin level plus elevated levels of proinsulin and C-peptide suggest insulinoma. Insulin levels generally decline in patients with type 1 diabetes mellitus. In the early stage of type 2 diabetes, insulin levels are either normal or elevated. In the late stage of type 2 diabetes, insulin levels decline. In normal individuals, insulin levels parallel blood glucose levels. To compare insulin and C-peptide concentrations (ie, insulin to C-peptide ratio): -Convert insulin to pmol/L: insulin concentration in mcIU/mL x 6.945 = insulin concentration in pmol/L. -Convert C-peptide to pmol/L: C-peptide concentration in ng/mL x 331 = C-peptide concentration in pmol/L.

Reference Values:
2.6-24.9 mcIU/mL

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Threatte GA, Henry JB. Carbohydrates. In: Henry JB, ed. Clinical Diagnosis and Management by Laboratory Methods. 19th ed. WB Saunders Company; 1996:194-207 2. Sacks DB. Diabetes mellitus. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1160-1200

IGFGP
36365

Insulin-Like Growth Factor 1 and Insulin-Like Growth Factor-Binding Protein 3 Growth Panel, Serum

Clinical Information: Insulin-like growth factor 1 (IGF1) is a 70-amino acid polypeptide (molecular weight [MW] 7.6 kDa). IGF1 is a member of a family of closely related growth factors with high homology to insulin that signal through a corresponding group of highly homologous tyrosine kinase receptors. IGF1 is produced by many tissues, with the liver being the main source of circulating IGF1. IGF1 is the major mediator of the anabolic and growth-promoting effects of growth hormone (GH). IGF1 is transported by IGF-binding proteins, in particular IGF-binding protein 3 (IGFBP3), which also controls its bioavailability and half-life. IGFBP3 is a 264-amino acid peptide (MW 29 kD) produced by the liver. It is the most abundant of a group of IGFBPs that transport and control bioavailability and half-life of IGFs, particularly IGF1, the major mediator of the anabolic- and growth-promoting effects of GH. In addition to its IGF binding-function, IGFBP3 also exhibits intrinsic growth-regulating effects that are not yet fully understood but have evoked interest with regards to a possible role of IGFBP3 as a prognostic tumor marker. Noncomplexed IGF1 and IGFBP3 have short half-lives (t1/2) of 10 minutes and 30 to 90 minutes, respectively, while the IGFBP3/IGF1 complex is cleared with a much slower t1/2 of 12 hours. The secretion patterns of IGF1 and IGFBP3 mimic each other, their respective syntheses being controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGF1 and IGFBP3 levels show only minor fluctuations. IGF1 and IGFBP3 serum levels, therefore, represent a stable and integrated measurement of GH production

and tissue effect. Low IGF1 and IGFBP3 levels are observed in GH deficiency or GH resistance. If acquired in childhood, these conditions result in short stature. Childhood GH deficiency can be an isolated abnormality or associated with deficiencies of other pituitary hormones. Some of the latter cases may be due to pituitary or hypothalamic tumors or result from either cranial radiation or intrathecal chemotherapy for childhood malignancies. Most GH resistance in childhood is mild to moderate, with causes ranging from poor nutrition to severe systemic illness (eg, kidney failure). These individuals may have IGF1 and IGFBP3 levels within the reference range. Severe childhood GH resistance is rare and usually due to defects of the GH-receptor, its downstream signaling cascades, or deleterious variants in IGF1, its binding proteins, or its receptor signaling cascades. Both GH deficiency and mild-to-moderate GH resistance can be treated with recombinant human GH (rhGH) injections, while severe resistance will usually not respond to GH. However, such patients might respond to recombinant IGF1 therapy, unless the underlying defect is in the IGF1 receptor or its downstream signaling systems. The exact prevalence and causes of adult GH resistance are uncertain, but adult GH deficiency is seen mainly in patients with pituitary tumors. It is associated with decreased muscle bulk and increased cardiovascular morbidity and mortality, but replacement therapy remains controversial. Elevated serum IGF1 and IGFBP3 levels often indicate either a sustained overproduction of GH or excessive rhGH therapy. Endogenous GH excess is caused mostly by GH-secreting pituitary adenomas, resulting in gigantism, if acquired before epiphyseal closure, and in acromegaly thereafter. Both conditions are associated with generalized organomegaly, hypertension, diabetes, cardiomyopathy, osteoarthritis, compression neuropathies, a mild increase in cancer risk (breast, colon, prostate, lung), and diminished longevity. It is plausible, but unproven, that long-term rhGH overtreatment may result in similar adverse outcomes. Malnutrition results in low serum IGF1 concentrations, which recover with restoration of adequate nutrition.

Useful For: Diagnosing growth disorders Diagnosing adult growth hormone deficiency Monitoring of recombinant human growth hormone treatment Insulin-like growth factor binding protein 3 can be used as a possible adjunct to insulin-like growth factor 1 and growth hormone in the diagnosis and follow-up of acromegaly and gigantism

Interpretation: Both insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3) measurements can be used to assess growth hormone (GH) excess or deficiency. However, for all applications, IGF1 measurement has generally been shown to have superior diagnostic sensitivity and specificity and should be used as the primary test. In particular, in the diagnosis and follow-up of acromegaly and gigantism, IGFBP3 measurement adds little, if anything, to IGF1 testing. The combination of IGF1 and IGFBP3 measurements might offer some benefits over either analyte alone in the diagnosis of GH deficiency and resistance, and in the monitoring of recombinant human GH (rhGH) therapy. Serum IGF1 and IGFBP3 concentrations below the 2.5th percentile (standard deviation score, Z-score of <-2) for age are consistent with GH deficiency or severe GH resistance, but patients with incomplete GH deficiency or mild-to-moderate GH resistance may have levels within the reference range. In GH deficiency, GH levels may also be low and can show suboptimal responses in stimulation tests (eg, exercise, clonidine, arginine, ghrelin, growth hormone-releasing hormone, insulin-induced hypoglycemia), while in severe GH resistance, GH levels might be substantially elevated. However, dynamic GH testing is not always necessary for diagnosis. If it is undertaken, it should be performed and interpreted in endocrine testing centers under the supervision of a pediatric or adult endocrinologist. The aim of both pediatric and adult GH replacement therapy is to achieve IGF1 and IGFBP3 levels within the reference range, ideally within the middle-to-upper third. Higher levels are rarely associated with any further therapeutic gains but could potentially lead to long-term problems of GH excess. Elevated IGF1 and IGFBP3 levels support the diagnosis of acromegaly or gigantism in individuals with appropriate signs or symptoms. In successfully-treated patients, both levels should be within the normal range, ideally within the lower third. In both diagnosis and follow-up, IGF1 levels correlate better with clinical disease activity than IGFBP3 levels. After transsphenoidal removal of pituitary tumors in patients with acromegaly, IGF-I concentration starts to decrease and returns to normal levels in most patients postoperatively by the fourth day. Persons with anorexia or malnutrition have low values of IGF1. IGF1 is a more sensitive indicator than prealbumin, retinol-binding protein, or transferrin for monitoring nutritional repletion.

Reference Values:

INSULIN-LIKE GROWTH FACTOR 1

Males:
0-11 months: 18-156 ng/mL
1 year: 14-203 ng/mL
2 years: 16-222 ng/mL
3 years: 22-229 ng/mL
4 years: 30-236 ng/mL
5 years: 39-250 ng/mL
6 years: 47-275 ng/mL
7 years: 54-312 ng/mL
8 years: 61-356 ng/mL
9 years: 67-405 ng/mL
10 years: 73-456 ng/mL
11 years: 79-506 ng/mL
12 years: 84-551 ng/mL
13 years: 90-589 ng/mL
14 years: 95-618 ng/mL
15 years: 99-633 ng/mL
16 years: 104-633 ng/mL
17 years: 107-615 ng/mL
18-22 years: 91-442 ng/mL
23-25 years: 66-346 ng/mL
26-30 years: 60-329 ng/mL
31-35 years: 54-310 ng/mL
36-40 years: 48-292 ng/mL
41-45 years: 44-275 ng/mL
46-50 years: 40-259 ng/mL
51-55 years: 37-245 ng/mL
56-60 years: 34-232 ng/mL
61-65 years: 33-220 ng/mL
66-70 years: 32-209 ng/mL
71-75 years: 32-200 ng/mL
76-80 years: 33-192 ng/mL
81-85 years: 33-185 ng/mL
86-90 years: 33-179 ng/mL
> or=91 years: 32-173 ng/mL

Females:
0-11 months: 14-192 ng/mL
1 year: 23-243 ng/mL
2 years: 28-256 ng/mL
3 years: 31-249 ng/mL
4 years: 33-237 ng/mL
5 years: 36-234 ng/mL
6 years: 39-246 ng/mL
7 years: 44-279 ng/mL
8 years: 51-334 ng/mL
9 years: 61-408 ng/mL
10 years: 73-495 ng/mL
11 years: 88-585 ng/mL
12 years: 104-665 ng/mL
13 years: 120-719 ng/mL
14 years: 136-729 ng/mL

15 years: 147-691 ng/mL
16 years: 153-611 ng/mL
17 years: 149-509 ng/mL
18-22 years: 85-370 ng/mL
23-25 years: 73-320 ng/mL
26-30 years: 66-303 ng/mL
31-35 years: 59-279 ng/mL
36-40 years: 54-258 ng/mL
41-45 years: 49-240 ng/mL
46-50 years: 44-227 ng/mL
51-55 years: 40-217 ng/mL
56-60 years: 37-208 ng/mL
61-65 years: 35-201 ng/mL
66-70 years: 34-194 ng/mL
71-75 years: 34-187 ng/mL
76-80 years: 34-182 ng/mL
81-85 years: 34-177 ng/mL
86-90 years: 33-175 ng/mL
> or =91 years: 25-179 ng/mL

Tanner Stage reference ranges:
Males
Stage I: 81-255 ng/mL
Stage II: 106-432 ng/mL
Stage III: 245-511 ng/mL
Stage IV: 223-578 ng/mL
Stage V: 227-518 ng/mL

Females
Stage I: 86-323 ng/mL
Stage II: 118-451 ng/mL
Stage III: 258-529 ng/mL
Stage IV: 224-586 ng/mL
Stage V: 188-512 ng/mL

Tanner Stage reference source: Bindlingmaier M, Friedrich N, Emeny RT, et al. Reference intervals for insulin-like growth factor-1 (igf-i) from birth to senescence: results from a multicenter study using a new automated chemiluminescence IGF-I immunoassay conforming to recent international recommendations. J Clin Endocrinol Metab. 2014;99(5):1712-1721

Note: Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN 3
1-7 days: < or =0.7 mcg/mL
8-14 days: 0.5-1.4 mcg/mL
15 days-11 months: Unavailable
1 year: 0.7-3.6 mcg/mL
2 years: 0.8-3.9 mcg/mL
3 years: 0.9-4.3 mcg/mL
4 years: 1.0-4.7 mcg/mL

5 years: 1.1-5.2 mcg/mL
6 years: 1.3-5.6 mcg/mL
7 years: 1.4-6.1 mcg/mL
8 years: 1.6-6.5 mcg/mL
9 years: 1.8-7.1 mcg/mL
10 years: 2.1-7.7 mcg/mL
11 years: 2.4-8.4 mcg/mL
12 years: 2.7-8.9 mcg/mL
13 years: 3.1-9.5 mcg/mL
14 years: 3.3-10 mcg/mL
15 years: 3.5-10 mcg/mL
16 years: 3.4-9.5 mcg/mL
17 years: 3.2-8.7 mcg/mL
18 years: 3.1-7.9 mcg/mL
19 years: 2.9-7.3 mcg/mL
20 years: 2.9-7.2 mcg/mL
21-25 years: 3.4-7.8 mcg/mL
26-30 years: 3.5-7.6 mcg/mL
31-35 years: 3.5-7.0 mcg/mL
36-40 years: 3.4-6.7 mcg/mL
41-45 years: 3.3-6.6 mcg/mL
46-50 years: 3.3-6.7 mcg/mL
51-55 years: 3.4-6.8 mcg/mL
56-60 years: 3.4-6.9 mcg/mL
61-65 years: 3.2-6.6 mcg/mL
66-70 years: 3.0-6.2 mcg/mL
71-75 years: 2.8-5.7 mcg/mL
76-80 years: 2.5-5.1 mcg/mL
81-85 years: 2.2-4.5 mcg/mL

Tanner Stages:
Males
Stage I: 1.4-5.2 mcg/mL
Stage II: 2.3-6.3 mcg/mL
Stage III: 3.1-8.9 mcg/mL
Stage IV: 3.7-8.7 mcg/mL
Stage V: 2.6-8.6 mcg/mL

Females
Stage I: 1.2-6.4 mcg/mL
Stage II: 2.8-6.9 mcg/mL
Stage III: 3.9-9.4mcg/mL
Stage IV: 3.3-8.1 mcg/mL
Stage V: 2.7-9.1 mcg/mL

Note: Puberty onset, ie, the transition from Tanner stage 1 (prepubertal) to Tanner stage 2 (early pubertal), occurs for girls at a median age of 10.5 (+/-2) years and for boys at a median age of 11.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. By contrast, for boys there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage 5 (young adult) should be reached by age 18.

Clinical References: 1. Wetterau L, Cohen P. Role of insulin-like growth factor monitoring in optimizing growth hormone therapy. J Ped Endocrinol Metab. 2000;13:1371-1376 2. Granada ML,

Murillo J, Lucas A, et al. Diagnostic efficiency of serum IGF-1, IGF-binding protein-3 (IGFBP-3), IGF/IGFBP-3 molar ratio and urinary GH measurements in the diagnosis of adult GH deficiency: importance of an appropriate reference population. Eur J Endocrinol. 2000;142:243-253 3. Parama C, Fluiters E, de la Fuente J, et al. Monitoring of treatment success in patients with acromegaly: the value of serum insulin-like growth factor binding protein-3 and serum leptin measurements in comparison to plasma insulin-like growth factor 1 determination. Metabolism. 2001;50:1117-1121 4. Monzavi R, Cohen P. IGFs and IGFBPs: role in health and disease. Best Pract Res Clin Endocrinol Metab. 2002;16:433-447 5. Boquete HR, Sobrado PG, Fideleff HL, et al. Evaluation of diagnostic accuracy of insulin-like growth factor (IGF)-1 and IGF-binding protein-3 in growth hormone-deficient children and adults using ROC plot analysis. J Endocrinol Metab. 2003;88:4702-4708 6. Brabant G. Insulin-like growth factor-I: marker for diagnosis of acromegaly and monitoring the efficacy of treatment. Eur J Endocrinol. 2003;148:S15-S20 7. Boscato LM, Stuart MC. Heterophilic antibodies: a problem for all immunoassays. Clin Chem. 1988;34:27-33 8. Maus A, Kemp J, Milosevic D, et al. Center of mass calculation in combination with MS/MS allows robust identification of single amino acid polymorphisms in clinical measurements of insulin-like growth factor-1. J Proteome Res. 2020;19(1):186-193. doi:10.1021/acs.jproteome.9b00494

IGFMS
62750

Insulin-Like Growth Factor-1, Mass Spectrometry, Serum

Clinical Information: Insulin-like growth factor 1 (IGF1) is a 70-amino acid polypeptide (molecular weight 7.6 kDa; Uniprot Accession P05019 [aa 49-118]). IGF1 is a member of a family of closely related growth factors with high homology to insulin that signal through a corresponding group of highly homologous tyrosine kinase receptors. IGF1 is produced by many tissues, with the liver being the main source of circulating IGF1. IGF1 is the major mediator of the anabolic and growth-promoting effects of growth hormone (GH). IGF1 is transported by IGF-binding proteins, in particular IGF-binding protein 3 (IGFBP3), which also controls its bioavailability and half-life. Noncomplexed IGF1 and IGFBP3 have short half-lives (t1/2) of 10 minutes and 30 to 90 minutes, respectively, while the IGFBP3/IGF1 complex is cleared with a much slower t1/2 of 12 hours. The secretion patterns of IGF1 and IGFBP3 mimic each other, their respective syntheses being controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGF1 and IGFBP3 levels show only minor fluctuations. IGF1 and IGFBP3 serum levels, therefore, represent a stable and integrated measurement of GH production and tissue effect. Low IGF1 and IGFBP3 levels are observed in GH deficiency or GH resistance. If acquired in childhood, these conditions result in short stature. Childhood GH deficiency can be an isolated abnormality or associated with deficiencies of other pituitary hormones. Some of the latter cases may be due to pituitary or hypothalamic tumors or result from either cranial radiation or intrathecal chemotherapy for childhood malignancies. Most GH resistance in childhood is mild-to-moderate, with causes ranging from poor nutrition to severe systemic illness (eg, kidney failure). These individuals may have IGF1 and IGFBP3 levels within the reference range. Severe childhood GH resistance is rare and usually due to defects of the GH-receptor, its downstream signaling cascades, or deleterious variants in IGF1, its binding proteins, or its receptor signaling cascades. Both GH deficiency and mild-to-moderate GH resistance can be treated with recombinant human GH (rhGH) injections, while severe resistance will usually not respond to GH. However, such patients might respond to recombinant IGF1 therapy, unless the underlying defect is in the IGF1 receptor or its downstream signaling systems. The exact prevalence and causes of adult GH resistance are uncertain, but adult GH deficiency is seen mainly in patients with pituitary tumors. It is associated with decreased muscle bulk and increased cardiovascular morbidity and mortality, but replacement therapy remains controversial. Elevated serum IGF1 and IGFBP3 levels often indicate either a sustained overproduction of GH or excessive rhGH therapy. Endogenous GH excess is caused mostly by GH-secreting pituitary adenomas, resulting in gigantism if acquired before epiphyseal closure and in acromegaly thereafter. Both conditions are associated with generalized organomegaly, hypertension, diabetes, cardiomyopathy, osteoarthritis, compression neuropathies, a mild increase in cancer risk (breast, colon, prostate, lung), and diminished longevity. It is plausible, but unproven, that long-term rhGH overtreatment may result in similar adverse outcomes. Malnutrition results in low serum IGF1 concentrations, which recover with restoration of adequate nutrition.

Useful For: Evaluation of growth disorders Evaluation of growth hormone deficiency or excess in children and adults Monitoring of recombinant human growth hormone treatment Follow-up of individuals with acromegaly and gigantism

Interpretation: Both insulin-like growth factor 1 (IGF1) and insulin-like growth factor-binding protein 3 (IGFBP3) measurements can be used to assess growth hormone (GH) excess or deficiency. However, for all applications, IGF1 measurement has generally been shown to have superior diagnostic sensitivity and specificity and should be used as the primary test. In particular, in the diagnosis and follow-up of acromegaly and gigantism, IGFBP3 measurement adds little, if anything, to IGF1 testing. The combination of IGF1 and IGFBP3 measurements might offer some benefits over either analyte alone in the diagnosis of GH deficiency and resistance, and in the monitoring of recombinant human GH (rhGH) therapy. Serum IGF1 and IGFBP3 concentrations below the 2.5th percentile (standard deviation score, Z-score of <-2) for age are consistent with GH deficiency or severe GH resistance, but patients with incomplete GH deficiency or mild-to-moderate GH resistance may have levels within the reference range. In GH deficiency, GH levels may also be low and can show suboptimal responses in stimulation tests (eg, exercise, clonidine, arginine, ghrelin, growth hormone-releasing hormone, insulin-induced hypoglycemia), while in severe GH resistance, GH levels might be substantially elevated. However, dynamic GH testing is not always necessary for diagnosis. If it is undertaken, it should be performed and interpreted in endocrine testing centers under the supervision of a pediatric or adult endocrinologist. The aim of both pediatric and adult GH replacement therapy is to achieve IGF1 and IGFBP3 levels within the reference range, ideally within the middle-to-upper third. Higher levels are rarely associated with any further therapeutic gains but could potentially lead to long-term problems of GH excess. Elevated IGF1 and IGFBP3 levels support the diagnosis of acromegaly or gigantism in individuals with appropriate signs or symptoms. In successfully-treated patients, both levels should be within the normal range, ideally within the lower third. In both diagnosis and follow-up, IGF1 levels correlate better with clinical disease activity than IGFBP3 levels. After transsphenoidal removal of pituitary tumors in patients with acromegaly, IGF-I concentration starts to decrease and returns to normal levels in most patients postoperatively by the fourth day. Persons with anorexia or malnutrition have low values of IGF1. IGF1 is a more sensitive indicator than prealbumin, retinol-binding protein, or transferrin for monitoring nutritional repletion.

Reference Values:

Males:
0-11 months: 18-156 ng/mL
1 year: 14-203 ng/mL
2 years: 16-222 ng/mL
3 years: 22-229 ng/mL
4 years: 30-236 ng/mL
5 years: 39-250 ng/mL
6 years: 47-275 ng/mL
7 years: 54-312 ng/mL
8 years: 61-356 ng/mL
9 years: 67-405 ng/mL
10 years: 73-456 ng/mL
11 years: 79-506 ng/mL
12 years: 84-551 ng/mL
13 years: 90-589 ng/mL
14 years: 95-618 ng/mL
15 years: 99-633 ng/mL
16 years: 104-633 ng/mL
17 years: 107-615 ng/mL
18-22 years: 91-442 ng/mL
23-25 years: 66-346 ng/mL
26-30 years: 60-329 ng/mL

31-35 years: 54-310 ng/mL
36-40 years: 48-292 ng/mL
41-45 years: 44-275 ng/mL
46-50 years: 40-259 ng/mL
51-55 years: 37-245 ng/mL
56-60 years: 34-232 ng/mL
61-65 years: 33-220 ng/mL
66-70 years: 32-209 ng/mL
71-75 years: 32-200 ng/mL
76-80 years: 33-192 ng/mL
81-85 years: 33-185 ng/mL
86-90 years: 33-179 ng/mL
> or =91 years: 32-173 ng/mL

Females:
0-11 months: 14-192 ng/mL
1 year: 23-243 ng/mL
2 years: 28-256 ng/mL
3 years: 31-249 ng/mL
4 years: 33-237 ng/mL
5 years: 36-234 ng/mL
6 years: 39-246 ng/mL
7 years: 44-279 ng/mL
8 years: 51-334 ng/mL
9 years: 61-408 ng/mL
10 years: 73-495 ng/mL
11 years: 88-585 ng/mL
12 years: 104-665 ng/mL
13 years: 120-719 ng/mL
14 years: 136-729 ng/mL
15 years: 147-691 ng/mL
16 years: 153-611 ng/mL
17 years: 149-509 ng/mL
18-22 years: 85-370 ng/mL
23-25 years: 73-320 ng/mL
26-30 years: 66-303 ng/mL
31-35 years: 59-279 ng/mL
36-40 years: 54-258 ng/mL
41-45 years: 49-240 ng/mL
46-50 years: 44-227 ng/mL
51-55 years: 40-217 ng/mL
56-60 years: 37-208 ng/mL
61-65 years: 35-201 ng/mL
66-70 years: 34-194 ng/mL
71-75 years: 34-187 ng/mL
76-80 years: 34-182 ng/mL
81-85 years: 34-177 ng/mL
86-90 years: 33-175 ng/mL
> or =91 years: 25-179 ng/mL

Tanner Stage reference ranges:
Males
Stage I: 81-255 ng/mL
Stage II: 106-432 ng/mL

Stage III: 245-511 ng/mL
Stage IV: 223-578 ng/mL
Stage V: 227-518 ng/mL

Females
Stage I: 86-323 ng/mL
Stage II: 118-451 ng/mL
Stage III: 258-529 ng/mL
Stage IV: 224-586 ng/mL
Stage V: 188-512 ng/mL

Tanner Stage reference source: Bindlingmaier M, Friedrich N, Emeny RT,et al. Reference intervals for insulin-like growth factor-1 (igf-i) from birth to senescence: results from a multicenter study using a new automated chemiluminescence IGF-I immunoassay conforming to recent international recommendations. J Clin Endocrinol Metab. 2014;99(5):1712-1721

Note: Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

Clinical References: 1. Wetterau L, Cohen P. Role of insulin-like growth factor monitoring in optimizing growth hormone therapy. J Ped Endocrinol Metab. 2000;13 Suppl 6:1371-1376. doi:10.1515/jpem-2000-s610 2. Granada ML, Murillo J, Lucas A, et al. Diagnostic efficiency of serum IGF-1, IGF-binding protein-3 (IGFBP-3), IGF/IGFBP-3 molar ratio and urinary GH measurements in the diagnosis of adult GH deficiency: importance of an appropriate reference population. Eur J Endocrinol. 2000;142(3):243-253. doi:10.1530/eje.0.1420243 3. Boquete HR, Sobrado PGV, Fideleff HL, et al. Evaluation of diagnostic accuracy of insulin-like growth factor (IGF)-1 and IGF-binding protein-3 in growth hormone-deficient children and adults using ROC plot analysis. J Endocrinol Metab. 2003;88(10):4702-4708. doi:10.1210/jc.2003-030412 4. Brabant G. Insulin-like growth factor-I: marker for diagnosis of acromegaly and monitoring the efficacy of treatment. Eur J Endocrinol. 2003;148 Suppl 2:S15-S20. doi:10.1530/eje.0.148s015 5. Bidlingmaier M, Friedrich N, Emeny RT, et,al. Reference intervals for insulin-like growth factor-1 (IGF-1) from birth to senescence: results from a multicenter study using a new automated chemiluminescence IGF-1 immunoassay conforming to recent international recommendations. J Clin Endocrinol Metab. 2014;99(5):1712-1721.doi:10.1210/jc.2013-3059

IGFB3
83300

Insulin-Like Growth Factor-Binding Protein 3, Serum

Clinical Information: Insulin-like growth factor-binding protein 3 (IGFBP-3) is a 264-amino acid peptide (molecular weight 29 kDa) produced by the liver. It is the most abundant of a group of IGFBPs that transport and control bioavailability and half-life of the insulin-like growth factors (IGF), in particular IGF-1, the major mediator of the anabolic- and growth-promoting effects of growth hormone (GH). Noncomplexed IGFBP-3 and IGF-1 have short half-lives (t1/2) of 30 to 90 minutes and 10 minutes, respectively, while the IGFBP-3/IGF-1 complex is cleared with a much slower t1/2 of 12 hours. In addition to its IGF-binding function, IGFBP-3 also exhibits intrinsic growth-regulating effects that are not yet fully understood but have evoked interest with regards to a possible role of IGFBP-3 as a prognostic tumor marker. The secretion patterns of IGFBP-3 and IGF-1 mimic each other; their respective syntheses are primarily controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGFBP-3 and IGF-1 levels show only minor fluctuations. IGFBP-3 and IGF-1 serum levels therefore represent a stable and integrated measurement of GH production and tissue effect. Low IGFBP-3 and IGF-1 levels are observed in GH deficiency or GH

resistance. If acquired in childhood, these conditions result in short stature. Childhood GH deficiency can be an isolated abnormality or associated with deficiencies of other pituitary hormones. Some of the latter cases may be due to pituitary or hypothalamic tumors or result from cranial radiation or intrathecal chemotherapy for childhood malignancies. Most GH resistance in childhood is mild to moderate, with causes ranging from poor nutrition to severe systemic illness (eg, kidney failure). These individuals may have IGF-1 and IGFBP-3 levels within the reference range. Severe childhood GH resistance is rare and usually due to GH-receptor defects. Both GH deficiency and mild-to-moderate GH resistance can be treated with recombinant human GH (rhGH) injections. The prevalence and causes of adult GH resistance are uncertain, but adult GH deficiency is seen mainly in pituitary tumor patients. It is associated with decreased muscle bulk and increased cardiovascular morbidity and mortality, but replacement therapy remains controversial. Elevated serum IGFBP-3 and IGF-1 levels indicate a sustained overproduction of GH or excessive rhGH therapy. Endogenous GH excess is caused mostly by GH-secreting pituitary adenomas, resulting in gigantism, if acquired before epiphyseal closure, and in acromegaly thereafter. Both conditions are associated with generalized organomegaly, hypertension, diabetes, cardiomyopathy, osteoarthritis, compression neuropathies, a mild increase in cancer risk, and diminished longevity. It is plausible, but unproven, that long-term rhGH-overtreatment may result in similar adverse outcomes.

Useful For: Diagnosing growth disorders Diagnosing adult growth hormone deficiency Monitoring of recombinant human growth hormone treatment As a possible adjunct to insulin-like growth factor 1 and growth hormone in the diagnosis and follow-up of acromegaly and gigantism

Interpretation: For all applications, insulin-like growth factor 1 (IGF-1) measurement has generally been shown to have superior diagnostic sensitivity and specificity compared with insulin-like growth factor-binding protein 3 (IGFBP-3). IGFBP-3 testing should, therefore, usually be combined with IGF-1 testing. The combination of IGF-1 and IGFBP-3 measurements appears superior to determining either analyte alone in the diagnosis of growth hormone (GH) deficiency and resistance and in the monitoring of recombinant human GH therapy. By contrast, in the diagnosis and follow-up of acromegaly and gigantism, IGFBP-3 measurement adds little if anything to IGF-1 testing. IGF-1 and IGFBP-3 levels below the 2.5th percentile for age are consistent with GH deficiency or severe resistance, but patients with incomplete GH deficiency or mild-to-moderate GH resistance may have levels within the reference range. In GH deficiency, GH levels are also low and show suboptimal responses in stimulation tests (eg, exercise, clonidine, arginine, ghrelin, growth hormone-releasing hormone, insulin-induced hypoglycemia), while in severe GH resistance, GH levels are substantially elevated. However, dynamic GH testing is not always necessary for diagnosis. If it is undertaken, it should be performed and interpreted in endocrine testing centers under the supervision of an endocrinologist. The aim of both pediatric and adult GH replacement therapy is to achieve IGF-1 and IGFBP-3 levels within the reference range, ideally within the middle to upper third. Higher levels are rarely associated with any further therapeutic gains but could potentially lead to long-term problems of GH excess. Elevated IGF-1 and IGFBP-3 levels support the diagnosis of acromegaly or gigantism in individuals with appropriate symptoms or signs. In successfully treated patients, both levels should be within the normal range, ideally within the lower third. In both diagnosis and follow-up, IGF-1 levels correlate better with clinical disease activity than IGFBP-3 levels.

Reference Values:

1-7 days: < or =0.7 mcg/mL
8-14 days: 0.5-1.4 mcg/mL
15 days-11 months: unavailable
1 year: 0.7-3.6 mcg/mL
2 years: 0.8-3.9 mcg/mL
3 years: 0.9-4.3 mcg/mL
4 years: 1.0-4.7 mcg/mL
5 years: 1.1-5.2 mcg/mL
6 years: 1.3-5.6 mcg/mL
7 years: 1.4-6.1 mcg/mL

8 years: 1.6-6.5 mcg/mL
9 years: 1.8-7.1 mcg/mL
10 years: 2.1-7.7 mcg/mL
11 years: 2.4-8.4 mcg/mL
12 years: 2.7-8.9 mcg/mL
13 years: 3.1-9.5 mcg/mL
14 years: 3.3-10 mcg/mL
15 years: 3.5-10 mcg/mL
16 years: 3.4-9.5 mcg/mL
17 years: 3.2-8.7 mcg/mL
18 years: 3.1-7.9 mcg/mL
19 years: 2.9-7.3 mcg/mL
20 years: 2.9-7.2 mcg/mL
21-25 years: 3.4-7.8 mcg/mL
26-30 years: 3.5-7.6 mcg/mL
31-35 years: 3.5-7.0 mcg/mL
36-40 years: 3.4-6.7 mcg/mL
41-45 years: 3.3-6.6 mcg/mL
46-50 years: 3.3-6.7 mcg/mL
51-55 years: 3.4-6.8 mcg/mL
56-60 years: 3.4-6.9 mcg/mL
61-65 years: 3.2-6.6 mcg/mL
66-70 years: 3.0-6.2 mcg/mL
71-75 years: 2.8-5.7 mcg/mL
76-80 years: 2.5-5.1 mcg/mL
81-85 years: 2.2-4.5 mcg/mL

Tanner Stages:

Males
Stage I: 1.4-5.2 mcg/mL
Stage II: 2.3-6.3 mcg/mL
Stage III: 3.1-8.9 mcg/mL
Stage IV: 3.7-8.7 mcg/mL
Stage V: 2.6-8.6 mcg/mL

Females
Stage I: 1.2-6.4 mcg/mL
Stage II: 2.8-6.9 mcg/mL
Stage III: 3.9-9.4 mcg/mL
Stage IV: 3.3-8.1 mcg/mL
Stage V: 2.7-9.1 mcg/mL

Note: Puberty onset, ie, the transition from Tanner stage I (prepubertal) to Tanner stage II (early pubertal), occurs for girls at a median age of 10.5 (+/-2) years and for boys at a median age of 11.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in girls who are obese and in African American girls. By contrast, for boys there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

Clinical References: 1. Boscato LM, Stuart MC. Heterophilic antibodies: a problem for all immunoassays. Clin Chem. 1988;34(1):27-33 2. Wetterau L, Cohen P. Role of insulin-like growth factor monitoring in optimizing growth hormone therapy. J Ped Endocrinol Metab. 2000;13 Suppl 6:1371-1376 3. Granada ML, Murillo J, Lucas A, et al. Diagnostic efficiency of serum IGF-1, IGF-

binding protein-3 (IGFBP-3), IGF/IGFBP-3 molar ratio and urinary GH measurements in the diagnosis of adult GH deficiency: importance of an appropriate reference population. Eur J Endocrinol. 2000;142(3):243-253 4. Parama C, Fluiters E, de la Fuente J, Andrade A, Garcia-Mayor RV. Monitoring of treatment success in patients with acromegaly: the value of serum insulin-like growth factor binding protein-3 and serum leptin measurements in comparison to plasma insulin-like growth factor 1 determination. Metabolism. 2001;50(9):1117-1121 5. Monzavi R, Cohen P. IGFs and IGFBPs: role in health and disease. Best Pract Res Clin Endocrinol Metab. 2002;16(3):433-447 6. Boquete HR, Sobrado PGV, Fideleff HL, et al: Evaluation of diagnostic accuracy of insulin-like growth factor (IGF)-1 and IGF-binding protein-3 in growth hormone-deficient children and adults using ROC plot analysis. J Endocrinol Metab. 2003;88(10):4702-4708 7. Shen Y, Zhang J, Zhao Y, Yan Y, Liu Y, Cai J. Diagnostic value of serum IGF-1 and IGFBP-3 in growth hormone deficiency: a systematic review with meta-analysis. Eur J Pediatr. 2015;174(4):419-427 8. Inoue-Lima TH, Vasques GA, Nakaguma M, et al. A Bayesian Approach to Diagnose Growth Hormone Deficiency in Children: Insulin-Like Growth Factor Type 1 Is Valuable for Screening and IGF-Binding Protein Type 3 for Confirmation. Horm Res Paediatr. 2020;93(3):197-205

FGBP1
75670

Insulin-like Growth Factor-binding Protein-1 (IGFBP-1)

Useful For: Identify women who are at high risk for developing preeclampsia.

Reference Values:

Age	Range (ng/mL)
	Fasting
Prepubertal	30-1000
Pubertal	20-200
Adults	10-150

INSM1
602573

Insulinoma-Associated Protein 1 (INSM1), Immunostain, Technical Component Only

Clinical Information: Insulinoma associated protein 1 (INSM1) is expressed in tissues with neuroendocrine differentiation. INSM1 is a sensitive and specific marker for neuroendocrine tumors.

Useful For: Identification of neuroendocrine tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Fujino K, Yasufuku K, Kudoh S, et al. INSM1 is the best marker for the diagnosis of neuroendocrine tumors: comparison with CGA, SYP and CD56. Int J Clin Exp Pathol. 2017;10(5):5393-5405 2. Rosenbaum J, Guo Z, Baus R, et al. INSM1: A novel immunohistochemical and molecular marker for neuroendocrine and neuroepithelial neoplasms. Am J Clin Pathol.

2015;144(4):579-591 3. Rooper L, Sharma R, Li Q, et al. INSM1 demonstrates superior performance to the individual and combined use of synaptophysin, chromogranin and CD56 for diagnosing neuroendocrine tumors of the thoracic cavity. Am J Surg Pathol. 2017;41(11):1561-1569 4. Lan M, Breslin M. Structure, expression, and biological function of INSM1 transcription factor in neuroendocrine differentiation. FASEB J. 2018;23(7):2024-2033 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

IFG23
607216

Intact Fibroblast Growth Factor 23, Serum

Clinical Information: Fibroblast growth factor 23 (FGF23) is a major regulator of phosphate (phosphorus) homeostasis. FGF23 is secreted primarily by bone, followed by thymus, heart, brain and, in low levels, by several other tissues. High serum phosphate (phosphorus) concentrations stimulate FGF23 expression and secretion through a yet poorly understood mechanism. Only intact FGF23 is considered bioactive. Intact FGF23 interacts with a specific receptor on renal tubular cells, decreasing expression of type IIa sodium/phosphate cotransporters, resulting in decreased phosphate reabsorption. In addition, gene transcription of 1-alpha-hydroxylase is downregulated, reducing bioactive 1,25-dihydroxy vitamin D, thereby further decreasing phosphate reabsorption. Eventually, falling serum phosphate concentrations lead to diminished FGF23 secretion, closing the feedback loop. Measurement of FGF23 can assist in diagnosis and management of disorders of phosphate and bone metabolism in patients with either normal or impaired kidney function. When FGF23 levels are pathologically elevated in individuals with normal kidney function, hypophosphatemia, with or without osteomalacia, ensues. This can occur in rare, usually benign, mixed connective tissue tumors that contain characteristic complex vascular structures, osteoclast-like giant cells, cartilaginous elements, and dystrophic calcifications. These neoplasms secrete FGF23 ectopically and autonomously (tumor-induced osteomalacia; TIO). In less than one-fourth of cases, a different benign or malignant soft tissue tumor type or, extremely rarely, a carcinoma may be the cause of paraneoplastic FGF23 secretion. In either scenario, complete removal of the tumor cures the TIO. Hypophosphatemia and skeletal abnormalities are also observed in X-linked hypophosphatemia (XLH) and autosomal dominant hypophosphatemic rickets (ADHR). In XLH, variants in the PHEX (phosphate-regulating neutral endopeptidase) gene, which encodes a cell-surface-bound protein-cleavage enzyme, affect bioactive FGF23 secretion. Although the pathogenesis of XLH is not fully understood, animal studies indicate that loss of PHEX function results in enhanced secretion of FGF23. In ADHR, FGF23 variants render the protein resistant to proteolytic cleavage, thereby increasing FGF23 levels. However, not all FGF23 variants increase renal phosphate secretions. Variants that impair FGF23 signaling, rather than increase its protease resistance, are associated with the syndrome of familial tumoral calcinosis (ectopic calcifications) with hyperphosphatemia. In patients with kidney failure, FGF23 contributes to renal osteodystrophy. The patient's kidneys can no longer excrete sufficient amounts of phosphate. This leads to marked increases in FGF23 secretion as a compensatory response, aggravating the 1,25-dihydroxy vitamin D deficiency of renal failure and the consequent secondary hyperparathyroidism. In circulation, intact FGF-23 is cleaved to generate 2 biologically inactive fragments: a N-terminal fragment and a C-terminal fragment. FGF23 has a rapid clearance and short half-life, which ranges between 46 and 58 min for intact and C-terminal fragments, respectively. Different types of FGF-23 immunoassays are available: those targeting the intact form (iFGF23) and those detecting C-terminal fragments (cFGF23). Various studies have suggested that iFGF23 assays are more sensitive than cFGF23 for the detection of FGF23 concentrations in patients with TIO and patients with XLH. In addition, iFGF23 concentrations are not affected by iron deficiency, which may lead to false-positive results when using cFGF23 assays.

Useful For: Diagnosing and monitoring tumor induced osteomalacia Diagnosing X-linked hypophosphatemia or autosomal dominant hypophosphatemic rickets Diagnosing familial tumoral calcinosis with hyperphosphatemia

Interpretation: Increased fibroblast growth factor 23 (FGF23) concentrations are present in

individuals with renal phosphate-wasting diseases such as autosomal dominant hypophosphatemic rickets (ADHR), autosomal recessive hypophosphatemic rickets (ARHR), X-linked hypophosphatemia rickets (XLH) and tumor induced osteomalacia (TIO). Clinically, FGF23 measurement is useful in the differential diagnosis of these hypophosphatemic diseases since the patient presents with high FGF23 levels along with hypophosphatemia. In other causes of hypophosphatemia, such as vitamin D deficiency, FGF23 levels are low. In FGF23-producing tumors, a decrease in FGF23 concentrations following surgery is a reliable indication of complete tumor resection. Intact FGF23 concentrations are elevated in patients with TIO or XLH. However, intact FGF23 concentrations within the reference interval do not exclude the disease and should be interpreted in the setting of phosphate concentrations (ie, an FGF23 concentration in the upper level of the reference interval in the context of hypophosphatemia might be indicative of XLH). In ADHR, FGF23 concentrations are not consistently elevated, and the severity of renal phosphate-wasting may wax and wane; FGF23 concentrations are normal during quiescent periods when serum phosphate levels are normal, and they are elevated during active, hypophosphatemic phases of the disease.(1) FGF23 concentrations are influenced by factors such as phosphate intake and vitamin D therapy. Therefore, intact FGF23 levels are most informative in untreated patients. In the setting of hypophosphatemia, an elevated FGF23 may be indicative of FGF23-mediated hypophosphatemia. In a Mayo Clinic study, using the Medfrontier (Minaris Medical Co, Ltd, Tokyo, Japan) and a cut-off of greater than or equal to 59 pg/mL, corresponding to the upper limit of the reference interval, intact FGF23 concentrations were elevated in 90% and 84% of TIO and XLH hypophosphatemia patients, respectively. In the TIO and XLH patients where the intact FGF23 concentration was not above the reference interval, the intact FGF23 concentrations were at the upper end of the reference interval and much higher than observed in the patients with FGF23-independent hypophosphatemia. In contrast in the patients with FGF23-independent hypophosphatemia, intact FGF23 concentrations were significantly lower than what was observed in the healthy cohort and the normophosphatemic patients.(2) A study using the same assay and a cut-off of 30.0 pg/mL, reported 100% sensitivity and 82% specificity for the differential diagnosis of FGF23-related hypophosphatemia rickets/osteomalacia without vitamin D deficiency versus non-FGF23-related hypophosphatemia.(3)

Reference Values:

Pediatric (<18 yrs): < or =52 pg/mL
Adults (> or =18 yrs): < or = 59 pg/mL

Clinical References: 1. Imel EA, Hui SL, Econs MJ. FGF23 concentrations vary with disease status in autosomal dominant hypophosphatemic rickets. J Bone Miner Res. 2007;22(4):520-526 2. Ramos P, Larson B, Ashrafzadeh-Kian S, et al. Intact fibroblast growth factor 23 concentrations in hypophosphatemic disorders. Endocr Pract. 2023;29(3):193-198. doi:10.1016/j.eprac.2023.01.003 3. Ito, N., Kubota, T., Kitanaka, S.et al. Clinical performance of a novel chemiluminescent enzyme immunoassay for FGF23. J Bone Miner Metab. 2021;39(6):1066-1075.doi.org/10.1007/s00774-021-01250-1 4. Ashrafzadeh-Kian SL, Ito N, Srivastava T, el al. The effect of burosumab on intact and C-terminal FGF23 measurements. Clin Endocrinol (Oxf). 2023;99(2):152-157. doi:10.1111/cen.14832 5. Imel EA, Gray AK, Padgett LR, Econs MJ. Iron and fibroblast growth factor 23 in X-linked hypophosphatemia. Bone. 2014;60:87-92 6. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphatemia. Nat Rev Nephrol. 2019;15(7):435-455. doi:10.1038/s41581-019-0152-5 7. Fauconnier C, Roy T, Gillerot G, Roy C, Pouleur AC, Gruson D: FGF23: Clinical usefulness and analytical evolution. Clin Biochem. 2019;66:1-12. doi:10.1016/j.clinbiochem.2019.03.002 8. Hartley IR, Gafni RI, Roszko KL, et al. Determination of FGF23 levels for the diagnosis of FGF23-mediated hypophosphatemia. J Bone Miner Res. 2022;37(11):2174-2185. doi:10.1002/jbmr.4702

INI1
70477

Integrase Interactor 1 (INI1/BAF47) Immunostain, Technical Component Only

Clinical Information: Integrase interactor 1 (INI1) is a member of the SWI/SNF (SWItch/sucrose non-fermentable) chromatin remodeling complex, which play an important role in regulation of transcription by modulating access of protein to DNA. Loss of function of these complexes has been implicated in human cancers. Point alterations and deletions of the INI BAF47 gene may be seen in pediatric rhabdoid tumors, rhabdomyosarcoma, chronic myeloid leukemia, and in central nervous system tumors (medulloblastomas and choroid plexus carcinomas) where loss of nuclear staining for INI1/BAF47 is seen. In normal tissues, nuclear expression of INI1/BAF4 should be present in all cell types.

Useful For: Part of a panel of immunostains where loss of staining can be used as a marker of various neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Judkins AR, Mauger J, Ht A, Rorke LB, Biegel JA. Immunohistochemical analysis of hSNF5/INI1 in pediatric CNS neoplasms. Am J Surg Pathol. 2004;28(5):644-650. doi:10.1097/00000478-200405000-00013 2. DeCristofaro MF, Betz BL, Rorie CJ, Reisman DN, Wang W, Weissman BE. Characterization of SWI/SNF protein expression in human breast cancer cell lines and other malignancies. J Cell Physiol. 2001;186:136-145. doi:10.1002/1097-4652(200101)186:1<136::AID-JCP1010>3.0.CO;2-4 3. Kleinschmidt-DeMaster BK, Meltesen L, McGavran L, Lillehei KO. Characterization of glioblastomas in young adults. Brain Pathol. 2006;16:273-286. doi:10.1111/j.1750-3639.2006.00029.x 4. Parham DM. Immunohistochemical markers of soft tissue tumors: pathologic diagnosis, genetic contributions, and therapeutic options. Anal Chem Insights. 2015;10(Suppl 1):1-10. doi:10.4137/ACI.S32730 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

IEHCG 606587 Interference Evaluation Heterophile, Beta-Human Chorionic Gonadotropin, Serum

Clinical Information: Due to exposure to animal antigens, some patients have developed antibodies that interfere with immunoassay testing. These heterophilic antibodies can bind to animal antibodies used in immunoassays. It has been found that a significant percentage of certain sandwich immunoassay results are false-positive results caused by heterophilic antibody interference. The most frequently reported assay interference effect of heterophilic antibodies is a false-positive assay result. False-negative assay results have also been reported in the literature. Manufacturers add blocking agents to their reagents, but occasional patient samples containing heterophile antibodies are incompletely blocked. Subsequent reporting of erroneous results can have adverse effects on patient management, especially with tumor marker assays. Among immunometric assays, human chorionic gonadotropin (hCG) assays have been found uniquely susceptible to heterophile antibody interference, resulting in occasional false-positive results. The current assay has proven robust in this respect, but rare interferences still occur. Typically, the observed false-positive elevations are modest, ranging from just above the reference range to levels of 50 to 60 IU/L. If such results are seen and are discordant with the clinical picture or other biochemical or imaging tests, then the laboratory should be alerted. After additional blocking treatment, repeat analysis of the specimen in question may resolve the issue. Dilution of the specimen prior to assay performance often yields unexpected nonlinear results in the presence of interfering substances, such as heterophile antibodies. Heterophile blocking tube treatment is used for troubleshooting samples that yield results that are either nonlinear or do not match the

clinical picture of the patient and are suspected of containing heterophile antibodies. Finally, assessment of an analyte, such as hCG with an alternative assay will often lead to apparent discrepant results in the presence of a heterophile antibody, as heterophile antibodies often interact differently with alternative assay antibodies. Human chorionic gonadotropin (hCG) is a glycoprotein hormone (molecular weight [MW] approximately 36,000 Da) consisting of 2 noncovalently bound subunits. The alpha subunit (92-amino acids; "naked" protein MW 10,205 Da) is essentially identical to that of luteinizing hormone (LH), follicle-stimulating hormone, and thyrotropin. The alpha subunit is essential for receptor transactivation. The different beta subunits of the above hormones are transcribed from separate genes, show less homology, and convey the receptor-specificity of the dimeric hormones. The chorionic gonadotropin, beta gene (coding for a 145-amino acid, "naked" protein MW 15,531 Da; glycosylated subunit MW approximately 22,500 Da) is highly homologous to the beta subunit of LH and acts through the same receptor. However, while LH is a classical tropic pituitary hormone, hCG does not usually circulate in significant concentrations. In pregnant primates (including humans), it is synthesized in the placenta and maintains the corpus luteum and, hence, progesterone production, during the first trimester. Thereafter, the placenta produces steroid hormones, diminishing the role of hCG. HCG concentrations fall, leveling off around week 20, significantly above prepregnancy levels. After delivery, miscarriage, or pregnancy termination, hCG levels fall, with a half-life of 24 to 36 hours, until prepregnancy levels are reached. Outside of pregnancy, hCG may be secreted by abnormal germ cell, placental, or embryonal tissues, in some seminomatous and nonseminomatous testicular tumors; ovarian germ cell tumors; gestational trophoblastic disease (hydatidiform mole and choriocarcinoma); and benign or malignant nontesticular teratomas. Rarely, other tumors, including hepatic, neuroendocrine, breast, ovarian, pancreatic, cervical, and gastric cancers may secrete hCG, usually in relatively modest quantities. During pathological hCG production, the highly coordinated secretion of alpha and beta subunits of hCG may be disturbed. In addition to secreting intact hCG, tumors may produce disproportionate quantities of free alpha-subunits or, more commonly, free beta-subunits. Assays that detect both intact hCG and free beta-hCG, including the electrochemiluminescent immunoassay assay, tend to be more sensitive in detecting hCG-producing tumors. With successful treatment of hCG-producing tumors, hCG levels should fall with a half-life of 24 to 36 hours and, eventually, return to the reference range. The alternate testing method is an enzymatic immunoassay. Values obtained with different assay methods or kits may be different and cannot be used interchangeably.

Useful For: Evaluating suspected interference from heterophile antibodies causing a falsely elevated human chorionic gonadotropin result This test is not to be used for pregnancy testing.

Interpretation: Specimens are evaluated for potential heterophile antibody interference in the Roche Elecsys total beta-human chorionic gonadotropin (hCG) immunoassay. Evaluation consists of pretreatment with commercial heterophile antibody blocking tube reagents, serial dilution of the sample, and testing on an alternate platform (Beckman Coulter DxI). The presence of heterophile antibody interference in the Roche Elecsys assay is not suspected when the results from the pretreatment, serial dilution, and the alternative platform agree within 20% of the original result. The presence of heterophile antibody interference in the Roche Elecsys assay is suspected when 1 or more of the following are observed: a significant decrease in hCG (>20%) upon treatment of the sample with heterophile antibody blocking reagents, lack of linearity upon serial dilutions, or a significant difference in hCG concentration on the alternate platform. When a heterophile antibody interference affecting the Roche Elecsys assay is suspected, the hCG results from this assay are considered false-positive results and should not be used in clinical management. Heterophile reagent blocking tubes (HBT-Scantibodies) contain a unique blocking reagent composed of specific binders, which inactivate heterophilic antibodies. Once the specific binders have bound to the heterophilic antibodies, the antibodies are no longer able to cause immunoassay interference. Blocking agents do not inhibit all heterophilic antibodies completely and cannot be used to rule out the presence of heterophile antibody interference. For patients with apparent serum hCG concentrations greater than 15 to 20 IU/L, hCG should also be detectable in urine if it is truly elevated. Failure to detect urinary hCG in such patients can support the suspicion of a false-positive serum hCG test. After delivery, miscarriage, or pregnancy termination, hCG levels fall with a half-life of 24 to 36 hours, until prepregnancy levels are reached. An absent or significantly slower decline is seen in patients

with retained products of conception. Gestational trophoblastic disease (GTD) is associated with very considerable elevations of hCG, usually above 2 multiples of the median for gestational age persisting, or even rising beyond, the first trimester. Serum hCG levels are elevated in approximately 40% to 50% of patients with nonseminomatous testicular cancer and 20% to 40% of patients with seminoma. Markedly elevated levels of hCG (>5000 IU/L) are uncommon in patients with pure seminoma and indicate the presence of a mixed testicular cancer. Ovarian germ cell tumors (approximately 10% of ovarian tumors) display elevated hCG levels in 20% to 50% of cases. Teratomas in children may overproduce hCG, even when benign, resulting in precocious pseudopuberty. Levels may be elevated to similar levels as seen in testicular cancer. Among nonreproductive tumors, hepatobiliary tumors (hepatoblastomas, hepatocellular carcinomas, and cholangiocarcinomas) and neuroendocrine tumors (eg, islet cell tumors and carcinoids) are those most frequently associated with hCG production. Many hCG-producing tumors also produce other embryonic proteins/antigens, in particular alpha fetoprotein (AFP). Therefore, AFP should also be measured in the diagnostic workup of such neoplasms. Complete therapeutic response in hCG-secreting tumors is characterized by a decline in hCG levels with an apparent half-life of 24 to 36 hours and eventual return to concentrations within the reference range. GTD and some tumors may produce hyperglycosylated hCG with a longer half-life, but an apparent half-life of greater than 3 days suggests the presence of residual hCG-producing tumor tissue. A rise in hCG levels above the reference range in patients with hCG-producing tumors that had previously been treated successfully suggests possible local or distant metastatic recurrence.

Reference Values:

BETA-HUMAN CHORIONIC GONADOTROPIN, QUANTITATIVE, SERUM

Children(1,2)

Males

Birth-3 months: < or =50 IU/L*

>3 months-<18 years: <1.4 IU/L

Females

Birth-3 months: < or =50 IU/L*

>3 months-<18 years: <1.0 IU/L

Pediatric reference values based on:

1. Chen RJ, Huang SC, Chow SN, Hsieh CY: Human chorionic gonadotropin pattern in maternal circulation. Amniotic fluid and fetal circulation in late pregnancy. J Reprod Med. 1993;38(2):151-154

2. Schneider DT, Calaminus G, Gobel U: Diagnostic value of alpha 1-fetoprotein and beta-human chorionic gonadotropin in infancy and childhood. Pediatr Hematol Oncol. 2001;18(1):11-26

*Human chorionic gonadotropin (hCG), produced in the placenta, partially passes the placental barrier. Newborn serum beta-hCG concentrations are approximately 1/400th of the corresponding maternal serum concentrations, resulting in neonate beta-hCG levels of 10-50 IU/L at birth. Clearance half-life is approximately 2 to 3 days. Therefore, by 3 months of age, levels comparable to adults should be reached.

Adults (97.5th percentile)

Males: <1.4 IU/L

Females

Premenopausal, nonpregnant: <1.0 IU/L

Postmenopausal: <7.0 IU/L

HUMAN CHORIONIC GONADOTROPIN, ALTERNATIVE METHOD

Males

Birth-3 months: Not established

>3 months-49 years: <0.6 IU/L

50 years-80 years: <1.6 IU/L

>80 years: Not established

Females

Birth-3 months: Not established
>3 months-40 years: <0.6 IU/L
41 years-50 years: <6.2 IU/L
51 years-150 years: <7.8 IU/L

Clinical References: 1. Cole LA, Khanlian SA, Muller CY: Detection of perimenopause or postmenopause human chorionic gonadotropin: an unnecessary source of alarm. Am J Obstet Gynecol. 2008 Mar;198(3):275.e1-7. doi: 10.1016/j.ajog.2007.09.034 2. Schneider DT, Calaminus G, Gobel U: Diagnostic value of alpha 1-fetoprotein and beta-human chorionic gonadotropin in infancy and childhood. Pediatr Hematol Oncol. 2001 Jan-Feb;18(1):11-26 3. Cole LA, Butler S: Detection of hCG in trophoblastic disease. The USA hCG reference service experience. J Reprod Med. 2002 Jun;47(6):433-444 4. von Eyben FE: Laboratory markers and germ cell tumors. Crit Rev Clin Lab Sci. 2003 Aug;40(4):377-427 5. Sturgeon CM, Duffy MJ, Stenman UH, et al: National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. Clin Chem. 2008 Dec;54(12):e11-79. doi: 10.1373/clinchem.2008.105601 6. Jara-Aguirre JC, Baumann NA, Block DR, Algeciras-Schimnich A: Human chorionic gonadotropin suspected heterophile interference investigations in immunoassays: a recommended approach. Clin Chem Lab Med. 2019 Jul 26;57(8):1192-1196. doi: 10.1515/cclm-2018-1142 7. Sturgeon CM, Viljoen A: Analytical error and interference in immunoassay: minimizing risk. Ann Clin Biochem. 2011 Sep;48(Pt 5):418-432. doi: 10.1258/acb.2011.011073 8. Marks V: False-positive immunoassay results: a multicenter survey of erroneous immunoassay results from assays of 74 analytes in 10 donors from 66 laboratories in seven countries. Clin Chem. 2002 Nov;48(11):2008-2016 9. Tate J, Ward G: Interferences in immunoassay. Clin Biochem Rev. 2004 May;25(2):105-120

IETG
610069

Interference Evaluation Heterophile, Thyroglobulin Tumor Marker, Serum

Clinical Information: Serum thyroglobulin (Tg) measurements are used in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is thyroid specific, serum Tg concentrations should be undetectable or very low after the thyroid gland is removed during treatment for thyroid cancer. Most often Tg is measured by immunometric assays as they are widely available in automated high-throughput instruments, have shorter turnaround times, and have functional sensitivities of 0.1 mcg/L or less. However, these immunoassays may be affected by the presence of both anti-thyroglobulin antibody (TgAb) and heterophile antibody interferences. The presence of TgAb might cause falsely low/undetectable Tg that can mask disease; whereas heterophile antibodies might cause falsely high Tg that can be mistaken for residual or recurrent disease. Some patients, due to exposure to animal antigens, have developed heterophile antibodies, such as human anti-mouse antibodies, that can interfere with immunoassay testing by binding to the animal antibodies used in immunoassays. In some sandwich immunoassays, including those for Tg, the presence of heterophile antibodies in the patient's sample might lead to a false-positive result. Although rare, false-negative assay results due to heterophile interference have also been reported in the literature. Manufacturers often add blocking agents to their reagents, but, occasionally, patient samples containing heterophile antibodies are incompletely blocked and exhibit heterophile antibody interference. Subsequent reporting of erroneous results can have adverse effects on patient management, especially with tumor marker assays. Dilution of the specimen prior to assay performance often yields unexpected nonlinear results in the presence of interfering substances such as heterophile antibodies and/or TgAb. Heterophile blocking tube treatment is also utilized for troubleshooting samples that exhibit potential heterophile interference. Finally, assessment of an analyte such as Tg with an alternative assay will often lead to apparent discrepant results in the presence of heterophile antibodies and/or TgAb interference. Measurement of Tg by liquid chromatography tandem mass spectrometry (Tg-MS) has been introduced as a method for accurate Tg quantitation in the presence of TgAb and heterophile antibodies. Tg-MS assays are based on peptide quantitation after tryptic

digestion and immunocapture of Tg-specific peptides. The advantage of trypsin digestion is that all proteins are cleaved, including both TgAb and heterophile antibodies, thus eliminating them as interferences.

Useful For: Evaluation of suspected interference from heterophile antibodies causing a falsely elevated thyroglobulin result

Interpretation: Specimens are evaluated for the presence of potential interfering anti-thyroglobulin (TgAb) and heterophile antibody interference in the Beckman Access thyroglobulin (Tg) immunoassay. While the presence of TgAb can result in falsely low Tg concentrations in the Beckman immunoassay, the presence of heterophile antibodies can result in falsely elevated Tg concentrations in the Beckman immunoassay. Following investigation of the presence of TgAb, heterophile antibody evaluation consists of pretreatment with commercial heterophile antibody blocking reagents, serial dilutions of the sample, and testing on an alternate platform generally unaffected by the presence of heterophile antibodies or TgAb (ie, Tg liquid chromatography tandem mass spectrometry [Tg-MS]). The presence of heterophile antibody interference in the Beckman Access Tg immunoassay is not suspected when the results from the pretreatment, serial dilutions, and the alternative platform (Tg-MS) agree with the original result. The presence of heterophile antibody interference in the Beckman Access Tg immunoassay is suspected when 1 or more of the following are observed: a significant decrease in Tg concentration (>20%) upon treatment of the sample with heterophile antibody blocking reagents, lack of linearity upon serial dilutions, or a significant difference in Tg concentration on the alternate platform (Tg-MS). When a heterophile antibody interference affecting the Beckman Access immunoassay is suspected, the Tg result from this assay is considered false positive and should not be used in clinical management. Thyroglobulin Antibody: Thyroglobulin antibody may interfere with the measurement of Tg. TgAb should be measured in conjunction with every measurement of serum Tg to rule out potential interference. Anti-Tg antibodies greater or equal to 1.8 IU/mL are likely to cause interference in the Tg immunoassay. In the Beckman Access Tg immunoassay utilized in this interference evaluation, the presence of TgAb is most likely to cause a reduction in measured Tg concentrations. Measurement of Tg by mass spectrometry is not affected by the presence of TgAb.

Reference Values:

THYROGLOBULIN TUMOR MARKER
< or =33 ng/mL

THYROGLOBULIN, MASS SPECTROMETRY
< or =33 ng/mL

THYROGLOBULIN ANTIBODY
<1.8 IU/mL
Reference values apply to all ages.

Clinical References: 1. Barbesino G, Algeciras-Schimnich A, Bornhorst JA. False positives in thyroglobulin determinations due to the presence of heterophile antibodies: an underrecognized and consequential clinical problem. Endocr Pract. 2021;27(5):396-400. doi:10.1016/j.eprac.2020.10.011 2. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-1214 3. Netzel BC, Grebe SKG, Algeciras-Schimnich A. Usefulness of a thyroglobulin liquid chromatography-tandem mass spectrometry assay for evaluation of suspected heterophile interference. Clin Chem. 2014;60(7):1016-1018 4. Algeciras-Schimnich A. Thyroglobulin measurement in the management of patients with differentiated thyroid cancer. Crit Rev Clin Lab Sci. 2018;55(3):205-218 5. Ward G, Simpson A, Boscato L, Hickman PE. The investigation of interferences in immunoassay. Clin Biochem. 2017;50(18):1306-1311

IRF8
620064

Interferon Regulatory Factor 8 (IRF8) Immunostain, Technical Component Only

Clinical Information: Interferon regulatory factor 8 (IRF8) is a marker for monocytic and dendritic cell progenitors. Expression of IRF8 is useful for detecting monoblasts in both acute monoblastic/monocytic leukemia and advancing chronic myelomonocytic leukemia. IRF8 expression is also observed in blastic plasmacytoid dendritic cell neoplasm and may be useful to distinguish classic Hodgkin lymphoma and anaplastic large cell lymphoma.

Useful For: Identification of monoblasts in acute monoblastic/monocytic leukemia and chronic myelomonocytic leukemia

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Katz SG, Edappallath S, Xu ML. IRF8 is a reliable monoblast marker for acute monocytic leukemias. Am J Surg Pathol. 2021;45(10):1391-1398 2. Tzankov A, Facchetti, F, Muhleisen B, Dirnhofer S. IRF8 is a reliable monoblast marker for acute monocytic leukemias, but does not discriminate between monoblasts and plasmacytoid dendritic cells. Am J Surg Pathol. 2022;46(5):725-727 3. McQuaid DC, Katz SG, Xu ML. IRF8 as a novel marker to differentiate between CD30-positive large cell lymphomas. Am J Clin Pathol. 2022;158(2):173-176

FIFNY
57586

Interferon-gamma (IFN-y) Serum

Reference Values:
<8.6 pg/mL

FIN1A
75908

Interleukin 1-Alpha

Clinical Information: The Interleukins belong to the family termed cytokines. They are peptides used by immune and inflammatory cells to communicate and control cell operations. The cytokines have some similar actions to the Growth Factors but Growth Factors regulate proliferation of non-immune cells. Interleukin 1a is a 17,500 molecular weight peptide derived primarily from macrophages, fibroblasts, endothelial cells, and B cells. The major target cells are T and B cells, Fibroblasts, and Hepatocytes. Interleukin 1a shares a receptor with Interleukin 1b although they are significantly different structurally. Interleukin 1a promotes antigen specific immune responses, inflammation, Prostaglandin secretion, Colony Stimulating Factors, proteoglycanase, collagenase, and gelatinase activity, and release of Interleukin 2 from T cells. Levels are stimulated by liposaccharide, endotoxins, inflammatory agents, lectin, Tumor Necrosis Factor, and Interferons. Levels are suppressed by Corticosteroids, Prostaglandin E2, and suppressant lymphocytes.

Reference Values:
Less than 3.9 pg/mL

Clinical References: 1. JT Whicher and SW Evans. Cytokines in Disease. Clinical Chemistry 36: 1269-1281, 1990. 2. MP Bevilacqua, JS Pober, GR Majeau, W Fiers, RS Cotran, and MA Gimbrone. Recombinant Tumor Necrosis Factor Induced Pro-Coagulant Activity in Cultured Human Vascular

Endothelium: Characterization and Comparison with Action of Interleukin-1. Proceedings of the National Academy of Science 83: 4533-4537, 1986.

FIL2M
57826

Interleukin 2

Interpretation: Interpretive Information: Cytokines Results are to be used for research purposes or in attempts to understand the pathophysiology of immune, infectious, or inflammatory disorders.

Reference Values:
2.1 pg/mL or less

IL28Q
610056

Interleukin 28B (IL28B) Variant (rs12979860), Varies

Clinical Information: Individuals with hepatitis C virus (HCV) genotype 1 infections have variable responses to treatment with pegylated-interferon and ribavirin combination therapy. Some individuals will respond to treatment with sustained viral response, while other patients have poor response and fail to achieve sustained viral clearance. Response to pegylated-interferon and ribavirin combination therapy in HCV genotype 1-infected individuals has been found to be closely associated with a single-nucleotide variant (SNV), designated rs12979860, located 3 kilobases upstream from the interleukin 28B gene locus (IL28B, also known as IFNL3) present on human chromosome 19. HCV genotype 1-infected individuals with the CC genotype, as compared to either the CT or TT genotypes, of this SNP in IL28B have approximately 2- to 3-fold greater rates of sustained viral response to combined pegylated-interferon and ribavirin therapy.(1) Similar increases in sustained viral response rates were observed across various racial groups, including European Americans (95% CI, 1.8- to 2.3-fold), African Americans (95% CI, 1.9- to 4.7-fold), and Hispanics (95% CI, 1.4- to 3.2-fold).(1) The CC genotype has also been associated with a 3-fold increase in rate of spontaneous clearance of HCV.(2,4) The SNV in IL28B is only one of many factors that can influence response rates to pegylated-interferon and ribavirin combination therapy in HCV genotype 1 infection, and the SNV genotype result should be interpreted in the context of other clinical factors present in a given patient. Frequency of the rs12979860 C allele varies across different racial and ethnic groups. The rs12979860 C variant is most frequently present in individuals from East Asia (allele frequency >0.9) and least common in individuals of African origin (allele frequency 0.2-0.5).(2) In a recent US-based study, the favorable CC genotype was observed in 37% of Whites, 29% Hispanics, and 14% of African Americans tested. The mechanism by which the IL28B genotype mediates response to pegylated-interferon and ribavirin combination therapy among HCV genotype 1-infected individuals is not yet understood and is the subject of intense ongoing research. The impact of the IL28B-related alteration on response rates in patients infected with HCV genotypes other than genotype 1 is still being investigated.

Useful For: Predicting responsiveness of genotype 1 hepatitis C viral infections to combined pegylated-interferon and ribavirin-based therapies

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009;461(7262):399-401 2. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature. 2009;461(7265):798-801 3. Charlton MR, Thompson A, Veldt BJ, et al. Interleukin-28B

polymorphisms are associated with histological recurrence and treatment response following liver transplantation in patients with hepatitis C virus infection. Hepatology. 2011;53(1):317-324 4. Thompson AJ, Muir AJ, Sulkowski MS, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. Gastroenterology. 2010;139(1):120-9.e18. doi:10.1053/j.gastro.2010.04.013

IL5P
36519

Interleukin 5, Plasma

Clinical Information: Interleukin-5 (IL-5), a homodimer composed of two 20-kDa subunits, is expressed primarily by CD4+ Th2 (helper T cells, subset 2) cells and, to a lesser extent, by activated mast cells.(1,2) IL-5 acts on mature eosinophils, leading to proliferation, activation, differentiation, and survival. IL-5 plays a critical role in the host immune response to helminthic infections and has been implicated in the pathology of certain allergic diseases, asthma, and vasculitis.(1-3) In these diseases, it is associated with significant increase in levels of eosinophils, a condition referred to as hypereosinophilia. IL-5 is known to activate eosinophils, which interact through their Fc receptors to bind helminths that have been opsonized by IgG or IgA specific antibodies.(1) Of the other diseases associated with IL-5 and hypereosinophilia, those of the skin and airways (urticaria, asthma, allergic bronchopulmonary aspergillosis, and eosinophilic granulomatosis with polyangiitis [EGPA]) have received considerable attention recently due to availability of therapies that target the IL-5 pathways.(4) In EPGA, increased levels of IL-5 have been seen in a subset of patients with implications for disease management.(4,5) The IL-5 pathway-directed therapies have been approved for use in patients with severe eosinophilic asthma. With availability of these therapies, it is likely that IL-5 cytokine testing may be used to identify patients at-risk for disease.

Useful For: Evaluation of patients with disorders known to be associated with hypereosinophilia

Interpretation: Elevated concentrations of interleukin-5 (IL-5) may indicate an expanded Th2 (helper T cells, subset 2)-immune response, which may be associated with hypereosinophilia.

Reference Values:
< or =1.0 pg/mL

Clinical References: 1. Nakayama T, Hirahara K, Onodera A, et al. Th2 cells in health and disease. Annu Rev Immunol. 2017;35:53-84 2. Yanagibashi T, Satoh M, Nagai Y, Koike M, Takatsu K. Allergic diseases: From bench to clinic - Contribution of the discovery of interleukin-5. Cytokine. 2017;98:59-70 3. Kandikattu HK, Venkateshaiah SU, Mishra A. Synergy of interleukin (IL)-5 and IL-18 in eosinophil mediated pathogenesis of allergic diseases. Cytokine Growth Factor Rev. 2019;47:83-98 4. Harish A, Schwartz SA: Targeted anti-IL-5 therapies and future therapeutics for hypereosinophilic syndrome and rare eosinophilic conditions. Clin Rev Allergy Immunol. 2020;59(2):231-247 5. Nishi R, Koike H, Ohyama K, et al. Association between IL-5 levels and the clinicopathologic features of eosinophilic granulomatosis with polyangiitis. Neurology. 2021;96(5):226-229 6. Melo JT Jr, Tunstall T, Pizzichini MMM, et al: IL-5 levels in nasosorption and sputosorption correlate with sputum eosinophilia in allergic asthma. Am J Respir Crit Care Med. 2019;199(2):240-243 7. Guntur VP, Manka LA, Denson JL, et al: Benralizumab as a steroid-sparing treatment option in eosinophilic granulomatosis with polyangiitis. J Allergy Clin Immunol Pract. 2021;9(3):1186-1193 8. Hillas G, Fouka E, Papaioannou AI: Antibodies targeting the interleukin-5 signaling pathway used as add-on therapy for patients with severe eosinophilic asthma: a review of the mechanism of action, efficacy, and safety of the subcutaneously administered agents, mepolizumab and benralizumab. Expert Rev Respir Med. 2020;14(4):353-365

IL1B
622327

Interleukin-1 Beta, Plasma

Clinical Information: Interleukin-1 (IL-1) beta is a potent pro-inflammatory cytokine that is crucial for host-defence responses to infection and injury. IL-1 beta binds to IL-1 receptor 1 (IL-1R1) and initiates inflammatory responses in T-lymphocytes, epithelial cells and endothelial cells.(1,2) Excess IL-1 beta signaling have been associated with acute inflammation and chronic autoinflammatory diseases.(3) Plasma IL-1 beta concentrations are elevated in some rheumatoid arthritis patients compared to healthy volunteers. There are increased concentrations of IL-1 beta and tumor necrosis factor-alpha in synovial fluid of rheumatoid arthritis patients. Several biologics, such as anakinra and canakinumab, have been developed to inhibit the IL-1 signaling pathway by blocking IL-1 beta binding to IL-1 receptors in rheumatoid arthritis, familial Mediterranean fever, cryopyrin-associated periodic syndromes, etc.(2,4)

Useful For: Measuring the concentration of interleukin-1 beta in plasma Evaluating patients experiencing inflammatory conditions, autoinflammatory disorders, and infection

Interpretation: Elevated interleukin-1 beta concentrations could indicate the presence of inflammatory or infectious condition.

Reference Values:
<18 years: Not established
> or =18 years: <20.0 pg/mL

Clinical References: 1. Pretre V, Papadopoulos D, Regard J, Pelletier M, Woo J. Interleukin-1 (IL-1) and the inflammasome in cancer. Cytokine. 2022;153:155850 2. Imazio M, Lazaros G, Gattorno M, et al. Anti-interleukin-1 agents for pericarditis: a primer for cardiologists. Eur Heart J. 2022;43(31):2946-2957 3. Carta S, Semino C, Sitia R, Rubartelli A. Dysregulated IL-1 beta Secretion in Autoinflammatory Diseases: A Matter of Stress?. Front Immunol. 2017;8:345 4. Kaneko N, Kurata M, Yamamoto T, Morikawa S, Masumoto J. The role of interleukin-1 in general pathology. Inflamm Regen. 2019;39:12

SIL2R
622328

Interleukin-2 Receptor Alpha Soluble, Plasma

Clinical Information: The interleukin-2 (IL-2) receptor (CD25) is a membrane protein that is upregulated on activated T cells. Its soluble form, IL-2 receptor alpha soluble (sIL-2r alpha, soluble CD25) is notably elevated in lymphoproliferative disorders, such as hemophagocytic lymphohistiocytosis (HLH), autoimmune lymphoproliferative syndrome (ALPS), T-cell related leukemia-lymphoma and other conditions associated with T-cell activation.(1) Based on the HLH-2004 trial, the diagnosis of HLH syndrome should be based on compatible clinical presentation in the context of significantly elevated inflammatory markers, including ferritin, sIL-2r alpha, and CXCL9 (C-X-C motif chemokine ligand 9). sIL-2r alpha elevation at a significant level (2SD above age-adjusted laboratory-specific reference range) is a crucial diagnostic criterion.(2) In addition to activated T cells, IL-2 receptor is also expressed on a certain subset of B cells, Regulatory Teg cells, granulocytes and natural killer (NK) cells.(3) Elevation of sIL-2r alpha can be observed in other chronic inflammatory conditions and malignancies.(4,5) In sarcoidosis patients with cardiac involvement, higher levels of sIL-2r alpha are associated with worse long-term clinical outcomes and increase systemic inflammatory activities.(6) In patients with hematological malignancies that express IL-2 receptors, sIL-2r alpha elevations are associated with poor prognosis or disease relapse.(4,7)

Useful For: Measuring the concentration of soluble interleukin-2 receptor alpha (sIL-2r alpha) in plasma Aids in the diagnosis and evaluation of patients for lymphoproliferative disorders, including autoimmune lymphoproliferative syndrome, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome May help monitor patients with sarcoidosis or hematologic malignancies with elevated sIL-2r alpha

Interpretation: A significant elevation in soluble interleukin-2 receptor alpha (sIL-2r alpha) concentration (2 standard deviations above age-adjusted laboratory-specific reference range) is one of the diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH) syndrome. The diagnosis of HLH syndrome should be based on compatible clinical presentation in the context of significantly elevated inflammatory markers, including ferritin, sIL-2r alpha, and CXCL9 (C-X-C motif chemokine ligand 9).

Reference Values:
<18 years: Not established
> or =18 years: <959 pg/mL

Clinical References: 1. Hayden A, Lin M, Park S, et al. Soluble interleukin-2 receptor is a sensitive diagnostic test in adult HLH. Blood Adv. 2017;1(26):2529-2534 2. Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124-131 3. Riley, R.S., R. Mageau, and J. Ben-Ezra, Laboratory Evaluation of the Cellular Immune System, in Henry's Clinical Diagnosis and Management by Laboratory Methods. 2011. p. 877-898 4. Yang ZZ, Grote DM, Ziesmer SC, et al. Soluble IL-2Ra facilitates IL-2-mediated immune responses and predicts reduced survival in follicular B-cell non-Hodgkin lymphoma. Blood. 2011;118(10):2809-2820 5. Seidler S, Zimmermann HW, Weiskirchen R, Trautwein C, Tacke F. Elevated circulating soluble interleukin-2 receptor in patients with chronic liver diseases is associated with non-classical monocytes. BMC Gastroenterol. 2012;12:38 6. Kobayashi Y, Sato T, Nagai T, et al. Association of high serum soluble interleukin 2 receptor levels with risk of adverse events in cardiac sarcoidosis. ESC Heart Fail. 2021;8(6):5282-5292 7. Zoref-Lorenz A, Murakami J, Hofstetter L, et al. An improved index for diagnosis and mortality prediction in malignancy-associated hemophagocytic lymphohistiocytosis. Blood. 2022;139(7):1098-1110

FIL4S
57585

Interleukin-4 (IL-4) Serum

Reference Values:
<0.5 pg/mL

IL6DX
618776

Interleukin-6, Serum

Clinical Information: Interleukin 6 (IL-6) has important roles in both innate and adaptive immunity.(1) IL-6 can be produced by a variety of different cell types, including macrophages, endothelial cells, and T cells. This production can be initiated in response to microbial invasion or other cytokines, such as tumor necrosis factor. As part of the innate immune system, IL-6 acts on hepatocytes to induce expression of C-reactive protein (CRP), fibrinogen, and serum amyloid A, also known as the acute phase response. Within the adaptive immune response, IL-6 plays a key role in activating antibody-producing B cells to proliferate, leading to an enhanced antibody response. Concentrations of IL-6 are elevated in patients with infection, sepsis, and septicemia. During inflammatory conditions, the concentration of IL-6 can increase severalfold, highlighting its clinical relevance as a major alarm signal in response to infections (sepsis/septicemia), inflammation, autoimmunity, and cancer, including Castleman disease. In addition, IL-6 concentrations appear to correlate with the severity of sepsis, as defined by clinical and laboratory parameters.(2) Elevations in IL-6 also appear to be associated with more localized infections, such as prosthetic joint infections (PJI).(3) A recent meta-analysis demonstrated that IL-6 had improved diagnostic accuracy for PJI compared to CRP, erythrocyte sedimentation rate, and white blood cell counts. IL-6 is also elevated in numerous chronic inflammatory disorders, including rheumatoid arthritis (RA), systemic lupus erythematosus, ankylosing spondylitis, and inflammatory bowel disease.(4) There is evidence that IL-6 is involved in the pathogenesis of certain chronic inflammatory disorders. Tocilizumab, an antibody that blocks IL-6 function by binding to the IL-6 receptor, has been approved for the treatment of RA. In a randomized trial, 50% to 60% of patients

receiving tocilizumab and methotrexate showed improvement in clinical signs and symptoms of RA, compared to only 25% of patients receiving methotrexate alone.(5) Siltuximab, a monoclonal antibody against IL-6, is also sometimes used to treat Castleman disease. However, the presence of Siltuximab may interfere with some IL-6 assays, leading to the proposed use of CRP as a surrogate marker to monitor Siltuximab efficacy.(6-8) IL-6 has also been shown to be elevated in COVID-19 patients. There is some indication that patients with more severe disease may develop elevated circulating IL-6. The significance of this finding is still being elucidated, including whether monitoring of circulating IL-6 levels can help with patient management, prognosis, or response to treatment.(9,10)

Useful For: Evaluating patients with suspected chronic inflammatory disorders, such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, or inflammatory bowel disease Evaluating patients with Castleman disease Evaluating patients with suspected systemic infection Evaluating patients with suspected localized infection, specifically prosthetic joint infection Assisting in identifying severe inflammatory response in patients with confirmed COVID-19 illness to aid in determining the risk of intubation with mechanical ventilation, in conjunction with clinical findings and the results of other laboratory testing

Interpretation: Elevated concentrations of interleukin 6 may indicate an ongoing inflammatory response and could be consistent with a systemic infection, localized infection, or chronic inflammatory disease.

Reference Values:
< 6.4 pg/mL

Clinical References: 1. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta. 2011;1813(5):878-888 2. Tsalik E, Jaggers B, Glickman SW, et al. Discriminative value of inflammatory biomarkers for suspected sepsis. J Emerg Med. 2012;43(1):97-106 3. Berbari E, Mabry T, Tsaras G, et al. Inflammatory blood laboratory levels as markers of prosthetic joint infection: a systematic review and meta-analysis. J Bone Joint Surg Am. 2010;92(11):2102-2109 4. Gabay C: Interleukin-6 and chronic inflammation. Arthritis Res Ther. 2006;8 Suppl 2:S3 5. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomized trial. Lancet. 2008;371(9617):987-997 6. Yoshizaki K, Murayama S, Ito H, Koga T. The Role of interleukin-6 in Castleman disease. Hematol Oncol Clin North Am. 2018;32(1):23-36. doi:10.1016/j.hoc.2017.09.003 7. Sarosiek S, Shah R, Munshi NC. Review of siltuximab in the treatment of multicentric Castleman's disease. Ther Adv Hematol. 2016;7(6):360-366. doi:10.1177/2040620716653745 8. Chen F, Teachey DT, Pequignot E, et al. Measuring IL-6 and sIL-6R in serum from patients treated with tocilizumab and/or siltuximab following CAR T cell therapy. J Immunol Methods. 2016;434:1-8. doi: 10.1016/j.jim.2016.03.005 9. Gubernatororova EO, Gorshkova EA, Polinova AI, Drutskava MS. IL-6: Relevance for immunopathology of SARS-CoV-2. Cytokine Growth Factor Rev. 2020;53:13-24 10. Ashrafzadeh-Kian S, Campbell MR, Jara Aguirre JC, et al. Role of immune mediators in predicting hospitalization of SARS-CoV-2 positive patients. Cytokine. 2022;150:155790. doi:10.1016/j.cyto.2021.155790

FIL8S
57563

Interleukin-8 (IL-8) Serum

Reference Values:
<12.4 pg/mL

IFBA
9335

Intrinsic Factor Blocking Antibody, Serum

Clinical Information: The cobalamins, also referred to as vitamin B12, are a group of closely related enzymatic cofactors involved in the conversion of methylmalonyl-coenzyme A to succinyl-coenzyme A and in the synthesis of methionine from homocysteine. Vitamin B12 deficiency can lead to megaloblastic anemia and neurological deficits. The latter may exist without, or precede, anemia. Adequate replacement therapy will generally improve or cure cobalamin deficiency. Unfortunately, many other conditions, which require different interventions, can mimic the symptoms and signs of vitamin B12 deficiency. Moreover, even when cobalamin deficiency has been established, clinical improvement may require different dosages or routes of vitamin B12 replacement, depending on the underlying cause. In particular, patients with pernicious anemia (PA), possibly the most common type of cobalamin deficiency in developed countries, require either massive doses of oral vitamin B12 or parenteral replacement therapy. This is due to patients with PA having gastric mucosal atrophy, most likely caused by a destructive autoimmune process. This results in diminished or absent gastric acid, pepsin, and intrinsic factor (IF) production. Gastric acid and pepsin are required for liberation of cobalamin from binding proteins, while IF binds the free vitamin B12, carries it to receptors on the ileal mucosa, and facilitates its absorption. Most PA patients have autoantibodies against gastric parietal cells or IF, with the latter being very specific but only present in approximately 50% of cases. By contrast, parietal cell antibodies are found in approximately 90% of PA patients, but are also found in a significant proportion of patients with other autoimmune diseases and in approximately 2.5% (4th decade of life) to approximately 10% (8th decade of life) of healthy individuals.

Useful For: Confirming the diagnosis of pernicious anemia

Interpretation: The aim of the work-up of patients with suspected vitamin B12 deficiency is to first confirm the presence of deficiency and then to establish its most likely etiology. Measurement of serum vitamin B12, either preceded or followed by serum methylmalonic acid measurement, is the first step in diagnosing pernicious anemia (PA). If these tests support deficiency, then intrinsic factor blocking antibody (IFBA) testing is indicated to confirm PA as the etiology. A positive IFBA test very strongly supports a diagnosis of PA. Since the diagnostic sensitivity of IFBA testing for PA is only around 50%, an indeterminate or negative IFBA test does not exclude the diagnosis of PA. In these patients, either PA or another etiology, such as malnutrition, may be present. Measurement of serum gastrin levels will help in these cases. In patients with PA, fasting serum gastrin is elevated to more than 200 pg/mL in an attempted compensatory response to the achlorhydria seen in this condition. For a detailed overview of the optimal testing strategies in PA diagnosis, see ACASM / Pernicious Anemia Cascade, Serum and associated Vitamin B12 Deficiency Evaluation.

Reference Values:
Negative

Clinical References: 1. Toh BH, Van Driel IR, Gleeson PA: Pernicious anemia. N Engl J Med. 1997;337:1441-1448. doi: 10.1056/NEJM199711133372007 2. Klee GG: Cobalamin and folate evaluation: measurement of methylmalonic acid and homocysteine vs vitamin B12 and folate. Clin Chem. 2000;46:1277-1283 3. Ward PC: Modern approaches to the investigation of vitamin B12 deficiency. Clin Lab Med. 2002:22;435-445. doi: 10.1016/s0272-2712(01)00003-8 4. Stabler SP, Allen RH: Vitamin B12 deficiency as a worldwide problem. Ann Rev Nutr. 2004;24:299-326. doi: 10.1146/annurev.nutr.24.012003.132440 5. Roberts NB, Taylor A, Sodi R: Vitamins and trace elements. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:639-718 6. Bizzaro N, Antico A: Diagnosis and classification of pernicious anemia. Autoimmun Rev. 2014;13(4-5):565-568. doi: 10.1016/j.autrev.2014.01.042

UIOD
9549

Iodine, 24 Hour, Urine

Clinical Information: Iodine is an essential element for thyroid hormone production. The

measurement of urinary iodine is preferred for assessment of toxicity, recent exposure, and monitoring iodine excretion rate as an index of replacement therapy.

Useful For: Assessing iodine toxicity or recent exposure in a 24-hour urine collection Monitoring iodine excretion rate as index of replacement therapy

Interpretation: Measurement of urinary iodine excretion provides the best index of dietary iodine intake and deficiency is generally indicated when the concentrations are below 100 mcg/L. World Healthcare Organization (WHO) Criteria for Assessing Iodine Status Children older than 6 years and adults(1) Median urinary iodine (mcg/L) Iodine intake Iodine status <20 Insufficient Severe deficiency 20-49 Insufficient Moderate deficiency 50-99 Insufficient Mild deficiency 100-199 Adequate Adequate nutrition 200-299 Above requirements May pose a slight risk of more than adequate >299 Excessive Risk of adverse health consequences Pregnant women(1) Median urinary iodine (mcg/L) Iodine intake <150 Insufficient 150-249 Adequate 250-499 Above requirements >499 Excessive Lactating women and children younger than 2 years(1) Median urinary iodine (mcg/L) Iodine intake <100 Insufficient >99 Adequate

Reference Values:
0-17 years: Not established
> or =18 years: 75-851 mcg/24 hour

Clinical References: 1. Department of Nutrition for Health and Development (NHD); World Health Organization. Urinary iodine concentrations for determining iodine status in populations. World Health Organization; 2013. Accessed April 25, 2025. Available at www.who.int/publications/i/item/WHO-NMH-NHD-EPG-13.1 2. Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 3. Knudsen N, Christiansen E, Brandt-Christensen M, et al. Age- and sex-adjusted iodine/creatinine ratio. A new standard in epidemiological surveys? Evaluation of three different estimates of iodine excretion based on casual urine samples and comparison to 24 h values. Eur J Clin Nutr. 2000;54(4):361-363 4. Liberman CS, Pino SC, Fang SL, et al. Circulating iodine concentrations during and after pregnancy. J Clin Endocrinol Metab. 1998;83(10):3545-3549 5. Pfeiffer CM, Sternberg MR, Schleicher RL, et al. CDC's Second National Report on Biochemical Indicators of Diet and Nutrition in the US Population is a valuable tool for researchers and policy makers. J Nutr. 2013;143(6):938S-947S 6. Leung AM, Braverman LE. Consequences of excess iodine. Nat Rev Endocrinol. 2014;10(3):136-142. doi:10.1038/nrendo.2013.251 7. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry: Toxicological Profile for Iodine. HHS, 2004. Accessed April 25, 2025. Available at www.atsdr.cdc.gov/ToxProfiles/tp158.pdf

IOD
81574

Iodine, Serum

Clinical Information: Iodine is an essential element required for thyroid hormone production. The measurement of iodine serves as an index of adequate dietary iodine intake and iodine overload, particularly from iodine-containing drugs, such as amiodarone.

Useful For: Determining iodine overload using serum specimens Monitoring iodine levels in individuals taking iodine-containing drugs

Interpretation: Values between 80 ng/mL and 250 ng/mL have been reported to indicate hyperthyroidism. Values above 250 ng/mL may indicate iodine overload.

Reference Values:
40-92 ng/mL

Clinical References: 1. Allain P, Berre S, Krari N, et al. Use of plasma iodine assay for diagnosing thyroid disorders. J Clin Pathol. 1993;46(5):453-455 2. Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 3. Leung AM, Braverman LE. Consequences of excess iodine. Nat Rev Endocrinol. 2014;10(3):136-142. doi: 10.1038/nrendo.2013.251 4. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry: Toxicological Profile for Iodine. HHS; 2004. Accessed March 20, 2025. Available at www.atsdr.cdc.gov/ToxProfiles/tp158.pdf

IODCU
610708

Iodine/Creatinine Ratio, Random, Urine

Clinical Information: Iodine is an essential element for thyroid hormone production. The measurement of urinary iodine is preferred for assessment of toxicity, recent exposure, and monitoring iodine excretion rate as an index of replacement therapy.

Useful For: Assessment of iodine toxicity or recent iodine exposure using a random urine collection Monitoring iodine excretion rate as index of replacement therapy

Interpretation: Measurement of urinary iodine excretion provides the best index of dietary iodine intake and deficiency is generally indicated when the concentrations are below 100 mcg/L. For deficiency, 10 repeat random urines are recommended. World Healthcare Organization (WHO) Criteria for Assessing Iodine Status Children older than 6 years and adults Median urinary iodine (mcg/L) Iodine intake Iodine status <20 Insufficient Severe deficiency 20-49 Insufficient Moderate deficiency 50-99 Insufficient Mild deficiency 100-199 Adequate Adequate nutrition 200-299 Above requirements May pose a slight risk of more than adequate >299 Excessive Risk of adverse health consequences Pregnant women Median urinary iodine (mcg/L) Iodine intake <150 Insufficient 150-249 Adequate 250-499 Above requirements >499 Excessive Lactating women and children younger than 2 years Median urinary iodine (mcg/L) Iodine intake <100 Insufficient >99 Adequate

Reference Values:
0-17 years: Not established
> or =18 years: <584 mcg/g creatinine

Clinical References: 1. Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 2. Knudsen N, Christiansen E, Brandt-Christensen M, Nygaard B, Perrild H. Age- and sex-adjusted iodine/creatinine ratio. A new standard in epidemiological surveys? Evaluation of three different estimates of iodine excretion based on casual urine samples and comparison to 24 h values. Eur J Clin Nutr. 2000;54(4):361-363 3. Liberman CS, Pino SC, Fang SL, Braverman LE, Emerson CH. Circulating iodide concentrations during and after pregnancy. J Clin Endocrinol Metab. 1998;83(10):3545-3549 4. Pfeiffer CM, Sternberg MR, Schleicher RL, Haynes BM, Rybak ME, Pirkle JL. The CDC's Second National Report on Biochemical Indicators of Diet and Nutrition in the U.S. Population is a valuable tool for researchers and policy makers. J Nutr. 2013;143(6):938S-947S 5. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry: Toxicological Profile for Iodine. HHS; 2004. Accessed March 21, 2025. Available at www.atsdr.cdc.gov/ToxProfiles/tp158.pdf 6. Leung AM, Braverman LE. Consequences of excess iodine. Nat Rev Endocrinol. 2014;10(3):136-142. doi:10.1038/nrendo.2013.251 7. Beckford K, Grimes CA, Margerison C, et al. A systematic review and meta-analysis of 24-h urinary output of children and adolescents: impact on the assessment of iodine status using urinary biomarkers. Eur J Nutr. 2020;59(7):3113-3131. doi:10.1007/s00394-019-02151-w

HEXP
606984

Iohexol, Plasma

Clinical Information: The assessment of glomerular filtration rate (GFR) is an important parameter of kidney function utilized by clinicians in the care of patients with varying kidney diseases, and for clinical research when precise assessment of kidney function is necessary. The GFR is the sum of all the filtration rates of the individual nephrons within the kidney and, as such, reflects the number of functioning nephrons. Plasma concentrations of iohexol can be used for measurement of GFR through multiple plasma iohexol determinations following an intravenous bolus injection of iohexol (plasma disappearance) or following a continuous infusion (or subcutaneous injection) of iohexol when used in conjunction with urine iohexol determinations (urinary clearance; HEXU / Iohexol, Timed Collection, Urine).

Useful For: Determining glomerular filtration rate in plasma specimens

Interpretation: Low glomerular filtration rate (GFR) values indicate abnormal kidney function, which may be either reversible/transient or irreversible/permanent. GFR tends to decline with age.

Reference Values:
Not applicable

Clinical References: 1. Brown SC, O'Reilly PH. Iohexol clearance for the determination of glomerular filtration rate in clinical practice: evidence for a new gold standard. J Urol. 1991;146:675-679 2. Gaspari F, Perico N, Ruggenenti P, et al. Plasma clearance of nonradioactive iohexol as a measure of glomerular filtration rate. J Am Soc Nephrol. 1995;6:257-263 3. Schwartz GJ, Abraham AG, Furth SL, et al. Optimizing iohexol plasma disappearance curves to measure the glomerular filtration rate in children with chronic kidney disease. Kidney Int. 2010;77:65-71 4. Schmit DJ, Carroll LJ, Eckfeldt JH, Seegmiller JC. Verification of separate measurement procedures where analytical determinations influence the clinical interpretation of GFR: Iohexol quantitation by HPLC and LC-MS/MS. Clin Biochem. 2019;67:16-23 5. Seegmiller JC, Burns BE, Schinstock CA, Lieske JC, Larson TS. Discordance between iothalamate and iohexol urinary clearances. Am J Kid Dis. 2016;67(1):49-55

HEXU
606985

Iohexol, Timed Collection, Urine

Clinical Information: The assessment of glomerular filtration rate (GFR) is an important parameter of kidney function utilized by clinicians in the care of patients with varying kidney diseases, and for clinical research when precise assessment of kidney function is necessary. The GFR is the sum of all the filtration rates of the individual nephrons within the kidney and, as such, reflects the number of functioning nephrons. Urine concentrations of iohexol can be used for measurement of GFR following a subcutaneous injection of iohexol (plasma disappearance), or during a continuous infusion of iohexol when used in conjunction with plasma iohexol determinations (HEXP / Iohexol, Plasma). The results can be used to determine the clearance of iohexol, which is a measure of GFR.

Useful For: Determining glomerular filtration rate in urine specimens

Interpretation: Low glomerular filtration rate (GFR) values indicate abnormal kidney function, which may be either reversible/transient or irreversible/permanent. GFR tends to decline with age.

Reference Values:
Not applicable

Clinical References: 1. Brown SC, O'Reilly PH. Iohexol clearance for the determination of glomerular filtration rate in clinical practice: evidence for a new gold standard. J Urol.

1991;146(3):675-679 2. Gaspari F, Perico N, Ruggenenti P, et al. Plasma clearance of nonradioactive iohexol as a measure of glomerular filtration rate. J Am Soc Nephrol. 1995;6(2):257-263 3. Schwartz GJ, Abraham AG, Furth SL, Warady BA, Munoz A. Optimizing iohexol plasma disappearance curves to measure the glomerular filtration rate in children with chronic kidney disease. Kidney Int. 2010;77(1):65-71 4. Schmit DJ, Carroll LJ, Eckfeldt JH, Seegmiller JC. Verification of separate measurement procedures where analytical determinations influence the clinical interpretation of GFR: Iohexol quantitation by HPLC and LC-MS/MS. Clin Biochem. 2019;67:16-23 5. Seegmiller JC, Burns BE, Schinstock CA, Lieske JC, Larson TS. Discordance between iothalamate and iohexol urinary clearances. Am J Kid Dis. 2016;67(1):49-55

SFEC
621385

Iron and Total Iron-Binding Capacity, Serum

Clinical Information:

Useful For: Screening for chronic iron overload diseases, particularly hereditary hemochromatosis Screening for iron deficiency as the cause of anemia Monitoring treatment for iron deficiency anemia This test should not be used as the primary test for iron deficiency.

Interpretation: Serum iron concentration is elevated in iron overload conditions including hemochromatosis.(1) Serum iron concentration is decreased in iron deficiency, iron deficiency anemia, and anemia of chronic disease.(1) Total iron-binding capacity values are elevated in anemia of chronic disease and iron overload conditions.(1) Total iron-binding capacity values are decreased in iron deficiency, iron deficiency anemia, and iron-refractory iron deficiency anemia.(1) Percent saturation often exceeds 45% in hereditary hemochromatosis and 90% in advanced iron overload states.(2) Percent saturation less than 16% is generally used to screen for iron deficiency, but a threshold of 20% is used in the presence of inflammation.(3) For more information about hereditary hemochromatosis testing, see Hereditary Hemochromatosis Algorithm.

Reference Values:

IRON
Males: 50-150 mcg/dL
Females: 35-145 mcg/dL

TOTAL IRON-BINDING CAPACITY
250-400 mcg/dL

PERCENT SATURATION
14-50%

Clinical References: 1. Swinkels DW. Iron metabolism. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 40 2. Kowdley KV, Brown KE, Ahn J, Sundaram V. ACG Clinical Guideline: Hereditary Hemochromatosis [published correction appears in Am J Gastroenterol. 2019 Dec;114(12):1927. doi:10.14309/ajg.0000000000000469]. Am J Gastroenterol. 2019;114(8):1202-1218. doi:10.14309/ajg.0000000000000315 3. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet. 2016;387(10021):907-916. doi:10.1016/S0140-6736(15)60865-0

FET
8350

Iron, Liver Tissue

Clinical Information: Hemosiderosis is the condition of excessive iron accumulation in tissues. Liver is the first organ affected in iron-overload diseases. Transient increases in iron first appear in Kupffer

cells. This finding is commonly related to sideroblastic anemia, excessive iron consumption, or chronic alcohol ingestion. Persistent hemosiderosis, as seen in hemochromatosis, causes iron accumulation in hepatocytes and is usually concentrated in biliary cells. Hereditary hemochromatosis is an autosomal recessive disease with estimated prevalence of 2 in 1000 in White population, with lower incidence in other races. The gene responsible for hereditary hemochromatosis (HFE) is located on chromosome 6; the majority of patients with hereditary hemochromatosis have variants in the HFE gene. Hereditary hemochromatosis is characterized by an accelerated rate of intestinal iron absorption and progressive iron deposition in various tissues that typically begins to be expressed in the third to fifth decades of life but may occur in children. The most common presentation is hepatic cirrhosis in combination with hypopituitarism, cardiomyopathy, diabetes, arthritis, or hyperpigmentation. Because of the severe sequelae of this disease, if left untreated and recognizing that treatment is relatively simple, early diagnosis before signs or symptoms appear is important. Screening for hemochromatosis is best done by measuring serum iron and transferrin saturation (FEC / Iron and Total Iron-Binding Capacity, Serum). If the serum iron concentration is above 175 mcg/dL and the transferrin saturation is above 55%, analysis of serum ferritin concentration (FERR1 / Ferritin, Serum) is indicated. A ferritin concentration above 400 ng/mL is suggestive of hemochromatosis but also can indicate other forms of hepatocyte injury, such as alcoholic or viral hepatitis, or other inflammatory disorders involving the liver. HFE analysis (HFET / Hereditary Hemochromatosis, HFE Variant Analysis, Varies) may be used to confirm the clinical diagnosis of hemochromatosis, to diagnose hemochromatosis in asymptomatic individuals with blood tests showing increased iron stores, or for predictive testing of individuals who have a family history of hemochromatosis. The alleles evaluated by HFE gene analysis are evident in approximately 80% of patients with hemochromatosis; a negative report for HFE gene does not rule-out hemochromatosis. In a patient with negative HFE gene testing, elevated iron status for no other obvious reason, and family history of liver disease, additional evaluation of liver iron concentration is indicated. Diagnosis of hemochromatosis may also be based on biochemical analysis and histologic examination of a liver biopsy. In this assay, results are reported as the hepatic iron index (HII) and dry weight of iron. The HII is considered the "gold standard" for diagnosis of hemochromatosis. This test is appropriate when: -Serum iron is above 160 mcg/dL -Transferrin saturation is above 55% -Ferritin is above 400 ng/mL in male patients or above 200 ng/mL in female patients -HFE gene test is negative for HFE variants For more information see Hereditary Hemochromatosis Algorithm.

Useful For: Diagnosis of hemochromatosis using liver tissue specimens

Interpretation: A hepatic iron concentration above 10,000 mcg/g dry weight is diagnostic for hemochromatosis. Hepatic iron concentrations above 3000 mcg/g are seen when there is iron overload without cellular injury and cirrhosis. Hepatic iron concentrations greater than the reference range are associated with hemosiderosis, thalassemia, and sideroblastic anemia. Some patients with hepatitis or cirrhosis without significant fibrosis will have hepatic iron concentrations at the top end of normal or just slightly above the normal range. Iron accumulates in the liver normally with aging. The hepatic iron index (HII) normalizes hepatic iron concentration for age. The HII is calculated from the hepatic iron concentration by converting the concentration from mcg/g to mcmol/g dry weight and dividing by years of age. The normal range for HII is less than 1.0. -Patients with homozygous hemochromatosis have an HII above 1.9. -Patients with heterozygous hemochromatosis often have an HII ranging from 1.0 to 1.9. -Patients with hepatitis and alcoholic cirrhosis usually have an HII below 1.0, although a small percentage of patients with alcoholic cirrhosis have an HII in the range of 1.0 to 1.9. -Patients with hemochromatosis who have been successfully treated with phlebotomy will have an HII below 1.0. Liver specimens collected from patients with cirrhosis containing a high degree of fibrosis have results near the low end of the reference range, even though they will show significant iron staining in hepatocytes. While it is true that iron accumulates in hepatocytes in advanced alcoholic cirrhosis with fibrosis, there are relatively few hepatocytes compared to other inert (fibrotic) tissue, so the quantitative iron determination, which is expressed as microgram of iron per gram of dry weight tissues, yields a low result. Histologic examination of all tissue specimens should be performed to facilitate correct interpretation. When structural heterogeneity is apparent histologically, variation in measured iron should be anticipated. In approximately 2% of cases, a high degree of hepatic heterogeneity has been

observed that makes quantitation highly variable.

Reference Values:

Iron
Males: 200-2,400 mcg/g dry weight
Females: 200-1,800 mcg/g dry weight

Iron Index
> or =13 years: <1.0 mcmol/g/year
Reference values have not been established for patients that are younger than 13 years.

Clinical References: 1. Brandhagen DJ, Fairbanks VF, Baldus W. Recognition and management of hereditary hemochromatosis. Am Fam Physician. 2002;65:853-860, 865-866 2. Summers KM, Halliday JW, Powell LW. Identification of homozygous hemochromatosis subjects by measurement of hepatic iron index. Hepatology. 1990;12:20-25 3. Ludwig J, Batts KP, Moyer TP, et al. Liver biopsy diagnosis of homozygous hemochromatosis: a diagnostic algorithm. Mayo Clin Proc. 1993;68:263-267 4. Pietrangelo A. Hemochromatosis: an endocrine liver disease. Hepatology. 2007;46:1291-1301 5. Ashley EA, Butte AJ, Wheeler MT, et al. Clinical assessment incorporating a personal genome. Lancet. 2010;375:1525-1535 6. McLaren CE, Barton JC, Eckfeldt JH, et al. Heritability of serum iron measures in the hemochromatosis and iron overload screening (HEIRS) family study. Am J Hematol. 2010;85:101-105 7. Radford-Smith DE, Powell EE, Powell LW. Haemochromatosis: a clinical update for the practising physician. Intern Med J. 2018;48(5):509-516. doi:10.1111/imj.13784

IRON
2502

Iron, Serum

Clinical Information: Iron (Fe) is involved in the function of all cells. Systemic iron homeostasis is maintained by the tight regulation of communication between cells that absorb iron from the diet (duodenal enterocytes), cells that consume iron (mainly erythroid precursors), and cells that store iron (hepatocyte and tissue macrophages). Once ingested iron is absorbed and temporarily stored in the mucosal cells within ferritin. Ferritin provides a soluble protein shell to encapsulate a complex of insoluble ferric hydroxide and ferric phosphate. Iron is released into the blood and transported as Fe (III)-transferrin.(1) The concentration of iron varies widely, both in normal healthy persons, and in various clinical disorders. The biologic variation of iron is notable in normal healthy persons and in various clinical disorders owing to both diurnal variation and post-prandial effects. Normally, intra-individual serum iron levels undergo significant within day and day-to-day variation. The intraindividual day-to-day variation of iron is approximately 25% to 30%.(1) Serum iron concentration is frequently highest in the morning and declines progressively during the day, to reach a low point near midnight. There are no definitive studies that suggest fasting from food is required; however, serum iron is commonly drawn in the fasting state. Drawing blood three hours after consuming oral iron supplements has been shown to significantly increase serum iron concentration 3 to 5-fold and therefore should be avoided for 24 hours prior to collection.(2)

Useful For: Aiding in the evaluation of iron deficiency and iron overload diseases in combination with total iron binding capacity and percent saturation Assessment of acute iron poisoning

Interpretation: Serum iron is elevated in iron overload conditions including hemochromatosis. Additional causes include oral or parenteral intake of medicinal iron, acute hepatitis, and chronic liver failure.(1) Serum iron is decreased in iron deficiency, iron deficiency anemia, and anemia of chronic disease.(1)

Reference Values:

Only orderable as part of profile. For more information see SFEC / Iron and Total Iron-Binding Capacity,

Serum

Males: 50-150 mcg/dL
Females: 35-145 mcg/dL

Clinical References: 1. Swinkels DW. Iron metabolism. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier, 2023:chap 40 2. Silay K, Akinci S, Yalcin A, et al. The status of iron absorption in older patients with iron deficiency anemia. Eur Rev Med Pharmacol Sci. 2015;19(17):3142-3145

FIVCZ
75575

Isavuconazole (CRESEMBA) LC-MS/MS

Clinical Information:

Reference Values:
The analytical measuring range is 0.1-10 mcg/mL. The therapeutic range has not yet been established.

Clinical References:

ISPCA
113306

ISH Additional (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

ISA26
113308

ISH Additional, Professional Only (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

ISTOA
113217

ISH Additional, Tech Only (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

ISPCI
113305

ISH Initial (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

ISH26
113307

ISH Initial, Professional Only (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

ISTOI
113216

ISH Initial, Tech Only (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

ISLET
70479

Islet 1 Immunostain, Technical Component Only

Clinical Information: Islet 1 is a homeobox-gene-related transcription factor involved in the development of the endocrine pancreas. Islet 1 is expressed in endocrine pancreas, subsets of neurons of the adrenal medulla, and dorsal root ganglion cell layers in the retina, the pineal gland, and some areas of the brain. Islet 1 is a useful marker as it is positive in the majority of pancreatic endocrine tumors.

Useful For: Identification of endocrine tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Du A, Hunter CS, Murray J, et al. Islet-1 is required for the maturation, proliferation, and survival of the endocrine pancreas. Diabetes. 2009;58:2059-2069. doi:10.2337/db08-0987 2. Schmitt AM, Riniker F, Anlauf M, et al. Islet 1 (Isl1) Expression is a reliable marker for pancreatic endocrine tumors and their metastases. Am J Surg Pathol. 2008;32(3):420-425. doi:10.1097/PAS.0b013e318158a397 3. Albarello L, Zerbi A, Capitanio V, et al. Transcription factors islet-1, Pax6, Nkx6.1, MafB and Pdx-1 in pancreatic endocrine tumors. JOP. 2008;9(6) Supplement:773 4. Koo J, Mertens R, Mirocha J, et al. Value of islet 1 and PAX8 in identifying metastatic neuroendocrine tumors of pancreatic origin. Mod Pathol. 2012;25:893-901. doi:10.1038/modpathol.2012.34 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

IA2
89588

Islet Antigen 2 (IA-2) Antibody, Serum

Clinical Information: Islet cell autoantibodies have been known to be associated with type 1 diabetes mellitus for many years. In recent years, several autoantigens against which islet antibodies are directed have been identified. These include the tyrosine phosphatase-related islet antigen 2 (IA-2), glutamic acid decarboxylase 65 (GAD65), zinc transporter 8 (ZnT8), and insulin. One or more of these autoantibodies are detected in 96% of patients with type 1 diabetes and are detectable before clinical onset, as well as in symptomatic individuals. A serological study of 50 individuals with type 1 diabetes and 50 control subjects conducted simultaneously across 43 laboratories in 16 countries demonstrated a median sensitivity of 57% and a median specificity of 99% for IA-2 antibody in type 1 diabetes. Prospective studies in relatives of patients with type 1 diabetes have shown that development of 1 or more islet autoantibodies (including IA-2 antibody) provides an early marker of progression to type 1 diabetes. Autoantibody profiles identifying patients destined to develop type 1 diabetes are usually detectable

before age 3 years. In one study of relatives seropositive for IA-2 antibody, the risk of developing type 1 diabetes within 5 years was 65.3%. Some patients with type 1 diabetes are initially diagnosed as having type 2 diabetes because of symptom onset in adulthood, societal obesity, and initial insulin-independence. These patients with "latent autoimmune diabetes in adulthood" may be distinguished from those patients with type 2 diabetes by detection of 1 or more islet autoantibodies (including IA-2).

Useful For: Clinical distinction of type 1 from type 2 diabetes mellitus Identification of individuals at risk of type 1 diabetes (including high-risk relatives of patients with diabetes) Prediction of future need for insulin treatment in adult-onset diabetic patients

Interpretation: Seropositivity for islet antigen 2 autoantibody (> 0.02 nmol/L) is supportive of: -A diagnosis of type 1 diabetes -A high risk for future development of diabetes -A current or future need for insulin therapy in patients with diabetes

Reference Values:
< or =0.02 nmol/L
Reference values apply to all ages.

Clinical References: 1. Shields BM, Shepherd M, Hudson M, et al. Population-based assessment of a biomarker-based screening pathway to aid diagnosis of monogenic diabetes in young-onset patients. Diabetes Care. 2017;40(8):1017-1025. doi:10.2337/dc17-0224 2. Bingley PJ. Clinical applications of diabetes antibody testing. J Clin Endocrinol Metab. 2010;95(1):25-33 3. Bingley PJ, Bonifacio E, Mueller PW. Diabetes Antibody Standardization Program: first assay proficiency evaluation. Diabetes 2003;52(5):1128-1136 4. Christie MR, Roll U, Payton MA, et al. Validity of screening for individuals at risk for type I diabetes by combined analysis of antibodies to recombinant proteins. Diabetes Care. 1997;20(6):965-970 5. Lampasona V, Petrone A, Tiberti C, et al: Zinc transporter 8 antibodies complement GAD and IA-2 antibodies in the identification and characterization of adult-onset autoimmune diabetes: Non insulin requiring autoimmune diabetes (NIRAD) 4. Diabetes Care. 2010;33(1):104-108

ATR
113383

Isoagglutinin Titer, Anti-A, Serum

Clinical Information: Isoagglutinins are antibodies produced by an individual that cause agglutination of red blood cells (RBCs) in other individuals. People possess isoagglutinins directed toward the A or B antigen absent from their own RBCs. For example, type B or O individuals will usually possess anti-A. The anti-A is formed in response to exposure to A-like antigenic structures found in ubiquitous non-RBC biologic entities (eg, bacteria). Isoagglutinins present in the newborn are passively acquired from maternal circulation. Such passively acquired isoagglutinins will gradually disappear, and the infant will begin to produce isoagglutinins at age 3 to 6 months. Isoagglutinin production may vary in patients with certain disease conditions. Decreased levels of isoagglutinins may be seen in patients with acquired and congenital hypogammaglobulinemia and agammaglobulinemia. Some individuals with roundworm infections will have elevated levels of anti-A.

Useful For: Evaluation of individuals with possible hypogammaglobulinemia Investigation of suspected roundworm infections

Interpretation: The result is reported as antiglobulin phase, in general representing IgG antibody. The result is the reciprocal of the highest dilution up to 1:1024 at which macroscopic agglutination (1+) is observed. Dilutions above 1:1024 are reported as greater than 1024.

Reference Values:
Interpretation depends on clinical setting. No defined reference values.

Clinical References: Cohn CS, Delaney M, Johnson ST, Katz LM, Schwartz J. eds: Technical Manual. 21st ed. AABB; 2023

BTR
113384

Isoagglutinin Titer, Anti-B, Serum

Clinical Information: Isoagglutinins are antibodies produced by an individual that cause agglutination of red blood cells (RBCs) in other individuals. People possess isoagglutinins directed toward the A or B antigen absent from their own RBCs. For example, type A or O individuals will usually possess anti-B. The anti-B is formed in response to exposure to B-like antigenic structures found in ubiquitous non-red blood cell biologic entities (eg, bacteria). Isoagglutinins present in the newborn are passively acquired from maternal circulation. Such passively acquired isoagglutinins will gradually disappear, and the infant will begin to produce isoagglutinins at age 3 to 6 months. Isoagglutinin production may vary in patients with certain pathologic conditions. Decreased levels of isoagglutinins may be seen in patients with acquired and congenital hypogammaglobulinemia and agammaglobulinemia.

IHDI
82773

Isocyanate HDI, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to isocyanate HDI Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive

5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

IMDI
82774

Isocyanate MDI, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to isocyanate MDI Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ITDT
82775

Isocyanate TDI, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to isocyanate TDI Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FISON
91349

Isoniazid (INH)

Reference Values:
Units: ug/mL

The effective concentration range of isoniazid is dependent upon the minimum inhibitory concentration of the pathogen being treated.

Toxic range: greater than 20 ug/mL

ISPG
82768

Ispaghula, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to ispaghula Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ITCON 81247 Itraconazole, Serum

Clinical Information: Itraconazole is a synthetic triazole antifungal drug approved for treatment and prophylaxis of a variety of fungal infections. Its activity results from inhibition of fungal synthesis of ergosterol, an integral component of fungal cell membranes. Concerns about adequate absorption and drug interactions are some of the major indications for therapeutic drug monitoring. Mean oral bioavailability approximates 55% but is highly variable; absorption can be enhanced by food or acidic drinks. Hepatic enzyme inducers can cause low serum itraconazole levels, and coadministration of these drugs has been associated with itraconazole therapeutic failure. Itraconazole therapeutic efficacy is greatest when serum concentrations exceed 0.5 mcg/mL for localized infections or 1.0 mcg/mL for systemic infections. An active metabolite, hydroxyitraconazole, is present in serum at roughly twice the level of the parent drug. These concentrations refer to analysis by high-performance liquid chromatography; quantitation by bioassay generates considerably higher apparent drug measurements due to reactivity with the active metabolite.

Useful For: Verifying systemic absorption of orally administered itraconazole Patients with life-threatening fungal infections Patients considered at risk for poor absorption or rapid clearance of itraconazole

Interpretation: A lower cutoff concentration has not been defined that applies in all cases. The serum concentration must be interpreted in association with other variables, such as the nature of the infection, the specific microorganism, and minimal inhibitory concentration results, if available. Localized infections are more likely to respond when serum itraconazole is more than 0.5 mcg/mL (by high-performance liquid chromatography); systemic infections generally require drug concentrations more than 1.0 mcg/mL. Consider target of more than 1.5 mcg/mL for itraconazole plus hydroxyitraconazole. Therapeutic drug monitoring should be done at steady state, which usually occurs in about 7 days. Timing of the serum collection is not as critical due to the drug's long half-life, but trough collections are recommended.

Reference Values:

ITRACONAZOLE (TROUGH):
>0.5 mcg/mL (localized infection)
>1 mcg/mL (systemic infection)

HYDROXYITRACONAZOLE:
Hydroxyitraconazole is an active metabolite; no defined therapeutic range has been established.

Clinical References: 1. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother. 2009;53(1):24-34. doi:10.1128/AAC.00705-08 2. Hope WW, Billaud EM, Lestner J, Denning DW. Therapeutic drug monitoring for triazoles. Curr Opin Infect Dis. 2008;21(6):580-586. doi:10.1097/QCO.0b013e3283184611 3. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

JCHAI 7048 J-Chain Immunostain, Technical Component Only

Clinical Information: J chain is a small, glycopeptide of 15 kDa that is structurally unrelated to heavy or light chains. It serves to structurally link the immunoglobulin components of polymeric immunoglobulins IgA and IgM, and it appears to play a role in secretion of antibodies at mucosal sites. B cells in the germinal center express J chain at an early stage of differentiation, with the expression persisting in the plasma cells destined to produce IgA or IgM.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Roberts C, Jack F, Angus B, Reid A, Thompson WD. Immunohistochemical detection of CD30 remains negative in nodular lymphocyte-predominant Hodgkin's disease using enhanced antigen retrieval. Histopathology. 2002;40(2):166-170. doi:10.1046/j.1365-2559.2002.01338.x 2. Isaacson P. Immunochemical demonstration of J chain: a marker of B-cell malignancy. J Clin Pathol. 1979;32(8):802-807. doi:10.1136/jcp.32.8.802 3. Rudigar T, Ott G, Ott MM, Muller-Deubert SM, Muller-Hermelink HK. Differential diagnosis between classic Hodgkin's lymphoma, T-cell-rich B-cell lymphoma, and paragranuloma by paraffin immunohistochemistry. Am J Surg Pathol. 1998;22(10):1184-1191. doi:10.1097/00000478-199810000-00003 4. Mestecky J, Preud'homme JL, Crago SS, Mihaesco E, Prchal JT, Okos AJ. Presence of J chain in human lymphoid cells. Clin Exp Immunol. 1980;39(2):371-385 5. Moore E, Swerdlow S, Gibson S. J chain and myocyte enhancer factor 2B are useful in differentiating classical Hodgkin lymphoma from nodular lymphocyte predominant Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Hum Pathol. 2017;68:47-53. doi:10.1016/j.humpath.2017.08.015 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

JMACK
82819

Jack Mackerel, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Jack mackerel Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

JAK2P
606821

JAK2 (9p24.1) Rearrangement, Hematologic Disorders, FISH, Tissue

Clinical Information: The JAK2 gene codes for a protein tyrosine kinase involved in cytokine signaling. Chromosomal translocations involving JAK2 can lead to the formation of chimeric oncoproteins in hematologic malignancies. Rearrangements involving 9p24.1 are rare abnormalities seen in various hematologic diseases and are typically aggressive. Identification of opportunities to apply targeted therapy with JAK2 inhibitors can be helpful for patients with JAK2 rearrangements.

Useful For: Providing diagnostic information for hematologic malignancies Aiding in the determination of whether a targeted JAK2 inhibitor could be useful for therapy

Interpretation: A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the JAK2 locus. A negative result suggests no rearrangement of the JAK2 gene region at 9p24.1.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Chase A, Bryant C, Score J, et al: Ruxolitinib as potential targeted therapy for patients with JAK2 rearrangements. Haematologica. 2013;98(3):404-408 2. Van Roosbroeck K, Cox L, Tousseyn T, et al: JAK2 rearrangements, including the novel SEC31A-JAK2 fusion, are recurrent in classical Hodgkin lymphoma. Blood. 2011;117(15):4056-4064 3. Roberts K, Li Y, Payne-Turner D, et al: Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med.

2014;371:1005-101 4. Springuel L, Renauld JC, Knoops L: JAK kinase targeting in hematologic malignancies: a sinuous pathway from identification of genetic alteration towards clinical indications. Haematologica. 2015;100:1240-1253 5. Reshmi SC, Harvey RC, Roberts KG, et al: Targetable kinase gene fusions in high-risk B-ALL: A study from the Children's Oncology Group. Blood. 2017;129:3352-3361

JAKXB 89189 JAK2 Exon 12 and Other Non-V617F Mutation Detection, Blood

JAKXM 60025 JAK2 Exon 12 and Other Non-V617F Mutation Detection, Bone Marrow

Clinical Information: DNA sequence mutations in the Janus kinase 2 (JAK2) gene are found in the hematopoietic cells of several myeloproliferative neoplasms (MPN), most frequently polycythemia vera (close to 100%), essential thrombocythemia (approximately 50%), and primary myelofibrosis (approximately 50%). Mutations in JAK2 have been reported at much lower frequency in other MPN, chronic myelomonocytic leukemia and mixed MPN/myelodysplastic syndromes, but essentially never in chronic myelogenous leukemia (CML), reactive cytoses, or normal patients. Mutations are believed to cause constitutive activation of the JAK2 protein, which is an intracellular tyrosine kinase important for signal transduction in many hematopoietic cells. Since it is often difficult to distinguish reactive conditions from the non-CML MPN, identification of a JAK2 mutation has diagnostic value. Potential prognostic significance of JAK2 mutation detection in chronic myeloid disorders has yet to be clearly established. The vast majority of JAK2 mutations occur as base pair 1849 in the gene, resulting in a JAK2 V617F protein change. In all cases being evaluated for JAK2 mutation status, the initial test that should be ordered is JAK2M / JAK2 V617F Mutation Detection, Bone Marrow, a sensitive assay for detection of the mutation. However, if no JAK2 V617F mutation is found, further evaluation of JAK2 may be clinically indicated. Over 50 different mutations have now been reported within exons 12 through 15 of JAK2 and essentially all of the non-V617F mutations have been identified in polycythemia vera. These mutations include point mutations and small insertions or deletions. Several of the exon 12 mutations have been shown to have biologic effects similar to those caused by the V617F mutation such that it is currently assumed other nonpolymorphic mutations have similar clinical effects. However, research in this area is ongoing. This assay for non-V617F/alternative JAK2 mutations is designed to obtain the sequence for JAK2 exons 12 through the first 90% of exon 15, which spans the region containing all mutations reported to date.

Useful For: Second-order testing to aid in the distinction between a reactive cytosis and a myeloproliferative neoplasm, particularly when a diagnosis of polycythemia is being entertained; for use with bone marrow specimens

Interpretation: The results will be reported as 1 of 2 states: 1. Negative for JAK2 mutation 2. Positive for JAK2 mutation If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Ma W, Kantarjian H, Zhang X, et al: Mutation profile of JAK2 transcripts in patients with chronic myeloid neoplasias. J Mol Diagn 2009;11:49-53 2. Kilpivaara O, Levine RL: JAK2 and MPL mutations in myeloproliferative neoplasms: discovery and science. Leukemia

2008;22:1813-1817 3. Kravolics R: Genetic complexity of myeloproliferative neoplasms. Leukemia 2008;22:1841-1848

JAK2R 38715 JAK2 Exon 12-15 Sequencing, Polycythemia Vera Reflex, Varies

Clinical Information: The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR::ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide variant in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). This variant is identified overall in approximately two-thirds of all MPN,(1-3) but the prevalence varies by MPN subtype. The JAK2 V617F variant is present in 95% to 98% of polycythemia vera patients, 50% to 60% of primary myelofibrosis patients, and 50% to 60% of essential thrombocythemia patients. It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome.(4) This variant is not seen in chronic myelogenous leukemia or in reactive conditions with elevated blood counts. Detection of the JAK2 V617F variant is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate absence of an MPN. Other important molecular markers in BCR::ABL1-negative MPN include CALR exon 9 variant (20%-30% of PMF and ET) and MPL exon 10 variant (5%-10% of PMF and 3%-5% of ET).(5-9) Variants in JAK2, CALR, and MPL are essentially mutually exclusive.

Useful For: Aiding in the distinction between a reactive blood cytosis and a chronic myeloproliferative disorder using peripheral blood specimens

Interpretation: The results will be reported as 1 of the 2 states: -Negative for JAK2 V617F variant -Positive for JAK2 V617F variant Positive variant status is highly suggestive of a myeloid neoplasm but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative variant status does not exclude the presence of a myeloproliferative neoplasm or other neoplasm. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. 2005;365(9464):1054-1061 2. James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive signaling causes polycythaemia vera. Nature. 2005;434(7037):1144-1148 3. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med. 2005;352:1779-1790 4. Steensma DP, Dewald GW, Lasho TL, et al. The JAK2 V617F activating tyrosine kinase mutation is an infrequent event in both "atypical" myeloproliferative disorders and the myelodysplastic syndrome. Blood. 2005;106:1207-1209 5. Gong, Jerald Z, Cook, James R, et al. Laboratory practice guidelines for detecting and reporting JAK2 and MPL mutations in myeloproliferative neoplasms. J Mol Diag. 2013;15(6):733-744 6. Stuckey R, Gomez-Casares MT. Recent advances in the use of molecular analyses to inform the diagnosis and prognosis of patients with polycythaemia vera. Int J Mol Sci. 2021;22(9):5042. doi:10.3390/ijms22095042

JAK2M 31155 JAK2 V617F Mutation Detection, Bone Marrow

Clinical Information: The Janus kinase 2 (JAK2) gene codes for a tyrosine kinase (JAK2) associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors

important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide variant in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). This variant is identified overall in approximately two-thirds of all MPN,(1-3) but the prevalence varies by MPN subtype. The JAK2 V617F variant is present in 95% to 98% of polycythemia vera patients, 50% to 60% of primary myelofibrosis (PMF) patients, and 50% to 60% of essential thrombocythemia (ET) patients. It has infrequently been described in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome.(4) This variant is not seen in chronic myelogenous leukemia or reactive conditions with elevated blood counts. Detection of the JAK2 V617F variant is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate absence of an MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 variant (20%-30% of PMF and ET) and MPL exon 10 variant (5%-10% of PMF and 3%-5% of ET). Variants in JAK2, CALR, and MPL are essentially mutually exclusive.

Useful For: Aiding in the distinction between a reactive blood cytosis and a chronic myeloproliferative disorder using bone marrow specimens

Interpretation: The results will be reported as 1 of the 2 states: -Negative for JAK2 V617F variant -Positive for JAK2 V617F variant Positive variant status is highly suggestive of a myeloid neoplasm but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative variant status does not exclude the presence of a myeloproliferative neoplasm or other neoplasm. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Baxter EJ, Scott LM, Campbell PJ, et al: Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. 2005 Mar;365(9464):1054-1061 2. James C, Ugo V, Le Couedic JP, et al: A unique clonal JAK2 mutation leading to constitutive signaling causes polycythaemia vera. Nature. 2005 Apr 28;434(7037):1144-1148 3. Kralovics R, Passamonti F, Buser AS, et al: A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med. 2005 Apr 28;352(17):1779-1790 4. Steensma DP, Dewald GW, Lasho TL, et al: The JAK2 V617F activating tyrosine kinase mutation is an infrequent event in both "atypical" myeloproliferative disorders and the myelodysplastic syndromes. Blood. 2005 Aug 15;106(4):1207-1209 5. Gong JZ, Cook JR, Greiner TC, et al: Laboratory practice guidelines for detecting and reporting JAK2 and MPL mutations in myeloproliferative neoplasms: a report of the Association for Molecular Pathology. J Mol Diagn. 2013 Nov;15(6):733-744

JAKFM
618647

JAK2 V617F Mutation Detection, Bone Marrow

Clinical Information: Mutations in the JAK2, CALR, and MPL genes are considered driver events in the BCR::ABL1 negative myeloproliferative neoplasms (MPN), including polycythemia vera (PV), primary myelofibrosis (PMF) and essential thrombocythemia (ET). The JAK2 V617F mutation occurs in 95% to 98% of patients with PV, 50% to 60% of patients with PMF and 50% to 60% of patients with ET respectively at diagnosis. Other JAK2 mutations in exons 12 through 15 occur in the remaining patients with PV. Mutations in the CALR gene occur in 20% to 30% of patients with PMF and 20% to 30% of patients with ET at diagnosis. A 52 base pair (bp) deletion (53%) and a 5 bp deletion (32%) are the most common mutations in the CALR gene while other types of mutations may occur in the remaining cases. MPL exon 10 mutations occur in 5% to 10% of patients with PMF and 5% to 10% of patients with ET. Mutations in JAK2, CALR, and MPL are mutually exclusive. The JAK2 V617F

mutation is detected by quantitative polymerase chain reaction (qPCR). The CALR mutations are detected by PCR targeting exon 9. The MPL mutations in exon 10 are detected by Sanger sequencing. All mutations in JAK2, CALR, and MPL can also be detected by next-generation sequencing (NGS). In addition to the mutations in JAK2, CALR, and MPL, mutations in many other genes including ASXL1, TET2, DNMT3A, SRSF2, SF3B1, U2AF1, ZRSR2, EZH2, IDH1, IDH2, CBL, KRAS, NRAS, STAG2, and TP53 can occur in MPN. These additional mutations are more frequent in PMF and advanced disease, as compared to PV and ET. It is known that mutations in the ASXL1, SRSF2, U2AF1, EZH2, IDH1, and IDH2 are correlated with a poor prognostic risk. While a single gene test on JAK2, CALR, and MPL can be clinically useful, all above mentioned gene mutations can be detected by NGS.

Useful For: Diagnosis or differential diagnosis of myeloproliferative disorders by JAK2 V617F variant detection in bone marrow specimens

Interpretation: The results will be reported as 1 of the 2 states: -Negative for JAK2 V617F variant -Positive for JAK2 V617F variant Positive variant status is highly suggestive of a myeloid neoplasm but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative variant status does not exclude the presence of a myeloproliferative neoplasm or other neoplasm. Results below the laboratory cutoff for positivity have unclear clinical significance at this time.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutation of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390 2. Rumi E, Pietra D, Ferretti V, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. Blood. 2014;123(10):1544-1551 3. Greenfield G, McMullin MF, Mils K. Molecular pathogenesis of the myeloproliferative neoplasms. J Hematol Oncol. 2021;14(1):103 4. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022;36(7):1703-1719

JAK2V
31156

JAK2 V617F Mutation Detection, Varies

Clinical Information: The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR::ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). This mutation is identified overall in approximately two-thirds of all MPN,(1-3) but the prevalence varies by MPN subtype. The JAK2 V617F is present in 95% to 98% of polycythemia vera, 50% to 60% of primary myelofibrosis (PMF), and 50% to 60% of essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome.(4) This mutation is not seen in chronic myelogenous leukemia or in reactive conditions with elevated blood counts. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate absence of an MPN. Other important molecular markers in BCR::ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET). Mutations in JAK2, CALR, and MPL are essentially mutually exclusive.

Useful For: Aiding in the distinction between a reactive blood cytosis and a chronic myeloproliferative disorder using extracted DNA specimens

Interpretation: The results will be reported as 1 of the 2 states: -Negative for JAK2 V617F mutation -Positive for JAK2 V617F mutation Positive mutation status is highly suggestive of a myeloid neoplasm but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplasm. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. 2005;365(9464):1054-1061 2. James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive signaling causes polycythaemia vera. Nature. 2005;434(7037):1144-1148 3. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med. 2005;352:1779-1790 4. Steensma DP, Dewald GW, Lasho TL, et al. The JAK2 V617F activating tyrosine kinase mutation is an infrequent event in both "atypical" myeloproliferative disorders and the myelodysplastic syndrome. Blood. 2005;106:1207-1209 5. Stuckey R, Gomez-Casares MT. Recent advances in the use of molecular analyses to inform the diagnosis and prognosis of patients with polycythaemia vera. Int J Mol Sci. 2021;22(9):5042. doi:10.3390/ijms22095042

FJPE
57921

Jalapeno/Chipotle (Capsicum annuum) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >=50 Very Strong Positive

Reference Values:
<0.35 kU/L

JCEDR
82865

Japanese Cedar, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Japanese cedar Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FJCQP 75758 JC Polyoma Virus DNA, Quantitative Real-Time PCR, Plasma

Clinical Information:

Reference Values:

JCV 70475 JC Virus Detection by In Situ Hybridization

Clinical Information: JC virus is the etiologic agent of progressive multifocal leukoencephalopathy (PML), a rare, demyelinating, fatal disorder of the central nervous system that occurs on a background of immune deficiency. PML is an infrequent complication of a wide variety of conditions, including lymphoproliferative disorders (Hodgkin disease, chronic lymphocytic leukemia), sarcoidosis, tuberculosis, and AIDS.

Useful For: Confirming a clinical and histopathologic diagnosis of progressive multifocal leukoencephalopathy

Interpretation: This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

Clinical References: 1. Fritzsche FR, Pianca S, Gaspert A, et al: Silver-enhanced in situ hybridization for detection of polyomavirus DNA in patients with BK virus nephropathy. Diagn Mol

Pathol. 2011 Jun;20(2):105-110 2. Aksamit AJ, Mourrain P, Sever JL, Major EO: Progressive multifocal leukoencephalopathy: investigation of 3 cases using in situ hybridization with JC virus biotinylated DNA probe. Ann Neurol. 1985 Oct;18(4):490-496 3. Aksamit AJ: Nonradioactive in situ hybridization in progressive multifocal leukoencephalopathy. Mayo Clin Proc. 1993 Sept;68(9):899-910 4. Muaoz-Marmol AM, Mola G, Fernandez-Vasalo A, et al: JC virus early protein detection by immunohistochemistry in progressive multifocal leukoencephalopathy: a comparative study with in situ hybridization and polymerase chain reaction. J Neuropathol Exp Neurol. 2004 Nov;63(11):1124-1130 5. Vago L, Cinque P, Sala E, et al: JCV-DNA and BKV-DNA in the CNS tissue and CSF of AIDS patients and normal subjects. Study of 41 cases and review of the literature. J Acquir Immune Defic Syndr Hum Retrovirol. 1996 Jun 1;12(2):139-146 6. Chen H, Chen XZ, Waterboer T, et al: Viral infections and colorectal cancer: a systematic review of epidemiological studies. Int J Cancer. 2015 Jul 1:137(1)12-24

LCJC
800170

JC Virus, Molecular Detection, PCR, Spinal Fluid

Clinical Information: JC virus (JCV), a member of the genus Polyomavirus, is a small nonenveloped DNA-containing virus. Primary infection occurs in early childhood, with a prevalence of greater than 80%.(1) The virus is latent but can reactivate in immunosuppressed patients, especially those with AIDS. JCV is recognized as the etiologic agent of progressive multifocal leukoencephalopathy (PML), a fatal demyelinating disease of the central nervous system.(2,3) Histologic examination of brain biopsy tissue may reveal characteristic pathologic changes localized mainly in oligodendrocytes and astrocytes. Detection of JCV DNA by polymerase chain reaction (PCR) (target gene, large T antigen) in the cerebrospinal fluid specimens of patients with suspected PML infection has replaced the need for biopsy tissue for laboratory diagnosis.(4) Importantly, the PCR test is specific with no cross-reaction with BK virus, a closely related polyomavirus.

Useful For: Aiding in diagnosing progressive multifocal leukoencephalopathy due to JC virus This test is not to be used as a diagnostic tool for Creutzfeldt-Jakob disease. This test is not recommended for screening asymptomatic patients

Interpretation: Detection of JC virus (JCV) DNA supports the clinical diagnosis of progressive multifocal leukoencephalopathy due to JCV.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Safak M, Khalili K: An overview: human polyomavirus JC virus and its associated disorders. J Neurovirol. 2006;9 Suppl 1:3-9. doi: 10.1080/13550280390195360 2. Khalili K, White MK: Human demyelinating disease and the polyomavirus JCV. Mult Scler. 2006 Apr;12(2):133-142 3. Ahsan N, Shah KV: Polyomaviruses and human diseases. Adv Exp Med Bio.l 2006;577:1-18. doi: 10.1007/0-387-32957-9_1 4. Romero JR, Kimberlin DW: Molecular diagnosis of viral infections of the central nervous system. Clin Lab Med. 2003 Dec;23(4):843-865 5. Chen Y, Bord E, Tompkins T, et al: Asymptomatic reactivation of JC virus in patients treated with natalizumab. N Engl J Med. 2009 Sep 10;361(11):1067-1074 6. Egli A, Infanti L, Dumoulin A, et al: Prevalence of polyomavirus BK and JC infection and replication in 400 healthy donors. J Infect Dis. 2009 Mar 15;199(6):837-846 7. Tan CS, Koralnik IJ: JC, BK, and other Polyomaviruses: Progressive multifocal leukoencephalopathy (PML). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:1931-1939

JCPCR
618305

JC Virus, Molecular Detection, PCR, Spinal Fluid

Clinical Information: JC virus (JCV), a member of the genus Polyomavirus, is a small nonenveloped DNA-containing virus. Primary infection occurs in early childhood, with a prevalence of greater than 80%.(1) The virus is latent but can reactivate in immunosuppressed patients, especially those with AIDS. JCV is recognized as the etiologic agent of progressive multifocal leukoencephalopathy (PML), a fatal demyelinating disease of the central nervous system.(2,3) Histologic examination of brain biopsy tissue may reveal characteristic pathologic changes localized mainly in oligodendrocytes and astrocytes. Detection of JCV DNA by polymerase chain reaction (PCR) (target gene, large T antigen) in the cerebrospinal fluid specimens of patients with suspected PML infection has replaced the need for biopsy tissue for laboratory diagnosis.(4) Importantly, the PCR test is specific with no cross-reaction with BK virus, a closely related polyomavirus.

Useful For: Aiding in diagnosing progressive multifocal leukoencephalopathy due to JC virus This test is not to be used as a diagnostic tool for Creutzfeldt-Jakob disease This test is not recommended for screening asymptomatic patients

Interpretation: Detection of JC virus (JCV) DNA supports the clinical diagnosis of progressive multifocal leukoencephalopathy due to JCV.

Reference Values:
Negative

Clinical References: 1. Safak M, Khalili K. An overview: human polyomavirus JC virus and its associated disorders. J Neurovirol. 2003;9 Suppl 1:3-9 2. Khalili K, White MK. Human demyelinating disease and the polyomavirus JCV. Mult Scler. 2006;12(2):133-142 3. Ahsan N, Shah KV. Polyomaviruses and human diseases. Adv Exp Med Biol. 2006;577:1-18 4. Romero JR, Kimberlin DW. Molecular diagnosis of viral infections of the central nervous system. Clin Lab Med. 2003;23(4):843-865 5. Chen Y, Bord E, Tompkins T, et al. Asymptomatic reactivation of JC virus in patients treated with natalizumab. N Engl J Med. 2009;361(11):1067-1074 6. Egli A, Infanti L, Dumoulin A, et al. Prevalence of polyomavirus BK and JC infection and replication in 400 healthy donors. J Infect Dis. 2009;199(6):837-846 7. Kartau M, Auvinen E, Verkkoniemi-Ahola A, et al. JC polyomavirus DNA detection in clinical practice. J Clin Virol. 2022;146:105051. doi:10.1016/j.jcv.2021.105051

JO1
80179

Jo 1 Antibodies, IgG, Serum

Clinical Information: Based on their specificity, autoantibodies in idiopathic inflammatory myopathies (IIM) are grouped into myositis specific (MSA) and myositis associated autoantibodies (MAA).(1-3) Among the MSA, autoantibodies against aminoacyl-tRNA synthetases (aaRSs) represent the most common antibodies and can be detected in 25% to 35% of patients with mainly anti-synthetase syndrome (ASSD).(1-4) ASSD is an autoimmune disease characterized by the presence of autoantibodies targeting one of several aaRSs along with clinical features including interstitial lung disease, myositis, Raynaud's phenomenon, arthritis, mechanic's hands, and fever.(3,4) The family of aaRSs consists of highly conserved cytoplasmic and mitochondrial enzymes, one for each amino acid, which are essential for the RNA translation machinery and protein synthesis. Along with their main functions, aaRSs are involved in the development of immune responses, regulation of transcription, and gene-specific silencing of translation.(4) Anti-Jo-1 autoantibody is the most frequently detected anti-aaRS antibody in ASSD and targets the histidyl tRNA synthetase which catalyses the binding of the histidine to its cognate tRNA during protein synthesis.(4,5). Other described anti-aaRSs reported in ASSD include PL-7 (threonyl), PL-12 (alanyl), OJ (isoleucyl), EJ (glycyl), KS (asparaginyl), Zo (phenylalanyl) and Ha (tyrosyl).(4) The presence these autoantibodies has become a key feature for classification and diagnosis of IIM and is increasingly used to define clinically distinguishable IIM subsets. Each anti-ARS antibody seems to define a distinctive clinical phenotype.(3) In addition to the characteristic features associated with the presence of anti-Jo-1 antibodies in patients with ASSD, testing for anti-aaRS autoantibodies including anti-

Jo-1 antibody maybe indicated with cytoplasmic speckled pattern using HEp-2 substrate by indirect immunofluorescence assay.(6,7) In the context of ASSD, their presence may be associated with positivity for anti-Ro52 antibodies which is an MAA.(8) In routine clinical testing, anti-Jo-1 antibody testing maybe performed using a variety of solid-phase immunoassays such as the enzyme-linked immunosorbent assay, line immunoassay, chemiluminescence immunoassay, fluorescent enzyme immunoassay, and multiplex immunoassay such as the BioPlex.(6,9,10) The performance characteristics of these assays for the detection of anti-Jo-1 antibody have not been extensively investigated to establish comparability.(9,10) For more information see Connective Tissue Disease Cascade.

Useful For: Evaluating patients with clinical features of idiopathic inflammatory myositis, especially those with clinical features suggestive of anti-synthetase syndrome or interstitial lung disease

Interpretation: A positive result for anti-Jo 1 antibody is suggestive of anti- synthetase syndrome or may indicate a risk for myositis with or without interstitial lung disease.

Reference Values:

<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References: 1. Satoh M, Tanaka S, Ceribelli A, Calise SJ, Chan EK. A comprehensive overview on myositis-specific antibodies: New and old biomarkers in idiopathic inflammatory myopathy. Clin Rev Allergy Immunol. 2017;52(1):1-19 2. Mariampillai K, Granger B, Amelin D, et al. Development of a new classification system for idiopathic inflammatory myopathies based on clinical manifestations and myositis-specific autoantibodies. JAMA Neurol. 2018;75(12):1528-1537 3. Cavagna L, Nuno L, Scire CA, et al. Clinical spectrum time course in anti Jo-1 positive antisynthetase syndrome: Results from an international retrospective multicenter study. Medicine (Baltimore). 2015;94(32):e1144 4. Galindo-Feria AS, Notarnicola A, Lundberg IE, Horuluoglu B. Aminoacyl-tRNA synthetases: On anti-synthetase syndrome and beyond. Front Immunol. 2022;13:866087 5. Freist W, Verhey JF, Ruhlmann A, Gauss DH, Arnez JG. Histidyl-tRNA synthetase. Biol Chem. 1999;380(6):623-646 6. Damoiseaux J, Andrade LEC, Carballo OG, et al. Clinical relevance of HEp-2 indirect immunofluorescent patterns: the International Consensus on ANA patterns (ICAP) perspective. Ann Rheum Dis. 2019;78(7):879-889 7. Tebo AE. Autoantibody testing in idiopathic inflammatory myopathies. J Appl Lab Med. 2022;7(1):387-390 8. Rutjes SA, Vree Egberts WT, Jongen P, et al. Anti-Ro52 antibodies frequently co-occur with anti-Jo-1 antibodies in sera from patients with idiopathic inflammatory myopathy. Clin Exp Immunol. 1997;109(1):32-40 9. Cavazzana I, Fredi M, Ceribelli A, et al. Testing for myositis specific autoantibodies: Comparison between line blot and immunoprecipitation assays in 57 myositis sera. J Immunol Methods. 2016;433:1-5 10. Espinosa-Ortega F, Holmqvist M, Alexanderson H, et al. Comparison of autoantibody specificities tested by a line blot assay and immunoprecipitation-based algorithm in patients with idiopathic inflammatory myopathies. Ann Rheum Dis. 2019;78(6):858-860

JOHN
82900

Johnson Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical

manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Johnson grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

JIP
621699

Joint Infection Panel, PCR, Synovial Fluid

Clinical Information: Joint infections (JI) occur when pathogens access bones and joints via hematogenous spread, contiguous spread of pathogens from an adjacent infection, or direct implantation (eg, open fracture, surgery, implanted medical devices). JI broadly encompasses multiple types of infections including, but not limited to, septic arthritis (SA), and prosthetic joint infection (PJI). These infections are commonly diagnosed by a combination of laboratory results, microbiological data, histological evaluation of tissue, intraoperative inspection, and in some cases radiographic results.(1) JI are most often caused by bacterial pathogens, though yeasts are also a significant cause. Serious morbidity can arise from JI, resulting in significant pain, permanent disability, or death.(2) Additionally, JI are often complicated and result in increased hospital stay length as well as higher rates of long-term rehabilitation and rehospitalization.(3,4) Globally, the prevalence of JI is estimated to be four to ten per 100,000 people

in developed countries, with the economic impact of such infections totaling hundreds of millions of dollars per year.(4,5) Timely diagnosis of JI and administration of effective treatment can significantly reduce the rates of serious complications, duration of hospital stays, and costs. The BIOFIRE JI Panel tests a single synovial fluid sample to simultaneously provide results for multiple aerobic and anaerobic bacteria and yeast that cause JI as well as genetic markers associated with antimicrobial resistance. Although JI is a broad category that includes multiple types of infections, the BIOFIRE JI Panel was primarily designed to detect organisms associated with SA and PJI. Rapid identification of the organism(s) in synovial fluid, along with information about antimicrobial resistance gene status for select microorganisms, may aid the physician in making timely and appropriate treatment and management decisions. The BIOFIRE JI Panel is indicated as an aid in the diagnosis of specific agents of JI and results should be used in conjunction with other clinical and laboratory findings. Negative results may be due to infection with pathogens that are not detected by this test, pathogens present below the limit of detection of the assay, or infection that may not be detected in a synovial fluid specimen. Positive results do not rule out co-infection with other organisms. The BIOFIRE JI Panel is not intended to monitor treatment for JI. Culture of synovial fluid is necessary to recover organisms for susceptibility testing and epidemiological typing, to identify organisms in the synovial fluid that are not detected by the BIOFIRE JI Panel, and to further identify species in the genus, complex, or group results.

Useful For: Rapid detection of synovial fluid infections caused by the following: Anaerococcus prevotii/vaginalis Finegoldia magna Streptococcus species Clostridium perfringens Parvimonas micra Streptococcus agalactiae Cutibacterium avidum/granulosum Peptoniphilus species Streptococcus pneumoniae Enterococcus faecalis Peptostreptococcus anaerobius Streptococcus pyogenes Enterococcus faecium Staphylococcus aureus Staphylococcus lugdunensis Bacteroides fragilis Kingella kingae Proteus species Citrobacter species Klebsiella aerogenes Pseudomonas aeruginosa Enterobacter cloacae complex Klebsiella pneumoniae complex Salmonella species Escherichia coli Morganella morganii Serratia marcescens Haemophilus influenzae Neisseria gonorrhoeae Candida species Candida albicans This test is not recommended as a test of cure.

Interpretation: Results are intended to aid in the diagnosis of illness and are meant to be used in conjunction with other clinical and epidemiological findings. Detected results do not distinguish between a viable or replicating organism and a nonviable organism or nucleic acid, nor do they exclude the potential for coinfection by organisms not included in the panel. Negative results do not exclude the possibility of infection and should not be used as the sole basis for diagnosis, treatment, or other management decisions. The antimicrobial resistance genes detected may or may not be associated with the agents responsible for disease. Undetected results for the included antimicrobial resistance genes do not guarantee susceptibility to corresponding classes of antimicrobials, as other mechanisms of antimicrobial resistance exist.

Reference Values:
Undetected

Clinical References: 1. Tande AJ, Patel R. Prosthetic Join Infection. Clin Micrbiol Rev. 2014;27(2):302-345. doi:10.1128/CMR.00111-13 2. Berendt T, Byren I. Bone and joint infection. Clin Med (Lond). 2004;4(6):510-518. doi:10.7861/clinmedicine.4-6-510 3. Lipsky BA, Weigelt JA, Gupta V, Killian A, Peng MM. Skin, Soft Tissue, Bone, and Joint Infections in Hospitalized Patients: Epidemiology and Microbiological, Clinical, and Economic Outcomes. Infect Control Hosp Epidemiol. 2007;28(11):1290-1298. doi:10.1086/520743 4. Grammatico-Guillon L, Baron S, Gettner S, et al. Bone and joint infections in hospitalized patients in France, 2008: clinical and economic outcomes. J Hosp Infect. 2012;82(1):40-48. doi:10.1016/j.jhin.2012.04.025 5. Faust SN, Clark J, Pallett A, Clarke NMP. Managing bone and joint infection in children. Arch Dis Child. 2012;97(6):545-553. doi:10.1136/archdischild-2011-301089 6. Esteban J, Salar-Vidal L, Schmitt BH. Multicenter evaluation of the BIOFIRE Joint Infection Panel for the detection of bacteria, yeast, and AMR genes in synovial fluid samples. J Clin Microbiol. 2023;61(11):e0035723. doi:10.1128/jcm.00357-23

JUNE
82893

June Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to June grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FWJR
57953

Juniper Western (Juniperus occidentalis) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

KLISH
70615

Kappa and Lambda Light Chain mRNA, In Situ Hybridization (ISH) Technical Component Only

Clinical Information: Restricted expression of immunoglobulin light chains can help support a diagnosis of a plasmacytic neoplasm.

Useful For: Aids in diagnosing plasma cell neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Akhtar N, Ruprai A, Pringle JH, et al. In situ hybridization detection of light chain mRNA in routine bone marrow trephines from patients with suspected myeloma. Br J Haematol. 1989;73:296-301 2. Weiss LM, Movahed LA, Chen YY, et al. Detection of immunoglobulin light-chain mRNA in lymphoid tissues using a practical in-situ hybridization method. Am J Pathol. 1990;137:979-988 3. Hristov AC, Comfere NI, Vidal CI, Sundram U. Kappa and lambda immunohistochemistry and in situ hybridization in the evaluation of atypical cutaneous lymphoid infiltrates. J Cutan Pathol. 2020;47(11):1103-1110. doi:10.1111/cup.13858 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

KAIHC
70482

Kappa Light Chain Immunostain, Technical Component Only

Clinical Information: Kappa or lambda immunoglobulin light chains pair with immunoglobulin heavy chains to form complete immunoglobulin molecules. These proteins serve as receptors for antigens in B lymphocytes and are secretory products of plasma cells, forming the humoral arm of the immune system. Because individual B cells or plasma cells synthesize immunoglobulin containing either kappa or lambda light chains, but not both, immunoperoxidase stains for light chains can be applied to lymphocyte and plasma cell populations as a marker of clonality and B-cell lineage.

Useful For: A marker of clonality and B-cell lineage

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Peterson LC, Brown BA, Crosson JT, Mladenovic J. Application of the immunoperoxidase technique to bone marrow trephine biopsies in the classification of patients with monoclonal gammopathies. Am J Clin Pathol. 1986;85:688-693 2. Taylor CR, Burns J. The demonstration of plasma cells and other immunoglobulin-containing cells in formalin-fixed, paraffin-embedded tissues using peroxidase labeled antibody. J Clin Pathol. 1974;27(1):14-20 3. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

KAIPC
113330

KappaLambda IHC (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

K11CS
610581

Kelch-Like Protein 11 Antibody, Cell Binding Assay, Serum

Clinical Information: Kelch-like protein 11 (KLHL11 or Kelch-like family member 11) IgG is a biomarker of paraneoplastic encephalitis, KLHL11 encephalitis is a unique paraneoplastic syndrome commonly associated with testicular germ cell tumors mainly seminoma. Ataxia, diplopia, dysarthria, and vertigo are common presenting features of the rhombencephalitis phenotype. Hearing loss and tinnitus may precede other neurological signs and symptoms by weeks to months. A subset of patients also has clinical and magnetic resonance imaging (MRI) presentations consistent with limbic encephalitis. Most patients with this syndrome have inflammatory spinal fluid profiles, especially elevated oligoclonal bands. MRI brain demonstrates T2 fluid attenuated inversion recovery (T2/FLAIR) abnormalities involving the brainstem or limbic system. The accompanying neurological disorder is usually severe. Clinical improvement following treatment of cancer or immunotherapy has been reported.

Useful For: Evaluating patients with paraneoplastic or autoimmune encephalitis (brainstem encephalitis or limbic encephalitis or cerebellar ataxia) using serum specimens

Interpretation: Evaluating patients with paraneoplastic or autoimmune encephalitis (brainstem encephalitis or limbic encephalitis or cerebellar ataxia) using serum specimens

Reference Values:
Negative

Clinical References: 1. Mandel-Brehm C, Dubey D, Kryzer TJ, et al: Kelch-like protein 11 antibodies in seminoma-associated paraneoplastic encephalitis. N Engl J Med. 2019;381:47-54 2. Dubey D, Wilson MR, Clarkson B, et al: Expanded clinical phenotype, oncological associations, and immunopathologic insights of paraneoplastic Kelch-like protein-11 encephalitis. JAMA Neurol. 2020 Aug 3;77(11):1-10

K11CC
610580

Kelch-Like Protein 11 Antibody, Cell Binding Assay, Spinal Fluid

Clinical Information: Kelch-like protein 11 (KLHL11, or Kelch-like family member 11) IgG is a biomarker of paraneoplastic encephalitis KLHL11 encephalitis is a unique paraneoplastic syndrome commonly associated with testicular germ cell tumors, mainly seminoma. Ataxia, diplopia, dysarthria, and vertigo are common presenting features of the rhombencephalitis phenotype. Hearing loss and

tinnitus may precede other neurological signs and symptoms by weeks to months. A subset of patients also has clinical and magnetic resonance imaging (MRI) presentations consistent with limbic encephalitis. Most patients with this syndrome have inflammatory spinal fluid profiles (especially elevated oligoclonal bands). MRI brain demonstrates T2 fluid attenuated inversion recovery (T2/FLAIR) abnormalities involving the brainstem or limbic system. The accompanying neurological disorder is usually severe. Clinical improvement following treatment of cancer or immunotherapy has been reported.

Useful For: Evaluating patients with paraneoplastic or autoimmune encephalitis (brainstem encephalitis or limbic encephalitis or cerebellar ataxia) using spinal fluid specimens

Interpretation: Positivity for Kelch-like protein 11 (KLHL11)-IgG is indicative of a paraneoplastic neurological syndrome. Positivity indicates a high likelihood of finding a testicular cancer. A rigorous search for cancer should be initiated after KLHL11 autoimmunity is confirmed.

Reference Values:
Negative

Clinical References: 1. Mandel-Brehm C, Dubey D, Kryzer TJ, et al: Kelch-like protein 11 antibodies in seminoma-associated paraneoplastic encephalitis. N Engl J Med. 2019;381:47-54 2. Dubey D, Wilson MR, Clarkson B, et al: Expanded clinical phenotype, oncological associations, and immunopathologic insights of paraneoplastic Kelch-like protein-11 encephalitis. JAMA Neurol. 2020 Aug 3;77(11):1-10

KRT34 Keratin (34BE12) Immunostain, Technical Component Only
70492

Clinical Information: Keratin 34 beta E12 (sometimes referred to as Keratin 903) is a monoclonal antibody that reacts with high-molecular-weight cytokeratin. In normal prostate, reactivity for keratin 34BE12 can be seen in the basal layer of prostatic glands in a membranous/cytoplasmic pattern. It is most useful as a basal cell-specific marker in the prostate, and shows loss of staining around glands of prostate cancer, which do not have a basal cell layer.

Useful For: Identification of cells expressing high-molecular-weight cytokeratin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Brimo F, Epstein JI: Immunohistochemical pitfalls in prostate pathology. Hum Pathol. 2012 Mar;43(3):313-324 2. Hameed O, Humphrey PA: Immunohistochemistry in the diagnosis of minimal prostate cancer. Current Diagn Pathol. 2006 Aug;12(4):279-291 3. Martens MB, Keller JH: Routine immunohistochemical staining for high-molecular weight cytokeratin 34-beta and alpha-methylacyl CoA racemase (P504S) in postirradiation prostate biopsies. Mod Pathol. 2006 Feb;19(2):287-290 4. Varma M, Morgan M, Amin MB, Wozniak S, Jasani B: High molecular weight cytokeratin antibody (clone 34beta12): a sensitive marker for differentiation of high-grade invasive urothelial carcinoma from prostate cancer. Histopathology. 2003 Feb;4292):167-172

KRTAE Keratin (AE1/AE3) Immunostain, Technical Component Only
70493

Clinical Information: Keratin clone AE1/AE3 is a broad-spectrum cytokeratin antibody that reacts with many low and high molecular weight keratins in a filamentous or membrane pattern in the epithelium of most organs. Diagnostically, antikeratin antibodies are usually applied as part of a panel to determine cell lineage of poorly differentiated malignant tumors.

Useful For: Identification of cells expressing a broad spectrum of cytokeratins (low and high molecular weight keratins)

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Cserni G, Bianchi S, Vezzosi V, et al. The value of cytokeratin immunohistochemistry in the evaluation of axillary sentinel lymph nodes in patients with lobular breast carcinoma. J Clin Pathol. 2006;59(5):518-522 2. Khan NR, Khan AN, Waris E, Suleman BA, Khan AA. Ck AE1/AE3 tumor marker expression in SCC of head and neck. Cell Biol Res.Ther. 2014;3:1-6 3. Listrom MB, Dalton LW. Comparison of keratin monoclonal antibodies MAK-6, AE1:AE3, and CAM-5.2. Am J Clin Pathol. 1987;88(3):297-301 4. Morice WG, Ferreiro JA. Distinction of basaloid squamous cell carcinoma from adenoid cystic and small cell undifferentiated carcinoma by immunohistochemistry. Hum Pathol. 1998;29(6):609-612 5. Pinkus GS, Etheridge CL, O'Connor EM. Are keratin proteins a better tumor marker than epithelial membrane antigen? A comparative immunohistochemical study of various paraffin-embedded neoplasms using monoclonal and polyclonal antibodies. Am J Clin Pathol. 1986;85(3):269-277 6. Badzio A, Czapiewski P, Gorczynski A, et al. Prognostic value of broad-spectrum keratin clones AE1/AE3 and CAM5. 2 in small cell lung cancer patients undergoing pulmonary resection. Acta Biochim Pol. 2019;66(1):111-1114 7. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

KRTOS
70495

Keratin (OSCAR) Immunostain, Technical Component Only

Clinical Information: The OSCAR cytokeratin antibody covers a wide spectrum of molecular weights; similar in expression pattern to CAM5.2, with greater coverage of high molecular weight range (eg, squamous epithelium). In normal tonsil, the squamous epithelium shows strong staining, and fibroblastic reticulum cells in interfollicular regions show weaker staining. Diagnostically, antikeratin antibodies are usually applied as part of a panel to determine cell lineage of poorly differentiated malignant tumors.

Useful For: Aids in determining primary site in carcinomas of unknown origin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Gown AM, Yaziji H, Barry TS, et al. OACAR, a novel broad anti-cytokeratin monoclonal antibody optimized for diagnostic immunohistochemistry. Poster, United States and Canadian Academy of Pathology Annual Meeting 2003 2. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

KRT19
70490

Keratin 19 (KRT19) Immunostain, Technical Component Only

Clinical Information: Cytokeratin19 (KRT19) is a low molecular weight cytoskeletal protein expressed in simple epithelium, transitional epithelium, and a few complex epithelia (myoepithelium, basal epithelium). Anti-KRT19 is useful in carcinomas with ductal or glandular differentiation.

Useful For: Aids in the identification of cells expressing low molecular weight cytokeratin (KRT19)

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Jain R, Fischer S, Serra S, Chetty R. The use of cytokeratin 19 (CK19) immunohistochemistry in lesions of the pancreas, gastrointestinal tract, and liver. Appl Immunohistochem Mol Morphol. 2010;18(1):9-15 2. Nasr MR, Mukhopadhyay S, Zhang S, Katzenstein AL. Immunohistochemical markers in diagnosis of papillary thyroid carcinoma: Utility of HBME1 combined with CK19 immunostaining. Mod Pathol. 2006;19:1631-1637 3. Prasad ML, Pellegata NS, Huang Y, et al. Galectin-3, fibronectin-1, CITED-1, HBME1 and cytokeratin-19 immunohistochemistry is useful for the differential diagnosis of thyroid tumors. Mod Pathol. 2005;18(1):48-57 4. Van Eyken P, Sciot R, Paterson A, et al. Cytokeratin expression in hepatocellular carcinoma: an immunohistochemical study. Hum Pathol. 1988;19(5):562-568 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

KRT20
70491

Keratin 20 (KRT20) Immunostain, Technical Component Only

Clinical Information: Cytokeratin 20 stains the cytoplasm of epithelial cells in a granular or filamentous pattern or may appear membrane associated (cytoskeletal) with expression primarily restricted to the epithelium of the lower gastrointestinal tract, urothelium, and Merkel-cells. When used together, cytokeratin 7 and cytokeratin 20 may be useful as an aid in determining primary site in carcinomas of unknown origin. Cytokeratin 20 is usually positive in colon carcinomas.

Useful For: Aids in determining the primary site in carcinomas of unknown origin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Berezowski K, Stastny JF, Kornstein MJ. Cytokeratins 7 and 20 and carcinoembryonic antigen in ovarian and colonic carcinoma. Mod Pathol. 1996;9(4):426-429 2. Bobos M, Hytiroglou P, Kostopoulos I, et al. Immunohistochemical distinction between merkel cell carcinoma and small cell carcinoma of the lung. Am J Dermatopath. 2006;28(2):99-104 3. Campbell F, Herrington CS. Application of cytokeratin 7 and 20 immunohistochemistry to diagnostic pathology. Curr Diagn Pathol. 2001;7:113-122 4. Chan JK, Suster S, Wenig BM, et al. Cytokeratin 20 immunoreactivity distinguishes Merkel cell (primary cutaneous neuroendocrine) carcinomas and salivary gland small cell carcinomas from small cell carcinomas of various sites. Am J Surg Pathol. 1997;21(2):226-234 5. Chu P, Wu E, Weiss LM. Cytokeratin 7 and cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases. Mod Pathol. 2000;13(9):962-972 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An

introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

KRT5
606999

Keratin 5 (KRT5) Immunostain, Technical Component Only

Clinical Information: Keratin 5 is a type II cytokeratin that dimerizes with the type I cytokeratin 14 forming intermediate filaments in the basal layer of the epidermis. Squamous epithelium of normal skin stains in a cytoplasmic pattern with keratin 5. Keratin 5 is usually positive in mesotheliomas and negative in adenocarcinomas, making it useful in separating mesotheliomas from pulmonary adenocarcinomas.

Useful For: Differentiation of mesothelioma and squamous cell carcinoma versus adenocarcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Boecker W, Stenman G, Loening T, et al. Squamous/epidermoid differentiation in normal breast and salivary gland tissues and their corresponding tumors originate from p63/K5/14-positive progenitor cells. Virchows Arch. 2015;466(1):21-36 2. Chu PG, Weiss LM. Expression of cytokeratin 5/6 in epithelial neoplasms: an immunohistochemical study of 509 cases. Mod Pathol. 2002;15(1):6-10 3. Kaufmann O, Fietze E, Mengs J, Dietel M. Value of p63 and cytokeratin 5/6 as immunohistochemical markers for the differential diagnosis of poorly differentiated and undifferentiated carcinomas. Am J Clin Pathol. 2001;116(6):823-830 4. Miettinen M, Sarlomo-Rikala M. Expression of calretinin, thrombomodulin, keratin 5, and mesothelin in lung carcinomas of different types: an immunohistochemical analysis of 596 tumors in comparison with epithelioid mesotheliomas of the pleura. Am J Surg Pathol. 2003;27(2):150-158 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

KRT7
70488

Keratin 7 (KRT7) Immunostain, Technical Component Only

Clinical Information: Keratin 7 (KRT7) stains the cytoplasm of epithelial cells in a granular or filamentous pattern or may appear membrane associated (cytoskeletal). In normal tissues, KRT7 is found in a large number of cell types including many ductal and glandular epithelia (biliary and pancreatic ducts, lung alveoli, breast, ovary, endometrium, renal collecting ducts, urothelium, thyroid, placental trophoblasts, and mesothelium). When used together, KRT7 and KRT20 may be useful as an aid in determining the primary site in carcinomas of unknown origin.

Useful For: Aiding in determining the primary site in carcinomas of unknown origin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

K818
622524

Keratin 8 and 18 (KRT8/18), Technical Component only

Clinical Information: Keratin 8 and 18 (KRT8/18) are expressed in a wide variety of epithelial cells. KRT8/18 is not expressed in mesenchymal cells or in endothelium. KRT8/18 is primarily used in the diagnosis of carcinomas including but not limited to mesotheliomas, renal cell carcinomas, small cell carcinomas, as well as most squamous cell carcinomas and adenocarcinomas.

Useful For: Aiding in the diagnosis of carcinomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chavez JD, Schweppe DK, Eng JK, et al. Quantitative interactome analysis reveals a chemoresistant edgotype. Nat Commun. 2015;6:7928. doi:10.1038/ncommx8928 2. Vyberg M, Diernaes C, Roge R, et al. NordiQC assessments of low molecular weight keratin 8/18 immunoassays. Appl Immunohistochem Mol Morphol. 2017;25(10):673-678 3. Morice WG, Ferreiro JA. Distinction of basaloid squamous cell carcinoma from adenoid cystic and small cell undifferentiated carcinoma by immunohistochemistry. Hum Pathol. 1998;29(6):609-612 4. Iwata J, Fletcher CD. Immunohistochemical detection of cytokeratin and epithelial membrane antigen in leiomyosarcoma: a systematic study of 100 cases. Pathol Int. 2000;50(1):7-14

FKEMS
75730

Ketamine and Metabolite Screen, Plasma

Reference Values:
Reporting limit determined each analysis

Units: ng/mL

Norketamine: None Detected
The intravenous administration of 2 mg/kg of Ketamine followed by continuous infusion of 41 mcg/kg/minute produced an average steady-state plasma concentration of 2200 ng Ketamine/mL and an average peak Norketamine level of 1050 ng/mL which occurred near the end of the 3 hour infusion.

Ketamine: None Detected
Reported levels during anesthesia: 500-6500 ng/mL

KETGP
608024

Ketone Disorders Gene Panel, Varies

Clinical Information: Ketones are a chemical energy source used by tissues when glucose is low. Disorders of impaired ketone body metabolism include beta-ketothiolase (BKT) deficiency and succinyl-CoA:3-ketoacid CoA transferase (SCOT) deficiency. Disorders of ketogenesis are mitochondrial 3-hydroxy-3-methyglutaric acid CoA (HMG-CoA) synthase (mHS) and HMG-CoA lyase (HL) deficiencies. BKT deficiency is caused by impaired activity of the enzyme acetoacetyl-CoA thiolase. Individuals with BKT deficiency are typically asymptomatic at birth, and symptoms are likely to develop from 6 to 18 months of age with illness or fasting, which appear as episodes of decompensation and severe ketoacidosis, vomiting, dehydration, and lethargy. Children are usually asymptomatic between episodes. SCOT deficiency is a more severe ketone utilization disorder, as all experience recurrent ketoacidotic episodes, and most individuals have chronic ketosis. About 50% of infants with

SCOT deficiency present in the first week of life, and the remaining 50% present between 6 to 24 months of age. mHS deficiency is due to reduced activity of a mitochondrial enzyme mHS. Infants with mHS deficiency have episodes of hypoketotic hypoglycemia, which can progress to coma. In mHS deficiency, there is no diagnostic pattern of organic acids in urine. The only biochemical diagnostic test is enzyme assay of mHS in liver. HL deficiency is due to reduced activity of mitochondrial and peroxisomal enzyme HL. Infants and children with HL deficiency also experience hypoketotic hypoglycemic episodes, and long-term impacts of these episodes can include epilepsy, intellectual disability, and white matter changes in the brain, usually due to hypoglycemia. Urine organic acids of individuals with HL are characteristic and demonstrate high levels of HMG and leucine metabolites. All 4 of these ketone disorders are inherited in an autosomal recessive manner. BKT deficiency is caused by variants in ACAT1, and SCOT deficiency is caused by variants in the OCT1. HMG-CoA synthase deficiency is due to variants in HMGCS2, and HMG-CoA lyase deficiency is due to variants in HMGCL. An additional disorder that impacts ketone metabolism and is included in this panel is monocarboxylate transporter 1 deficiency, due to 2 variants in SLC16A1 and resulting in severe episodes of ketoacidosis with illness or fasting. Treatment for these ketone disorders involves avoidance of fasting and provision of oral or intravenous carbohydrate to correct hypoglycemia and ketoacidosis. Long term neurologic sequelae occur in some individuals and are a consequence of hypoglycemia during ketoacidotic episodes. Urine organic acids (OAU / Organic Acids Screen, Random, Urine) and plasma acylcarnitine profile (ACRN / Acylcarnitines, Quantitative, Plasma) are the recommended first-tier tests for assessment of ketone disorders. However, as these may be normal in all but severe BKT deficiency, molecular genetic testing is a rapid and effective tool to diagnose individuals with ketone disorder.

Useful For: Follow up for abnormal biochemical results suggestive of a ketone disorder Establishing a molecular diagnosis for patients with ketone disorders Identifying variants within genes known to be associated with ketone disorders, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. 2. Mitchell GA, Fukao T: Inborn errors of ketone body metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease McGraw-Hill Education; 2019. Accessed March 8,2024. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225087757 3. Hori T, Yamaguchi S, Shinkaku H, et al. Inborn errors of ketone body utilization. Pediatr Int. 2015;57(1):41-48 4. Fukao T, Mitchell G, Sass JO, Hori T, Orii K, Aoyama Y. Ketone body metabolism and its defects. J Inherit Metab Dis. 2014;37(4):541-551

SKETC
606546

Ketones, Urine

Clinical Information: The body normally metabolizes fats to carbon dioxide and water. Inadequate carbohydrate in the diet or defects in carbohydrate metabolism or absorption cause the body to metabolize fatty acids. Ketones (acetoacetic acid, acetone, and beta-hydroxybutyric acid) are produced during fat metabolism and are excreted in urine. Patients with untreated or inadequately treated diabetes mellitus are unable to efficiently utilize glucose due to insufficient insulin. Under these conditions, large amounts of

fatty acids are metabolized, and abnormal amounts of ketones are excreted in the urine (ketonuria). Increased ketones may occur during physiological stress conditions such as fasting, starvation, pregnancy, strenuous exercise, fever, frequent vomiting, anorexia, and some inborn errors of metabolism.

Useful For: Screening for the presence of ketoacidosis

Interpretation: Detection of ketones in the urine of a diabetic is significant and indicates a change in insulin dosage or other alteration in treatment is necessary. Ketones may appear in urine in large amounts before serum ketone is elevated.

Reference Values:
Negative

Clinical References: 1. Free HM: Modern Urine Chemistry Manual. Bayer Corp; 1996:47-49 2. Morton A: Review article: Ketoacidosis in the emergency department. Emerg Med Australas. 2020 Jun;32(3):371-376. doi: 10.1111/1742-6723.13503

KI67
70481

Ki-67 (MIB-1) Immunostain, Technical Component Only

Clinical Information: Ki-67 (antibody clone MIB-1) is a nuclear protein playing a pivotal role in maintaining cell proliferation. Ki-67 is present in all non-G0 phases of the cell cycle. Beginning in the mid-G1 phase, the level increases through the S and G2 phases to reach a peak in M phase. In the end of M phase, it is rapidly catabolized. Ki-67 has been employed as a marker of proliferation and, hence, prognosis in neoplasms of many types, such as malignant lymphomas, prostatic and breast adenocarcinomas, astrocytic neoplasms, and soft tissue neoplasms.

Useful For: A marker of proliferation in neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Yerushalmi R, Woods R, Ravdin PM et al. Ki67 in breast cancer: prognostic and predictive potential. Lancet. 2010;11(2):174-183 2. Leonardo E, Volante M, Barbareschi M, et al. Cell membrane reactivity of MIB-1 antibody to Ki67 in human tumors: fact or artifact? Appl Immunohistochem Mol Morphol. 2007;15(2):220-223 3. Potemski P, Pluciennik E, Bednarek AK, et al. Ki-67 expression in operable breast cancer: a comparative study of immunostaining and a real-time RT-PCR assay. Pathol Res Pract. 2006;202(7):491-495 4. Li R, Heydon K, Hammond ME, et al. Ki-67 staining index predicts distant metastasis and survival in locally advanced prostate cancer treated with radiotherapy: an analysis of patients in Radiation Therapy Oncology Group Protocol 86-10. Clin Cancer Res. 2004;10(12 Pt 1):4118-4124 5. Trihia H, Murray S, Price K, et al. Ki-67 expression in breast carcinoma-its association with grading systems, Clinical parameters, and other prognostic factors-a surrogate marker? Cancer. 2003;97(5):1321-1331 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

KI67B
70588

Ki-67(MIB-1), Breast, Quantitative Immunohistochemistry, Automated

Clinical Information: Ki-67 (MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67 (MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic and predictive information in various tumor types.

Useful For: Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with breast carcinoma

Interpretation: Results will be reported as a percentage of tumor cells staining positive for Ki-67 (MIB-1). Quantitative Ki-67 (MIB-1) results should be interpreted within the clinical context for which the test was ordered. The scoring method using Aiforia artificial intelligence for image analysis was developed and validated in the Biomarker and Image Analysis Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic (see Method Description).

Reference Values:
Varies by tumor type; values reported from 0% to 100%

Clinical References: 1. Urruticoechea A, Smith IE, Dowsett M: Proliferation marker Ki-67 in early breast cancer. J Clin Oncol 2005 Oct 1;23(28):7212-7220 2. de Azambuja E, Cardoso F, de Castro G, et al: Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients. Br J Cancer 2007 May 21;96(10):1504-1513 3. Nielsen TO, Leung SCY, Rimm DL, et al: Assessment of Ki67 in breast cancer: updated recommendations from the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst. 2021 Jul 1;113(7):808-819. doi: 10.1093/jnci/djaa201 4. Zhang A, Wang X, Fan C, et al: The role of Ki67 in evaluating neoadjuvant endocrine therapy of hormone receptor-positive breast cancer. Front. Endocrinol. 2021 Nov 3;12:687244 5. Polewski MD, Nielsen GB, Gu Y, et al: A standardized investigational Ki-67 immunohistochemistry assay used to assess high-risk early breast cancer patients in the monarchE Phase3 Clinical Study identifies a population with greater risk of disease recurrence when treated with endocrine therapy alone. Appl Immunohistochem Mol Morphol. 2022 Apr 1;30(4):237-245. doi: 10.1097/PAI.0000000000001009

KIBM
71668

Ki-67(MIB-1), Breast, Semi-Quantitative Immunohistochemistry, Manual

Clinical Information: Ki-67 (MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67 (MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

Useful For: Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with breast carcinoma

Interpretation: Results will be reported as a percentage of tumor cells staining positive for Ki-67(MIB-1). Quantitative Ki-67 (MIB-1) results should be interpreted within the clinical context for which the test was ordered.

Reference Values:
This is not an orderable test. Order PATHC / Pathology Consultation. The consultant will determine the need for special stains.

Varies by tumor type; values reported from 0% to 100%

Clinical References: 1. Urruticoechea A, Smith IE, Dowsett M: Proliferation marker Ki-67 in early breast cancer. J Clin Oncol 2005 Oct 1;23(28):7212-7220 2. de Azambuja E, Cardoso F, de Castro G Jr, et al: Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients. Br J Cancer 2007 May 21;96(10):1504-1513

KINET 71503 Ki-67(MIB-1), Gastrointestinal/Pancreatic Neuroendocrine Tumors, Quantitative Immunohistochemistry, Automated

Clinical Information: Ki-67(MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67(MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

Useful For: Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with neuroendocrine tumors of the pancreas or gastrointestinal tract including metastases

Interpretation: Results will be reported as a percentage of tumor cells staining positive for Ki-67(MIB-1). Quantitative Ki-67(MIB-1) results should be interpreted within the clinical context for which the test was ordered. The scoring method using Aiforia artificial intelligence for image analysis was developed and validated in the Biomarker and Image Analysis Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic (see Method Description).

Reference Values:
Varies by tumor type; values reported from 0% to 100%

Clinical References: 1. La Rosa S. Diagnostic, Prognostic, and Predictive Role of Ki67 Proliferative Index in Neuroendocrine and Endocrine Neoplasms: Past, Present, and Future. Endocr Pathol. 2023;34(1):79-97. doi:10.1007/s12022-023-09755-3 2. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76(2):182-188. doi:10.1111/his.13975

KINM 71667 Ki-67(MIB-1), Gastrointestinal/Pancreatic Neuroendocrine Tumors, Quantitative Immunohistochemistry, Manual

Clinical Information: Ki-67(MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67(MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

Useful For: Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with neuroendocrine tumors of the pancreas or gastrointestinal tract including metastases

Interpretation: Results will be reported as a percentage of tumor cells staining positive for

Ki-67(MIB-1). Semi-quantitative Ki-67(MIB-1) results should be interpreted within the clinical context for which the test was ordered.

Reference Values:
This is not an orderable test. Order PATHC / Pathology Consultation. The consultant will determine the need for special stains.

Varies by tumor type; values reported from 0% to 100%

Clinical References: 1. La Rosa S. Diagnostic, Prognostic, and Predictive Role of Ki67 Proliferative Index in Neuroendocrine and Endocrine Neoplasms: Past, Present, and Future. Endocr Pathol. 2023;34(1):79-97. doi:10.1007/s12022-023-09755-3 2. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76(2):182-188. doi:10.1111/his.13975

KI67P
72130

Ki-67(MIB-1), Pulmonary, Quantitative Immunohistochemistry, Automated

Clinical Information: Ki-67(MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67(MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

Useful For: Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with carcinoid or atypical carcinoid of the lung including metastases

Interpretation: Results will be reported as a percentage of tumor cells staining positive for Ki-67(MIB-1). Quantitative Ki-67(MIB-1) results should be interpreted within the clinical context for which the test was ordered. The scoring method using Aiforia artificial intelligence for image analysis was developed and validated in the Biomarker and Image Analysis Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic (see Method Description).

Reference Values:
Varies by tumor type; values reported from 0% to 100%

Clinical References: 1. Boland JM, Kroneman TN, Jenkins SM, et al. Ki-67 Labeling index in pulmonary carcinoid tumors: Comparison between small biopsy and resection using tumor tracing and hot spot methods. Arch Pathol Lab Med. 2020;144(8):982-990 2. La Rosa S. Diagnostic, Prognostic, and Predictive Role of Ki67 Proliferative Index in Neuroendocrine and Endocrine Neoplasms: Past, Present, and Future. Endocr Pathol. 2023;34(1):79-97. doi:10.1007/s12022-023-09755-3

KIPM
72131

Ki-67(MIB-1), Pulmonary, Quantitative Immunohistochemistry, Manual

Clinical Information: Ki-67(MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67(MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

Useful For: Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with carcinoid or atypical carcinoid of the lung including metastases, using a manual method

Interpretation: Results will be reported as a percentage of tumor cells staining positive for Ki-67(MIB-1). Semi-quantitative Ki-67(MIB-1) results should be interpreted within the clinical context for which the test was ordered.

Reference Values:
Only orderable as a reflex. For more information see KI67P / Ki-67 (MIB-1), Pulmonary, Quantitative Immunohistochemistry, Automated.

Varies by tumor type; values reported from 0% to 100%

Clinical References: 1. Boland JM, Kroneman TN, Jenkins SM, et al. Ki-67 Labeling index in pulmonary carcinoid tumors: comparison between small biopsy and resection using tumor tracing and hot spot methods. Arch Pathol Lab Med. 2020;144(8):982-990. doi:10.5858/arpa.2019-0374-OA 2. La Rosa S. Diagnostic, Prognostic, and Predictive Role of Ki67 Proliferative Index in Neuroendocrine and Endocrine Neoplasms: Past, Present, and Future. Endocr Pathol. 2023;34(1):79-97. doi:10.1007/s12022-023-09755-3

KIMEL
70483

Ki67 + Melan A Immunostain, Technical Component Only

Clinical Information: Ki-67 (clone MIB-1) is a nuclear protein (detected by the chromogen DAB) playing a pivotal role in maintaining cell proliferation. Ki-67 is present in late G1-, S-, M-, and G2-phases of the cell cycle. Cells in the G0 (quiescent) phase are negative for this protein. Melan-A or melanoma antigen recognized by T cells (MART-1) (detected by the chromogen Fast Red) is expressed in the cytoplasm of melanocytes. It is a sensitive and specific marker for the diagnosis of melanoma. Melan A is also found in other tumors of melanocytic origin, such as clear cell sarcoma, melanotic neurofibroma, melanotic schwannoma, as well as in perivascular epithelioid cell tumor. Melan A (clone A103) cross-reacts with steroid hormone-producing cells and tumors. Consequently, adrenocortical adenomas/carcinomas and sex cord-stromal tumors of the ovary and testis may exhibit staining.

Useful For: Ki67 is a marker of proliferation in neoplasms Melan A aids in the identification of melanoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Puri PK, Valdes CL, Burchette JL, et al. Accurate identification of proliferative index in melanocytic neoplasms with Melan-A/Ki-67 double stain. J Cutan Pathol. 2010;37(9):1010-1012 2. Nielsen PS, Riber-Hansen R, Steiniche T. Immunohistochemical double stains against Ki67/MART1 and HMB45/MITF: promising diagnostic tools in melanocytic lesions. Am J Dermatopathol. 2011;33(4):361-370 3. Nielsen PS, Riber-Hansen R, Jensen TO, et al. Proliferation indices of phosphohistone H3 and Ki67: strong prognostic markers in a consecutive cohort with stage I/II melanoma. Mod Pathol. 2013;26:404-413 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

KIDBN
82619

Kidney Bean (Red), IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to red kidney bean Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

KIDST
605761

Kidney Stone Analysis

Clinical Information: The composition of urinary stones may vary from a simple crystal to a complex mixture containing several different species of crystals. The composition of the nidus (center) may be entirely different from that of the peripheral layers. Eighty percent of patients with kidney stones have a history of recurrent stone formation. Knowledge of stone composition can be useful to guide therapy of patients with recurrent stone formation. Treatment of urinary calculi can be complex.(1) In an overly simplified format, the following patterns are often treated as follows: -Hyperuricuria and predominately uric acid stones: Alkalinize urine to increase uric acid solubility -Hypercalciuria and predominately hydroxyapatite stones: Acidify urine to increase calcium solubility However, treatment also depends on urine pH and urine phosphate, sulfate, oxalate, and citrate concentrations. -Hyperoxaluria and calcium oxalate stones: Increase daily fluid intake and consider reduction of daily calcium However, daily requirements for calcium to maintain good bone formation complicate the treatment. -Magnesium ammonium phosphate stones (struvite): Investigate and treat urinary tract infection.

Useful For: Managing patients with recurrent renal calculi (kidney stones)

Interpretation: The interpretation of stone analysis results is complex and beyond the scope of this text. For more information see the second Clinical Reference. Calcium oxalate stones: -Production of calcium oxalate stones consisting of oxalate dihydrate indicates that the stone is newly formed, and current urine constituents can be used to assess the importance of supersaturation. -Production of calcium oxalate stones consisting of oxalate monohydrate indicates an old (>2 months since formed) stone, and current urine composition may not be meaningful. Magnesium ammonium phosphate stones (struvite): -Production of magnesium ammonium phosphate stones (struvite) indicates that the cause of stone formation was infection. -Treatment of the infection is the only way to inhibit further stone formation. Ephedrine/guaifenesin stones: -Certain herbal and over-the-counter preparations (eg, Mah Jung) contain high levels of ephedrine and guaifenesin. Excessive consumption of these products can lead to the formation of ephedrine/guaifenesin stones.

Reference Values:
The presence of a kidney stone is abnormal. A quantitative report will be provided after analysis.

Clinical References: 1. Mandel NS, Mandel IC, Kolbach-Mandel AM. Accurate stone analysis: the impact on disease diagnosis and treatment. Urolithiasis. 2017;45(1):3-9. doi:10.1007/s00240-016-0943-0 2. Smith LH: In: Schrier RW, Gottscholk CW, eds. Diseases of the Kidney. 4th ed. Little, Brown and Company; 1987:chap 25 3. Lieske JC, Segura JW. Evaluation and medical management of kidney stones. In: Potts JM, ed: Essential Urology: A Guide to Clinical Practice. Humana Press; 2004:117-152 4. Lieske JC. Pathophysiology and evaluation of obstructive uropathy. In: Smith AD, Gopal Badlani B, Bagley D, et al. Smith's Textbook of Endourology. 2nd ed. BC Decker Inc; 2007:101-106

KKBRP
65202

Kingella kingae, Molecular Detection, PCR, Blood

Clinical Information: Kingella kingae is a fastidious short gram-negative bacillus that may colonize the oropharynx of young children. Colonization may occasionally lead to invasive disease via hematogenous dissemination, primarily in children younger than 4 years of age. This most commonly results in bone and joint infection; K kingae is the most frequent cause of osteomyelitis and septic arthritis in children aged 6 to 36 months. K kingae may also cause endocarditis, involving both native and prosthetic valves, in patients of any age and is considered part of the HACEK (Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species) group of organisms, known for causing culture-negative endocarditis. K kingae produces a repeat-in-toxin (RTX) toxin. Diagnosis of K kingae infection may be challenging due to the fastidious nature of the organism in culture. Evaluation of blood by polymerase chain reaction is a useful tool for the

diagnosis of some cases of K kingae infection.

Useful For: Aiding in the diagnosis of Kingella kingae infection using whole blood specimens

Interpretation: A positive result indicates the presence of Kingella kingae DNA. A negative result indicates the absence of detectable K kingae DNA, but it does not negate the presence of the organism and may occur due to inhibition of polymerase chain reaction, sequence variability underlying primers or probes, or the presence of K kingae DNA in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. El Houmami N, Bzdreng J, Durand GA, et al: Molecular tests that target the RTX locus do not distinguish between Kingella kingae and the recently described Kingella negevensis species. J Clin Microbiol. 2017 Oct;55(10):3113-3122 2. Murphy TF: Moraxella catarrhalis, Kingella, and other gram-negative cocci. In: Bennett JE. Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:chap 213 3. Zbinden R: Aggregatibacter, Capnocytophaga, Eikenella, Kingella, Pasteurella, and other fastidious or rarely encountered gram-negative rods. In: Jorgensen JH, Carroll KC, Funke G, Pfaller MA, eds. Manual of Clinical Microbiology. 11th ed. ASM Press; 2015:652-666 4. Yagupsky P: Kingella kingae: carriage, transmission, and disease. Clin Microbiol Rev. 2015 Jan;28(1):54-79 5. Madigan T, Cunningham SA, Ramanan P, et al: Real-time PCR assay for detection of Kingella kingae in children. J Pediatr Infect Dis. 2018;13(3):216-233. doi: 10.1055/s-0038-1641603

KKRP
65201

Kingella kingae, Molecular Detection, PCR, Varies

Clinical Information: Kingella kingae is a fastidious short gram-negative bacillus that may colonize the oropharynx of young children. Colonization may occasionally lead to invasive disease via hematogenous dissemination, primarily in children younger than 4 years of age. This most commonly results in bone and joint infection; K kingae is the most frequent cause of osteomyelitis and septic arthritis in children aged 6 to 36 months. K kingae may also cause endocarditis, involving both native and prosthetic valves, in patients of any age and is considered part of the HACEK (Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species) group of organisms, known for causing culture-negative endocarditis. K kingae produces a repeat-in-toxin (RTX) toxin. Diagnosis of K kingae infection may be challenging due to the fastidious nature of the organism in culture. Evaluation of cardiac, bone, joint tissue, or fluid by polymerase chain reaction is a useful tool for the diagnosis of some cases of K kingae infection.

Useful For: Aiding in the diagnosis of Kingella kingae infection using tissue or synovial fluid specimens

Interpretation: A positive result indicates the presence of Kingella kingae DNA. A negative result indicates the absence of detectable K kingae DNA but does not negate the presence of the organism and may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of K kingae DNA in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. El Houmami N, Bzdreng J, Durand GA, et al: Molecular tests that target the RTX locus do not distinguish between Kingella kingae and the recently described Kingella negevensis

species. J Clin Microbiol. 2017 Oct;55(10):3113-3122 2. Murphy TF: Moraxella catarrhalis, Kingella, and other gram-negative cocci. In: Bennett JE. Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:chap 213 3. Yagupsky P: Kingella kingae: carriage, transmission, and disease. Clin Microbiol Rev. 2015 Jan;28(1):54-79 4. Madigan T, Cunningham SA, Ramanan P, et al: Real-time PCR assay for detection of Kingella kingae in children. J Pediatr Infect Dis. 2018;13(3):216-233. doi: 10.1055/s-0038-1641603

KIT
70485

KIT Immunostain, Technical Component Only

Clinical Information: KIT (CD117) membrane protein is a type III tyrosine kinase growth factor receptor for stem cell factor (SCF), also known as mast cell growth factor. It is expressed in mast cells, melanocytes, and interstitial cells of Cajal. KIT is expressed in various epithelia (breast, sweat glands and salivary glands, renal tubular cells, thyroid follicular cells), testicular and ovarian interstitial cells, neurons of the central nervous system, immature myeloid cells, and trophoblastic cells. KIT staining is useful in the diagnosis of gastrointestinal stromal tumors (GIST), germ cell tumors, mast cell disorders and acute myeloid leukemias.

Useful For: Aids in the identification of gastrointestinal stromal tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Lau SK, Weiss LM, Chu PG. D2-40 immunohistochemistry in the differential diagnosis of seminoma and embryonal carcinoma: a comparative immunohistochemical study with KIT (CD117) and CD30. Mod Pathol. 2007;20:320-325 2. Miettinen M, Sobin LH, Sarloma-Rikala M. Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT). Mod Pathol. 2000;13(10):1134-1142 3. Sarlomo-Rikala M, Kovatich AJ, Barusevicius A, Miettinen M. CD117: a sensitive marker for gastrointestinal stromal tumors that is more specific than CD34. Mod Pathol. 1998;11(8):728-734 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

KITQ
620901

KIT p.Asp816Val Variant Analysis, Quantitative, Varies

Clinical Information: Systemic mastocytosis (SM) is a hematopoietic neoplasm that is now recognized as a distinct entity in the current World Health Organization and International Consensus Classifications. SM is characterized by a proliferation of neoplastic mast cells in the bone marrow and rarely in extramedullary sites. SM may present with variable degrees of clinical severity and can sometimes be associated with a non-mast cell hematologic neoplasm. SM is diagnosed using a combination of major and minor criteria, encompassing morphologic, biochemical and molecular genetic features. An important minor criterion is the presence of an activating somatic mutation in the KIT gene, encoding the tyrosine kinase receptor for stem cell factor, which is a critical growth factor in early myeloid cell proliferation and development. In SM, the most common KIT alteration is a missense change in exon 17 at codon 816, p.Asp816Val (D816V). Much less frequently, other missense mutations involving the D816 codon or adjacent amino acids are encountered and rarely, KIT genetic alterations can occur in other exons. A subset of acute myeloid leukemias (AML) with core-binding factor gene fusions can also acquire activating KIT gene mutations, including D816V in many cases. Detection of KIT D816V is critical to help establish a diagnosis of SM and is optimally determined by

molecular testing. Because mast cell lesions are typically sparse and fibrotic in bone marrow and circulating tumor mast cells are in low abundance, highly sensitive and specific assays are required for optimal detection of KIT D816V. This can be achieved using quantitative allele-specific polymerase chain reaction (PCR) or droplet digital PCR (ddPCR) methods. The presence of KIT D816V mutation in the appropriate clinical and pathologic context is highly supportive of SM. In addition, although the D816V in SM is insensitive to targeted therapy with imatinib, other tyrosine kinase inhibitors such as avapritinib have demonstrated significant therapeutic efficacy in advanced SM, indicating that this mutation may also be a theranostic marker for these patients.

Useful For: Diagnosing systemic mastocytosis

Interpretation: The test will be interpreted as positive or negative for KIT p.Asp816Val and a quantitative result will be included if positive.

Reference Values:
An interpretive report will be provided indicating the status as positive or negative for KIT p.Asp816Val (D816V).
KIT gene (NCBI accession NM_000222.3)

Clinical References: 1. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022;36(7):1703-1719 2. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228 3. Reiter A, George TI, Gotlib J. New developments in diagnosis, prognostication, and treatment of advanced systemic mastocytosis. Blood. 2020;135(16):1365-1376 4. Arock M, Sotlar K, Broesby-Olsen S, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. Leukemia. 2015;29:1223-1232 5. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017;129(11):1420-1427 6. Munoz-Gonzalez JI, Alvarez-Twose I, Jara-Acevedo M, et al. Frequency and prognostic impact of KIT and other genetic variants in indolent systemic mastocytosis. Blood. 2019;134(5):456-468 7. Gotlib J, Reiter A, DeAngelo DJ. Avapritinib for advanced systemic mastocytosis. Blood. 2022;140(15):1667-1673

KIWI
82761

Kiwi Fruit, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to kiwi fruit Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists

or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

XYMF
35307

Known 45,X, Mosaicism Reflex Analysis, FISH, Whole Blood

Clinical Information: This test is appropriate for use in individuals with a karyotype of 45, X. Ullrich-Turner syndrome (UTS), also called Turner syndrome, is a genetic disorder associated with the apparent loss of a sex chromosome. Routine cytogenetic methods have identified 3 types of chromosomal abnormalities in UTS patients: loss of an entire X chromosome (45,X), structural X chromosome abnormalities, and mosaicism with an X or Y abnormality. In mosaicism, 2 or more populations of cells with different karyotypes are present (eg, 45,X/47,XXX). The incidence of UTS is approximately 1 in 3000 phenotypic female newborns. Many of these patients demonstrate the 45,X karyotype. About 30% to 50% are mosaic, with either a 45,X/46,XX karyotype or a structurally abnormal X chromosome. Fewer than 15% of patients with UTS appear to have mosaicism with a 46,XY cell population or a Y chromosome rearrangement. Identifying the mosaic status of patients with UTS is of clinical importance because phenotypic expression and clinical management are dependent upon the karyotype result. Patients with a Y chromosome have a 15% to 25% increased risk of gonadoblastoma. Failure to identify an XY signal pattern does not rule out the possibility of less than 0.6% Y chromosome mosaicism.

Useful For: Detecting sex chromosome mosaicism in patients with a 45,X karyotype

Interpretation: An XX clone is confirmed when at least 1.0% of cells display with 2 X chromosome signals. An XY clone is confirmed when at least 0.6% of cells display a 1 X and 1 Y signal pattern.

Phenotypic females with a 45,X/46,XX karyotype have no increased risk of gonadoblastoma and generally have a more moderate expression of Turner syndrome features than phenotypic females with a nonmosaic 45,X karyotype. The presence of a Y chromosome confers increased risk of gonadoblastoma.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Canto P, Kofman-Alfaro S, Jiminez AL, et al. Gonadoblastoma in Turner syndrome patients with nonmosaic 45,X karyotype and Y chromosome sequences. Cancer Genet Cytogenet. 2004;150(1):70-72 2. Wiktor A, Van Dyke DL. FISH analysis helps identify low-level mosaicism in Ullrich-Turner syndrome patients. Genet Med. 2004;6(3):132-135 3. Sybert VP, McCauley E. Turner syndrome. N Engl J Med. 2004;351:1227-1238 4. Gravholt CH, Andersen NH, Conway GS, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017;177(3):G1-G70

KRABZ 35433 Krabbe Disease, Full Gene Analysis and Large (30 kb) Deletion, Varies

Clinical Information: Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of galactocerebrosidase (GALC, galactosylceramide beta-galactosidase). GALC is encoded by the GALC gene located on 14q31. Krabbe disease occurs in approximately 1 in 100,000 live births with a carrier frequency of about 1 in 150 in the general population. Deficiency of GALC activity leads to an accumulation of galactosylceramide in globoid cells (multinucleated macrophages) causing severe demyelination throughout the brain. The toxic metabolite galactosylsphingosine (psychosine), an apoptotic compound, accumulates in oligodendrocytes and Schwann cells and contributes to disease pathogenicity. Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration follows, with death usually occurring by age 13 months. There are later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression. The clinical course of Krabbe disease can be variable even within the same family. Treatment is mostly supportive, although hematopoietic stem cell transplantation has shown some success if treatment begins before neurologic damage has occurred. The recommended first-tier test for Krabbe disease is GALCW / Galactocerebrosidase, Leukocytes. Individuals with GALC activity below the reference range for these assays are more likely to have variants in the GALC gene that are identifiable by molecular genetic testing. The above test is not reliable for detection of carriers of Krabbe disease. Additionally, measurement of the psychosine biomarker can aid in diagnosis and ongoing therapeutic monitoring (PSY / Psychosine, Blood Spot). This assay includes DNA sequencing of all 17 exons within the GALC gene as well as evaluation for the common 30-kb deletion spanning intron 10 through the end of the gene. This deletion accounts for a significant proportion of disease alleles that contribute to infantile Krabbe disease. While enzyme activity is not predictive of age of onset, there are known genotype-phenotype correlations. Individuals who are homozygous for the deletion or compound heterozygous for the deletion and a second GALC alteration (with the exception of late-onset variants) are predicted to have infantile Krabbe disease. The c.857G->A (p.Gly286Asp) alteration, on the other hand, is only associated with a late-onset phenotype.

Useful For: Second-tier test for confirming a diagnosis of Krabbe disease Carrier testing for individuals with a family history of Krabbe disease in the absence of known sequence variants in the family

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known

significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Newborn Screening ACT Sheet [Decreased galactocerebrosidase, elevated psychosine] Krabbe Disease (infantile form). American College of Medical Genetics and Genomics; 2021. Updated May 2022. Accessed June 10, 2024. Available at www.acmg.net/PDFLibrary/Krabbe-Infantile.pdf 2. Newborn Screening ACT Sheet [Decreased galactocerebrosidase, mildly elevated psychosine] Krabbe Disease (late-onset form). American College of Medical Genetics and Genomics; 2021. Updated May 2022. Accessed June 10, 2024. Available www.acmg.net/PDFLibrary/Krabbe-Later-Onset.pdf 3. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 4. Orsini JJ, Escolar ML, Wasserstein MP, Caggana M: Krabbe disease. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated October 11, 2018. Accessed June 30, 2020. Available at ncbi.nlm.nih.gov/books/NBK1238/ 5. Luzi P, Rafi MA, Wenger DA: Structure and organization of the human galactocerebrosidase (GALC) gene. Genomics. 1995;26:407-409 6. Luzi P, Rafi MA, Wenger DA: Characterization of the large deletion in the GALC gene found in patients with Krabbe disease. Hum Mol Genet. 1995;4(12):2335-2338 7. Spiegel R, Bach G, Sury V, et al: A mutation in the saposin A coding region of the prosaposin gene in an infant presenting as Krabbe disease: report of saposin A deficiency in humans. Molec Genet Metab. 2005,84:160-166

KRASW 616452 KRAS Somatic Mutation Analysis, Peritoneal Fluid

Clinical Information: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with predilection for peritoneal dissemination. Accurate peritoneal staging is important for management of patients with PDAC. The KRAS oncogene is the most frequently mutated oncogene in PDAC. Detection of KRAS mutations within peritoneal fluid has been associated with clinically positive laparoscopic findings (gross metastases and/or positive peritoneal cytology) and elevated peritoneal fluid carbohydrate antigen 19-9 and/or carcinoembryonic antigen and may portend an increased risk of residual/recurrent pancreatic cancer metastases within the peritoneal cavity. This test uses DNA extracted from cells shed into the peritoneum to evaluate for the presence of KRAS (G12A, G12C, G12D, G12R, G12S, G12V, G13D, Q61K, Q61L, Q61R, Q61H, and A146T) mutations. A positive result indicates the presence of an activating KRAS mutation and can be a useful marker to aid in the staging of pancreatic ductal adenocarcinoma.

Useful For: Staging of the pancreatic ductal adenocarcinoma(1)

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Yonkus JA, Alva-Ruiz R, Abdelrahman AM, et al. Molecular peritoneal staging for pancreatic ductal adenocarcinoma using mutant KRAS droplet-digital polymerase chain reaction: Results of a prospective clinical trial. J Am Coll Surg. 2021;233(1):73-80.e1. doi:10.1016/j.jamcollsurg.2021.05.009 2. Kim NH, Kim HJ. Preoperative risk factors for early recurrence in patients with resectable pancreatic ductal adenocarcinoma after curative intent surgical resection. Hepatobiliary Pancreat Dis Int. 2018;17(5):450-455 doi:10.1016/j.hbpd.2018.09.003 3. Avula

LR, Hagerty B, Alewine C. Molecular mediators of peritoneal metastasis in pancreatic cancer. Cancer Metastasis Rev. 2020;39(4):1223-1243. doi:10.1007/s10555-020-09924-4

KRASP 610679 KRAS Somatic Mutation Analysis, Tumor

Clinical Information: Strategies that focus on early detection and prevention effectively decrease the risk of mortality associated with cancer. In addition, an increase in survival rate for individuals with advanced stage disease has been observed as a result of advancements in standard chemotherapeutic agents and the development of specialized targeted therapies. Monoclonal antibodies against epidermal growth factor receptor (EGFR), such as cetuximab and panitumumab, represent an area of targeted therapy for patients with colorectal and non-small cell lung cancer (NSCLC). However, studies have shown that not all individuals with colorectal cancer or NSCLC respond to EGFR targeted molecules. Because the combination of targeted therapy and standard chemotherapy leads to an increase in toxicity and cost, strategies that help to identify the individuals most likely to benefit from such targeted therapies are desirable. Epidermal growth factor receptor is a growth factor receptor that is activated by the binding of specific ligands (epiregulin and amphiregulin), resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately regulating a number of cellular processes including cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression. Targeted therapies directed to EGFR, which inhibit activation of the RAS/MAPK pathway, have demonstrated some success (increased progression-free and overall survival) in patients with cancer, in particular, colorectal cancer and NSCLC. One of the most common somatic mutations in colon cancer and NSCLC is the presence of activating mutations in the protooncogene KRAS. KRAS is recruited by ligand-bound (active) EGFR to initiate the signaling cascade induced by the RAS/MAPK pathway. Because altered KRAS constitutively activates the RAS/MAPK pathway downstream of EGFR, agents such as cetuximab and panitumumab, which prevent ligand-binding to EGFR, do not appear to have any meaningful inhibitor activity on cell proliferation in the presence of altered KRAS. Current data suggest that the efficacy of EGFR-targeted therapies in colon cancer and NSCLC is confined to patients with tumors lacking KRAS mutations. An exception is the KRAS G12C variant, which is targetable with variant-specific inhibitors. This test uses DNA extracted from tumor tissue to evaluate for the presence of KRAS (G12A, G12C, G12D, G12R, G12S, G12V, G13D, Q61K, Q61L, Q61R, Q61H, and A146T) mutations. A positive result indicates the presence of an activating KRAS mutation and can be a useful marker by which patients are selected for EGFR-targeted therapy.

Useful For: Detecting molecular markers associated with response or resistance to specific cancer

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1.Allegra CJ, Rumble BR, Hamilton SR, et al. Extended RAS gene mutation testing in metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy: ASCO Provisional Clinical Opinion update 2015. J Clin Oncol. 2016;34(2):179-185 2.Spano JP, Milano G, Vignot S, Khayat D. Potential predictive markers of response to EGFR-targeted therapies in colorectal cancer. Crit Rev Oncol Hematol. 2008;66(1)21-30 3.Lam DC: Clinical testing for molecular targets for personalized treatment in lung cancer. Respirology. 2013;18(2):233-237 4.Hong DS, Fakih MG, Strickler JH, et al. KRAS G12C inhibition with sotorasib in advanced solid tumors. N Engl J Med. 2020;383(13):1207-1217

LBCS 620895 Labile Bound Copper, Serum

Clinical Information: Copper (Cu) is an important trace element that is associated with a number of metalloproteins. Copper in biological material is complexed with proteins, peptides, and other organic ligands. The majority of copper in plasma is bound to the enzyme ceruloplasmin, a copper-dependent multifunction oxidase enzyme. Up to 90% of copper exported from the liver into peripheral blood is tightly protein bound. The remaining copper fraction is often referred to as "free" copper, however a more accurate description is labile bound copper (LBC), as it is not truly circulating freely but is loosely bound to various smaller proteins, including albumin, transcuprein, tetrapeptides, and other amino acids. This test involves measurement of both the LBC concentration and total copper. The LBC will be divided by the measured total copper concentration to calculate a LBC fraction result. The LBC fraction (%) may be more useful than LBC in some disease states, such as Wilson disease, as it represents the fraction of LBC normalized against potential variation in total copper burden. Low serum copper, most often due to excess iron or zinc ingestion and infrequently due to dietary copper deficit, may result in altered growth and in impaired erythropoiesis. Low total serum copper is also observed in hepatolenticular degeneration (Wilson disease) due to a decrease in the synthesis of ceruloplasmin and allelic variances in cellular metal ion transporters. In Wilson disease, the albumin-bound copper may actually be increased, but ceruloplasmin-bound copper is low, resulting in low serum copper. However, during the acute phase of Wilson disease (fulminant hepatic failure), ceruloplasmin and copper levels may be normal; in this circumstance, hepatic inflammation causes increased release of ceruloplasmin. It is useful to relate the degree of liver inflammation to ceruloplasmin and copper (see the following discussion on hypercupremia). Significant hepatic inflammation with normal ceruloplasmin and copper suggest acute Wilson disease. As WD is characterized by a loss of ceruloplasmin-copper binding function, the concentration of non-ceruloplasmin bound labile copper (NCC) is an attractive target as a diagnostic aid. NCC has been historically estimated by the following formula: NCC = total serum copper (mcg/dL) - [3.15 x ceruloplasmin (mcg/dL)]. This calculated estimate has limitations, as it is difficult to directly measure ceruloplasmin, and assumes that all available ceruloplasmin is fully saturated with copper. As such, a clinical assay that can directly quantify the proportion of "free" or labile bound (LBC fraction) of total copper in serum may be preferable. While measurement of LBC fraction has been shown to be a promising diagnostic tool for Wilson disease, it may be applicable to other copper-related disorders as well. Additional disorders associated with decreased serum copper concentrations include malnutrition, hypoproteinemia, malabsorption, nephrotic syndrome, Menkes disease, copper toxicity, and megadosing of zinc-containing vitamins (zinc interferes with normal copper absorption from the gastrointestinal [GI] tract). Hypercupremia is found in primary biliary cholangitis (formerly primary biliary cirrhosis), primary sclerosing cholangitis, hemochromatosis, malignant diseases (including leukemia), thyrotoxicosis, and various infections. Serum copper concentrations are also elevated in patients taking contraceptives or estrogens and during pregnancy. Since the GI tract effectively excludes excess copper, it is the GI tract that is most affected by copper ingestion. Increased copper serum concentration, LBC copper, and LBC fraction alone do not directly indicate copper toxicity.

Useful For: May be useful in the evaluation of copper-related disorders, including Wilson disease

Interpretation: This test measures the labile bound copper (LBC) in serum and calculates the fraction (%) of labile bound copper to total copper (LBC fraction). Serum copper results below the normal range and LBC fraction above the normal range are associated with Wilson disease. Abnormal total copper and LBC fraction may also be associated with a variety of other copper-related disorders (see Clinical Information).

Reference Values:
Labile Bound Copper: <105 ng/mL

Labile Bound Copper Fraction:
Males: <10.5 %
Females: <8.1 %

Copper, Total:
0-2 months: 40-140 mcg/dL
3-6 months: 40-160 mcg/dL
7-9 months: 40-170 mcg/dL
10-12 months: 80-170 mcg/dL
13 months-10 years: 80-180 mcg/dL
11-17 years: 75-145 mcg/dL
Males:
> or =18 years: 73-129 mcg/dL
Females:
> or =18 years: 77-206 mcg/dL

Clinical References: 1. Woimant F, Djebrani-Oussedik N, Poujois A. New tools for Wilson's disease diagnosis: exchangeable copper fraction. Ann Transl Med. 2019;7(Suppl 2):S70. doi:10.21037/atm.2019.03.02 2. McMillin GA, Travis JJ, Hunt JW. Direct measurement of free copper in serum or plasma ultrafiltrate. Am J Clin Pathol. 2009;131(2):160-5. doi:10.1309/AJCP7Z9KBFINVGYF 3. Quarles CD Jr, Macke M, Michalke B, et al. LC-ICP-MS method for the determination of "extractable copper" in serum. Metallomics. 2020;12(9):1348-1355 4. Shribman S, Marjot T, Sharif A, et al. Investigation and management of Wilson's disease: a practical guide from the British Association for the Study of the Liver. Lancet Gastroenterol Hepatol. 2022;7(6):560-575 5. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 7th ed. Elsevier; 2023:chap 44 6. Alman B, Fay M, Antezana A, et al. Toxicological Profile for Copper. ATSDR; 2022. Accessed January 22, 2024. Available atwww.atsdr.cdc.gov/toxprofiles/tp132.pdf

LACO
62905

Lacosamide, Serum

Clinical Information: Lacosamide is approved for adjunctive therapy to treat partial-onset seizures in epileptic patients aged 17 years and older. In clinical trials, the most common side effects were dizziness, headache, nausea, and double vision. Lacosamide is completely absorbed after oral administration with negligible first-pass metabolism. Peak serum concentrations occur 1 to 4 hours after oral dosing, and the elimination half-life is approximately 13 hours. Steady-state serum concentrations are achieved after 3 days of twice daily repeated administration. About 40% of the administered dose is eliminated by the renal system unchanged, and 30% is metabolized by hepatic isoenzymes (CYP2C9, CYP2C19, and CYP3A4) to the O-desmethyl inactive metabolite. The relationship between lacosamide serum concentrations and its efficacy or adverse effects is not well established. However, central nervous system toxicity has been associated with higher drug concentrations in serum.

Useful For: Monitoring serum concentrations of lacosamide to ensure compliance and appropriate dosing in specific clinical conditions (ie, severe kidney impairment, mild-to-moderate hepatic impairment, and kidney failure)

Interpretation: The serum concentration should be interpreted in the context of the patient's clinical response and may provide useful information in patients showing poor response or adverse effects, particularly when lacosamide is co-administered with other anticonvulsant drugs. Toxic ranges are not well established but occur more frequently when concentrations are greater or equal to 20 mcg/mL.

Reference Values:
Patients receiving therapeutic doses usually have lacosamide concentrations of 1.0 to 10.0 mcg/mL.

Clinical References: 1. VIMPAT Medication Guide. Harris FRC Corporation. UCB, Inc; Revised 09/2022. Accessed April 23, 2024. Available at www.ucb-usa.com/vimpat-prescribing-information.pdf 2.

Patsalos PN, Berry DJ. Pharmacotherapy of the third-generation AEDs: lacosamide, retigabine and eslicarbazepine acetate. Expert Opin Pharmacother. 2012;13(5):699-715 3. Chung SS. New treatment option for partial-onset seizures: efficacy and safety of lacosamide. Ther Adv Neurol Disord. 2010;3(2):77-83 4. Sattler A, Schaefer M, May TW, Rambeck B, Brandt C. Fluctuation of lacosamide serum concentrations during the day and occurrence of adverse drug reactions-first clinical experience. Epilepsy Res. 2011;95(3):207-212 5. Greenaway C, Ratnaraj N, Sander JW, Patsalos PN. Saliva and serum lacosamide concentrations in patients with epilepsy. Epilepsia. 2011;52(2):258-263 6. McMullin M, Dalrymple R. Analysis for lacosamide in human serum by LC/MS/MS and a summary of 8,000 patient values. Ther Drug Monit. 2011;33(4):520-521 7. Hiemke C, Bergemann N, Clement HW, et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62. doi:10.1055/s-0043-116492

LDBF
606612

Lactate Dehydrogenase (LDH), Body Fluid

Clinical Information: Lactate dehydrogenase (LDH) activity is present in all cells of the body with the highest concentrations in the heart, liver, muscle, kidney, lung, and erythrocytes. Pleural fluid: Pleural fluid is normally present within the pleural cavity surrounding the lungs, serving as a lubricant between the lungs and inner chest wall. Pleural effusion develops when the pleural cavity experiences an overproduction of fluid due to increased capillary hydrostatic and osmotic pressure that exceeds the ability of the lymphatic or venous system to return the fluid to circulation. Laboratory-based criteria are often used to classify pleural effusions as either exudative or transudative. Exudative effusions form due to infection or inflammation of the capillary membranes allowing excess fluid into the pleural cavity. Patients with these conditions benefit from further investigation and treatment of the local cause of inflammation. Transudative effusions form due to systemic conditions such as volume overload, end stage kidney disease, and heart failure that can lead to excess fluid accumulation in the pleural cavity. Patients with transudative effusions benefit from treatment of the underlying condition.(1) Measurement of LDH in body fluids is primarily indicated to aid in the differentiation of transudative and exudative effusions as LDH activity is considered an indicator of the extent of inflammation. Dr. Richard Light derived criteria in the 1970s for patients with pleural effusions that are still used today.(2) The criteria include the measurement of total protein and LDH in pleural fluid and serum. Exudates are defined as meeting one of the following criteria: 1. Pleural fluid-to-serum protein ratio above 0.5 2. Pleural fluid LDH above two-thirds the upper limit of normal serum LDH 3. Pleural fluid-to-serum LDH ratio above 0.6 Pericardial fluid: The routine analysis of LDH to differentiate exudative and transudative pericardial effusions is not considered helpful.(3) Peritoneal fluid: Spontaneous bacterial peritonitis or ascitic fluid infection is common (12%) at the time of admission of a patient with cirrhosis and ascites. The diagnosis is made in the presence of an elevated ascitic fluid absolute polymorphonuclear (PMN) leukocyte count (ie, >250 cells/mm(3) [0.25 x 10(9)/L]) without an evident intra-abdominal, surgically treatable source of infection.(4) Secondary bacterial peritonitis (ie, ascitic fluid infection caused by a surgically treatable intra-abdominal source) can masquerade as spontaneous bacterial peritonitis. Signs and symptoms do not help separate patients who need surgical intervention from those who have spontaneous bacterial peritonitis and need only antibiotic treatment. In contrast, the initial ascitic fluid analysis and the response to treatment can assist with this important distinction. The characteristic analysis in the setting of free perforation is PMN count of 250 cells/mm(3) (usually many thousands) or higher, multiple organisms (frequently including fungi and enterococcus) on Gram stain and culture, and at least 2 of the following criteria: total protein above 1 g/dL, LDH above the upper limit of normal for serum, and glucose below 50 mg/dL. Studies have reported higher than 95% sensitivity but low specificity using these criteria; a computerized tomographic scan was diagnostic in 85% of patients with secondary peritonitis.(5)

Useful For: Identification of exudative pleural effusions Lactate dehydrogenase in pericardial fluids is not diagnostically useful.

Interpretation: Pleural fluid lactate dehydrogenase (LDH) to serum LDH ratios above 0.6 are most

consistent with exudative effusions.(2,6) Peritoneal fluid LDH above 220 U/L suggests secondary, rather than spontaneous bacterial peritonitis, in conjunction with other laboratory, imaging, and clinical findings.(4,5) Synovial fluid LDH may be elevated greater than plasma or serum LDH due to inflammatory causes. Values should be interpreted in conjunction with other clinical findings.(7) All other fluids: LDH may be used to differentiate transudative from exudative effusions. The decision limits are not well defined in fluids other than pleural fluid and should be interpreted in conjunction with other clinical findings.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Block DR, Florkowski CM. Body fluids. In: Rifai N, Horvath AR, Wittwer CT. eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:chap 43 2. Light RW, Macgregor I, Luchsinger PC, Ball WC. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med. 1972;77(4):507-513 3. Ben-Horin S, Bank I, Shinfeld A, et al. Diagnostic value of the biochemical composition of pericardial effusions in patients undergoing pericardiocentesis. Am J Cardiol. 2007;99(9):1294-1297 4. Soriano G, Castellote J, Alvarez C, et al. Secondary bacterial peritonitis in cirrhosis: a retrospective study of clinical and analytical characteristics, diagnosis and management. J Hepatol. 2010;52(1):39-44 5. Sahn, SA. Getting the most from pleural fluid analysis. Respirology. 2012;17(2):270-277 6. Tarn AC, Lapworth R. Biochemical analysis of ascitic (peritoneal) fluid: what should we measure? Ann Clin Biochem. 2010;47:397-407 7. Pejovic M, Stankovic A, Mitrovic DR. Lactate dehydrogenase activity and its isoenzymes in serum and synovial fluid of patients with rheumatoid arthritis and osteoarthritis. J Rheumatol. 1992;19:529-533 8. Nandakumar V, Dolan C, Baumann NA, et al. Effect of pH on the quantification of body fluid analytes for clinical diagnostic testing. Am J Clin Path. 2019;152(1):S10-S11

LD
8344

Lactate Dehydrogenase (LDH), Serum

Clinical Information: Lactate dehydrogenase (LDH) activity is present in all cells of the body with highest concentrations in heart, liver, muscle, kidney, lung, and erythrocytes. Serum LDH is elevated in a number of clinical conditions.

Useful For: Investigation of a variety of diseases involving the heart, liver, muscle, kidney, lung, and blood Monitoring changes in tumor burden after chemotherapy; lactate dehydrogenase elevations in patients with cancer are too erratic to be of use in the diagnosis of cancer

Interpretation: Marked elevations in lactate dehydrogenase (LDH) activity can be observed in megaloblastic anemia, untreated pernicious anemia, Hodgkin disease, abdominal and lung cancers, severe shock, and hypoxia. Moderate to slight increases in LDH levels are seen in myocardial infarction, pulmonary infarction, pulmonary embolism, leukemia, hemolytic anemia, infectious mononucleosis, progressive muscular dystrophy (especially in the early and middle stages of the disease), liver disease, and kidney disease. In liver disease, elevations of LDH are not as great as the increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Increased levels of the enzyme are found in about one-third of patients with kidney disease, especially those with tubular necrosis or pyelonephritis. However, these elevations do not correlate well with proteinuria or other parameters of kidney disease. On occasion a raised LDH level may be the only evidence to suggest the presence of a hidden pulmonary embolus.

Reference Values:
1-30 days: 135-750 U/L
31 days-11 months: 180-435 U/L
1-3 years: 160-370 U/L

4-6 years: 145-345 U/L
7-9 years: 143-290 U/L
10-12 years: 120-293 U/L
13-15 years: 110-283 U/L
16-17 years: 105-233 U/L
> or =18 years: 122-222 U/L

Clinical References: Panteghini M, Bais R: Serum enzymes. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:407-431

LAPYP
616609

Lactate Pyruvate Panel, Plasma

Clinical Information: Lactic acid (lactate) is primarily produced from glucose metabolism via the glycolytic pathway. Although primarily metabolized by the liver, other tissues also use small amounts of lactate. Typically, the amount of lactate produced parallels the amount utilized. Both the rates of lactate production and liver clearance impact the lactate concentration in blood. Lactic acidosis, or the accumulation of excess lactate, results from a combination of increased lactate production with decreased utilization. Patients experiencing lactic acidosis present with tachypnea, weakness, and fatigue. Untreated, patients may develop confusion and progress to coma. Lactic acidosis may be associated with hypoxic conditions (eg, shock, hypovolemia, heart failure, pulmonary insufficiency), metabolic disorders (eg, diabetic ketoacidosis, malignancies, inborn errors of metabolism), and toxin exposures (eg, ethanol, methanol, salicylates). Pyruvic acid, an intermediate metabolite, plays an important role in linking carbohydrate and amino acid metabolism to the tricarboxylic acid cycle, the fatty acid beta-oxidation pathway, and the mitochondrial respiratory chain complex. However, pyruvic acid levels alone have little clinical utility. Combined analysis of lactate and pyruvate may suggest an inborn error of metabolism when elevations of both analytes are observed or when there is an abnormal lactate-to-pyruvate (L:P) ratio. For example, several mitochondrial respiratory chain disorders exhibit elevated L:P ratios. Mitochondrial disorders vary widely in both clinical presentation and age of onset. Patients commonly present with neurologic and myopathic features. In addition, patients may experience involvement of multiple organ systems with features such as myopathy, ophthalmoplegia, ptosis, cardiomyopathy, sensorineural hearing loss, optic atrophy, pigmentary retinopathy, diabetes mellitus, encephalomyopathy, seizures, and stroke-like episodes. A low L:P ratio is observed in inherited disorders of pyruvate metabolism including pyruvate dehydrogenase complex (PDHC) deficiency. Clinical presentation of PDHC deficiency can range from fatal congenital lactic acidosis to relatively mild ataxia or neuropathy. The most common features observed in infants and children with PDHC deficiency are developmental delay, hypotonia, seizures, and ataxia. Other manifestations may include congenital brain malformations, degenerative changes including Leigh disease, and facial dysmorphism.

Useful For: Diagnosing and monitoring patients with lactic acidosis Monitoring lactate-to-pyruvate ratios

Interpretation: An elevated lactate-to-pyruvate (L:P) ratio may indicate inherited disorders of the respiratory chain complex, tricarboxylic acid cycle disorders, and pyruvate carboxylase deficiency. Respiratory chain defects usually result in L:P ratios above 20. A low L:P ratio (disproportionately elevated pyruvic acid) may indicate an inherited disorder of pyruvate metabolism. Defects of the pyruvate dehydrogenase complex result in L:P ratios below 10. The L:P ratio is characteristically normal in other patients. An artifactually high ratio can be found if the patient is acutely ill. Cerebrospinal fluid (CSF) L:P ratio may assist in evaluation of patients with neurologic dysfunction and normal blood L:P ratios. Blood and CSF specimens should be collected at the same time.

Reference Values:
Lactic Acid
< or = 4000.0 nmol/mL

Pyruvic Acid
< or = 350.0 nmol/mL

Clinical References: 1. Munnich A, Rotig A, Cormier-Daire V, Rustin P. Clinical presentation of respiratory chain deficiency. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed July 5, 2024. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225086827 2. Robinson BH. Lactic acidemia: Disorders of pyruvate carboxylase and pyruvate dehydrogenase. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed July 5, 2024. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225087140 3. Shoffner JM. Oxidative phosphorylation diseases. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019 Accessed July 5, 2024. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225088339

LACS1
601685

Lactate, Plasma

Clinical Information: Anaerobic glycolysis markedly increases blood lactate and causes some increase in pyruvate levels, especially with prolonged exercise. The common cause for increased blood lactate and pyruvate is anoxia resulting from such conditions as shock, pneumonia, and congestive heart failure. Lactic acidosis may also occur in kidney failure and leukemia. Thiamine deficiency and diabetic ketoacidosis are associated with increased levels of lactate and pyruvate. Lactate measurements that evaluate the acid-base status are used in the diagnosis and treatment of lactic acidosis (abnormally high acidity in the blood).

Useful For: Diagnosing and monitoring patients with lactic acidosis

Interpretation: While no definitive concentration of lactate has been established for the diagnosis of lactic acidosis, lactate concentrations exceeding 5 mmol/L and pH below 7.25 are generally considered indicative of significant lactic acidosis.

Reference Values:
0-90 days (<3 months): 0.0-3.3 mmol/L
3-24 months: 0.0-3.1 mmol/L
>24 months-18 years: 0.0-2.2 mmol/L
>18 years: 0.5-2.2 mmol/L

Clinical References: 1. Mizock BA. The hepatosplanchnic area and hyperlactatemia: A tale of two lactates. Crit Care Med. 2001;29(2):447-449. doi:10.1097/00003246-200102000-00047 2. Duke T: Dysoxia and lactate. Arch Dis Child. Oct;81(4):343-350. doi:10.1136/adc.81.4.343 3. Sacks D: Carbohydrates. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 6th ed. Elsevier; 2018:518-538

LASF1
601821

Lactic Acid, Spinal Fluid

Clinical Information: Anaerobic glycolysis markedly increases lactate concentrations. Lactate concentrations in cerebrospinal fluid (CSF) are increased in the presence of cerebral glycolysis or hypoxia

associated with bacterial meningitis, cerebral infarction, cerebral arteriosclerosis, intracranial hemorrhage, hydrocephalus, traumatic brain injury, cerebral edema, epilepsy, and inborn errors of metabolism. Lactate found in CSF is predominantly produced by central nervous system anaerobic glycolysis and is independent of blood lactate. Lactate measurement in CSF has been proposed as a test to differentiate bacterial from viral meningitis.

Useful For: Aid in differentiating between bacterial and viral meningitis Aid in identifying increased anaerobic glycolysis or hypoxia associated with bacterial meningitis, cerebral infarction, cerebral arteriosclerosis, intracranial hemorrhage, hydrocephalus, traumatic brain injury, cerebral edema, epilepsy, and inborn errors of metabolism

Interpretation: In addition to reference intervals, published meta-analysis of 33 studies concluded concentrations greater than 3.9 mmol/L are suggestive of bacterial meningitis, with lower concentrations suggestive of viral meningitis.(1)

Reference Values:
0-2 days: 1.1-6.7 mmol/L
3-10 days: 1.1-4.4 mmol/L
11 days-17 years: 1.1-2.8 mmol/L
>17 years: 1.1-2.4 mmol/L

Clinical References: 1. Sakushima K, Hayashino Y, Kawaguchi T, et al: Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: A meta-analysis. J Infect. 2011;62:255-262 2. Zhang W, Natowicz MR: Cerebrospinal fluid lactate and pyruvate concentrations and their ratio. Clin Biochem. 2013;46:694-697

FLACF
57827

Lactoferrin, Fecal by ELISA

Interpretation: A positive result is indicative of the presence of lactoferrin, a marker for fecal leukocytes. A negative result does not exclude the presence of intestinal inflammation.

Reference Values:
Negative

FLACQ
75813

Lactoferrin, Quantitative, Stool

Reference Values:
Less than 7.25 mcg/mL

LACTO
70625

Lactotransferrin Immunostain, Technical Component Only

Clinical Information: Lactotransferrin (also referred to as lactoferrin) is a secreted iron-binding glycoprotein found in milk, tears, and leukocytes. It has been shown to be expressed in various tissues including tonsil, intestinal epithelium, kidney, and various regions of the brain where it is thought to play a role in iron metabolism and defense against bacteria. Lactotransferrin also plays a role in amyloidosis, specifically of the cornea, but has been observed in other tissue types.

Useful For: Identifying the presence of lactotransferrin in amyloid deposits An adjunct to amyloid-subtyping analysis by mass spectrometry

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Ando Y, Nakamura M, Kai H, et al. A novel localized amyloidosis associated with lactoferrin in the cornea. Lab Invest. 2002;82(6):757-765 2. Furuya S, Masurmori N, Furuya R, et al. Characterization of localized seminal vesicle amyloidosis causing hemospermia: An analysis using immunohistochemistry and magnetic resonance imaging. J Urol. 2005;173:1273-1277 3. Kebbel A, Rocken C. Immunohistochemical classification of amyloid in surgical pathology revisited. Am J Surg Pathol. 2006;30(6):673-683 4. Tuccari G, Barresi G. Lactoferrin in human tumours: immunohistochemical investigations during more than 25 years. Biometals. 2011;24:775-784 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FLBAE
57572

Ladybeetle Multicolored Asian (Harmonia axyridis) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >=50 Very Strong Positive

Reference Values:
<0.35 kU/L

LAMQ
82682

Lamb's Quarter, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to lamb's quarter Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

LAMB
82699

Lamb, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to lamb Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

LAIHC
70499

Lambda Light Chain Immunostain, Technical Component Only

Clinical Information: Kappa or lambda immunoglobulin light chains pair with immunoglobulin heavy chains to form complete immunoglobulin molecules. These proteins serve as receptors for antigens in B lymphocytes and are the secretory products of plasma cells, forming the humoral arm of the immune system. Because individual B cells or plasma cells synthesize immunoglobulin containing either kappa or lambda light chains, but not both, immunoperoxidase stains for light chains can be applied to lymphocyte and plasma cell populations as a marker of clonality and B-cell lineage.

Useful For: A marker of B-cell and plasma cell clonality and B-cell lineage

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Peterson LC, Brown BA, Crosson JT, Mladenovic J. Application of the immunoperoxidase technique to bone marrow trephine biopsies in the classification of patients with monoclonal gammopathies. Am J Clin Pathol. 1986;85:688-693 2. Taylor CR, Burns J. The demonstration of plasma cells and other immunoglobulin-containing cells in formalin-fixed, paraffin-embedded tissues using peroxidase labeled antibody. J Clin Pathol. 1974;27(1):14-20 3. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

LAMO
80999

Lamotrigine, Serum

Clinical Information: Lamotrigine (Lamictal) is approved for therapy of bipolar I disorder and a wide variety of seizure disorders including Lennox-Gastaut syndrome, primary generalized tonic-clonic

seizures, and partial seizures. Its many off-label uses include treatment of migraine, trigeminal neuralgia, and treatment-refractory depression. Lamotrigine inhibits glutamate release (an excitatory amino acid) and voltage-sensitive sodium channels to stabilize neuronal membranes; it also weakly inhibits the 5-HT3 (serotonin) receptor. Lamotrigine oral bioavailability is very high (approximately 98%). The drug is metabolized by glucuronic acid conjugation to inactive metabolites. The half-life is 25 to 33 hours in adults but decreases with concurrent use of phenytoin or carbamazepine (13-14 hours) and increases with concomitant valproic acid therapy (59-70 hours), kidney dysfunction, or hepatic impairment. The therapeutic range is relatively wide, 3 to 15 mcg/mL for most individuals. Common adverse effects are dizziness, ataxia, blurred or double vision, nausea, or vomiting.

Useful For: Monitoring serum concentration of lamotrigine Assessing compliance Adjusting lamotrigine dose in patients receiving other anticonvulsant drugs that interact pharmacokinetically with lamotrigine

Interpretation: The serum concentration should be interpreted in the context of the patient's clinical response and may provide useful information in patients showing poor response, noncompliance, or adverse effects, particularly when lamotrigine is coadministered with other anticonvulsant drugs. While most patients show response to the drug when the trough concentration is in the range of 3.0 to 15.0 mcg/mL and show signs of toxicity when the peak serum concentration is greater than 20 mcg/mL, some patients can tolerate peak concentrations as high as 70 mcg/mL.

Reference Values:
Patients receiving therapeutic doses usually have lamotrigine concentrations of 3.0-15.0 mcg/mL.

Clinical References: 1. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453 2. Johannessen SI, Battino D, Berry DJ, et al. Therapeutic drug monitoring of the newer antiepileptic drugs. Ther Drug Monit. 2003;25(3):347-363. doi:10.1097/00007691-200306000-00016 3. Johannessen SI, Landmark CJ. Value of therapeutic drug monitoring in epilepsy. Expert Rev Neurother. 2008;8(6):929-939. doi:10.1586/14737175.8.6.929 4. Johannessen SI, Tomson T. Pharmacokinetic variability of newer antiepileptic drugs: When is monitoring needed? Clin Pharmacokinet. 2006;45(11):1061-1075. doi:10.2165/00003088-200645110-00002 5. Physician's Desk Reference. 71st ed. Thomson PDR; 2017 6. Hardman JG, Limbird LE, Gilman AG, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. McGraw-Hill Book Company; 2001 7. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62. doi:10.1055/s-0043-116492

LANGR
70496

Langerin Immunostain, Technical Component Only

Clinical Information: Langerhans cells are specialized antigen-presenting cells residing in the skin, usually as scattered cells along the dermal-epidermal junction. Langerin is expressed in both normal and neoplastic Langerhans cells and is specifically associated with the assembly of Birbeck granules in these cells. Langerin positivity also has been noted in lymph node sinuses and hepatic sinusoids in which CD1a is negative.

Useful For: Visualization of normal and neoplastic Langerhans cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the

patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chikwava K, Jaffe R. Langerin (CD207) staining in normal pediatric tissues, reactive lymph node, and childhood histiocytic disorders. Pediatr Dev Pathol. 2004;7(6):607-614 2. Valladeau J, Dezuter-Dambuyant C, Saeland S, et al. Langerin/CD207 sheds light on formation of birbeck granules and their possible function in Langerhans cells. Immunol Res. 2003;28(2):93-107 3. Bohn OL, Ruiz-Arguelles G, Navarro L, et al. Cutaneous Langerhans cell sarcoma: a case report and review of the literature. Int J Hematol. 2007;85(2):116-120 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

LANG
82349

Langust (Lobster), IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to langust (lobster) Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive

6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

LATX
82787

Latex, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to latex Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FLDLD
75160

LDL Cholesterol, Direct

Interpretation: CHD Risk Factors: +1 Age: Men 45 years and older; Women 55 years and older or premature menopause without estrogen therapy +1 Family history of premature CHD +1 Current smoking +1 Hypertension +1 Diabetes mellitus +1 Low HDL Cholesterol: 39 mg/dL or less - 1 High HDL Cholesterol: 60 mg/dL or greater LDL Cholesterol: Therapeutic goal 99 mg/dL or less if CHD is present (Optional 69 mg/dL or less) 129 mg/dL or less if no CHD and two or more risk factors 159 mg/dL or less if no CHD (Circulation 2004; 110:227-39)

Reference Values:
0-19 years:
Desirable: 109 mg/dL or less
Borderline: 110-129 mg/dL
Higher risk: 130 mg/dL or greater

20 years and older:
Desirable: 129 mg/dL or less (99 mg/dL or less if patient has CHD)
Borderline: 130-159 mg/dL
Higher risk: 160 mg/dL or greater

PBOU
608894

Lead Occupational Exposure, Random, Urine

Clinical Information: Lead toxicity primarily affects the gastrointestinal, neurologic, and hematopoietic systems. Increased urine lead concentration per gram of creatinine indicates significant lead exposure. Measurement of urine lead concentration per gram of creatinine before and after chelation therapy has been used as an indicator of significant lead exposure. An increase in lead concentration per gram of creatinine in the post-chelation specimen of up to 6 times the concentration in the pre-chelation specimen is normal. Blood lead measurement is the best test for clinical correlation of toxicity. For more information, see PBDV / Lead, Venous, with Demographics, Blood.

Useful For: Detecting clinically significant lead exposure due to occupational exposure in random urine specimens This test is not a substitute for blood lead screening.

Interpretation: Urinary excretion of less than 4 mcg/g creatinine is not associated with any significant lead exposure. Urinary excretion of more than 4 mcg/g creatinine is usually associated with pallor, anemia, and other evidence of lead toxicity.

Reference Values:
Only orderable as part of profile. For more information see:
-PBUOE / Lead Occupational Exposure, Random, Urine
-HMUOE / Heavy Metal Occupational Exposure, with Reflex, Random, Urine

Biological Exposure Index (BEI): <150 mcg/g creatinine

Clinical References: 1. Kosnett MJ, Wedeen RP, Rotherberg SJ, et al. Recommendations for medical management of adult lead exposure. Environ Health Perspect. 2007;115(3):463-471 2. de Burbane C, Buchet JP, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and

arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590 3. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44 4. Hauptman M, Bruccoleri R, Woolf AD. An update on childhood lead poisoning. Clin Pediatr Emerg Med. 2017;18(3):181-192. doi:10.1016/j.cpem.2017.07.010

PBUOE
608898

Lead Occupational Exposure, Random, Urine

Clinical Information: Lead toxicity primarily affects the gastrointestinal, neurologic, and hematopoietic systems. Increased urine lead concentration per gram of creatinine indicates significant lead exposure. Measurement of urine lead concentration per gram of creatinine before and after chelation therapy has been used as an indicator of significant lead exposure. However, the American College of Medical Toxicology (ACMT 2010) position statement on post-chelator challenge urinary metal testing states that "post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning. Lead blood measurement is the best test for clinical correlation of toxicity. For more information see PBDV / Lead, Venous, with Demographics, Blood.

Useful For: Detecting clinically significant lead exposure due to occupational exposure This test is not a substitute for blood lead screening.

Interpretation: Measurements of urinary lead levels have been used to assess lead exposure. However, like blood lead, urinary lead excretion mainly reflects recent exposure and, thus, shares many of the same limitations for assessing lead body burden or long-term exposure.(1,2) Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations.(3,4)

Reference Values:
LEAD/CREATININE:
Biological Exposure Index (BEI): <150 mcg/g creatinine

CREATININE:
> or =18 years: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Sakai T. Biomarkers of lead exposure. Ind Health. 2000;38(2):127-142 2. Skerfving S. Biological monitoring of exposure to inorganic lead. In: Clarkson TW, Friberg L, Nordberg GF, Sager PR, eds. Biological Monitoring of Toxic Metals. Rochester Series on Environmental Toxicity. Springer; 1988:169-197 3. Gulson BL, Jameson CW, Mahaffey KR, et al. Relationships of lead in breast milk to lead in blood, urine, and diet of the infant and mother. Environ Health Perspect. 1998;106(10):667-674 4. Skerfving S, Ahlgren L, Christoffersson JO. Metabolism of inorganic lead in man. Nutr Res. 1985;Suppl 1:601-607 5. Kosnett MJ, Wedeen RP, Rotherberg SJ, et al. Recommendations for medical management of adult lead exposure. Environ Health Perspect. 2007;115(3):463-471 6. De Burbane C, Buchet JP, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590 7. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44 8. Hauptman M, Bruccoleri R, Woolf AD. An update on childhood lead poisoning. Clin Pediatr Emerg Med. 2017;18(3):181-192. doi:10.1016/j.cpem.2017.07.010

PBPFD
619722

Lead Profile Occupational Exposure, Blood

Clinical Information: Lead is a heavy metal commonly found in man's environment that can be an acute and chronic toxin. Lead was banned from household paints in 1978 but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids, such as vinegar and fruit juices. Lead is found in dirt from areas adjacent to homes painted with lead-based paints and highways where lead accumulates from use of leaded gasoline. Use of leaded gasoline has diminished significantly since the introduction of nonleaded gasolines that have been required in personal automobiles since 1972. Lead is found in soil near abandoned industrial sites where lead may have been used. Water transported through lead or lead-soldered pipe will contain some lead with higher concentrations found in water that is weakly acidic. Some foods/beverages (eg, moonshine distilled in lead pipes) and some traditional home medicines contain lead. Lead expresses its toxicity by several mechanisms. It avidly inhibits aminolevulinic acid dehydratase and ferrochelatase, 2 of the enzymes that catalyze synthesis of heme; the end result is decreased hemoglobin synthesis resulting in anemia and increased levels of erythrocyte zinc protoporphyrin. Lead is also an electrophile that avidly forms covalent bonds with the sulfhydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense tissues such as the central nervous system being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease. Oral dimercaprol may be used in the outpatient setting except in the most severe cases.

Useful For: Detecting lead toxicity due to occupational exposure

Interpretation:

Reference Values:
LEAD: <3.5 mcg/dL
The Occupational Safety and Health Administration (OSHA) recommended limit for blood lead level is 40 mcg/dL (OSHA 1978).
The biological exposure index (BEI) for Pb in blood of exposed workers is 20 mcg/dL (ACGIH 2018).

Critical Values:
Pediatrics (< or =15 years): > or =20.0 mcg/dL
Adults (> or =16 years): > or =70.0 mcg/dL

PROTOPORPHYRINS, FRACTIONATION
Free Protoporphyrin: <20 mcg/dL
Zinc-Complexed Protoporphyrin: <60 mcg/dL

Clinical References: 1. Centers for Disease Control and Prevention. National Report on Human Exposure to Environmental Chemicals. CDC; Updated September 2023. Accessed December 5, 2023. Available at www.cdc.gov/exposurereport 2. Occupational Safety and Health Administration. Medical surveillance guidelines. Occupational Health and Safety Standards Toxic and Hazardous Substances from 1910.1025 App C. OSHA; 2001. Accessed December 5, 2023. Available at https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1025AppC 3. de Burbure C, Buchet J-P, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects

and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590 4. Kosnett MJ, Wedeen RP, Rothenberg SJ, et al. Recommendations for medical management of adult lead exposure. Environ Health Perspect. 2007;115(3):463-471 5. Jusko T, Henderson C, Lanphear B, et al. Blood lead concentrations <10 mcg/dL and child intelligence at 6 years of age. Environ Health Perspect. 2008;116(2):243-248

PBU
8600

Lead, 24 Hour, Urine

Clinical Information: Increased urine lead excretion rate indicates significant lead exposure. Measurement of urine lead excretion rate before and after chelation therapy has been used as an indicator of lead exposure. However, the American College of Medical Toxicology position statement (ACMT 2010) on post-chelator challenge urinary metal testing states that "post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning."(1) For more information see PBDV/ Lead, Venous, with Demographics, Blood.

Useful For: Detecting clinically significant lead exposure in 24-hour specimens This test is not a substitute for blood lead screening.

Interpretation: Measurements of urinary lead (Pb) levels have been used to assess lead exposure. However, like lead blood, urinary lead excretion mainly reflects recent exposure and thus shares many of the same limitations for assessing lead body burden or long-term exposure.(2,3) Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations.(4,5)

Reference Values:
0-17 years: Not established
> or =18 years: <2 mcg/24 h

Clinical References: 1. American College of Medical Toxicology. American College of Medical Toxicology position statement on post-chelator challenge urinary metal testing. J Med Toxicol. 2010;6(1):74-75. doi:10.1007/s13181-010-0039-0 2. Sakai T. Biomarkers of lead exposure. Ind Health. 2000;38(2):127-142 3. Skerfving S. Biological monitoring of exposure to inorganic lead. In: Clarkson TW, Friberg L, Nordberg GF, Sager PR, eds. Biological Monitoring of Toxic Metals. Rochester Series on Environmental Toxicity. Springer; 1988:169-197 4. Gulson BL, Jameson CW, Mahaffey KR, et al. Relationships of lead in breast milk to lead in blood, urine, and diet of the infant and mother. Environ Health Perspect. 1998;106(10):667-674 5. Skerfving S, Ahlgren L, Christoffersson JO, et al. Metabolism of inorganic lead in man. Nutr Res. 1985;Suppl 1:601-607 6. Kosnett MJ, Wedeen RP, Rotherberg SJ, et al. Recommendations for medical management of adult lead exposure. Environ Health Perspect. 2007;115(3):463-471 7. de Burbane C, Buchet JP, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590 8. Pascal DC, Ting BG, Morrow JC, et al. Trace metals in urine of United States residents: reference range concentrations. Environ Res. 1998;76(1):53-59 9. Hauptman M, Bruccoleri R, Woolf AD. An update on childhood lead poisoning. Clin Pediatr Emerg Med. 2017;18(3):181-192. doi:10.1016/j.cpem.2017.07.010 10. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

PBDC
113400

Lead, Capillary, with Demographics, Blood

Clinical Information: Lead is a heavy metal naturally found in the environment that can be an acute and chronic toxin. Lead can enter the environment through releases from mining lead and other metals, and from factories that make or use lead, lead alloys, or lead compounds. Lead is released into the air during burning coal, oil, or waste. Before the use of leaded gasoline in motor vehicles was banned (January 1, 1996), most of the lead released into the United States environment came from vehicle exhaust. Lead was banned from household paints in 1978 but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids, such as vinegar and fruit juices. Lead is commonly found in soil especially near roadways, older houses, old orchards, mining areas, industrial sites, near power plants, incinerators, landfills, and hazardous waste sites. Recent data has shown that inexpensive cosmetic jewelry pieces sold to the general public may contain high levels of lead, which can be transferred to the skin through routine handling. However, not much lead can get into your body through your skin. People may be exposed to lead by eating food or drinking water that contains lead. Drinking (tap) water in houses containing lead pipes may contain lead, especially if the water is acidic or "soft". Foods may contain small amounts of lead. Leafy fresh vegetables grown in lead-containing soils may have lead-containing dust on them. Lead may also enter foods if they are put into improperly glazed pottery or ceramic dishes and from leaded-crystal glassware. However, since lead solder is no longer used in cans, very little lead is typically found in food. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is incorporated into bone (approximately 94% adults; approximately 73% children) and erythrocytes, lead ultimately distributes among all tissues with lipid-dense tissues, such as the central nervous system, being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Other alternative sources of lead include moonshine distilled in lead pipes, some traditional home medicines, non-Western cosmetics (eg, surma and kohl), and some types of hair colorants, cosmetics, and dyes. Lead expresses its toxicity by several mechanisms: 1. It avidly inhibits aminolevulinic acid dehydratase and ferrochelatase, 2 of the enzymes involved in the synthesis of heme. In the end, this inhibition causes decreased hemoglobin synthesis resulting in anemia. 2. Lead is also an electrophile that avidly forms covalent bonds with the sulfhydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease and may be necessary especially in children if the blood lead is higher than 25 mcg/dL. The standard chelating agents currently in use are dimercaprol (British Anti-Lewisite), CaNa2-EDTA (or EDTA), penicillamine, and 2,3-dimercaptosuccinic acid (DMSA; succimer).

Useful For: Detecting lead toxicity with capillary collections

Interpretation: No safe blood lead level in children has been identified. Lead exposure can affect nearly every system in the body. Because lead exposure often occurs with no obvious symptoms, it frequently goes unrecognized. The current reference level at which the Centers for Disease Control and Prevention recommends public health actions be initiated is 3.5 mcg/dL in patients aged 0 to 5 years and 5 mcg/dL for patients aged 6 years and older. The most recent National Health and Nutrition Examination Survey (NHANES) data shows that 97.5 percentile for blood lead levels in US adults aged 16 years and older is 3.46 mcg/dL. In concurrence with the reference value concept that there is no safe level of lead in blood, the Council of State and Territorial Epidemiologists Occupational Health Subcommittee approved lowering the blood lead threshold from 5 to 3.5 mcg/dL for adults. Chelation therapy is generally indicated in children when whole blood lead concentrations are above 25 mcg/dL. The Occupational Safety and Health Administration (OSHA) has published the following standards for employees working in industry. OSHA Standards for General Industry (CFR 1910.1025) and Construction (CFR 1926.62) apply to workers exposed to airborne lead levels 30 mcg/m(3) or greater time-weighted average and

require the removal of workers if a periodic and follow-up blood lead level is 60 mcg/dL (2.9 mcmol/L) or greater, 50 mcg/dL (2.4 mcmol/L) or greater for construction, or the average blood lead level of all tests over a 6-month period (or if there are fewer than 3 tests over a 6-month period, the average of 3 consecutive tests) is 50 mcg/dL (2.4 mcmol/L) or greater. Workers with a single blood lead level meeting the numerical criteria for medical removal must have their blood lead level retested within 2 weeks. If a worker is medically removed, a new blood lead level must be measured monthly during the removal period. Workers are permitted to return to work when their blood lead level is 40 mcg/dL (1.9 mcmol/L) or less. According to OSHA Lead Standards, a zinc protoporphyrin is also required on each occasion a blood lead level measurement is made.

Reference Values:

<3.5 mcg/dL
Critical values
Pediatrics (< or =15 years): > or =20.0 mcg/dL
Adults (> or =16 years): > or =70.0 mcg/dL

Clinical References: 1. Centers for Disease Control and Prevention (CDC). National Report on Human Exposure to Environmental Chemicals. CDC; Updated March 28, 2024. Accessed November 22, 2024. Available at www.cdc.gov/exposurereport 2. Agency for Toxic Substances and Disease Registry: Toxicological Profile for Lead. US Department of Health and Human Services; August 2020. Accessed November 22, 2024. Available at: www.atsdr.cdc.gov/ToxProfiles/tp13.pdf 3. de Burbure C, Buchet JP, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590 4. Kosnett MJ, Wedeen RP, Rothenberg SJ, et al. Recommendations for medical management of adult lead exposure. Environ Health Perspect. 2007;115(3):463-471 5. Jusko T, Henderson C, Lanphear B, et al. Blood lead concentrations <10 mcg/dL and child intelligence at 6 years of age. Environ Health Perspect. 2008;116(2):243-248 6. Strathmann FG, Blum LM. Toxic elements. In Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018: 907-910 7. Cantor AG, Hendrickson R, Blazina I, Griffin J, Grusing S, McDonagh MS. Screening for elevated blood lead levels in childhood and pregnancy: Updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2019;321(15):1510-1526. doi:10.1001/jama.2019.1004 8. CSTE Occupational Subcommittee. Management Guidelines for Blood Lead Levels in Adults. 2021. November 22, 2024. Available at:https://cdn.ymaws.com/www.cste.org/resource/resmgr/occupationalhealth/publications/ManagementGuidelinesforAdult.pdf

PBHA
8495

Lead, Hair

Clinical Information: Hair analysis for lead can be used to corroborate blood analysis or to document past lead exposure. If the hair is collected and segmented in a time sequence (based on length from root), the approximate time of exposure can be assessed.

Useful For: Detecting lead exposure using hair specimens

Interpretation: Normal hair lead content is below 4.0 mcg/g. While hair lead content above 10.0 mcg/g may indicate significant lead exposure, hair is also subject to potential external contamination with environmental lead and contaminants in artificial hair treatments (eg, dyeing, bleaching, or permanents). Ultimately, the hair lead content needs to be interpreted in addition to the overall clinical scenario including symptoms, physical findings, and other diagnostic results when determining further actions.

Reference Values:

<4.0 mcg/g of hair

Reference values apply to all ages.

Clinical References: 1. Strumylaite L, Ryselis S, Kregzdyte R. Content of lead in human hair from people exposed to lead. Int J Hyg Environ Health. 2004;207:345-351 2. Barbosa F, Tanus-Santos J, Gerlach R, Parsons P. A Critical review of biomarkers used for monitoring human exposure to lead: advantages, limitations, and future needs. Environ Health Perspect. 2005;113:1669-1674 3. Sanna E, Liguori A, Palmes L, et al. Blood and hair lead levels in boys and girls living in two Sardinian towns at different risks of lead pollution. Ecotoxicol Environ Saf. 2003;55:293-299 4. DiPietro ES, Phillips DL, Paschal DC, Neese JW. Determination of trace elements in human hair. Biol Trace Elem Res. 1989;22:83-100 5. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

PBNA
89857

Lead, Nails

Clinical Information: Nail analysis of lead can be used to corroborate blood analysis.

Useful For: Detecting lead exposure using nail specimens

Interpretation: Normally, the nail lead content is below 4.0 mcg/g. While nail lead content above 10.0 mcg/g may indicate significant lead exposure, nails are also subject to potential external contamination with environmental lead. Ultimately, the nail lead content needs to be interpreted in addition to the overall clinical scenario including symptoms, physical findings, and other diagnostic results when determining further actions.

Reference Values:
<4.0 mcg/g of nails

Reference values apply to all ages.

Clinical References: 1. Strumylaite L, Ryselis S, Kregzdyte R. Content of lead in human hair from people exposed to lead. Int J Hyg Environ Health. 2004;207(4):345-351 2. Barbosa F, Tanus-Santos J, Gerlach R, Parsons P. A critical review of biomarkers used for monitoring human exposure to lead: advantages, limitations, and future needs. Environ Health Perspect.2005;113(12):1669-1674 3. Sanna E, Liguori A, Palmes L, Soro MR, Floris Ge Blood and hair lead levels in boys and girls living in two Sardinian towns at different risks of lead pollution. Ecotoxicol Environ Saf. 2003;55(3):293-299 4. Strathmann FG, Blum LM: Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

PBDV
113401

Lead, Venous, with Demographics, Blood

Clinical Information: Lead is a heavy metal naturally found in the environment that can be an acute and chronic toxin. Lead can enter the environment through releases from mining lead and other metals, and from factories that make or use lead, lead alloys, or lead compounds. Lead is released into the air during burning coal, oil, or waste. Before the use of leaded gasoline in motor vehicles was banned (January 1, 1996), most of the lead released into the United States environment came from vehicle exhaust. Lead was banned from household paints in 1978 but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids, such as vinegar and fruit juices. Lead is commonly found in soil especially near roadways,

older houses, old orchards, mining areas, industrial sites, near power plants, incinerators, landfills, and hazardous waste sites. Recent data has shown that inexpensive cosmetic jewelry pieces sold to the general public may contain high levels of lead, which can be transferred to the skin through routine handling. However, not much lead can get into your body through your skin. People may be exposed to lead by eating food or drinking water that contains lead. Drinking (tap) water in houses containing lead pipes may contain lead, especially if the water is acidic or "soft". Foods may contain small amounts of lead. Leafy fresh vegetables grown in lead-containing soils may have lead-containing dust on them. Lead may also enter foods if they are put into improperly glazed pottery or ceramic dishes and from leaded-crystal glassware. However, since lead solder is no longer used in cans, very little lead is typically found in food. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is incorporated into bone (approximately 94% adults; approximately 73% children) and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense tissues such as the central nervous system being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Other alternative sources of lead include moonshine distilled in lead pipes, some traditional home medicines, non-Western cosmetics (eg, surma and kohl), and some types of hair colorants, cosmetics, and dyes. Lead expresses its toxicity by several mechanisms: 1) It avidly inhibits aminolevulinic acid dehydratase and ferrochelatase, 2 of the enzymes involved in the synthesis of heme. In the end, this inhibition causes decreased hemoglobin synthesis resulting in anemia. 2) Lead is also an electrophile that avidly forms covalent bonds with the sulfhydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease and may be necessary especially in children if the blood lead is higher than 25 mcg/dL. The standard chelating agents currently in use are dimercaprol (British Anti-Lewisite), CaNa2-EDTA (or EDTA), penicillamine, and 2,3-dimercaptosuccinic acid (DMSA; succimer).

Useful For: Detecting lead toxicity in venous blood specimens

Interpretation: No safe blood lead level in children has been identified. Lead exposure can affect nearly every system in the body. Because lead exposure often occurs with no obvious symptoms, it frequently goes unrecognized. The current reference level at which the Centers for Disease Control and Prevention recommends public health actions be initiated is 3.5 mcg/dL in patients 0 to 5 years old and 5 mcg/dL for patients 6 years and older. The most recent National Health and Nutrition Examination Survey (NHANES) data shows that 97.5 percentile for blood lead levels in US adults aged 16 years and older is 3.46 mcg/dL. In concurrence with the reference value concept that there is no safe level of lead in blood, the Council of State and Territorial Epidemiologists Occupational Health Subcommittee approved lowering the blood lead threshold from 5 to 3.5 mcg/dL for adults. Chelation therapy is generally indicated in children when whole blood lead concentrations are above 25 mcg/dL. The Occupational Safety and Health Administration (OSHA) has published the following standards for employees working in industry. OSHA Standards for General Industry (CFR 1910.1025) and Construction (CFR 1926.62) apply to workers exposed to airborne lead levels 30 mcg/m(3) or greater time-weighted average and require the removal of workers if a periodic and follow-up blood lead level is 60 mcg/dL (2.9 mcmol/L) or greater, 50 mcg/dL (2.4 mcmol/L) or greater for construction, or the average blood lead level of all tests over a 6-month period (or if there are fewer than 3 tests over a 6-month period, the average of 3 consecutive tests) is 50 mcg/dL (2.4 mcmol/L) or greater. Workers with a single blood lead level meeting the numerical criteria for medical removal must have their blood lead level retested within 2 weeks. If a worker is medically removed, a new blood lead level must be measured monthly during the removal period. Workers are permitted to return to work when their blood lead level is 40 mcg/dL (1.9 mcmol/L) or less. According to OSHA Lead Standards, a zinc protoporphyrin is also required on each occasion a blood lead level measurement is made.

Reference Values:
<3.5 mcg/dL
Critical values
Pediatrics (< or =15 years): > or =20.0 mcg/dL
Adults (> or =16 years): > or =70.0 mcg/dL

Clinical References: 1. Centers for Disease Control and Prevention (CDC). National Report on Human Exposure to Environmental Chemicals. CDC; Updated September 29, 2023. Accessed October 24, 2023. Available at www.cdc.gov/exposurereport 2. Agency for Toxic Substances and Disease Registry: Toxicological Profile for Lead. US Department of Health and Human Services; August 2020. Accessed October 24, 2023. Available at www.atsdr.cdc.gov/ToxProfiles/tp13.pdf 3. de Burbure C, Buchet JP, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590 4. Kosnett MJ, Wedeen RP, Rothenberg SJ, et al. Recommendations for medical management of adult lead exposure. Environ Health Perspect. 2007;115(3):463-471 5. Jusko T, Henderson C, Lanphear B, et al. Blood lead concentrations <10 mcg/dL and child intelligence at 6 years of age. Environ Health Perspect. 2008;116(2):243-248 6. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:907-910 7. Cantor AG, Hendrickson R, Blazina I, Griffin J, Grusing S, McDonagh MS. Screening for elevated blood lead levels in childhood and pregnancy: Updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2019;321(15):1510-1526. doi:10.1001/jama.2019.1004 8. CSTE Occupational Subcommittee. Management Guidelines for Blood Lead Levels in Adults. 2021.Accessed October 24, 2023. Available at: https://cdn.ymaws.com/www.cste.org/resource/resmgr/occupationalhealth/publications/ManagementGuidelinesforAdult.pdf

PBUCR
608908

Lead/Creatinine Ratio, Random, Urine

Clinical Information: Increased urine lead concentration per gram of creatinine indicates significant lead exposure. Measurement of urine lead concentration per gram of creatinine before and after chelation therapy have been used as an indicator of significant lead exposure. However, the American College of Medical Toxicology (ACMT 2010) position statement on post-chelator challenge urinary metal testing states that "post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning." Blood lead measurement is the best test for clinical correlation of toxicity. For more information see PBDV / Lead, Venous, with Demographics, Blood.

Useful For: Detecting clinically significant lead exposure, a toxic heavy metal, using random urine specimens

Interpretation: Measurements of urinary lead (Pb) levels have been used to assess lead exposure. However, like lead blood, urinary Pb excretion mainly reflects recent exposure and thus shares many of the same limitations for assessing lead body burden or long-term exposure.(1,2) Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations.(3,4)

Reference Values:
LEAD/CREATININE:
0-17 years: Not established
> or =18 years: <2 mcg/g creatinine

CREATININE:

> or =18 years: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Sakai T. Biomarkers of lead exposure. Ind Health. 2000;38(2):127-142 2. Skerfving S. Biological monitoring of exposure to inorganic lead. In: Clarkson TW, Friberg L, Nordberg GF, Sager PR, eds. Biological Monitoring of Toxic Metals. Rochester Series on Environmental Toxicity. Springer; 1988:169-197 3. Gulson BL, Jameson CW, Mahaffey KR, et al. Relationships of lead in breast milk to lead in blood, urine, and diet of the infant and mother. Environ Health Perspect. 1998;106(10):667-674 4. Skerfving S, Ahlgren L, Christoffersson JO. Metabolism of inorganic lead in man. Nutr Res. 1985;Suppl 1:601-607 5. Kosnett MJ, Wedeen RP, Rotherberg SJ, et al. Recommendations for medical management of adult lead exposure. Environ Health Perspect. 2007;115(3):463-471 6. de Burbane C, Buchet JP, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590 7. Strathmann FG, Blum LM: Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44 8. Hauptman M, Bruccoleri R, Woolf AD. An update on childhood lead poisoning. Clin Pediatr Emerg Med. 2017;18(3):181-192. doi:10.1016/j.cpem.2017.07.010

PBCU
608904

Lead/Creatinine Ratio, Urine

Clinical Information: Increased urine lead concentration per gram of creatinine indicates significant lead exposure. Measurement of urine lead concentration per gram of creatinine before and after chelation therapy have been used as an indicator of significant lead exposure. An increase in lead concentration per gram of creatinine in the post-chelation specimen of up to 6 times the concentration in the pre-chelation specimen is normal. Blood lead is the best clinical correlation of toxicity. For more information see PBDV / Lead, Venous, with Demographics, Blood.

Useful For: Detecting clinically significant lead exposure using random urine specimens This test is not a substitute for blood lead screening.

Interpretation: Urinary excretion of less than 4 mcg/g creatinine is not associated with any significant lead exposure. Urinary excretion greater than 4 mcg/g creatinine is usually associated with pallor, anemia, and other evidence of lead toxicity. Measurements of urinary lead levels have been used to assess lead exposure. However, like lead blood, urinary lead excretion mainly reflects recent exposure and thus shares many of the same limitations for assessing lead body burden or long-term exposure.(1,2) Urinary lead concentration increases exponentially with blood lead and can exhibit relatively high intra-individual variability, even at similar blood lead concentrations.(3,4)

Reference Values:
Only orderable as part of profile. For more information see:
-PBUCR / Lead/Creatinine Ratio, Random, Urine
-HMUCR / Heavy Metal/Creatinine Ratio, with Reflex, Random, Urine

0-17 years: Not established
> or =18 years: <2 mcg/g creatinine

Clinical References: 1. Sakai T. Biomarkers of lead exposure. Ind Health. 2000;38(2):127-142. doi:10.2486/indhealth.38.127 2. Skerfving S. Biological monitoring of exposure to inorganic lead. In: Clarkson TW, Friberg L, Nordberg GF, Sager PR, eds. Biological Monitoring of Toxic Metals. Rochester Series on Environmental Toxicity. Springer; 1988:169-197 3. Gulson BL, Jameson CW, Mahaffey KR, et al. Relationships of lead in breast milk to lead in blood, urine, and diet of the infant

and mother. Environ Health Perspect. 1998;106(10):667-667. doi:10.1289/ehp.98106667 4. Skerfving S, Ahlgren L, Christoffersson JO. Metabolism of inorganic lead in man. Nutr Res 1985;Suppl 1:601-607 5. Kosnett MJ, Wedeen RP, Rotherberg SJ, et al. Recommendations for medical management of adult lead exposure. Environ Health Perspect. 2007;115(3):463-471. doi:10.1289/ehp.9784 6. de Burbane C, Buchet JP, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590. doi:10.1289/ehp.8202 7. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44 8. Hauptman M, Bruccoleri R, Woolf AD. An update on childhood lead poisoning. Clin Pediatr Emerg Med. 2017;18(3):181-192. doi:10.1016/j.cpem.2017.07.010

LEFLU
60292

Leflunomide Metabolite (Teriflunomide), Serum

Clinical Information: Leflunomide is a disease-modifying antirheumatic drug approved for therapy of rheumatoid arthritis and used off-label to reduce viral nephritis in kidney transplant. It is a prodrug: rapid and complete metabolism converts leflunomide to its active metabolite, teriflunomide (also called A77 1726), which acts by inhibiting pyrimidine synthesis. Teriflunomide has a very long half-life, greater than 2 weeks on average. There is marked interindividual variability in leflunomide pharmacokinetics, thus therapeutic monitoring of serum teriflunomide concentrations may be helpful in optimizing therapy. Therapeutic targets remain only loosely defined and appear to vary depending on the purpose of therapy, but serum teriflunomide concentrations greater than 40 mcg/mL have been associated with better clinical outcomes. Due to the long half-life, serum specimens for therapeutic monitoring may be collected at any point in the dosing cycle, although trough (immediately before next schedule dose) sampling is preferred for consistency. Adverse reactions to leflunomide do not correlate well with serum drug concentration but include diarrhea, hypertension, and liver toxicity. Enhanced elimination of the drug may be required in patients who are or who wish to become pregnant, or who are experiencing toxicity; teriflunomide can persist up to 2 years after ceasing therapy unless elimination is accelerated. This can be accomplished through use of activated charcoal or a bile acid sequestrant such as cholestyramine, reducing the half-life of teriflunomide to approximately 1 day. Serum concentrations less than 0.020 mcg/mL (<20 ng/mL) on 2 independent tests at least 2 weeks apart are preferred for patients anticipating pregnancy to minimize the potential risk of teratogenesis associated with the drug.

Useful For: Therapeutic monitoring of patients actively taking leflunomide Assessment of elimination in patients requiring enhanced elimination of the drug

Interpretation: Therapy: clinical targets for serum teriflunomide (leflunomide metabolite) concentrations are still being determined, but levels greater than 40 mcg/mL appear to correlate with better outcome. Elimination: serum concentrations less than 0.020 mcg/mL (20 ng/mL) are preferred to minimize potential teratogenesis for patients considering pregnancy.

Reference Values:
Therapeutic: >40 mcg/mL
Elimination: <0.020 mcg/mL

Clinical References: 1. Cannon GW, Kremer JM. Leflunomide. Rheum Dis Clin North Am. 2004;30(2):295-309 2. Chan V, Charles BG, Tett SE. Population pharmacokinetics and association between A77 1726 plasma concentrations and disease activity measures following administration of leflunomide to people with rheumatoid arthritis. Br J Clin Pharmacol. 2005 Sep;60(3):257-264 3. Teschner S, Gerke P, Geyer M, et al. Leflunomide therapy for polyomavirus-induced allograft nephropathy: efficient BK virus elimination without increased risk of rejection. Transplant Proc. 2009;41(6):2533-2538 4. Temprano KK, Bandlamudi R, Moore TL. Antirheumatic drugs in pregnancy and lactation. Semin Arthritis Rheum. 2005;35(2):112-121 5. Hirsch HH, Randhawa PS; AST Infectious

Diseases Community of Practice: BK polyomavirus in solid organ transplantation-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13528. doi:10.1111/ctr.13528

LAGU
81268

Legionella Antigen, Random, Urine

Clinical Information: Legionnaires disease, named after the outbreak in 1976 at the American Legion convention in Philadelphia, is caused by Legionella pneumophila and is an acute febrile respiratory illness ranging in severity from mild illness to fatal pneumonia. Since that time, it has been recognized that the disease occurs in both epidemic and endemic forms, and that sporadic cases are not readily differentiated from other respiratory infections by clinical symptoms. It is estimated that about 25,000 to 100,000 Legionella infections occur annually. Known risk factors include immunosuppression, cigarette smoking, alcohol consumption, and concomitant pulmonary disease. The resulting mortality rate, which ranges up to 40% in untreated immunocompetent patients, can be lowered if the disease can be rapidly diagnosed and appropriate antimicrobial therapy instituted early. L pneumophila is estimated to be responsible for 80% to 85% of reported cases of Legionella infections with the majority of cases being caused by L pneumophila serogroup 1 alone. A variety of laboratory techniques (culture, direct fluorescent antibody, DNA probes, immunoassay, antigen detection), using a variety of specimen types (respiratory specimens, serum, urine), have been used to help diagnose Legionella pneumonia. Respiratory specimens are preferred. Unfortunately, one of the presenting signs of Legionnaires disease is the relative lack of productive sputum. This necessitates the use of invasive procedures to obtain adequate specimens (eg, bronchial washing, transtracheal aspirate, lung biopsy) in many patients. Serology may also be used but is often retrospective in nature. It was shown as early as 1979 that a specific soluble antigen was present in the urine of patients with Legionnaires disease.(1) The presence of Legionella antigen in urine makes this an ideal specimen for collection, transport, and subsequent detection in early, as well as later, stages of the disease. The antigen may be detectable in the urine as early as 3 days after onset of symptoms.

Useful For: An adjunct to culture for the detection of past or current Legionnaires disease (Legionella pneumophila serogroup 1)

Interpretation: Positive: Positive for Legionella pneumophila serogroup 1 antigen in urine, suggesting current or past infection. Culture is recommended to confirm infection. Negative: Negative for L pneumophila serogroup 1 antigen in urine, suggesting no recent or current infection. Infection with Legionella cannot be ruled out because: -Other serogroups (other than serogroup 1, which is detected by this assay) and other Legionella species (other than L pneumophila) can cause disease -Antigen may not be present in urine in early infection -The level of antigen may be below the detection limit of the test Legionella culture is recommended for cases of suspected Legionella pneumonia due to organisms other than L pneumophila serogroup 1.

Reference Values:
Negative

Clinical References: 1. Berdal BP, Farshy CE, Feeley JC. Detection of Legionella pneumonophila antigen in urine by enzyme-linked immunospecific assay. J Clin Microbiol. 1979;9(5):575-578 2. Fraser DW, Tsai TR, Orenstein W, et al. Legionnaires' disease: description of an epidemic of pneumonia. N Engl J Med. 1977;297(22):1189-1197 3. Stout JE, Yu VL. Legionellosis. N Engl J Med. 1997;337(10):682-687 4. Edelstein PH, Roy CR. Legionnaires disease and Pontiac fever. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2807-2817

LEGI
8204

Legionella Culture, Varies

Clinical Information: The Legionellaceae are ubiquitous in natural freshwater habitats, allowing them to colonize artificial water supplies (eg, reservoirs), which may then serve as the source for human infections. Legionella pneumophila and the related species, Legionella bozemanii, Legionella dumoffii, Legionella gormanii, Legionella micdadei, Legionella longbeachae, and Legionella jordanis have been isolated from patients with pneumonia (Legionnaires disease). The organism has been isolated from lung tissue, bronchoalveolar lavage, pleural fluid, and sputum. The signs, symptoms, and radiographic findings of Legionnaires disease are generally nonspecific.

Useful For: Diagnosis of Legionnaires disease

Interpretation: Identification of Legionella species from respiratory specimens provides a definitive diagnosis of Legionnaires disease. Organisms isolated are identified as Legionella species via matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry and/or 16S ribosomal RNA (rRNA) gene sequencing.

Reference Values:
No growth of Legionella species after 7 days of incubation

Clinical References: 1. Edelstein PH. Legionella In: Carroll KC, Pfaller MA, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:905-920 2. Clinical and Laboratory Standards Institute. Interpretive Criteria for Identification of Bacteria and Fungi by Targeted DNA Sequencing. 2nd ed. CLSI Guideline MM18. CLSI; 2018 3. Rucinski SL, Murphy MP, Kies KD, Cunningham SA, Schuetz AN, Patel R. Eight years of clinical Legionella PCR testing illustrates a seasonal pattern. J Infect Dis. 2018;218(4):669-670. doi:10.1093/infdis/jiy201

SLEG
8122

Legionella pneumophila (Legionnaires Disease), Antibody, Serum

Clinical Information: Legionella pneumophila may cause pulmonary disease in normal and immunocompetent individuals. The disease may occur sporadically in the form of community acquired pneumonia or as an epidemic. Pneumonia (often referred to as Legionnaires disease) occurs more frequently in individuals who are severely immunosuppressed; however, a milder form of the illness, Pontiac fever, is more prevalent in normal hosts. Extrapulmonary infection with L pneumophila is rare. Legionnaires disease, Pontiac fever, and extrapulmonary infection have been collectively referred to as legionellosis. Approximately 85% of the documented cases of legionellosis have been caused by L pneumophila. Serogroups 1 and 6 of L pneumophila, by themselves, account for up to 75% of cases of legionellosis. The definitive diagnosis of L pneumophila is made by isolation of the organism on specialized culture medium (buffered charcoal yeast extract agar) or detection by a nucleic acid amplification test. In the absence of invasive procedures (eg, bronchial alveolar lavage), evaluation of patient urine samples for L pneumophila serotype 1 antigen may be useful. Testing for antibodies to L pneumophila may be helpful to establish prior exposure or infection, however, does not differentiate between acute and past infection.

Useful For: Evaluating possible legionellosis (Legionnaires disease, Pontiac fever, extrapulmonary legionella infection caused by Legionella pneumophila)

Interpretation: A negative result indicates that IgG, IgA, and IgM antibodies to Legionella pneumophila serogroups 1-6 were not detected. Negative results do not exclude Legionella infection. It may require 4 to 8 weeks to develop a detectable antibody response; serum specimens taken early in the

course of infection may not yet have significant antibody titers. Furthermore, antibody levels can fall to undetectable levels within a month of infection, early antibiotic therapy may suppress antibody response, and some individuals may not develop antibodies above detectable limits. Some culture-positive cases of Legionella do not develop Legionella antibody. Positive results are suggestive of Legionella infection. A positive result only indicates immunologic exposure at some point in time. It does not distinguish between previous or current infection. The level of antibody response may not be used to determine active infection. Other laboratory procedures or additional clinical information are necessary to establish a diagnosis. Specimens with equivocal results are retested prior to reporting. Repeat testing on a second specimen should be considered in patients with equivocal results, if clinically indicated.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Koneman EW, Allen SD, Janda WM, eds. Color Atlas and Textbook of Diagnostic Microbiology. 5th ed. Lippincott-Raven Publishers; 1997 2. Edelstein PH, Roy CR. Legionnaires' disease and Pontiac fever. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020

LEGRP 89564 Legionella species, Molecular Detection, PCR, Varies

Clinical Information: Legionnaires disease was first recognized during a pneumonia outbreak at the Legionnaires convention in Philadelphia in 1976. Investigators with the Centers for Disease Control and Prevention isolated a novel, gram-negative bacillus, later named Legionella pneumophila. It is now widely recognized that L pneumophila (and other members of the genus Legionella) cause Legionnaires disease.

Useful For: Sensitive and rapid diagnosis of pneumonia caused by Legionella species The assay is not recommended as a test of cure because bacteria nucleic acids may persist after successful treatment.

Interpretation: A positive polymerase chain reaction (PCR) result for the presence of a specific sequence found within the Legionella 5S ribosomal RNA gene indicates the presence of a Legionella species DNA, which may be due to Legionella infection or environmental/water Legionella DNA in the specimen. A negative PCR result indicates the absence of detectable Legionella DNA in the specimen but does not rule-out legionellosis as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of Legionella species in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. Hayden RT, Uhl JR, Qian X, et al. Direct detection of Legionella species from bronchoalveolar lavage and open lung biopsy specimens: comparison of LightCycler PCR, in situ hybridization, direct fluorescence antigen detection, and culture. J Clin Microbiol. 2001;39(7):2618-2626. doi:10.1128/JCM.39.7.2618-2626.2001. 2. Diederen BM, Kluytmans JA, Vandenbroucke-Grauls CM, Peeters MF. Utility of real-time PCR for diagnosis of Legionnaires' disease in routine clinical practice. J Clin Microbiol. 2008;46(2):671-677. doi:10.1128/JCM.01196-07. 3. MacDonell MT, Colwell RR. The nucleotide sequence of the 5S rRNA from Legionella pneumophila. Nucleic Acids Res. 1987;15(3):1335. doi:10.1093/nar/15.3.1335

LEIS
86219

Leishmaniasis (Visceral) Antibody, Serum

Clinical Information: Visceral leishmaniasis (kala azar) is a disseminated intracellular protozoal infection that targets primarily the reticuloendothelial system (liver, spleen, bone marrow) and is caused by Leishmania donovani, Leishmania chagasi, or Leishmania infantum (L donovani complex). Transmission is by the bite of sandflies. Clinical symptoms include fever, weight loss, and splenomegaly; pancytopenia and hypergammaglobulinemia are often present. Most (90%) new cases each year arise in rural areas of India, Nepal, Bangladesh, Sudan, and Brazil, but the disease has a worldwide distribution, including the Middle East. Definitive diagnosis has required the microscopic documentation of characteristic intracellular amastigotes in stained smears from culture of aspirates of tissue (spleen, lymph node) or bone marrow. The detection of serum antibodies to the recombinant K39 antigen of L donovani is an alternative noninvasive sensitive (95%-100%) method for the diagnosis of active, visceral leishmaniasis.

Useful For: Aiding in the diagnosis of active visceral leishmaniasis This test should not be used as the sole criteria for diagnosis.

Interpretation: Negative: Negative results indicate the absence of antibodies to members of the Leishmania donovoni complex. Repeat testing in 2 to 3 weeks if clinically indicated. Immunocompromised patients frequently have low or undetectable antibodies to Leishmania species. Positive: Positive results indicate the presence of antibodies to members of the L donovoni complex, the causative agents of visceral leishmaniasis. Results should not be used as the sole criterion for diagnosis or treatment of visceral leishmaniasis and should not be used to diagnose other forms of leishmaniasis. False-positive reactions due to malaria infection have been reported.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Sundar S, Sahu M, Mehta H, et al. Noninvasive management of Indian visceral leishmaniasis: clinical application of diagnosis of K39 antigen strip testing at a kala-azar referral unit. Clin Infect Dis. 2002;35(5):581-586 2. Aronson NE, Copeland NK, Magill AJ. Leishmania species: visceral (Kala-Azar), cutaneous, and mucosal leishmaniasis. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3321-3339

FLEMG
57643

Lemon IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

LEM
82678

Lemon, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to lemon Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FLENG
57685

Lentil IgG

Interpretation:

Reference Values:

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

LEN
82885

Lentil, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to lentil Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

LEPD
82849

Lepidoglyphus destructor, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Lepidoglyphus destructor Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FLEP
91339

Leptin

Reference Values:
Units: ng/mL
Adults (BMI=22)
Males: 0.7-5.3
Females: 3.3-18.3

Contact laboratory for other BMI reference ranges.

LEPDT
65183

Leptospira, IgM, Serum

Clinical Information: Leptospirosis is a zoonotic disease of worldwide prevalence, though the majority of infections occur in warm, tropical climates. Wild mammals, typically rodents, are the primary, natural reservoir for disease-causing strains of Leptospira; however, domestic animals (eg, dogs) also represent a major source of human infection. Leptospira are gram-negative spirochetes with at least 20 different species in the genus. Of these, at least 9 species are considered disease-causing, including the most common agent of leptospirosis, Leptospira interrogans. Transmission occurs through indirect human contact (eg, via mucous membranes or abraded skin) with water, food, or soil contaminated with animal urine containing the Leptospira spirochetes. Following infection, the incubation period can range from 3 to 30 days, depending on the inoculum dose and immune status of the individual. The clinical manifestations of leptospirosis can vary, ranging from a mild, flu-like illness (eg, headache, malaise, fever, arthralgia, fatigue) to fulminant disease with severe liver and kidney involvement. The latter manifestation was previously referred to as Weil disease. Leptospira organisms may be found in the blood at the onset of disease and can persist for approximately 1 week. Subsequently, spirochetes may be found in the urine and can persist for 2 to 3 months; however, shedding may be intermittent, and the number of organisms present may be low. While Leptospira can be grown in culture, this is a fastidious organism that requires immediate transport to the laboratory. Additionally, detectable growth requires prolonged incubation (1-6 weeks), limiting the utility of culture for acute diagnosis. For this reason, serologic detection for antibodies to Leptospira remains the method of choice for rapid diagnosis. IgM-class antibodies to this spirochete are detectable by day 6 of illness and remain detectable for 2 to 3 months following symptom onset.

Useful For: Aiding in the diagnosis of leptospirosis This test is not useful for establishing cure or response to therapy.

Interpretation: Positive: IgM antibodies to Leptospira species detected, suggesting recent infection. Antibody presence alone cannot be used to definitively diagnose acute infection, as antibodies from a prior exposure or infection may remain detectable for a prolonged period. Borderline: Result should be interpreted with caution. Additional testing of a second, convalescent specimen is recommended. If the specimen remains borderline reactive, a second serological method should be considered if leptospirosis infection is still suspected. Negative: No IgM antibodies to Leptospira detected. Since antibodies may not be present or may be present at undetectable levels during early disease, repeat testing of a convalescent sample collected in 2 to 3 weeks is recommended.

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of High-Consequence Pathogens and Pathology (DHCPP): Leptospriosis. Reviewed June 24, 2024. Accessed September 5, 2024. Available at www.cdc.gov/leptospirosis/ 2. Costa F, Hagan JE, Calcagno J, et al. Global morbidity and mortality of

leptospirosis: a systemic review. PLoS Negl Trop Dis. 2015;9(9):e0003898. doi:10.1371/journal.pntd.0003898

FLETG
57639

Lettuce IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

LETT
82805

Lettuce, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to lettuce Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal

2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

LLTOT 621505 Leukemia and Lymphoma Immunophenotyping, Technical Only, Tissue

Clinical Information: Cellular immunophenotyping, characterizing cells by using antibodies directed against cell surface markers, is generally regarded as a fundamental element in establishing a diagnosis of tissue involvement by hematolymphoid malignancies when used in conjunction with morphologic assessment. It is also an essential component in subclassification of hematolymphoid malignancies when present. This is a technical only test and does not include interpretation. At any point, clients may request to have a Mayo Clinic hematopathologist provide an interpretation at an additional charge.

Useful For: Evaluation of tissues for potential involvement by: -Chronic lymphoproliferative disorders -Malignant lymphomas -Acute lymphoblastic leukemia -Acute myelogenous leukemia

Interpretation: Report will include a summary of the procedure. Normal tissues typically contain a mixture of B cells with polytypic surface immunoglobulin light chain expression and T cells with unremarkable expression of the T cell-associated antigens CD3, CD5, and CD7. Typically, no appreciable blast population is present by CD45 and side scatter analysis.

Reference Values:
Not applicable

Clinical References: 1. Morice WG, Hodnefield JM, Kurtin PJ, Hanson CA. An unusual case of leukemic mantle cell lymphoma with a blastoid component showing loss of CD5 and aberrant expression of CD10. Am J Clin Pathol. 2004;122(1):122-127 2. Hanson CA. Acute leukemias and myelodysplastic syndromes. In: McClatchey KD, ed. Clinical Laboratory Medicine. Williams and Wilkins; 1994:939-969 3. Jaffe ES, Cossman J. Immunodiagnosis of lymphoid and mononuclear phagocytic neoplasms. In: Rose NR, Friedman H, Fahey JL, eds. Manual of Clinical Immunology. 3rd ed. ASM Press; 1987:779-790 4. Witzig TE, Banks PM, Stenson MJ, et al. Rapid immunotyping of B-cell non-Hodgkin's lymphomas by flow cytometry. A comparison with the standard frozen-section method. Am J Clin Pathol. 1990;94(3):280-286 5. Jevremovic D, Dronca RS, Morice WG, et al. CD5+ B-cell lymphoproliferative disorders: Beyond chronic lymphocytic leukemia and mantle cell lymphoma. Leuk Res. 2010;34(9):1235-1238 6. Jevremovic D, Olteanu H. Flow cytometry applications in the diagnosis of T/NK-cell lymphoproliferative disorders. Cytometry B Clin Cytom. 2019;96(2):99-115 7. Shi M, Jevremovic D, Otteson GE, Timm MM, Olteanu H, Horna P. Single antibody detection of T-Cell receptor alpha beta clonality by flow cytometry rapidly identifies mature T-Cell neoplasms and monotypic small CD8-positive subsets of uncertain significance. Cytometry B Clin Cytom. 2020;98(1):99-107

LLTOF 34488 Leukemia and Lymphoma Phenotyping, Technical Only, Varies

LLPB 800433 Leukemia/Lymphoma Immunophenotyping, Flow Cytometry, Blood

Clinical Information: Diagnostic hematopathology has become an increasingly complex subspecialty, particularly with neoplastic disorders of blood and bone marrow. While morphologic assessment of blood smears, bone marrow smears, and tissue sections remains the cornerstone of lymphoma and leukemia diagnosis and classification, immunophenotyping is a very valuable and important complementary tool. Immunophenotyping hematopoietic specimens can help resolve many differential diagnostic problems posed by the clinical or morphologic features.

Useful For: Evaluating lymphocytoses of undetermined etiology Identifying B- and T-cell lymphoproliferative disorders involving blood Distinguishing acute lymphoblastic leukemia (ALL) from acute myeloid leukemia (AML) using whole blood specimens Immunologic subtyping of ALL Distinguishing reactive lymphocytes and lymphoid hyperplasia from malignant lymphoma using whole blood specimens Distinguishing between malignant lymphoma and acute leukemia using whole blood specimens Phenotypic subclassification of B- and T-cell chronic lymphoproliferative disorders, including chronic lymphocytic leukemia, mantle cell lymphoma, and hairy cell leukemia Recognizing AML with minimal morphologic or cytochemical evidence of differentiation Recognizing monoclonal plasma cells

Interpretation: Report will include a morphologic description, a summary of the procedure, the percent positivity of selected antigens, and an interpretive conclusion based on the correlation of the clinical history with the morphologic features and immunophenotypic results.

Reference Values:
An interpretive report will be provided.

This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist for every case.

Clinical References: 1. Hanson CA, Kurtin PJ, Katzman JA, et al. Immunophenotypic analysis of peripheral blood and bone marrow in the staging of B-cell malignant lymphoma. Blood. 1999;94(11):3889-3896 2. Hanson CA. Acute leukemias and myelodysplastic syndromes. In: McClatchey KD, ed. Clinical Laboratory Medicine. Williams and Wilkins; 1994:939-969 3. Morice WG, Leibson PJ, Tefferi A. Natural killer cells and the syndrome of chronic natural killer cell lymphocytosis. Leuk Lymphoma. 2001;41(3-4):277-284. doi:10.3109/10428190109057982 4. Langerak, van Den Beemd, Wolvers-Tettero, et al. Molecular and flow cytometric analysis of the Vbeta repertoire for clonality assessment in mature TCRalphabeta T-cell proliferations. Blood. 2001;98(1):165-173. doi:10.1182/blood.v98.1.165 5. Hoffman RA, Kung PC, Hansen QP, Goldstein G. Simple and rapid measurement of human T lymphocytes and their subclass in peripheral blood. Proc Natl Acad Sci USA. 1980;77(8):4914-4917. doi:10.1073/pnas.77.8.4914 6. Jaffe ES, Cossman J. Immunodiagnosis of lymphoid and mononuclear phagocytic neoplasms. In: Rose NR, Friedman H, Fahey JD, eds. Manual of Clinical Immunology. 3rd ed. ASM Press; 1987:779-790 7. Morice WG, Kimlinger T, Katzmann JA, et al. Flow cytometric assessment of TCR-Vbeta expression in the evaluation of peripheral blood involvement by T-cell lymphoproliferative disorders: a comparison with conventional T-cell immunophenotyping and molecular genetic techniques. Am J Clin Pathol. 2004;121(3):373-383. doi:10.1309/3A32-DTVM-H640-M2QA 8. Stelzer GT, Shultz KE, Loken MR. CD45 gating for routine flow cytometric analysis of bone marrow specimens. Ann NY Acad Sci. 1993;677:265-280. doi:10.1111/j.1749-6632.1993.tb38783.x 9. Jevremovic D, Olteanu H. Flow

cytometry applications in the diagnosis of T/NK-cell lymphoproliferative disorders. Cytometry B Clin Cytom. 2019;96(2):99-115. doi:10.1002/cyto.b.21768 10. Shi M, Jevremovic D, Otteson GE, Timm MM, Olteanu H, Horna P. Single antibody detection of T-cell receptor alpha beta clonality by flow cytometry rapidly identifies mature T-Cell neoplasms and monotypic small CD8-positive subsets of uncertain significance. Cytometry B Clin Cytom. 2020;98(1):99-107

LLPT 19499 Leukemia/Lymphoma Immunophenotyping, Flow Cytometry, Tissue

Clinical Information: Cellular immunophenotyping, characterizing cells by using antibodies directed against cell surface markers, is generally regarded as a fundamental element in establishing a diagnosis of tissue involvement by hematolymphoid malignancies, when used in conjunction with morphologic assessment. It is also an essential component in subclassification of hematolymphoid malignancies when present.

Useful For: Evaluation of tissues for potential involvement by: -Chronic lymphoproliferative disorders -Malignant lymphomas -Acute lymphoblastic leukemia -Acute myelogenous leukemia

Interpretation: This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist for every case. Normal tissues typically contain a mixture of B cells with polytypic surface immunoglobulin light chain expression and T cells with unremarkable expression of the T cell-associated antigens CD3, CD5, and CD7. Typically, no appreciable blast population is present by CD45 and side scatter analysis.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Morice WG, Hodnefield JM, Kurtin PJ, Hanson CA. An unusual case of leukemic mantle cell lymphoma with a blastoid component showing loss of CD5 and aberrant expression of CD10. Am J Clin Pathol. 2004;122(1):122-127 2. Hanson CA. Acute leukemias and myelodysplastic syndromes. In: McClatchey KD, ed. Clinical Laboratory Medicine. Williams and Wilkins; 1994:939-969 3. Jaffe ES, Cossman J. Immunodiagnosis of lymphoid and mononuclear phagocytic neoplasms. In: Rose NR, Friedman H, Fahey JL, eds. Manual of Clinical Immunology. 3rd ed. ASM Press; 1987:779-790 4. Witzig TE, Banks PM, Stenson MJ, et al. Rapid immunotyping of B-cell non-Hodgkin's lymphomas by flow cytometry. A comparison with the standard frozen-section method. Am J Clin Pathol. 1990;94(3):280-286 5. Jevremovic D, Dronca RS, Morice WG, et al. CD5+ B-cell lymphoproliferative disorders: Beyond chronic lymphocytic leukemia and mantle cell lymphoma. Leuk Res. 2010;34(9):1235-1238 6. Jevremovic D, Olteanu H. Flow cytometry applications in the diagnosis of T/NK-cell lymphoproliferative disorders. Cytometry B Clin Cytom. 2019;96(2):99-115 7. Shi M, Jevremovic D, Otteson GE, Timm MM, Olteanu H, Horna P. Single antibody detection of T-Cell receptor alpha beta clonality by flow cytometry rapidly identifies mature T-Cell neoplasms and monotypic small CD8-positive subsets of uncertain significance. Cytometry B Clin Cytom. 2020;98(1):99-107

LCMS 3287 Leukemia/Lymphoma Immunophenotyping, Flow Cytometry, Varies

Clinical Information: Diagnostic hematopathology has become an increasingly complex subspecialty, particularly with neoplastic disorders of blood and bone marrow. While morphologic assessment of blood smears, bone marrow smears, and tissue sections remains the cornerstone of

lymphoma and leukemia diagnosis and classification, immunophenotyping is a very valuable and important complementary tool. Immunophenotyping hematopoietic specimens can help resolve many differential diagnostic problems posed by the clinical or morphologic features. This test is appropriate for only hematopoietic specimens.

Useful For: Evaluating lymphocytoses of undetermined etiology Identifying B- and T-cell lymphoproliferative disorders involving blood and bone marrow Distinguishing acute lymphoblastic leukemia (ALL) from acute myeloid leukemia (AML) Immunologic subtyping of acute leukemias Distinguishing reactive lymphocytes and lymphoid hyperplasia from malignant lymphoma Distinguishing between malignant lymphoma and acute leukemia Phenotypic subclassification of B- and T-cell chronic lymphoproliferative disorders, including chronic lymphocytic leukemia, mantle cell lymphoma, and hairy cell leukemia Recognizing AML with minimal morphologic or cytochemical evidence of differentiation Recognizing monoclonal plasma cells This test is not intended for detection of minimal residual disease below 5% blasts. This test is not appropriate for and cannot support diagnosis of sarcoidosis, hypersensitivity pneumonitis, interstitial lung diseases, or differentiating between pulmonary tuberculosis and sarcoidosis.

Interpretation: This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist for every case. Report will include a morphologic description, a summary of the procedure, the percent positivity of selected antigens, and an interpretive conclusion based on the correlation of the clinical history with the morphologic features and immunophenotypic results.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Jevremovic D, Dronca RS, Morice WG, et al. CD5+ B-cell lymphoproliferative disorders: Beyond chronic lymphocytic leukemia and mantle cell lymphoma. Leuk Res. 2010;34(9):1235-1238. doi:10.1016/j.leukres.2010.03.020 2. Hanson CA. Acute leukemias and myelodysplastic syndromes. In: McClatchey KD, ed. Clinical Laboratory Medicine. Williams and Wilkins; 1994:939-969 3. Jevremovic D, Olteanu H. Flow cytometry applications in the diagnosis of T/NK-Cell lymphoproliferative disorders. Cytometry B Clin Cytom. 2019;96(2):99-115. doi:10.1002/cyto.b.21768 4. Rosado FG, Morice WG, He R, Howard MT, Timm M, McPhail ED. Immunophenotypic features by multiparameter flow cytometry can help distinguish low grade B-cell lymphomas with plasmacytic differentiation from plasma cell proliferative disorders with an unrelated clonal B-cell process. Br J Haematol. 2015;169(3):368-376. doi:10.1111/bjh.13303 5. Shi M, Ternus JA, Ketterling RP, et al. Immunophenotypic and laboratory features of t(11;14)(q13;q32)-positive plasma cell neoplasms. Leuk Lymphoma. 2018;59(8):1913-1919. doi:10.1080/10428194.2017.1410885 6. Morice WG, Kimlinger T, Katzmann JA, et al. Flow cytometric assessment of TCR-Vbeta expression in the evaluation of peripheral blood involvement by T-cell lymphoproliferative disorders: a comparison with conventional T-cell immunophenotyping and molecular genetic techniques. Am J Clin Pathol. 2004;121(3):373-383. doi:10.1309/3A32-DTVM-H640-M2QA 7. Shi M, Jevremovic D, Otteson GE, Timm MM, Olteanu H, Horna P. Single antibody detection of T-Cell receptor alpha beta clonality by flow cytometry rapidly identifies mature T-Cell neoplasms and monotypic small CD8-positive subsets of uncertain significance. Cytometry B Clin Cytom. 2020;98(1):99-107. doi:10.1002/cyto.b.21782

LAD1
81155

Leukocyte Adhesion Deficiency Type 1, CD11a/CD18 and CD11b/CD18 Complex Immunophenotyping, Blood

Clinical Information: Leukocyte adhesion deficiency syndrome type 1 (LAD-1) is an autosomal recessive disorder caused by variants in the common chain (CD18) of the beta2-integrin family. LAD-1 is clinically characterized by recurrent infections, impaired wound healing, delayed umbilical cord

separation, persistent leukocytosis, and recurrent soft tissue and oral infections. Each of the beta2-integrins is a heterodimer composed of an alpha chain (CD11a, CD11b, or CD11c) noncovalently linked to a common beta2-subunit (CD18). The alpha-beta heterodimers of the beta2-integrin family include lymphocyte function-associated antigen 1 (CD11a/CD18), Mac-1/CR3 (CD11b/CD18), and p150/95 (CD11c/CD18).(1-4) The CD18 gene, ITGB2, and its product are required for normal expression of the alpha-beta heterodimers. Therefore, defects in CD18 expression lead to either very low or no surface membrane expression of CD11a, CD11b, and CD11c. Severe and moderate forms of LAD-1 exist, differing in the degrees of protein deficiency, which are caused by different ITGB2 variants. Two relatively distinct clinical phenotypes of LAD-1 have been described. Patients with the severe phenotype (<1% of normal expression of CD18 on neutrophils) characteristically have delayed umbilical stump separation (>30 days), infection of the umbilical stump (omphalitis), persistent leukocytosis (>15,000/microliter) in the absence of overt active infection, and severe destructive gingivitis with periodontitis and associated tooth loss, and alveolar bone resorption. Patients with the moderate phenotype of LAD-1 (1%-30% of normal expression of CD18 on neutrophils) tend to be diagnosed later in life. Normal umbilical separation, lower risk of life-threatening infections, and longer life expectancy are common in these patients. However, leukocytosis, periodontal disease, and delayed wound healing are still very significant clinical features. Patients with LAD-1 (and other primary immunodeficiency diseases) are unlikely to remain undiagnosed in adulthood. Consequently, this test should not be typically ordered in adults for LAD-1. However, it may be also used to assess immune competence by determining CD18, 11a, and 11b expression.

Useful For: Aiding in the diagnosis of leukocyte adhesion deficiency syndrome type 1, primarily in patients younger than 18 years CD11a, CD11b, and CD18 phenotyping

Interpretation: The report will include a summary interpretation of the presence or reduction in the level of expression of the individual markers (CD11a, CD11b, and CD18). Expression of the individual markers provides indirect information on the presence or absence of the CD11a/CD18 and CD11b/CD18 complexes. Specimens obtained from patients with leukocyte adhesion deficiency syndrome type 1 (LAD-1) show significant reduction (moderate phenotype) or near absence (severe phenotype) of CD18 and its associated molecules, CD11a and CD11b, on neutrophils and other leukocytes. CD11c expression also is low in LAD-1. The analytical sensitivity of the CD11c assay is insufficient to allow interpretation of CD11c surface expression. Therefore, this test is only for the expression of CD18, CD11a, and CD11b.

LECT2
70497

Leukocyte Cell-Derived Chemotaxin 2 (LECT2), Immunostains Without Interpretation

Clinical Information: Immunohistochemical staining for leukocyte cell-derived chemotaxin 2 (LECT2) is useful in the process of confirming amyloid subtype. Antibodies to LECT2 stain the amyloid deposits in patients with LECT2 amyloidosis. LECT2 amyloidosis typically involves the kidney, liver, and spleen.

Useful For: Identification and classification of amyloid subtypes in tissue

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 11. Benson MD, James S, Scott K, et al. Leukocyte chemotactic factor 2: A novel renal amyloid protein. Kidney Int. 2008;74(2):218-222 2. Uchida T, Nagai H, Gotoh K, et al. Expression pattern of a newly recognized protein, LECT2, in hepatocellular carcinoma and its

premalignant lesion. Pathol Int. 1999;49(2):147-151 3. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TLTE4
606355

Leukotriene E4, 24 Hour, Urine

Clinical Information: Leukotrienes (LT) are eicosanoids generated from arachidonic acid via the 5-lipoxygenase pathway. Leukotriene E4 (LTE4) is the stable end product of this pathway and, therefore, regarded as a biomarker of total cysteinyl leukotriene production.(1-3) Assessment of LTE4 in urine allows for noninvasive specimen collection and avoids artifactual formation of LT during phlebotomy. Generation of LTE4 occurs nonspecifically from active mast cells (MC), basophils, eosinophils, and macrophages and is modulated through a variety of mechanisms.(1) Elevated concentrations of LTE4 are associated with both clonal (primary) and nonclonal (secondary and idiopathic) MC activation syndromes (MCAS).(1-3) MCAS have been defined as a group of disorders in which patients experience symptoms precipitated by MC proinflammatory and vasoactive mediator release.(1) Some of these MC mediators contribute to physiologic processes and maintenance of tissue homeostasis. Primary MCAS have clonal markers, such as the KIT Asp816Val variant or aberrant expression of CD25 or CD2 on MC. The 2 primary groups of MCAS are mastocytosis (cutaneous and systemic [SM]) and monoclonal MCAS. Patients with mastocytosis should fulfill the World Health Organization diagnostic criteria for this disorder. Diagnosis requires either the major plus one minor criterion or 3 minor criteria.(1,4,5) The consensus diagnostic criteria for SM include: Major criterion: Imaging of the multifocal infiltrates Minor criteria: 1. Identifying morphological features of above 25% of MC from bone marrow biopsy 2. Detection of the point alteration at codon 816 in the KIT gene 3. CD2, CD25, and/or CD30 expression in MC 4. Persistently elevated serum tryptase (>20 ng/mL) The 2 main nonclonal MCAS categories include secondary MCAS, for which there is a known trigger for MC activation (IgE-dependent and independent allergic reactions, atopic disorders, autoimmune processes), and idiopathic, in which the etiology for MC activation is undefined.(1-3,5-7) Based on consensus criteria, the diagnosis of MCAS can be established when typical clinical symptoms arising from recurrent (episodic) acute systemic MC activation (typically in the form of recurrent anaphylaxis in at least 2 organ systems) have been documented; MC-derived mediators increase substantially in serum or urine over the individual's baseline; and the symptoms respond to drugs blocking MC activation, MC mediators, mediator production, or mediator effects.(6) A recently proposed diagnostic algorithm for the evaluation of patients with suspected MCAS considers 2 main diagnoses that may underlie severe forms of MC activation (anaphylaxis), namely, IgE-dependent allergies and clonal MC disorders.(1-3,5-7) A serum tryptase level, which has long been used in diagnosing these disorders, has several drawbacks, including the need to obtain acute and baseline specimens to fulfill diagnostic criteria. Furthermore, an increased baseline tryptase level has been reported in hereditary alpha tryptasemia, complicating the diagnostic possibilities.(1,3) In addition to the limitations of serum tryptase, there are reports of symptomatic patients with features of MC activation who do not meet all the criteria for MCAS but have elevated baseline mediator metabolites.(3,5,7) In these patients, there is evidence that their symptoms respond to drugs that target MC activation, the mediators released by MC, and/or the effects of these mediators. Based on these observations, validated biomarkers suggestive of MC activation, such as an increase in the histamine metabolite (N-methylhistamine) or the prostaglandin D2 metabolite (2,3-dinor 11 beta-prostaglandin F2 alpha), have been recommended for testing when tryptase is not available, or the result is inconclusive.(7) With respect to urine LTE4, there is increasing clinical evidence for its use in patients at risk for aspirin intolerance in asthma (aspirin-exacerbated respiratory disease) and other forms of asthma.(8,9) For example, elevated LTE4 concentrations have been shown to correlate with traditional markers and represent a noninvasive approach to asthma phenotyping in patients with type 2 asthma mediated in part by MC and eosinophils.(9) In this study, increased urine LTE4 levels were associated with lower lung function and increased amounts of exhaled nitric oxide and eosinophil markers in blood, sputum, and urine in adult and adolescent patients with asthma. Based on these and other findings, there is interest for the use of therapeutics that target the production of inflammatory eicosanoids, such as LTE4, in the management of these diseases.(10-12)

Useful For: Aiding in the evaluation of patients at-risk for mast cell activation syndrome (eg, systemic mastocytosis, IgE-mediated allergies, or aspirin-exacerbated respiratory disease) using 24-hour urine collections

Interpretation: Elevated urinary leukotriene E4 concentrations above 104 pg/mg creatinine may be suggestive of mast cell activation syndrome if compatible features of disease are present.

Reference Values:

LEUKOTRIENE E4:
< or =104 pg/mg creatinine

CREATININE:
Normal values mg per 24 hours:
Males: 930-2955 mg/24 hours
Females: 603-1783 mg/24 hours
Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Weiler CR. Mast cell activation syndrome: Tools for diagnosis and differential diagnosis. J Allergy Clin Immunol Pract. 2020;8(2):498-506 2. Gulen T, Akin C, Bonadonna P, et al. Selecting the right criteria and proper classification to diagnose mast cell activation syndromes: A critical review. J Allergy Clin Immunol Pract. 2021;9(11):3918-3928 3. Butterfield JH. Nontryptase urinary and hematologic biomarkers of mast cell expansion and mast cell activation: Status 2022. J Allergy Clin Immunol Pract. 2022;10(8):1974-1984 4. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017;129(11):1420-1427 5. Valent, P, Akin, C, Hartmann, K., et.al. Updated diagnostic criteria and classification of mast cell disorders: A consensus proposal. Hemasphere. 2021;5(11): e646 6. Divekar R, Hagan J, Rank M, et al. Diagnostic utility of urinary LTE4 in asthma, allergic rhinitis, chronic rhinosinusitis, nasal polyps, and aspirin sensitivity. J Allergy Clin Immunol Pract. 2016;4(4):665-670 7. Valent P, Hartmann K, Bonadonna P, et al. Global classification of mast cell activation disorders: An ICD-10-CM-adjusted proposal of the ECNM-AIM Consortium. J Allergy Clin Immunol Pract. 2022;10(8):1941-1950 8. Kolmert J, Gomez C, Balgoma D, et al. Urinary leukotriene E(4) and prostaglandin D(2) metabolites increase in adult and childhood severe asthma characterized by type 2 inflammation. A clinical observational study. Am J Respir Crit Care Med. 2021;203(1):37-53 9. Hagan JB, Laidlaw TM, Divekar R, et al: Urinary leukotriene E4 to determine aspirin intolerance in asthma: A systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2017;5(4):990-997.e1. doi:10.1016/j.jaip.2016.11.004 10. Hayashi H, Fukutomi Y, Mitsui C, et al. Omalizumab for aspirin hypersensitivity and leukotriene overproduction in aspirin-exacerbated respiratory disease. A randomized controlled trial. Am J Respir Crit Care Med. 2020;201(12):1488-1498 11. Buchheit KM, Lewis E, Gakpo D, et al: Mepolizumab targets multiple immune cells in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2021;148(2):574-584 12. Buchheit KM, Sohail A, Hacker J, et al: Rapid and sustained effect of dupilumab on clinical and mechanistic outcomes in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2022;150(2):415-424

RLTE4
606354

Leukotriene E4, Random, Urine

Clinical Information:

Useful For: Aiding in the evaluation of patients at-risk for mast cell activation syndrome (eg, systemic mastocytosis, IgE-mediated allergies, or aspirin-exacerbated respiratory disease) using random urine collections

Interpretation: Elevated urinary leukotriene E4 concentrations above 104 pg/mg creatinine may be

suggestive of mast cell activation syndrome if compatible features of disease are present.

Reference Values:
LEUKOTRIENE E4
< or =104 pg/mg creatinine

CREATININE
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Weiler CR. Mast cell activation syndrome: Tools for diagnosis and differential diagnosis. J Allergy Clin Immunol Pract. 2020;8(2):498-506 2. Gulen T, Akin C, Bonadonna P, et al. Selecting the right criteria and proper classification to diagnose mast cell activation syndromes: A critical review. J Allergy Clin Immunol Pract. 2021;9(11):3918-3928 3. Butterfield JH. Nontryptase urinary and hematologic biomarkers of mast cell expansion and mast cell activation: Status 2022. J Allergy Clin Immunol Pract. 2022;10(8):1974-1984 4. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017;129(11):1420-1427 5. Valent, P, Akin, C, Hartmann, K., et.al. Updated diagnostic criteria and classification of mast cell disorders: A consensus proposal. Hemasphere. 2021;5(11): e646 6. Divekar R, Hagan J, Rank M, et al. Diagnostic utility of urinary LTE4 in asthma, allergic rhinitis, chronic rhinosinusitis, nasal polyps, and aspirin sensitivity. J Allergy Clin Immunol Pract. 2016;4(4):665-670 7. Valent P, Hartmann K, Bonadonna P, et al. Global classification of mast cell activation disorders: An ICD-10-CM-adjusted proposal of the ECNM-AIM Consortium. J Allergy Clin Immunol Pract. 2022;10(8):1941-1950 8. Kolmert J, Gomez C, Balgoma D, et al. Urinary leukotriene E(4) and prostaglandin D(2) metabolites increase in adult and childhood severe asthma characterized by type 2 inflammation. A clinical observational study. Am J Respir Crit Care Med. 2021;203(1):37-53 9. Hagan JB, Laidlaw TM, Divekar R, et al: Urinary leukotriene E4 to determine aspirin intolerance in asthma: A systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2017;5(4):990-997.e1. doi:10.1016/j.jaip.2016.11.004 10. Hayashi H, Fukutomi Y, Mitsui C, et al. Omalizumab for aspirin hypersensitivity and leukotriene overproduction in aspirin-exacerbated respiratory disease. A randomized controlled trial. Am J Respir Crit Care Med. 2020;201(12):1488-1498 11. Buchheit KM, Lewis E, Gakpo D, et al: Mepolizumab targets multiple immune cells in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2021;148(2):574-584 12. Buchheit KM, Sohail A, Hacker J, et al: Rapid and sustained effect of dupilumab on clinical and mechanistic outcomes in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2022;150(2):415-424

FLEVA
75401

Levamisole, Urine

Clinical Information: Levamisole is used as a veterinary antihelminthic (worming agent) in animals. It is no longer available in North America for human use. However, from July-September 2008 approximately 30% of cocaine seized by the DEA was contaminated with levamisole.

Reference Values:
Reporting limit determined each analysis
Units: mcg/mL

LEV1P
113309

Level 1 Gross only (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

LEV2P
113310

Level 2 Gross and microscopic (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

LEV3P
113311

Level 3 Gross and microscopic (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

LEV4P
113312

Level 4 Gross and microscopic (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

LV4RP
113313

Level 4 Gross and Microscopic, RB (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

LEV5P
113314

Level 5 Gross and microscopic (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

LEV6P
113315

Level 6 Gross and microscopic (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

LEVE
83140

Levetiracetam, Serum

Clinical Information: Levetiracetam is approved for treatment of partial, myoclonic, and tonic-clonic seizures and is used off-label for manic states and migraine prophylaxis. Levetiracetam has very favorable pharmacokinetics with good bioavailability and rapid achievement of steady state. Its hepatic metabolism is minimal and nonoxidative, making it safe for use with hepatic enzyme inducers or inhibitors. The major metabolite is a carboxylic acid derivate, which is inactive and accounts for roughly one quarter of the administered dose. Levetiracetam is excreted renally, with a mean half-life of 7 hours in adults and slightly less than that in children. Kidney dysfunction may warrant therapeutic monitoring and/or dose

adjustment. Given the lack of drug interactions and favorable pharmacokinetics, the primary uses for therapeutic drug monitoring of levetiracetam are compliance assurance and management of physiological changes such as puberty, pregnancy, and aging. Toxicities associated with levetiracetam use include decreased hematocrit and red blood cell count, decreased neutrophil count, somnolence, asthenia, and dizziness. These toxicities may be associated with blood concentrations in the therapeutic range.

Useful For: Monitoring serum concentration of levetiracetam, particularly in patients with kidney disease Assessing compliance with levetiracetam therapy Assessing potential toxicity of levetiracetam

Interpretation: Most individuals display optimal response to levetiracetam with serum levels 10.0 to 40.0 mcg/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Toxic levels have not been well established. Therapeutic ranges are based on specimen collected at trough (ie, immediately before the next dose).

Reference Values:
10.0-40.0 mcg/mL

Clinical References: 1. Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs-best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring. ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239-1276 2. Johannessen SI, Tomson T. Pharmacokinetic variability of newer antiepileptic drugs: when is monitoring needed? Clin Pharmacokinet. 2006;45(11):1061-1075 3. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62

LID
8382

Lidocaine, Serum

Clinical Information: Lidocaine is commonly used as a local anesthetic, but it is also effective at controlling ventricular arrhythmia and ventricular fibrillation in children and adults. For cardiac therapy, optimal therapeutic response is seen when serum concentrations are between 1.5 and 5.0 mcg/mL. Lidocaine is protein-bound (60-80%), primarily to alpha-1-acid glycoprotein; concentrations of this protein increase after myocardial infarction, which may decrease the amount of free lidocaine and, thus, its efficacy. Lidocaine undergoes extensive first-pass hepatic metabolism and, therefore, is not administered orally. It is eliminated via renal clearance, with a half-life of approximately 1.5 to 2 hours. Diseases that reduce hepatic or renal function reduce clearance and prolong elimination of lidocaine. Toxicity occurs when the serum concentration of lidocaine is greater than 6.0 mcg/mL and is usually associated with symptoms of central nervous system excitation, light-headedness, confusion, dizziness, tinnitus, and blurred or double vision. This can be accompanied by bradycardia and hypotension leading to cardiovascular collapse.

Useful For: Assessing optimal lidocaine dosing during the acute management of ventricular arrhythmias following myocardial infarction or during cardiac manipulation such as surgery Assessing potential lidocaine toxicity

Interpretation: Optimal response to lidocaine occurs when the serum concentration is between 1.5 and 5.0 mcg/mL. Toxicity is more likely when concentrations exceed 6.0 mcg/mL.

Reference Values:
Therapeutic: 1.5-5.0 mcg/mL
Critical value: >6.0 mcg/mL

Clinical References: 1. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 42 2. Brunton LL, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 14th ed. McGraw-Hill Education; 2023

LMO2
70501

LIM Domain Only 2 (LMO2) Immunostain, Technical Component Only

Clinical Information: LIM domain only 2 (LMO2) is a transcription factor that regulates vascular and hematopoietic systems and is involved in hematolymphoid neoplasia. LMO2 is preferentially expressed by germinal center B cells and may also be expressed in erythroid and myeloid precursors and in megakaryocytes. Expression has been observed in cases of lymphoblastic and acute myeloid leukemia. It is rarely expressed in mature T, natural killer, and plasma cell neoplasms and is absent from nonhematolymphoid tissues except for endothelial cells. In the diagnosis of B-cell lymphomas, LMO2 can be useful in an immunohistochemical panel to assign a germinal center phenotype.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Natkunam Y, Zhao S, Mason DY, et al. The oncoprotein LMO2 is expressed in normal germinal-center b cells and in human b-cell lymphomas. Blood. 2007;109(4):1636-1642 2. Blenk S, Engelmann J, Weniger M, et al. Germinal center b cell-like and activated b cell-like type of diffuse large b cell lymphoma: Analysis of molecular predictors, signatures, cell cycle state and patient survival. Cancer Inform. 2007;3:399-420 3. Natkunam Y, Farinha P, His ED, et al. LMO2 protein expression predicts survival in patients with diffuse large b -cell lymphoma treated with anthracycline-based chemotherapy with and without rituximab. J Clin Oncol. 2008;26(3):447-454 4. Gratzinger D, Zhao S, West R, et al. The transcription factor LMO2 is a robust marker of vascular endothelium and vascular neoplasms and selected other entities. Am J Clin Pathol. 2009;131(2):264-278 5. Younes SF, Beck AH, Lossos IS, et al. Immunoarchitectural patterns in follicular lymphoma: efficacy of HGAL and LMO2 in the detection of the interfollicular and diffuse components. Am J Surg Pathol. 2010;34(9):1266-1276 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

LIME
82360

Lime, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to lime Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ALBLI
603181

Limited Bleeding Diathesis Profile Interpretation

Clinical Information:

Useful For: Interpretation of testing performed as part of a profile to detect of the more common potential causes of abnormal bleeding (eg, factor deficiencies/hemophilia, von Willebrand disease, factor-specific inhibitors) and a simple screen to evaluate for an inhibitor or severe deficiency of factor XIII (rare) This test is not useful for assessing platelet function (eg, congenital or acquired disorders such as Glanzmann thrombasthenia, Bernard-Soulier syndrome, storage pool disease, myeloproliferative disease, associated platelet dysfunction), which requires fresh platelets

Interpretation: An interpretive report will be provided when testing is completed, noting a presence or absence of a bleeding diathesis disease state.

Reference Values:
Only orderable as part of a profile. For more information see ALBLD / Bleeding Diathesis Profile,

Limited, Plasma.

An interpretive report will be provided.

Clinical References: Boender J, Kruip MJ, Leebeek FW. A diagnostic approach to mild bleeding disorders. J Thromb Haemost. 2016;14(8):1507-1516. doi:10.1111/jth.13368

LDPU
615289

Limited Drug Profile, 3 Drug Classes, Immunoassay, Random, Urine

Clinical Information: This test uses the simple screening technique that involves immunoassay testing for drugs by class. All positive immunoassay screening results can be confirmed by gas chromatography mass spectrometry or liquid chromatography tandem mass spectrometry and quantitated if applicable. This assay was designed to test for the following: -Barbiturates -Cocaine -Carboxy-tetrahydrocannabinol

Useful For: Detecting drug use involving barbiturates, cocaine, and carboxy-tetrahydrocannabinol This test is not intended for use in employment-related testing.

Interpretation: For information about drug testing, including estimated detection times, see Drug Class Testing on MayoClinicLabs.com.

Reference Values:
Only orderable as part of profile. For more information see CSMHU / Controlled Substance Monitoring Hybrid Drug Profile, 20 Drug Classes, High-Resolution Mass Spectrometry and Immunoassay Screen, Random, Urine.

Negative
Screening cutoff concentrations:
Barbiturates: 200 ng/mL
Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

Clinical References: 1. Physicians' Desk Reference. 60th ed. Medical Economics Company; 2006 2. Bruntman LL Lazo JS, Parker KL, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Book Company; 2006 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 4. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline-using clinical laboratory tests to monitor drug therapy in pain management patients. J Appl Lab Med. 2018;2(4):489-526

LIND
82862

Linden, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an

allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to linden Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

LINS
86311

Linseed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations.

In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to linseed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

LPSBF
606615

Lipase, Body Fluid

Clinical Information: Lipases are enzymes that hydrolyze glycerol esters of long-chain fatty acids and produce fatty acids and 2-acylglycerol. The pancreas is the primary source of serum lipase. Pancreatic injury results in increased serum lipase levels. Serum lipase is measured to aid in the diagnosis of pancreatitis. Peritoneal fluid: The digestive enzymes amylase and lipase can be measured in the identification of pancreatic fluid in the peritoneal cavity. Concentrations are expected to be elevated and at least several-fold times higher in fluid of pancreatic origin compared to simultaneous concentrations in serum.(1,2) Drain fluid: Lipase is expected to be elevated in drain fluids formed due to chronic pancreatitis or formation of a fistula following surgery.(1,3,4) Comparison to serum concentrations is recommended with elevations several-fold higher than blood being suggestive of the presence of

pancreatic fluid in the drained cavity.(5)

Useful For: Determining whether pancreatic inflammation or pancreatic fistula may be contributing to a pathological accumulation of fluid

Interpretation: Fluids (peritoneal, drain): Lipase concentrations several-fold higher than serum lipase concentrations is suggestive of the presence of pancreatic fluid in the drained cavity. All other fluids: Body fluid lipase activity may become elevated due to the presence of pancreatic fluid in the drained cavity. Results should be interpreted in conjunction with serum lipase and other clinical findings.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Block DR, Florkowski CM. Body Fluids. In: Rifai N, Horvath AR, Wittwer CT. eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier;2018:chap 43 2. Robert JH, Meyer P, Rohner A. Can serum and peritoneal amylase and lipase determinations help in the early prognosis of acute pancreatitis? Ann Surg. 1986;203(2):163-168. doi:10.1097/00000658-198602000-00009 3. Lipsett PA, Cameron JL. Internal pancreatic fistula. Am J Surg. 1992;163(2):216-220. doi:10.1016/0002-9610(92)90104-y 4. Kaman L, Behera A, Singh R, Katariya RN. Internal pancreatic fistulas with pancreatic ascites and pancreatic pleural effusions: recognition and management. ANZ J Surg. 200;71(4):221-225. doi:10.1046/j.1440-1622.2001.02077.x 5. Sileo AV, Chawla SK, LoPresti PA: Pancreatic ascites: Diagnostic importance of ascitic lipase. Am J Dig Dis. 1975 Dec;20(12):1110-1114. doi:10.1007/BF01070753 6. Nandakumar V, Dolan C, Baumann NA, et al. Effect of pH on the quantification of body fluid analytes for clinical diagnostic testing. Am J Clin Path. 2019; 152(1):S10-S11

FLIPR
90347

Lipase, Random Urine

Reference Values:
Adult: < or = 4 U/L

LPS
8328

Lipase, Serum

Clinical Information: Lipases are enzymes that hydrolyze glycerol esters of long-chain fatty acids and produce fatty acids and 2-acylglycerol. Bile salts and a cofactor, colipase, are required for full catalytic activity and greatest specificity. The pancreas is the primary source of serum lipase. Both lipase and colipase are synthesized in the pancreatic acinar cells and secreted by the pancreas in roughly equimolar amounts. Lipase is filtered and reabsorbed by the kidneys. Pancreatic injury results in increased serum lipase levels.

Useful For: Investigating pancreatic disorders, usually pancreatitis

Interpretation: In pancreatitis, lipase becomes elevated at about the same time as amylase (4-8 hours). But lipase may rise to a greater extent and remain elevated much longer (7-10 days) than amylase. Elevations 2 to 50 times the upper reference have been reported. The increase in serum lipase is not necessarily proportional to the severity of the attack. Normalization is not necessarily a sign of resolution. In acute pancreatitis, normoamylasemia may occur in up to 20% of such patients. Likewise, the existence of hyperlipemia may cause a spurious normoamylasemia. For these reasons, it is suggested that the 2 assays complement and not exclude each other, and that both enzymes should be assayed.

Reference Values:
13-60 U/L

Clinical References: 1. Rifai N, Horvath AR, Wittwer CT: Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics. Eighth edition. St. Louis, Elsevier, 2018, pp 323-324 2. Swaroop VS, Chari ST, Clain JE: Acute pancreatitis. JAMA 2004;291:2865-2868

BFLA1
614164

Lipid Analysis, Body Fluid

Clinical Information: Measurement of cholesterol and triglycerides combined with detection of chylomicrons in body fluids is useful for diagnosing chylous effusion or differentiating from pseudochylous effusion.(1) Chylous effusions are characterized by the presence of chyle, which contains chylomicrons circulating through the lymphatic system. Pseudochylous effusions do not have chylomicrons. Cholesterol concentrations in serous effusions increase over time due to chronic exudative processes that cause cell lysis or increased vascular permeability. These fluids have a milky appearance can be confused with chylous effusions. While chylous effusions often have elevated triglyceride concentrations and decreased cholesterol concentrations, identification of chylomicrons is considered the gold standard for the diagnosis. Pleural Fluid: Chylothorax is the name given to pleural effusions containing chylomicrons. They develop when chyle accumulates from disruption of the lymphatic system, often the thoracic duct, caused mainly by malignancy or trauma.(1) Lymph fluid contains chylomicron-rich chyle characterized by high concentrations of triglycerides. Pseudochylous effusions are the name given to milky appearing effusions that do not contain lymphatic contents but rather form gradually through the breakdown of cellular lipids in long-standing effusions such as rheumatoid pleuritis, tuberculosis, or myxedema, and, by definition, the effluent contains high concentrations of cholesterol.(2) Differentiation of pseudochylothorax from chylothorax is important as their milky or opalescent appearance is similar, however therapeutic management strategies differ. Peritoneal Fluid: Chylous ascites is the name given to peritoneal effusions containing chylomicrons. Obstruction of lymph flow causing leakage from dilated subserosal lymphatics, exudation through the walls of retroperitoneal megalymphatics, and direct leakage of chyle due to a lymphoperitoneal fistula have been proposed as possible mechanisms causing chylous ascites.(3) Elevated triglyceride concentrations have the best correlation with detection of chylomicrons, while cholesterol is not useful at predicting the presence or absence of chylomicrons.

Useful For: Distinguishing between chylous and nonchylous effusions

Interpretation: Pleural Fluid: Pleural fluid cholesterol concentrations 46 to 65 mg/dL are consistent with exudative effusions. Cholesterol concentrations greater than 200 mg/dL suggest pseudochylous effusion. Triglyceride concentrations greater than 110 mg/dL are consistent with chylous effusions. Triglyceride concentrations less than 50 mg/dL are usually not due to chylous effusions. Peritoneal Fluid: Peritoneal fluid triglyceride concentrations greater than 187 mg/dL are most consistent with chylous effusion. Cholesterol concentrations 33 to 70 mg/dL suggest malignant causes of ascites.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Hooper C, Lee YC, Maskell N; BTS Pleural Guideline Group. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii4-ii17 2. Staats BA, Ellefson RD, Budahn LL, Dines DE, Prakash UB, Offord K. The lipoprotein profile of chylous and nonchylous pleural effusions. Mayo Clin Proc. 1980;55(11):700-704 3. Thaler MA, Bietenbeck A, Schulz C, Luppa PB. Establishment of triglyceride cut-off values to detect chylous ascites and pleural effusions. Clin Biochem. 2017;50(3) 134-138 4. Burtis CA, Ashwood ER, Bruns DE, Tietz NW, eds. In: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 5th ed.

Elsevier; 2012:1 (xviii, 2238) 5. Noble RP. Electrophoretic separation of plasma lipoproteins in agarose gel. J Lipid Res 1968;9(6):693-700 6. Sepiashvili L, Dahl AR, Meeusen JM, Loftus CG, Donato LJ. A man with recurrent ascites after laparoscopic cholecystectomy. Clin Chem. 2017;63(7):1199-1203 7. Ellefson RD, Elveback L, Weidman W. Application of methods used for lipoprotein analysis: plasma lipoproteins of children and youths in Rochester, MN. DHEW Publication No. (NIH). 1978;78-1472

LPSC1
616696

Lipid Panel, Serum

Clinical Information: Lipoprotein cholesterol measurements are essential in managing risk for atherosclerotic cardiovascular disease (ASCVD). Atherosclerosis is defined by a buildup of plaque within arterial walls. ASCVD includes coronary heart disease, strokes, and peripheral artery disease. ASCVD develops over decades and is often asymptomatic until the patient experiences a life-threatening event such as a heart attack, stroke, or aneurysm. Cholesterol is a lipid that is synthesized in most tissues and actively absorbed from the diet. There is a strong association between serum cholesterol concentrations and cardiovascular disease. Cholesterol is carried in the blood by lipoproteins. Some lipoproteins carry a stronger risk of cardiovascular disease while others are associated with reduced cardiovascular risk. Total cholesterol concentration includes the sum of all "good" and "bad" cholesterol. Therefore, total cholesterol is recommended to be interpreted in context of a lipid panel that includes high-density lipoprotein cholesterol (HDL-C) and triglyceride measurements. Low-density lipoprotein cholesterol (LDL-C) is the primary lipoprotein responsible for atherogenic plaque. Very low-density lipoprotein cholesterol (VLDL-C) is also atherogenic and the combination of LDL-C and VLDL-C is called non-HDL cholesterol and often referred to as "bad" cholesterol. Serum total cholesterol, LDL-C, and non-HDL cholesterol are all directly associated with risk for ASCVD. HDL-C is associated with lower risk of cardiovascular disease. Excess cholesterol is actively pumped into HDL to be carried in the blood circulation and cleared by the liver in a process known as reverse cholesterol transport. For these reasons, HDL-C is often referred to as "good" cholesterol. Triglycerides are oily lipids carried in the blood by lipoproteins. Triglycerides are primarily carried by VLDL, chylomicrons, and remnant lipoproteins. Recent evidence supports triglycerides as an independent risk factor for ASCVD. Several conditions are associated with increased plasma triglycerides, including obesity, pregnancy, physical inactivity, excess alcohol intake, kidney disease, and diabetes. Elevated triglycerides are often associated with reduced HDL-C, insulin resistance, hypertension, fatty liver disease, and increased waist circumference. In addition to cardiovascular risk, elevated triglycerides confer a risk for acute pancreatitis.

Useful For: Managing atherosclerotic cardiovascular disease risk using serum specimens

Interpretation: Maintaining desirable concentrations of lipids lowers atherosclerotic cardiovascular disease (ASCVD) risk. Establishing appropriate treatment strategies and lipid goals require blood lipid values be considered in context with other risk factors including, age, sex, smoking status, and medical history of hypertension, diabetes, and cardiovascular disease. Triglycerides results of 500 mg/dL or above are severely elevated increasing the risk of pancreatitis. Triglycerides can be lowered by increasing physical activity, low-fat diet, weight loss, and/or triglyceride lowering pharmaceuticals. Low high-density lipoprotein cholesterol is a risk factor for cardiovascular disease. High density lipoprotein (HDL) cholesterol can be increased by the same lifestyle changes that reduce risk for cardiovascular disease; physical activity, smoking cessation, and eating healthier. However, medications that specifically increase HDL levels have failed to reduce cardiovascular disease. Extremely low HDL values (<20 mg/dL) may indicate liver disease or inherited dyslipidemia. Low-density lipoprotein cholesterol results of 190 mg/dL or above in adults (> or =160 mg/dL in children) are severely elevated and may indicate familial hypercholesterolemia. For non-HDL cholesterol results of 220 mg/dL or above, a possible inherited hyperlipidemia diagnosis should be considered.

Reference Values:

The National Lipid Association and the National Cholesterol Education Program have set the following guidelines for lipids in a context of cardiovascular risk for adults 18 years and older:

TOTAL CHOLESTEROL
Desirable: <200 mg/dL
Borderline High: 200-239 mg/dL
High: > or =240 mg/dL

TRIGLYCERIDES
Normal: <150 mg/dL
Borderline High: 150-199 mg/dL
High: 200-499 mg/dL
Very High: > or =500 mg/dL

HIGH DENSITY LIPOPROTEIN (HDL) CHOLESTEROL
Males
> or =40 mg/dL
Females
> or =50 mg/dL

LOW DENSITY LIPOPROTEIN (LDL) CHOLESTEROL
Desirable: <100 mg/dL
Above Desirable: 100-129 mg/dL
Borderline High: 130-159 mg/dL
High: 160-189 mg/dL
Very High: > or =190 mg/dL

NON-HDL CHOLESTEROL
Desirable: <130 mg/dL
Above Desirable: 130-159 mg/dL
Borderline High: 160-189 mg/dL
High: 190-219 mg/dL
Very High: > or =220 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids in a context of cardiovascular risk for children ages 2-17:
Reference values have not been established for patients who are younger than 24 months.

TOTAL CHOLESTEROL
Acceptable: <170 mg/dL
Borderline High: 170-199 mg/dL
High: > or =200 mg/dL

TRIGLYCERIDES
2-9 years:
Acceptable: <75 mg/dL
Borderline High: 75-99 mg/dL
High: > or =100mg/dL

10-17 years:
Acceptable: <90 mg/dL
Borderline High: 90-129 mg/dL
High: > or =130 mg/dL

HDL CHOLESTEROL
Low HDL: <40 mg/dL
Borderline Low: 40-45 mg/dL
Acceptable: >45 mg/dL

LDL CHOLESTEROL
Acceptable: <110 mg/dL
Borderline High: 110-129 mg/dL
High: > or =130 mg/dL

NON-HDL CHOLESTEROL
Acceptable: <120 mg/dL
Borderline High: 120-144 mg/dL
High: > or =145 mg/dL

Clinical References: 1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1082-e1143 2. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1-executive summary. J Clin Lipidol. 2014;8(5):473-488. doi:10.1016/j.jacl.2014.07.007 3. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics. 2011;128 Suppl 5(Suppl 5):S213-S256. doi:10.1542/peds.2009-2107C 4. Sampson M, Ling C, Sun Q, et al. A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia. JAMA Cardiol. 2020;5(5):540-548

LIPOG
617337

Lipodystrophy Gene Panel, Varies

Clinical Information: Lipodystrophies are rare conditions characterized primarily by the inability to properly store adipose tissue in the absence of nutritional deficit or catabolic state.(1) Lipodystrophies can be genetic (hereditary) or acquired (caused by environmental factors such as illness). The two most common forms of hereditary lipodystrophies are congenital generalized lipodystrophy (CGL) and familial partial lipodystrophy (FPLD), which are named according to the regions of the body they affect.(1) Congenital generalized lipodystrophy (also known as Berardinelli-Seip congenital lipodystrophy) is an autosomal recessive condition characterized by generalized absence fat throughout the entire body, generalized muscular appearance, and metabolic complications such as diabetes mellitus and dyslipidemia.(1,2) The prevalence of autosomal recessive CGL is not well-established, with estimates ranging from 1:10,000,000 to 1:25,000 depending on the population being considered.(2) Severe CGL is also a feature of Keppen-Lubinsky syndrome (KPLBS), an extremely rare autosomal dominant condition caused by biallelic, disease-causing variants in the KCNJ6 gene. KPLBS is a syndromic condition characterized by severe generalized lipodystrophy, microcephaly, progeroid appearance, and intellectual disability.(3) Familial partial lipodystrophy can be inherited in an autosomal dominant or autosomal recessive manner and is characterized by localized absence of fat in the limbs with possible metabolic complications.(1,4) FPLD can be isolated or can be a feature of a syndromic condition such as autosomal dominant SHORT syndrome (short stature, hyperextensibility of joints, ocular depression, Rieger anomaly, and teething delay) and autosomal recessive Mandibuloacral dysplasia with type B lipodystrophy.(4) The prevalence of FPLD is not known but thought to be rare.(4) Disease-causing variants in the LMNA gene can lead to autosomal recessive and autosomal dominant forms of lipodystrophies, but variants in this gene are also associated with several autosomal dominant cardiac, connective tissue, and muscular dystrophy phenotypes.(4) Often, lipodystrophy is a single

feature of a more syndromic condition when caused by disease-causing LMNA variants.(4) The FBN1 gene is primarily associated with autosomal dominant Marfan syndrome without features of lipodystrophy. However, literature suggests that specific disease-causing variants in the FBN1 gene may lead to an overlapping phenotype characterized by partial features of Marfan syndrome, progeroid appearance, and clinical features of lipodystrophy.(5)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of a hereditary lipodystrophy Establishing a diagnosis of a hereditary lipodystrophy

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Brown RJ, Araujo-Vilar D, Cheung PT, et al. The diagnosis and management of lipodystrophy syndromes: a multi-society practice guideline. J Clin Endocrinol Metab. 2016;101(12):4500-4511. doi:10.1210/jc.2016-2466 2. Van Maldergem L. Berardinelli-Seip congenital lipodystrophy. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated December 8, 2016. Accessed July 26, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1212/ 3. Masotti A, Uva P, Davis-Keppen L, et al. Keppen-Lubinsky syndrome is caused by mutations in the inwardly rectifying K+ channel encoded by KCNJ6. Am J Hum Genet. 2015;96(2):295-300. doi:10.1016/j.ajhg.2014.12.011 4. Bagias C, Xiarchou A, Bargiota A, Tigas S. Familial partial lipodystrophy (FPLD): recent insights. Diabetes Metab Syndr Obes. 2020;13:1531-1544. doi:10.2147/DMSO.S206053 5. Innes A, Dyment D. SHORT Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated June 4, 2020. Accessed January 22, 2025. Available at https://www.ncbi.nlm.nih.gov/books/NBK201365/ 6. Passarge E, Robinson PN, Graul-Neumann LM. Marfanoid-progeroid-lipodystrophy syndrome: a newly recognized fibrillinopathy. Eur J Hum Genet. 2016;24(9):1244-1247. doi:10.1038/ejhg.2016.6 7. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30

LRBA
608113

Lipopolysaccharide-Responsive Beige-Like Anchor Protein (LRBA) Deficiency, Blood

Clinical Information: Lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency is a rare autosomal recessive primary immunodeficiency disease (also known as inborn errors of immunity) caused by homozygous or compound heterozygous loss-of-function variants in the LRBA gene. It has a wide spectrum of clinical manifestations, including immune dysregulation and autoimmunity, inflammatory bowel disease, early-onset hypogammaglobulinemia, recurrent infections and organomegaly.

Useful For: Aiding in the diagnosis of lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency This test is not useful for identifying a carrier status for LRBA deficiency.

Interpretation: The results are reported as the percentage and MFI (mean fluorescence intensity) of lipopolysaccharide-responsive beige-like anchor protein (LRBA) expression in T cells and B cells. The

majority of genetically confirmed cases of LRBA deficiency lead to the absence of LRBA expression. Therefore, the lack of LRBA expression in T and B cells is consistent with LRBA deficiency. In this case, genetic analysis of LRBA to confirm the diagnosis and to identify the underlying variant will be recommended. In addition, there are reported cases of LRBA deficiency where the protein is expressed but at lower intensity. Therefore, the expression of LRBA at diminished intensity could be due to a disease-causing LRBA variant, which would have to be confirmed or ruled out by genetic and functional analysis.

Reference Values:
The appropriate reference values will be provided on the report.

Clinical References: 1. Lopez-Herrera G, Tampella G, Pan-Hammarstrom Q, et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. Am J Hum Genet. 2012;90(6):986-1001 2. Gamez-Diaz L, August D, Stepensky P, et al. The extended phenotype of LPS-responsive beige-like anchor protein (LRBA) deficiency. J Allergy Clin Immunol. 2016;137(1):223-230 3. Habibi S, Zaki-Dizaji M, Rafiemanesh H, et al. Clinical, Immunologic, and Molecular Spectrum of Patients with LPS-Responsive Beige-Like Anchor Protein Deficiency: A Systematic Review. J Allergy Clin Immunol Pract. 2019;7(7):2379-86.e5 4. Serwas NK, Kansu A, Santos-Valente E, et al. Atypical manifestation of LRBA deficiency with predominant IBD-like phenotype. Inflamm Bowel Dis. 2015;21(1):40-47 5. Revel-Vilk S, Fischer U, Keller B, et al. Autoimmune lymphoproliferative syndrome-like disease in patients with LRBA mutation. Clin Immunol. 2015;159(1):84-92 6. Kiykim A, Ogulur I, Dursun E, et al. Abatacept as a Long-Term Targeted Therapy for LRBA Deficiency. J Allergy Clin Immunol Pract. 2019;7(8):2790-2800.e15 7. Tesch VK, Abolhassani H, Shadur B, et al. Long-term outcome of LRBA deficiency in 76 patients after various treatment modalities as evaluated by the immune deficiency and dysregulation activity (IDDA) score. J Allergy Clin Immunol. 2020;145(5):1452-1463

LPALD
610738

Lipoprotein (a) and Low-Density Lipoprotein Cholesterol, Serum

Clinical Information: The cholesterol within lipoprotein(a) (Lp[a]) is included in every method that measures low-density lipoprotein cholesterol (LDL-C). Therefore, in patients that express high concentrations of Lp(a) the interpretation of LDL-C and the resulting clinical diagnoses and treatment strategies may be inaccurate. This panel reports 3 values: 1) the cholesterol measured within LDL by beta quantitation (this result contains both LDL-C and Lp[a]), 2) the cholesterol within Lp(a), and 3) a calculated "true" LDL-C where Lp(a)-C is subtracted from the beta quantitation LDL-C. The abnormal lipoprotein-X (LpX) is visible on lipoprotein electrophoresis. If LpX is present, the measurement of LDL-C is inaccurate and will not be reported.

Useful For: Evaluation of the contribution of lipoprotein (a) (Lp[a])-cholesterol within measured low-density lipoprotein cholesterol Evaluation of increased risk for cardiovascular disease and events: -Most appropriately measured in individuals at intermediate risk for cardiovascular disease -Patients with early atherosclerosis or strong family history of early atherosclerosis without explanation by traditional risk factors should also be considered for testing -Follow-up evaluation of patients with elevations in Lp(a) mass

Interpretation: Results of this panel can be used to determine the cholesterol content of low-density lipoprotein (LDL) and lipoprotein (a) (Lp[a]) separately. Interpretations of lipoprotein disorders can be made within the other clinical context. Lipoprotein-X (LpX) is an abnormal lipoprotein that appears in the sera of patients with obstructive jaundice and is an indicator of cholestasis. The presence of LpX will be reported if noted during Lp(a) cholesterol analysis. The other values (LDL-C and Lp(a)-C) will not be reported if LpX is present.

Reference Values:
Lipoprotein (a) Cholesterol: Normal: <5 mg/dL
Lipoprotein-X: Undetectable
Low-Density Lipoprotein Cholesterol (LDL-C):
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for LDL-C in adults (ages 18 years and older):
Desirable: <100 mg/dL
Above desirable: 100-129 mg/dL
Borderline high: 130-159 mg/dL
High: 160-189 mg/dL
Very high: > or =190 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for LDL-C in children and adolescents (ages 2-17 years):
Acceptable: <110 mg/dL
Borderline high: 110-129 mg/dL
High: > or =130 mg/dL

Clinical References: 1. Fatica EM, Meeusen JW, Vasile VC, Jaffe AS, Donato LJ. Measuring the contribution of Lp(a) cholesterol towards LDL-C interpretation. Clin Biochem. 2020;86:45-51. doi:10.1016/j.clinbiochem.2020.09.007. Erratum in: Clin Biochem. 2021;88:56-57 2. Willeit P, Yeang C, Moriarty P, et al. Low-density lipoprotein cholesterol corrected for lipoprotein (a) cholesterol, risk thresholds, and cardiovascular events. J Am Heart Assoc. 2020;9(23):e016318 3. Yeang C, Witztum JL, Tsimikas S: 'LDL-C'=LDL-C+Lp(a)-C: implications of achieved ultra-low LDL-C levels in the proprotein convertase subtilisin/kexin type 9 era of potent LDL-C lowering. Curr Opin Lipidol. 2015;26(3):169-178. doi:10.1097/MOL.0000000000000171 4. Kinpara K, Okada H, Yoneyama A, Okubo M, Murase T. Lipoprotein(a)-cholesterol: a significant component of serum cholesterol. Clin Chim Acta. 2011;412(19-20):1783-1787. doi:10.1016/j.cca.2011.05.036 5. Yeang C, Willeit P, Tsimikas S. The interconnection between lipoprotein(a), lipoprotein(a) cholesterol and true LDL-cholesterol in the diagnosis of familial hypercholesterolemia. Curr Opin Lipidol. 2020;31(6):305-312. doi:10.1097/MOL.0000000000000713

LMPP
83673

Lipoprotein Metabolism Profile, Serum

Clinical Information: Lipoprotein metabolism profile analysis provides information about the causes of elevated serum cholesterol or triglycerides. In some patients, increased serum lipids reflect elevated levels of intermediate-density lipoprotein (IDL), very-low-density lipoprotein (VLDL), lipoprotein a [Lp(a)], or even the abnormal lipoprotein complex, lipoprotein X (LpX). These elevations can signal genetic abnormalities in lipid metabolism or transport, nephrotic syndrome, endocrine dysfunction, or even cholestasis. Identifying the lipoproteins associated with lipid elevation is done using the gold-standard methods, including ultracentrifugation, selective precipitation, and electrophoresis. Proper characterization of a patient's dyslipidemic phenotype aids clinical decisions and treatment. Classifying the hyperlipoproteinemias into phenotypes places disorders that affect plasma lipid and lipoprotein concentrations into convenient groups for evaluation and treatment. A clear distinction must be made between primary (inherited) and secondary (liver disease, alcoholism, metabolic diseases) causes of dyslipoproteinemia. Lipoprotein profiling will identify the presence of Lp(a) and LpX and distinguish between the following dyslipidemias: -Exogenous hyperlipemia (Type I) -Familial hypercholesterolemia (Type IIa) -Familial combined hyperlipidemia (Type IIb) -Familial dysbetalipoproteinemia (Type III) -Endogenous hyperlipemia (Type IV) -Mixed hyperlipemia (Type V)

Useful For: Diagnosing dyslipoproteinemia Quantifying cholesterol and triglycerides in very-low-density lipoprotein, low-density lipoprotein (LDL), high-density lipoproteins (HDL), and chylomicrons Identifying lipoprotein-X Classifying hyperlipoproteinemias (lipoprotein phenotyping) Evaluating

patients with abnormal lipid values (cholesterol, triglyceride, HDL, LDL) for specific phenotypes

Interpretation: Patients with increased lipoprotein a [Lp(a)] cholesterol values have been associated with increased risk for the development of atherothrombotic disease. If not previously tested, it is recommended to order the immunoassay for Lp(a) (Test ID LIPA1 / Lipoprotein [a], Serum) to fully assess cardiovascular risk associated with Lp(a). Aggressive low-density lipoprotein reduction is the recommended treatment approach in most patients with increased Lp(a). Lipoprotein-X (LpX) is an abnormal lipoprotein that appears in the sera of patients with obstructive jaundice and is an indicator of cholestasis. The presence of LpX will be reported if noted during Lp(a) cholesterol analysis.

Reference Values:

	2-9 years	10-17 years	> or =18 years
Total cholesterol	* Acceptable: or =200 mg/dL	** Desirable: or = 240 mg/dL	
Triglycerides	* Acceptable: or =100 mg/dL	* Acceptable: or =130 mg/dL	** Normal: or =500 mg/dL
Low-density lipoprotein (LDL) cholesterol	* Acceptable: or =130 mg/dL	*** Desirable: or =190 mg/dL	
LDL triglycerides	< or =50 mg/dL	< or =50 mg/dL	
Apolipoprotein B	* Acceptable: or =110 mg/dL	*** Desirable: or =140 mg/dL	
High-density lipoprotein (HDL) cholesterol	* Low: 45 mg/dL	*** Males: > or =40mg/dL Females: > or =50mg/dL	
Very low-density lipoprotein (VLDL) cholesterol			
VLDL triglycerides			
Beta VLDL cholesterol			
Beta VLDL triglycerides			
Chylomicron cholesterol	Undetectable	Undetectable	
Chylomicron triglycerides	Undetectable	Undetectable	
Lp(a) cholesterol			
LpX	Undetectable	Undetectable	

Clinical References: 1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1082-e1143 2. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents; National Heart, Lung, and Blood Institute: Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128 Suppl 5:S213-S256 3. Rosenson RS, Najera SD, Hegele RA. Heterozygous familial

hypercholesterolemia presenting as chylomicronemia syndrome. J Clin Lipidol. 2017;11(1):294-296. doi:10.1016/j.jacl.2016.12.005 4. Hopkins PN, Brinton EA, Nanjee MN. Hyperlipoproteinemia type 3: the forgotten phenotype. Curr Atheroscler Rep. 2014;16(9):440. doi:10.1007/s11883-014-0440-2 5. Gotoda T, Shirai K, Ohta T, et al. Diagnosis and management of type I and type V hyperlipoproteinemia. J Atheroscler Thromb. 2012;19(1):1-12 6. Gonzales KM, Donato LJ, Shah P, Simha V. Measurement of apolipoprotein B levels helps in the identification of patients at risk for hypertriglyceridemic pancreatitis. J Clin Lipidol. 2021;15(1):97-103. doi:10.1016/j.jacl.2020.11.010 7. Fatica EM, Meeusen JW, Vasile VC, Jaffe AS, Donato LJ. Measuring the contribution of Lp(a) cholesterol towards LDL-C interpretation. Clin Biochem. 2020;86:45-51. doi:10.1016/j.clinbiochem.2020.09.007 8. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140(11):e596-e646

LIPA1
615007

Lipoprotein(a), Serum

Clinical Information: Lipoprotein (a) [Lp(a)] consists of a low-density lipoprotein (LDL) particle that is covalently bound to an additional protein, apolipoprotein (a) [Apo(a)]. Apo(a) has high sequence homology with the coagulation factor plasminogen, and like LDL, Lp(a) contains apolipoprotein B100 (ApoB). Thus, Lp(a) is both proatherogenic and prothrombotic. Lp(a) is an independent risk factor for coronary heart disease (CHD), ischemic stroke, and aortic valve stenosis. Lp(a) has been referred to as "the most atherogenic lipoprotein". The mechanism of increased risk is unclear but most likely involves progression of atherosclerotic stenosis via intimal deposition of cholesterol and promotion of thrombosis via homology to plasminogen. Accurate immunochemical measurement of Lp(a) is complicated by the heterogeneity of Lp(a) molecular size. Due to the large number of polymorphisms (varying number of kringle domain repeats in the Apo[a] protein) in the population, any given individual can have an Apo(a) protein between 240 to 800 kDa. This heterogeneity leads to inaccuracies in all immunoassays. In addition, the degree of atherogenicity of the Lp(a) particle may depend on the molecular size of the Lp(a)-specific protein. However, the measurement of Lp(a) using immunoassays calibrated to molar units is recommended to minimize assay inaccuracies caused by Apo(a) isoform size. Serum concentrations of Lp(a) are related to genetic factors, specifically the expression of Apo(a), and are largely unaffected by diet, exercise, and lipid-lowering pharmaceuticals. However, in a patient with additional modifiable CHD risk factors, more aggressive therapy to normalize these factors may be indicated if the Lp(a) value is also increased. In cases of extremely elevated Lp(a), lipoprotein apheresis may be considered.

Useful For: Cardiovascular disease (CVD) risk refinement in patients with moderate or high risk based on conventional risk factors or patients with clinical suspicion of residual CV risk not identified by other lipid parameters

Interpretation: Lipoprotein (a) [Lp(a)] concentrations of 75 nmol/L and above are linearly related to increased risk of cardiovascular events independent of conventional risk markers. Values > or =75 nmol/L may suggest increased risk of coronary heart disease. Values > or =125 nmol/L are considered a risk-enhancing factor for cardiovascular disease by several professional societies. Clinician-patient discussion of therapeutic strategy is warranted.

Reference Values:
> or =18 years: <75 nmol/L

Reference values have not been established for patients who are less than 18 years of age.

Clinical References: 1. Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009;302(4):412-423 2. Tsimikas S. A test in context: Lipoprotein(a): Diagnosis, prognosis,

controversies, and emerging therapies. J Am Coll Cardiol. 2017;69(6):692-711. doi:10.1016/j.jacc.2016.11.042 3. Marcovina SM, Koschinsky ML, Albers JJ, Skarlatos S. Report of the National Heart, Lung, and Blood Institute Workshop on Lipoprotein (a) and Cardiovascular Disease: recent advances and future directions. Clin Chem. 2003;49(11):1785-1796 4. Wilson DP, Jacobson TA, Jones PH, et al. Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidol. 2019;13(3):374-392. doi:10.1016/j.jacl.2019.04.010

LUCHM
622811

LiquidHALLMARK ctDNA and ctRNA

Clinical Information: LiquidHALLMARK detects clinically significant and actionable alterations associated with US Food and Drug Administration (FDA)-approved and emerging therapies, including tissue-agnostic targets BRAF, RET, NTRK, and MSI, and guideline-recommended biomarkers. The identification of these alterations allows healthcare professionals to make informed decisions to guide care from diagnosis and initial therapy selection, monitoring of therapy response, to the detection of emergent mutations that drive disease burden over time. The use of next-generation sequencing of circulating tumor DNA and RNA enables both minimal invasive testing and broad genomic coverage to maximize therapeutic benefit to patients. This test is intended for the genomic profiling of solid tumors via the use of circulating-free DNA and RNA.

Useful For: As an alternative to invasive tissue biopsies to assist in tumor profiling for diagnosis, predicting prognosis, and identifying targeted therapies for the treatment and management of patients with a solid tumor This test is not useful for prenatal screening.

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Pascual J, Attard G, Bidard FC, et al. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2022;33(8):750-768. doi:10.1016/j.annonc.2022.05.520 2. Iams WT, Mackay M, Ben-Shachar R, et al. Concurrent tissue and circulating tumor DNA molecular profiling to detect guideline-based targeted mutations in a multicancer cohort. JAMA Netw Open. 2024;7(1):e2351700. Published 2024 Jan 2. doi:10.1001/jamanetworkopen.2023.51700 3. Benayed R, Offin M, Mullaney K, et al. High yield of RNA sequencing for targetable kinase fusions in lung adenocarcinomas with no mitogenic driver alteration detected by DNA sequencing and low tumor mutation burden. Clin Cancer Res. 2019;25(15):4712-4722. doi:10.1158/1078-0432.CCR-19-0225 4. Heeke S, Gandhi S, Tran HT, et al. Brief Report: Longitudinal tracking of ALK rearranged non-small cell lung cancer from plasma using circulating-tumor RNA and circulating-tumor DNA. JTO Clin Res Rep. 2025;in press. doi:10.1016/j.jtocrr.2025.100795 5. Poh J, Ngeow KC, Pek M, et al. Analytical and clinical validation of an amplicon-based next generation sequencing assay for ultrasensitive detection of circulating tumor DNA. PLoS One. 2022;17(4):e0267389. Published 2022 Apr 29. doi:10.1371/journal.pone.0267389

FLISD
75638

Lisdexamfetamine as Metabolite, Urine

Clinical Information: Amphetamine is a drug as well as the metabolite of Methamphetamine. Benzphetamine is rapidly metabolized to Amphetamine and Methamphetamine.

Reference Values:
Reporting limit determined each analysis.
None Detected ng/mL

LITH
37046

Lithium, Serum

Clinical Information: Lithium alters the intraneuronal metabolism of catecholamines by an unknown mechanism. It is used to suppress the manic phase of manic-depressive psychosis. Lithium is distributed throughout the total water spaces of the body and is excreted primarily by the kidney. Toxicity from lithium salts leads to ataxia, slurred speech, and confusion. Since the concentration of lithium in the serum varies with the time after the dose, blood for lithium determination should be drawn at a standard time, preferably 8 to 12 hours after the last dose (trough values).

Useful For: Monitoring therapy of patients with bipolar disorders, including recurrent episodes of mania and depression Evaluating lithium toxicity

Interpretation: The therapeutic range for lithium has been established at 0.5 to 1.2 mmol/L. Within this range, most people will respond to the drug without symptoms of toxicity. However, response and side effects are individual. Lithium concentrations and side effects can increase with the loss of salt and water from the body, which can occur with a salt-free diet, excessive sweating, or an illness that causes vomiting and diarrhea. A variety of prescribed drugs, over-the-counter medications, and supplements can also increase, decrease, or interfere with the concentrations of lithium.

Reference Values:
Therapeutic: 0.5-1.2 mmol/L (trough concentration)
Critical value: >1.6 mmol/L
There is no relationship between peak concentration and degree of intoxication.

Clinical References: 1. Judd LL: The therapeutic use of psychotropic medications: lithium and other mood-normalizing medications. In Harrison's Principles of Internal Medicine. 12th edition. Edited by JD Wilson, E Braunwald, KJ Isselbacher, et al. New York, McGraw-Hill Book Company, 1991, pp 2141-2143 2. Gelenberg AJ, Kane JM, Kekller MB, et al: Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. N Engl J Med 1989;321:1489-1493 3. Lithium Product Monograph. Physicians' Desk Reference (PDR). 61st edition. Montvale, NJ: Thomson PDR, 2007

LFABP
70429

Liver Fatty Acid-Binding Protein (L-FABP) Immunostain, Technical Component Only

Clinical Information: Liver fatty acid-binding protein (L-FABP) is a cytoplasmic protein that binds free fatty acids and their coenzyme A derivative, bilirubin, and other hydrophobic ligands. It may have roles in lipid transport, uptake, and metabolism. L-FABP can be used with a panel of immunohistochemical markers (beta-catenin, glutamine synthetase, C-reactive protein, and amyloid A) to distinguish hepatic adenoma from focal nodular hyperplasia and non-neoplastic liver. L-FABP is downregulated in type 1 adenomas but is expressed in normal liver and other adenoma types.

Useful For: Classification of hepatic adenomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. van Aalten SM, Verheij J, Terkivatan T, et al. Validation of a liver adenoma classification system in a tertiary referral centre: implications for clinical practice. J Hepatol. 2011;55(1):120-125 2. Bioulac-Sage P, Cubel G, Balabaud C, et al. Revisiting the pathology of resected benign hepatocellular nodules using new immunohistochemical markers. Semin Liver Dis. 2011;31(1):91-103 3. Bioulac-Sage P, Rebouissou S, Thomas C, et al. Hepatocellular adenoma subype classification using molecular markers and immunohistochemistry. Hepatology. 2007;46(3):740-748 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

LIVPR
113633

Liver Profile, Serum

Clinical Information: The hepatic function panel may be used to help diagnose liver disease if a person has signs and symptoms that indicate possible liver dysfunction. If a person has a known condition or liver disease, testing may be performed at intervals to monitor the health of the liver and to evaluate the effectiveness of any treatments. Abnormal tests on a liver panel may prompt a repeat analysis of one or more tests, or of the whole panel, to see if the elevations or decreases persist and may indicate the need for additional testing to determine the cause of the liver dysfunction.

Useful For: Screening for liver damage, especially if someone has a condition or is taking a drug that may affect the liver

Interpretation: Hepatic function panel results are not diagnostic of a specific condition; they indicate that there may be a problem with the liver. In a person who does not have symptoms or identifiable risk factors, abnormal liver test results may indicate a temporary liver injury or reflect something that is happening elsewhere in the body, such as in the skeletal muscles, pancreas, or heart. It may also indicate early liver disease and the need for further testing and periodic monitoring. Results of liver panels are usually evaluated together. Several sets of results from tests performed over a few days or weeks are often assessed together to determine if a pattern is present. Each person will have a unique set of test results that will typically change over time. A healthcare practitioner evaluates the combination of liver test results to gain clues about the underlying condition. Often, additional testing is necessary to determine what is causing the liver damage or disease.

Reference Values:

TOTAL BILIRUBIN
0-6 days: Refer to http://bilitool.org/ for information on age-specific (postnatal hour of life) serum bilirubin values.
7-14 days: 0.0-14.9
15 days to 17 years: 0.0 -1.0
>18 years: 0.0-1.2

DIRECT BILIRUBIN
> or =12 months: 0.0-0.3 mg/dL
Reference values have not been established for patients who are younger than 12 months of age.

ASPARTATE AMINOTRANSFERASE
Males
0-11 months: Not established
1-13 years: 8-60 U/L
> or =14 years: 8-48 U/L

Females
0-11 months: Not established

1-13 years: 8-50 U/L
> or =14 years: 8-43 U/L

ALANINE AMINOTRANSFERAASE
Males
> or =1 year: 7-55 U/L
Reference values have not been established for patients who are younger than 12 months of age.

Females
> or =1 year: 7-45 U/L
Reference values have not been established for patients who are younger than 12 months of age.

ALKALINE PHOSPHATASE
Males
4 years: 149-369 U/L
5 years: 179-416 U/L
6 years: 179-417 U/L
7 years: 172-405 U/L
8 years: 169-401 U/L
9 years: 175-411 U/L
10 years: 191-435 U/L
11 years: 185-507 U/L
12 years: 185-562 U/L
13 years: 182-587 U/L
14 years: 166-571 U/L
15 years: 138-511 U/L
16 years: 102-417 U/L
17 years: 69-311 U/L
18 years: 52-222 U/L
> or =19 years: 45-115 U/L

Females
4 years: 169-372 U/L
5 years: 162-355 U/L
6 years: 169-370 U/L
7 years: 183-402 U/L
8 years: 199-440 U/L
9 years: 212-468 U/L
10 years: 215-476 U/L
11 years: 178-526 U/L
12 years: 133-485 U/L
13 years: 120-449 U/L
14 years: 153-362 U/L
15 years: 75-274 U/L
16 years: 61-264 U/L
17-23 years: 52-144 U/L
24-45 years: 37-98 U/L
46-50 years: 39-100 U/L
51-55 years: 41-108 U/L
56-60 years: 46-118 U/L
61-65 years: 50-130 U/L
> or =66 years: 55-142 U/L
Reference values have not been established for patients who are younger than 4 years of age.

ALBUMIN
> or =12 months: 3.5-5.0 g/dL
Reference values have not been established for patients who are younger than 12 months of age.

TOTAL PROTEIN
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients who are younger than 12 months of age.

Clinical References: Kampfrath T. Liver Panel Test. Testing.com; Updated September 28, 2022. Accessed September 19, 2023. Available at https://www.testing.com/tests/liver-panel/

LKM
80387

Liver/Kidney Microsome Type 1 Antibodies, Serum

Clinical Information: Autoimmune hepatitis (AIH) is chronic liver disease that results from a loss of immune system tolerance and recognition of self-antigens.(1) AIH occurs in children and adults, with a significant female predominance. The clinical presentation of AIH varies significantly from asymptomatic liver dysfunction to acute liver failure. Evidence of liver dysfunction manifests as elevated aspartate aminotransferase, alanine aminotransferase, and gamma glutaryl transferase in the context of normal alkaline phosphatase. In addition, most individuals with AIH display increased concentrations of total IgG. AIH is associated with the production of diverse autoantibodies which also serves to subcategorize patients.(2) AIH type 1 is associated with F-actin reactive smooth muscle autoantibody (SMA), antinuclear autoantibody (ANA) (60% of patients), and autoantibody to SLA/LP (15% to 20% of patients), while AIH type 2 is associated with LKM-1 and LC-1 autoantibodies.(3) AIH type I occurs in children and adults and usually has a relatively mild course that is responsive to steroids and azathioprine. In contrast, AIH type 2 occurs predominantly in children, with a more moderate/severe disease course. Most of the autoantibodies associated with AIH were originally detected and characterized by indirect immunofluorescence (IIF).(4) Anti-LKM-1 antibodies can be detected by IIF using rodent stomach/liver/kidney composite tissue; anti-LKM-1 antibodies display staining of the proximal tubules in the kidney and cytoplasmic staining of the hepatocytes, with no reactivity on the stomach tissue. The major target for anti-LKM-1 antibodies is the cytochrome P450 2D6 (CYP2D6).(5) Following the identification of this autoantibody target, a number of solid-phase immunoassays have been developed for the evaluation of anti-LKM-1 antibodies. Although not diagnostic in isolation, the presence of certain autoantibodies has been reported to be important in establishing the diagnosis of AIH. Published diagnostic criteria for AIH which include testing for autoantibodies (ANA, SMA, anti-LKM-1, and anti-SLA), determination of serum immunoglobulin, histopathology, evaluation for viral hepatitis, and other indices have been developed based on scoring systems.(6-8). These diagnostic scoring systems are useful in AIH research studies and may not substitute appropriate clinical assessment in routine patient evaluation.

Useful For: Evaluation of patients with liver disease of unknown etiology Evaluation of patients with suspected autoimmune hepatitis

Interpretation: Seropositivity for anti-liver/kidney microsomal antibodies type 1 antibodies is consistent with a diagnosis of autoimmune hepatitis type 2, in patients with compatible clinical symptoms and histopathology.

Reference Values:
< or =20.0 Units (Negative)
20.1-24.9 Units (Equivocal)
> or =25.0 Units (Positive)
Reference values apply to all ages.

Clinical References: 1. Mieli-Vergani G, Vergani D, Czaja AJ, et al. Autoimmune hepatitis. Primer. 2018;4:18017. doi:10.1038/nrdp.2018.17 2. Beretta-Piccoli BT, Mieli-Vergani G, Vergani D. Serology in autoimmune hepatitis: A clinical-practice approach. Eur J Intern Med. 2018;48:35-43. doi:10.1016/j.ejim.2017.10.006 3. Toh BH. Diagnostic autoantibodies for autoimmune liver diseases. Clin Transl Immunology. 2017;6(5):e139. doi:10.1038/cti.2017.14 4. Liberal R, Mieli-Vergani G, Vergani D. Clinical significance of autoantibodies in autoimmune hepatitis. J Autoimmun. 2013;46:17-24. doi:10.1016/j.jaut.2013.08.001 5. Manns MP, Johnson EF, Griffin KJ, Tan EM, Sullivan KF. Major antigen of liver kidney microsomal autoantibodies in idiopathic autoimmune hepatitis is cytochrome P450db1. J Clin Invest. 1989;83(3):1066-1072. doi:10.1172/JCI1139496 6. Hennes EM, Zeniya M, Czaja AJ, et. Al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008;48(1):169-76. doi:10.1002/hep.22322 7. Ducazu O, Degroote H, Geerts A, et al. Diagnostic and prognostic scoring systems for autoimmune hepatitis: a review. Acta Gastroenterol Belg. 2021;84(3):487-495. doi:10.51821/84.3.014. 8. Harrington C, Krishnan S, Mack CL, Cravedi P, Assis DN, Levitsky J. Noninvasive biomarkers for the diagnosis and management of autoimmune hepatitis. Hepatology. 2022;76(6):1862-1879. doi:10.1002/hep.32591

LOB
82744

Lobster, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to lobster Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive

3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

LQTSG
617351

Long QT Syndrome Gene Panel, Varies

Clinical Information: Long QT syndrome (LQTS) is a genetic cardiac arrhythmia condition characterized by QT prolongation and T-wave abnormalities on an electrocardiogram (ECG). LQTS may result in or present with recurrent syncope, ventricular arrhythmia (commonly torsade de pointes), sudden cardiac arrest, and sudden cardiac death. Some subtypes of LQTS are also referred to as Romano-Ward syndrome (RWS).(1) LQTS has a prevalence of approximately 1:2000 and is caused by loss-of-function, disease-causing variants in genes that encode cardiac ion channels or associated proteins. It is estimated that up to 75% of individuals meeting clinical diagnostic criteria for LQTS are found to harbor a disease-causing variant in one of three genes: KCNQ1, KCNH2, and SCN5A.(2) Disease-causing variants in additional genes contribute to a minority of LQTS cases.(2) In most cases, LQTS follows an autosomal dominant pattern of inheritance. Jervell and Lange-Nielsen syndrome (JLNS) is a rare condition characterized by prolonged QT interval and congenital profound bilateral sensorineural hearing loss. JLNS follows an autosomal recessive inheritance pattern and is caused by homozygous or compound heterozygous disease-causing variants in either KCNQ1 or KCNE1.(1) Andersen-Tawil syndrome is a rare condition characterized by prolonged QT interval, ventricular arrhythmias, episodic muscle weakness, and congenital anomalies that may include facial dysmorphology, clinodactyly, hand/foot syndactyly, short stature, and scoliosis. Andersen-Tawil syndrome follows an autosomal dominant inheritance pattern and is caused by disease-causing variants in the KCNJ2 gene.(3) Timothy syndrome is a rare, systemic condition involving prolonged QT interval in association with seizures, neurodevelopmental delays, recurrent infections, and congenital anomalies that may include hand/foot syndactyly, structural heart defects, and facial dysmorphology. Timothy syndrome follows an autosomal dominant patten of inheritance and is caused by disease-causing variants in the CACNA1C gene.(4) Genetic testing in LQTS is recommended and supported by multiple consensus statements to confirm the clinical diagnosis, assist with risk stratification, guide management, and identify at-risk family members. Even individuals with a normal QT interval may still be at risk for a cardiac event and sudden cardiac death and, thus, ECG analysis alone is insufficient to rule out the diagnosis and genetic testing is necessary to confirm the presence or absence of disease in at-risk family members.(1-4)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of long QT syndrome (LQTS) Establishing a diagnosis of LQTS

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Alders M, Bikker H, Christiaans I: Long QT syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003 . Updated February 8, 2018. Accessed July 27, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1129/ 2. Giudicessi JR, Ackerman MJ: Genetic testing in heritable cardiac arrhythmia syndromes: differentiating pathogenic mutations from background genetic noise. Curr Opin Cardiol. 2013 Jan;28(1):63-71. doi:10.1097/HCO.0b013e32835b0a41 3. Veerapandiyan A, Statland JM, Tawil R: Andersen-Tawil syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated June 7, 2018. Accessed July 27, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1264/ 4. Napolitano C, Timothy KW, Bloise R, Priori SG: CACNA1C-related disorders. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated February 11, 2021. Accessed July 27, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1403/ 5. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

LORAZ
80459

Lorazepam (Ativan), Serum

Reference Values:
Reference Range: 50.0 - 240.0 ng/mL

LDLD
606898

Low-Density Lipoprotein (LDL) Cholesterol, Beta-Quantification, Serum

Clinical Information: Low-density lipoprotein cholesterol (LDL-C) is acknowledged as being causally related with atherosclerotic cardiovascular disease. LDL-C remains the primary focus for cardiovascular risk assessment and effectiveness of risk reduction interventions including diet, physical activity, and pharmacologic therapies. Low-density lipoproteins are a heterogeneous population of lipid particles classically defined as having a density of 1.006 to 1.063 kg/L obtained by preparative ultracentrifugation. The gold standard beta-quantification (beta-quant or BQ) method combines ultracentrifugation with precipitation and yields a direct quantitative measurement of LDL-C, intermediate-density lipoprotein cholesterol, and lipoprotein(a) cholesterol. Extremely low concentrations of LDL-C are associated with abetalipoproteinemia and hypobetalipoproteinemia. In both cases, individuals will have very low total cholesterol and diminished or absent LDL-C, apolipoprotein B, and very low-density lipoprotein cholesterol. Patients may exhibit clinical signs and symptoms of polyneuropathy, intestinal fat malabsorption, hepatosteatosis, and fat-soluble vitamin deficiencies.

Useful For: Evaluation of cardiovascular risk Verification of estimated low-density lipoprotein cholesterol (LDL-C) in patients with hypertriglyceridemia or extremely low LDL-C Diagnosis of familial hypobetalipoproteinemia and abetalipoproteinemia

Interpretation: Mayo Clinic has adopted the National Lipid Association classifications, which are included as reference values on Mayo Clinic and Mayo Clinic Laboratories reports (see Reference Values). Lipids are most commonly measured to assess cardiovascular risk. Maintaining desirable concentrations of lipids lowers the risk of heart attacks or strokes. Establishing appropriate treatment strategies and lipid goals requires consideration of low-density lipoprotein cholesterol (LDL-C) in context with other risk factors including age, sex, smoking status, family and personal history of heart disease. All guidelines recommend aggressive lipid lowering for patients with LDL cholesterol above 190 mg/dL. Values below 20 mg/dL in untreated patients may be consistent with hypobetalipoproteinemia. Complications due to fat malabsorption may be present in affected individuals. Undetectable LDL-C is highly suggestive of abetalipoproteinemia. Related polyneuropathy may exist in affected individuals.

Reference Values:
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for LDL-C in adults (ages 18 years and up):
Desirable: <100 mg/dL
Above desirable: 100-129 mg/dL
Borderline high: 130-159 mg/dL
High: 160-189 mg/dL
Very high: > or =190 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for LDL-C in children and adolescents (ages 2-17 years):
Acceptable: <110 mg/dL
Borderline high: 110-129 mg/dL
High: > or =130 mg/dL

Clinical References: 1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-2497 2. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. J Clin Lipidol. 2014;8(5):473-488 3. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128(Suppl 5):S213-S256 4. Grundy SM, Stone NJ, Bailey AL, et al: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1046-e1081. doi:10.1161/CIR.0000000000000624

FUSF 35304 Low-Grade Fibromyxoid Sarcoma (LGFMS), 16p11.2 (FUS or TLS) Rearrangement, FISH, Tissue

Clinical Information: Low-grade fibromyxoid sarcoma (LGFMS) is a rare malignant soft tissue tumor characterized by a bland fibroblastic spindle cell proliferation arranged in alternating fibrous and myxoid areas, with or without giant collagen rosettes. These tumors are characterized by the chromosome translocation t(7;16)(q33-34;p11), which results in the fusion of FUS (also called TLS) on chromosome 16 to CREB3L2 (also called BBF2H7) on chromosome 7. Greater than 70% of LGFMS are cytogenetically characterized by this translocation. In rare cases, a variant t(11;16)(p11;p11) has been described in which FUS is fused to CREB3L1 (OASIS), a gene structurally related to CREB3L2. Testing of FUS locus rearrangement should be concomitant with histologic evaluation, and positive results may support the diagnosis of LGFMS.

Useful For: Supporting the diagnosis of low-grade fibromyxoid sarcoma when used in conjunction with an anatomic pathology consultation

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the FUS probe set. A positive result is consistent with the diagnosis of low-grade fibromyxoid sarcoma (LGFMS). A negative result suggests that a FUS gene rearrangement is not present, but does not exclude the diagnosis of LGFMS.

Reference Values:
An interpretative report will be provided.

Clinical References: 1. Fletcher CDM, Unni K, Mertens F: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. IARC: Lyon 2002, pp 104-105 2. Downs-Kelly E, Goldblum JR, Patel RM, et al: The utility of fluorescence in situ hybridization (FISH) in the diagnosis of myxoid soft tissue neoplasms. Am J Surg Pathol 2008;32:8-13 3. Mertens F, Fletcher CD, Antonescu CR, et al: Clinicopathologic and molecular genetic characterization of low-grade fibromyxoid sarcoma, and cloning of a novel FUS/CREB3L1 fusion gene. Lab Invest 2005;85:408-415 4. Vernon SE, Bejarano PA: Low-grade fibromyxoid sarcoma: a brief review. Arch Pathol Lab Med 2006;130:1358-1360 5. Storlazzi CT, Mertens F, et al: Fusion of the FUS and BBF2H7 genes in low grade fibromyxoid sarcoma.Hum Mol Genet. 2003 Sep 15;12(18):2349-58. Epub 2003 Jul 22

LOX 80462 Loxapine (Loxitane) and 8-Hydroxyloxapine

Reference Values:
Loxapine:
Reference Range: 5.0 - 30.0 ng/mL

8-Hydroxy-Loxapine:
Reference Range: 20.0 - 100.0 ng/mL

FLSDA 75680 LSD Trace Analysis, Urine

Reference Values:
Reporting limit determined each analysis.
None Detected ng/mL

LCAF 35282 Lung Cancer, ALK (2p23) Rearrangement, FISH, Tissue

Clinical Information: Rearrangements of the anaplastic lymphoma kinase (ALK) gene are found in approximately 3% to 5% of non-small cell lung carcinomas with the majority in adenocarcinoma and younger female patients who were light or nonsmokers. Clinical studies have shown that lung cancers harboring ALK rearrangements are resistant to epidermal growth factor receptor tyrosine kinase inhibitors, but may be highly sensitive to directed tyrosine kinase inhibitors.

Useful For: Identifying patients with non-small cell lung carcinoma who may benefit from treatment with directed tyrosine kinase inhibitors

Interpretation:

Reference Values:
An interpretative report will be provided.

Clinical References:

RETF 35846 Lung Cancer, RET (10q11) Rearrangement, FISH, Tissue

Clinical Information: Chromosomal rearrangements of the RET proto-oncogene at chromosome 10q11 resulting in fusion of the RET gene with various partner genes has been identified as a recurrent

abnormality in several tumor types including but not limited to some non-small cell carcinomas of the lung, thyroid carcinomas, salivary gland carcinomas, and soft tissue tumors Clinical data has shown that tumors harboring RET fusions may be sensitive to directed inhibitor therapy.

Useful For:

Interpretation: RET will be clinically interpreted as positive or negative. A result is considered positive when the percent of cells with separation of the RET fluorescence in situ hybridization (FISH) probes exceeds the normal cutoff for the RET FISH probe set. A positive result is consistent with rearrangement of the RET gene and likely reflects RET fusion with a partner gene. The significance of this FISH result is dependent on additional clinical and pathologic features. A positive result may support a certain diagnosis in a particular clinical and pathologic context. A positive result suggests that the tumor may be sensitive to directed kinase inhibitors. While results may indicate the potential response to directed tyrosine kinase inhibitors, selection of treatment remains a clinical decision. A negative result does not exclude the presence of a RET fusion or exclude the possible sensitivity to targeted therapy.

Reference Values:
An interpretive report will be provided.

Clinical References:

ROS1F
35845

Lung Cancer, ROS1 (6q22) Rearrangement, FISH, Tissue

Clinical Information:

Useful For: Fluorescence in situ hybridization (FISH) testing for ROS1 allows for the detection of most ROS1 rearrangements, therefore, is useful for identifying tumors that may be sensitive to directed therapy ROS1 FISH testing may also support the diagnosis of inflammatory myofibroblastic tumor, certain cutaneous melanocytic tumors, or other neoplasms when used in conjunction with pathologic assessment

Interpretation: A result is considered positive when the percent of cells separation of the ROS1 FISH probes exceeds the normal cutoff for the ROS1 FISH probe set. A positive result is consistent with rearrangement of the ROS1 gene and likely reflects ROS1 fusion with a partner gene. The significance of this finding is dependent on the clinical and pathologic features. A positive result suggests that the tumor may be responsive to directed therapy in the proper clinical and pathologic context. While results may indicate the potential response to directed tyrosine kinase inhibitors, selection of treatment remains a clinical decision. A positive result may support a certain diagnosis in a particular clinical and pathologic context. A negative result does not exclude the presence of a ROS1 fusion or exclude the possible sensitivity to targeted therapy.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Cui M, Han Y, Li P, et al. Molecular and clinicopathological characteristics of ROS1-rearranged non-small-cell lung cancers identified by next-generation sequencing. Molecular Oncology. 2020;14(11):2787-95 2. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol. 2012;30(8):863-870. doi:10.1200/JCO.2011.35.6345 3. Antonescu CR, Suurmeijer AJ, Zhang L, et al. Molecular characterization of inflammatory myofibroblastic tumors with frequent ALK and ROS1 gene fusions

and rare novel RET rearrangement. Am J Surg Pathol. 2015;39(7):957-967 4. Wiesner T, He J, Yelensky R, et al. Kinase fusions are frequent in Spitz tumours and spitzoid melanomas. Nature communications. 2014;5(1):3116 5. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med. 2014;371(21):1963-1971

LUPN
82613

Lupin, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to lupin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier;

2022:chap 56

FLUPV 91714 Lupus Anticoagulant Evaluation with Reflex

Reference Values:

Lupus Anticoagulant	Not Detected

This interpretation is based on the following test results:

PTT-LA Screen	< or = 40 seconds
DRVVT Screen	< or = 45 seconds

ALUPO 603465 Lupus Anticoagulant Profile Interpretation

Clinical Information: Lupus anticoagulant (LAC) is an antibody to negatively charged phospholipid that interferes with phospholipid-dependent coagulation tests. LAC is found in, but not limited to, patients with systemic lupus erythematosus; LAC is associated with other autoimmune disorders and collagen vascular disease and occurs in response to medications or certain infections (eg, respiratory tract infections in children) and in individuals with no obvious underlying disease. LAC has been associated with arterial and venous thrombosis and fetal loss. Individuals with thrombocytopenia or factor II deficiency associated with LAC may be at risk for bleeding.

Useful For: Interpretation of testing performed as part of a profile to confirme or exclude the presence of lupus anticoagulant (LAC), distinguishing LAC from specific coagulation factor inhibitors and nonspecific inhibitors Interpretation of testing performed as part of a profile to investigatie a prolonged activated thromboplastin time, especially when combined with other coagulation studies This test is not useful for the detection of antiphospholipid antibodies that do not affect coagulation tests. We recommend separate testing for serum phospholipid (cardiolipin) antibodies.

Interpretation: An interpretive report will be provided when testing is complete, noting a presence or absence of a lupus anticoagulant.

Reference Values:
Only orderable as a reflex. For more information see ALUPP / Lupus Anticoagulant Profile, Plasma.

An interpretive report will be provided.

Clinical References: 1. Arnout J, Vermylen J. Current status and implications of autoimmune antiphospholipid antibodies in relation to thrombotic disease. J Thromb Haemost. 2003;1(5):931-942 2. Levin JS, Branch DW, Rauch J.: The antiphospholipid syndrome. New Engl J Med. 2002;346(10):752-763 3. Proven A, Bartlett RP, Moder KG, et al. Clinical importance of positive tests for lupus anticoagulant and anticardiolipin antibodies. Mayo Clin Proc. 2004;79(4):467-475 4. Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. Humana Press; 2017

ALUPP 603463 Lupus Anticoagulant Profile, Plasma

Clinical Information: Lupus anticoagulant (LA) is an antibody to negatively charged phospholipid that interferes with phospholipid-dependent coagulation tests. LA is found in, but not limited to, patients with systemic lupus erythematosus; LA is associated with other autoimmune disorders and collagen

vascular disease and occurs in response to medications or certain infections (eg, respiratory tract infections in children) and in individuals with no obvious underlying disease. Lupus anticoagulant has been associated with arterial and venous thrombosis and fetal loss. Individuals with thrombocytopenia or factor II deficiency associated with LA may be at risk for bleeding.

Useful For: Confirming or excluding the presence of lupus anticoagulant (LA), distinguishing LA from specific coagulation factor inhibitors and nonspecific inhibitors Investigating a prolonged activated thromboplastin time, especially when combined with other coagulation studies This test is not useful for the detection of antiphospholipid antibodies that do not affect coagulation tests. We recommend separate testing for serum phospholipid (cardiolipin), IgG and IgM (CLPMG) and beta-2 glycoprotein 1, IgG and IgM (B2GMG).

Interpretation: An interpretive report will be provided when testing is complete.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Arnout J, Vermylen J. Current status and implications of autoimmune antiphospholipid antibodies in relation to thrombotic disease. J Thromb Haemost. 2003;1(5):931-942 2. Levin JS, Branch DW, Rauch J. The antiphospholipid syndrome. New Engl J Med. 2002;346(10):752-763 3. Proven A, Bartlett RP, Moder KG et al. Clinical importance of positive tests for lupus anticoagulant and anticardiolipin antibodies. Mayo Clin Proc. 2004;79(4):467-475 4. Kitches CS, Kessler CM, Konkle BA, et al. Consultative Hemostasis and Thrombosis. 4th ed. Elsevier; 2019:374-395

ALUPI
603464

Lupus Anticoagulant Profile, Technical Interpretation

Clinical Information: Lupus anticoagulant (LAC) is an antibody to negatively charged phospholipid that interferes with phospholipid-dependent coagulation tests. LAC is found in, but not limited to, patients with systemic lupus erythematosus; LAC is associated with other autoimmune disorders and collagen vascular disease, occurs in response to medications or certain infections (eg, respiratory tract infections in children), and in individuals with no obvious underlying disease. LAC has been associated with arterial and venous thrombosis and fetal loss. Individuals with thrombocytopenia or factor II deficiency associated with LAC may be at risk for bleeding.

Useful For: Technical interpretation of testing to confirm or exclude the presence of lupus anticoagulant (LAC) Distinguishing LAC from specific coagulation factor inhibitors and nonspecific inhibitors Investigating a prolonged activated thromboplastin time, especially when combined with other coagulation studies This test is not useful for the detection of antiphospholipid antibodies that do not affect coagulation tests. We recommend separate testing for serum phospholipid (cardiolipin) antibodies.

Interpretation: When testing is complete, if the prothrombin time, activated partial thromboplastin time, and dilute Russell's viper venom time fall within clinically normal ranges, an interpretive comment will be provided noting no evidence of a lupus anticoagulant.

Reference Values:
Only orderable as part of a profile. For more information see ALUPP / Lupus Anticoagulant Profile, Plasma.

An interpretive report will be provided.

Clinical References: 1. Arnout J, Vermylen J. Current status and implications of autoimmune

antiphospholipid antibodies in relation to thrombotic disease. J Thromb Haemost 2003;1(5):931-942 2. Levin JS, Branch DW, Rauch J. The antiphospholipid syndrome. New Engl J Med 2002;346(10):752-763 3. Proven A, Bartlett RP, Moder KG, et al. Clinical importance of positive tests for lupus anticoagulant and anticardiolipin antibodies. Mayo Clin Proc 2004;79(4):467-475

LUTHI 70498 Luteinizing Hormone (LH) Beta Immunostain, Technical Component Only

Clinical Information: In male individuals, luteinizing hormone (LH) stimulates androgen production by Leydig cells in the testis. In female individuals, LH stimulates androgen and progesterone synthesis in ovarian follicles and corpus luteum and promotes ovulation. A sparse population of cells (approximately 10%) stain positively in normal pituitary gland. This population of gonadotrophs also produces follicle-stimulating hormone. Immunohistochemical detection of LH beta may be useful in the classification of pituitary adenomas.

Useful For: Classification of pituitary adenomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Casar-Borota O, Oystese KA, Sundstrom M, et al. A high-throughput analysis of the IDH1(R132H) protein expression in pituitary adenomas. Pituitary. 2016;19(4):407-414 2. Buslei R, Strissel PL, Henke C, et al. Activation and regulation of endogenous retroviral genes in the human pituitary gland and related endocrine tumours. Neuropathol Appl Neurobiol. 2015;41(2):180-200 3. Zada G, Woodmansee WW, Ramkissoon S, et al. Atypical pituitary adenomas: incidence, clinical characteristics, and implications. J Neurosurg. 2011;114:336-344 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

LHPED 62999 Luteinizing Hormone (LH), Pediatrics, Serum

Clinical Information: Luteinizing hormone (LH) is a glycoprotein hormone consisting of 2 noncovalently bound subunits (alpha and beta). LH is produced by the anterior pituitary gland under regulation of the hypothalamic gonadotropin releasing hormone (GnRH) and feedback from gonadal steroid hormones. In children, LH, along with follicle-stimulating hormone (FSH), is used to diagnose precocious (early) and delayed puberty. Precocious puberty refers to the appearance of physical and hormonal signs of pubertal development at an earlier age than is considered normal (before 8 years of age in girls and 9 years of age in boys). Evaluation of precocious puberty includes measurement of LH and FSH to determine whether gonadotropins are increased in relation to chronologic age (gonadotropin-dependent) or whether sex steroid secretion is occurring independent of LH and FSH (gonadotropin-independent). In gonadotropin-dependent precocious puberty, basal LH levels are often elevated into the pubertal range and show a pubertal (heightened) response to GnRH stimulation. In gonadotropin-independent precocious puberty, the LH level is low at baseline and fails to respond to GnRH stimulation. Delayed puberty is defined clinically by the absence or incomplete development of secondary sexual characteristics by age 14 years in boys and by age 12 years in girls. Delayed puberty usually results from inadequate gonadal steroid secretion that, in turn, is most often caused by a defective gonadotropin secretion from the anterior pituitary, due to defective production of GnRH from the hypothalamus. Random measurements of LH and FSH, together with estradiol (girls) or testosterone

(boys), are useful to distinguish between primary and secondary causes of delayed puberty.

Useful For: Diagnosis of precocious puberty and delayed puberty in children

Interpretation: In young children, high levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), along with the development of secondary sexual characteristics at an unusually young age, are an indication of gonadotropin-dependent precocious puberty (also called central precocious puberty). Prepubertal levels of LH and FSH in children exhibiting some signs of pubertal changes may be an indication of gonadotropin-independent precocious puberty (also refer as precocious pseudopuberty). In precocious pseudopuberty the signs and symptoms are the result of elevated levels of estrogen in girls or testosterone in boys. In delayed puberty, LH and FSH levels can be normal or below what is expected for a youth within this age range. The test for LH response to gonadotropin releasing hormone in addition to other testing may help to diagnose the reason for the delayed puberty.

Reference Values:

Females
<1 year: <0.02-18.3 IU/L
1-8 years: <0.02-0.3 IU/L
9-10 years: <0.02-4.8 IU/L
11-13 years: <0.02-11.7 IU/L
14-17 years: <0.02-16.7 IU/L

Tanner Stages*
Stage I (1-8 years): <0.02-0.3 IU/L
Stage II: <0.02-4.1 IU/L
Stage III: 0.6-7.2 IU/L
Stage IV-V: 0.9-13.3 IU/L
*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African-American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

Males
<1 year: <0.02-5.0 IU/L
1-8 years: <0.02-0.5 IU/L
9-10 years: <0.02-3.6 IU/L
11-13 years: 0.1-5.7 IU/L
14-17 years: 0.8-8.7 IU/L

Tanner Stages*
Stage I (1-8 years): <0.02-0.5 IU/L
Stage II: 0.03-3.7 IU/L
Stage III: 0.09-4.2 IU/L
Stage IV-V: 1.3-9.8 IU/L
*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

Clinical References: 1. Jameson JL, ed. Reproductive Endocrinology. In: Harrison's Endocrinology. 2nd ed. McGraw-Hill. 2010;144-241 2. Wei C, Davis N, Honour J, Crowne E: The investigation of children and adolescents with abnormalities of pubertal timing. Ann Clin Biochem. 2017 Jan;54(1):20-32

LH
602752

Luteinizing Hormone (LH), Serum

Clinical Information: Luteinizing hormone (LH) is a glycoprotein hormone consisting of 2 noncovalently bound subunits (alpha and beta). The alpha subunit of LH, follicle-stimulating hormone (FSH), thyrotropin (formerly known as thyroid-stimulating hormone), and human chorionic gonadotropin (hCG) are identical and contain 92 amino acids. The beta subunits of these hormones vary and confer the hormones' specificity. LH has a beta subunit of 121 amino acids and is responsible for interaction with the LH receptor. This beta subunit contains the same amino acids in sequence as the beta subunit of hCG, and both stimulate the same receptor; however, the hCG-beta subunit contains an additional 24 amino acids, and the hormones differ in the composition of their sugar moieties. Gonadotropin-releasing hormone from the hypothalamus controls the secretion of the gonadotropins, FSH, and LH, from the anterior pituitary. In both male and female populations, LH is essential for reproduction. In girls and women, the menstrual cycle is divided by a midcycle surge of both LH and FSH into a follicular phase and a luteal phase. This "LH surge" triggers ovulation thereby not only releasing the egg but also initiating the conversion of the residual follicle into a corpus luteum that, in turn, produces progesterone to prepare the endometrium for a possible implantation. LH is necessary to maintain luteal function for the first 2 weeks. In case of pregnancy, luteal function will be further maintained by the action of hCG (a hormone very similar to LH) from the newly established pregnancy. LH supports thecal cells in the ovary that provide androgens and hormonal precursors for estradiol production. LH in boys and men acts on testicular interstitial cells of Leydig to cause increased synthesis of testosterone.

Useful For: An adjunct in the evaluation of menstrual irregularities Evaluating patients with suspected hypogonadism Predicting ovulation Evaluating infertility Diagnosing pituitary disorders

Interpretation: In both male and female patients, primary hypogonadism results in an elevation of basal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Postmenopausal LH levels are generally above 40 IU/L. FSH and LH are generally elevated in: -Primary gonadal failure -Complete testicular feminization syndrome -Precocious puberty (either idiopathic or secondary to a central nervous system lesion) In female patients: -Menopause -Primary ovarian hypodysfunction -Polycystic ovary disease In male patients: -Primary hypogonadism LH is decreased in: -Primary ovarian hyperfunction in female patients -Primary hypergonadism in male patients FSH and LH are both decreased in failure of the pituitary or hypothalamus.

Reference Values:

Males
< or =4 weeks: Not established
>1 month-< or =12 months: < or =0.4 IU/L
>12 months-< or =6 years: < or =1.3 IU/L
>6-< or =11 years: < or =1.4 IU/L
>11-< or =14 years: 0.1-7.8 IU/L
>14-< or =18 years: 1.3-9.8 IU/L
>18 years: 1.3-9.6 IU/L

Females
< or =4 weeks: Not established
>1-< or =12 months: < or =0.4 IU/L
>12 months-< or =6 years: < or =0.5 IU/L
>6-< or =11 years: < or =3.1 IU/L
>11-< or =14 years: < or =11.9 IU/L
>14-< or =18 years: 0.5-41.7 IU/L

Premenopausal:
Follicular: 1.9-14.6 IU/L

Midcycle: 12.2-118.0 IU/L
Luteal: 0.7-12.9 IU/L
Postmenopausal: 5.3-65.4 IU/L

Clinical References: 1. Kaplan LA, Pesce AJ. The gonads. In: Kazmierczak SC, ed. Clinical Chemistry: Theory, Analysis, and Correlation. 3rd ed. Mosby-Year Book, Inc; 1996:894 2. Dumesic DA. Hyperandrogenic anovulation: a new view of polycystic ovary syndrome. Postgrad Ob Gyn. 1995;15:1-5 3. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

SLYME
602732

Lyme Antibody Modified 2-Tier with Reflex, Serum

Clinical Information: Lyme disease (LD) is caused by infection with a member of the Borrelia burgdorferi sensu lato complex, which includes B burgdorferi sensu stricto (herein referred to as B burgdorferi), Borrelia afzelii, and Borrelia garinii. Among these species, B burgdorferi is the most frequent cause of LD in North America. These tick-borne spirochetes are transmitted to humans through the bite of Ixodes species ticks. Endemic areas for LD in the United States correspond with the distribution of 2 tick species, Ixodes scapularis (Northeastern and Upper Midwestern US) and Ixodes pacificus (West Coast US). Transmission of LD-associated Borrelia requires at least 36 hours of tick attachment. Approximately 80% of infected individuals will develop a unique expanding skin lesion with a central zone of clearing, referred to as erythema migrans (EM; stage 1). In the absence of treatment, patients may progress to early disseminated disease (stage 2), which is characterized by neurologic manifestations (eg, meningitis, cranial neuropathy, radiculoneuropathy) and is often associated with B garinii infection. Patients with late LD often present with intermittent or persistent arthralgia, most often associated with B burgdorferi infection, or with acrodermatitis chronica atrophicans (ACA), typically due to infection with B afzelii. Diagnosis of LD is currently based on either the standard or modified 2-tiered serologic testing algorithm (STTTA or MTTTA, respectively). For the STTTA, see LYME / Lyme Disease Serology, Serum. The MTTTA starts with an initial enzyme immunoassay (EIA) screen for detection of total antibodies against the Borrelia Vlse/pepC10 proteins. Samples that are screen positive or equivocal by this first tier EIA are subsequently reflexed for supplemental assessment using 2 separate EIAs for detection of IgM and IgG antibodies against B burgdorferi whole cell sonicate material. Importantly, while serologic assessment for LD may be negative in the early weeks following infection, over 90% of patients with later stages of infection are seropositive by serology, which remains the diagnostic method of choice for this disease.

Useful For: Diagnosis of Lyme disease This test should not be used as a screening procedure for the general population.

Interpretation:

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Theel ES. The past, present and (possible) future of serologic testing for Lyme disease. J Clin Microbiol. 2016;54(5):1191-1196. doi:10.1128/JCM.03394-15 2. Dattwyler RJ. Lyme borreliosis: An overview of clinical manifestations. Lab Med. 1990;21:290-292 3. Schwan TG, Burgdorfer W, Rosa PA. Borrelia. In: Murray PR, ed. Manual of Clinical Microbiology. 7th ed. ASM Press; 1999:746-758 4. Centers for Disease Control and Prevention (CDC). Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep. 1995;44(31):590-591

LNBAB
63502

Lyme Central Nervous System Infection IgG with Antibody Index Reflex, Serum and Spinal Fluid

Clinical Information: Lyme disease is a multisystem and multistage tick-transmitted infection caused by spirochetal bacteria in the Borrelia burgdorferi sensu lato (Bbsl) complex. Nearly all human infections are caused by 3 Bbsl species; B burgdorferi sensu stricto (hereafter referred to as B burgdorferi) is the primary cause of Lyme disease in North America, while Borrelia afzelii and Borrelia garinii are the primary causes of Lyme disease in Europe and parts of Asia. Lyme disease is the most commonly reported tick-borne infection in North America and Europe, causing an estimated 300,000 cases in the United States each year and 85,000 cases in Europe. The clinical features of Lyme disease are broad and may be confused with various immune and inflammatory disorders. The classic presenting sign of early localized Lyme disease caused by B burgdorferi is erythema migrans, which occurs in approximately 80% of individuals. Other early signs and symptoms include malaise, headache, fever, lymphadenopathy, and myalgia. Arthritis, cardiac disease, and neurological disease may be later stage manifestations. Neuroinvasive Lyme disease (NLD) can affect either the peripheral or central nervous system, with patients classically presenting with the triad of lymphocytic meningitis, cranial neuropathy (especially facial nerve palsy) and radiculoneuritis, which can affect the motor or sensory nerves, or both. These symptoms can occur in any combination or alone. Some patients may present with Bannwarth syndrome, which includes painful radiculoneuritis with variable motor weakness. NLD should be considered in individuals presenting with appropriate symptoms who have had exposure to ticks in a Lyme endemic region of the United States, Europe, or Asia. Patients meeting these criteria should be evaluated for the presence of anti-Bbsl antibodies in serum using the standard 2-tiered testing algorithm (LYME / Lyme Disease Serology, Serum) as recommended by the Centers for Disease Control and Prevention. Briefly, the LYME test includes testing of serum specimens by an anti-Bbsl antibody enzyme-linked immunosorbent assay, followed by supplemental testing of all reactive samples using an immunoblot or western blot for detection of IgM- and IgG-class antibodies to Bbsl. Notably, the majority of patients with NLD will be seropositive in serum. Therefore, it is recommended that all patients tested by this assay also have LYME / Lyme Disease Serology, Serum performed. Results from these assays, alongside appropriate exposure history and clinical presentation, may be used to establish a diagnosis of NLD. Spinal fluid (CSF) should not be tested for the presence of antibodies to Bbsl using the current 2-tiered testing algorithm as there are no interpretive criteria for assessment of anti-Bbsl IgM and IgG immunoblot banding patterns in CSF. Additionally, while the presence of antibodies to Bbsl in CSF may be due to true intrathecal antibody synthesis, thus indicating central nervous system (CNS) infection, antibodies may alternatively be present as a result of passive diffusion through the blood-brain barrier or due to blood contamination of CSF during a traumatic lumbar puncture. The Lyme CNS infection antibody index is performed as a reflex and quantitatively measures the level of anti-Bbsl antibodies in CSF and serum, ideally collected within 24 hours of each other, and normalizes those levels to total IgG and albumin in both specimen sources. A positive Lyme CNS AI indicates true intrathecal antibody synthesis of antibodies to Bbsl, which alongside clinical and exposure history can be used to establish a diagnosis of NLD.

Useful For: Aiding in the diagnosis of neuroinvasive Lyme disease or neuroborreliosis due to Borrelia species associated with Lyme disease (eg, Borrelia burgdorferi, Borrelia garinii, Borrelia afzelli)

Interpretation: Negative: No antibodies to Lyme disease causing Borrelia species detected in spinal fluid. A negative result in a patient with appropriate exposure history and symptoms consistent with neuroinvasive Lyme disease should not be used to exclude infection. Testing for antibodies to Lyme disease-causing Borrelia species in serum should be performed. Reactive: Supplemental testing to determine a Lyme central nervous system antibody index has been ordered. Diagnosis of neuroinvasive Lyme disease should not be established solely based on a reactive screening result.

Reference Values:

Negative

Reference values apply to all ages.

Clinical References: 1. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006;43(9):1089-1134 2. Halperin JJ, Shapiro ED, Logigian E, et al. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2007;69(1):91-102 3. Halperin JJ. Neuroborreliosis: J Neurol. 2017;264(6):1292-1297 4. Theel ES: The past, present and (possible) future of serologic testing for Lyme disease. J Clin Microbiol. 2016;54(5):1191-1196 5. Theel ES, Aguero-Rosenfeld ME, Pritt B, Adem PV, Wormser GP. Limitations and confusing aspects of diagnostic testing for neurologic Lyme disease in the United States. J Clin Microbiol. 2019;57(1): e01406-18. doi:10.1128/JCM.01406-18

LNBAI
63249

Lyme Central Nervous System Infection IgG, Antibody Index, Spinal Fluid

Clinical Information: Lyme disease is a multisystem and multistage tick-transmitted infection caused by spirochetal bacteria in the Borrelia burgdorferi sensu lato (Bbsl) complex. Nearly all human infections are caused by 3 Bbsl species; B burgdorferi sensu stricto (hereafter referred to as B burgdorferi) is the primary cause of Lyme disease in North America, while Borrelia afzelii and Borrelia garinii are the primary causes of Lyme disease in Europe and parts of Asia. Lyme disease is the most commonly reported tick-borne infection in North America and Europe, causing an estimated 300,000 cases in the United States each year and 85,000 cases in Europe. The clinical features of Lyme disease are broad and may be confused with various immune and inflammatory disorders. The classic presenting sign of early localized Lyme disease caused by B burgdorferi is erythema migrans, which occurs in approximately 80% of individuals. Other early signs and symptoms include malaise, headache, fever, lymphadenopathy, and myalgia. Arthritis, cardiac disease, and neurological disease may be later stage manifestations. Neuroinvasive Lyme disease (NLD) can affect either the peripheral or central nervous system, with patients classically presenting with the triad of lymphocytic meningitis, cranial neuropathy (especially facial nerve palsy) and radiculoneuritis, which can affect the motor or sensory nerves, or both. These symptoms can occur in any combination or alone. Some patients may present with Bannwarth syndrome, which includes painful radiculoneuritis with variable motor weakness. Neuroinvasive Lyme disease should be considered in individuals presenting with appropriate symptoms who have had exposure to ticks in a Lyme endemic region of the United States, Europe, or Asia. Patients meeting these criteria should be evaluated for the presence of anti-Bbsl antibodies in serum using the standard 2-tiered testing algorithm (LYME / Lyme Disease Serology, Serum) as recommended by the Centers for Disease Control and Prevention. Briefly, the LYME test includes testing of serum specimens by an anti-Bbsl antibody enzyme-linked immunosorbent assay, followed by supplemental testing of all reactive samples using an immunoblot or western blot for detection of IgM- and IgG- class antibodies to Bbsl. Notably, the majority of patients with NLD, will be seropositive in serum. Therefore, it is recommended that all patients tested by this assay also have LYME / Lyme Disease Serology, Serum performed. Results from these assays, alongside appropriate exposure history and clinical presentation, may be used to establish a diagnosis of NLD. Cerebrospinal fluid (CSF) may also be tested for the presence of antibodies to Bbsl using the current 2-tiered testing algorithm as defined for serum samples. However, there are currently no interpretive criteria for assessment of anti-Bbsl IgM and IgG immunoblot banding patterns in CSF. Additionally, while the presence of antibodies to Bbsl in CSF may be due to true intrathecal antibody synthesis, thus indicating central nervous system (CNS) infection, antibodies may alternatively be present as a result of passive diffusion through the blood-brain barrier or due to blood contamination of CSF during a traumatic lumbar puncture. The Lyme CNS antibody index quantitatively measures the level of anti-Bbsl antibodies in CSF and serum, ideally collected within 24 hours of each other, and normalizes

those levels to total IgG and albumin in both specimen sources. A positive Lyme CNS AI indicates true intrathecal antibody synthesis of antibodies to Bbsl, which alongside clinical and exposure history can be used to establish a diagnosis of NLD.

Useful For: Providing antibody index information to aid in the diagnosis of neuroinvasive Lyme disease or neuroborreliosis due to Borrelia species associated with Lyme disease (eg, Borrelia burgdorferi, Borrelia garinii, Borrelia afzelli)

Interpretation: Negative (Lyme CNS antibody index [AI] 0.6 to <1.3): Results indicate lack of intrathecal antibody synthesis to Lyme disease associated Borrelia species. This suggests the absence of neuroinvasive Lyme disease. The initial screen reactive result may be due to anti-Borrelia species antibodies present in the cerebrospinal fluid (CSF) due to increased permeability of the blood-brain barrier or transient introduction during lumbar puncture. Equivocal (Lyme CNS AI 1.3 to 1.5): Low level of intrathecal antibody synthesis to Lyme disease associated Borrelia species detected. Results should be correlated with exposure history and clinical presentation to establish a diagnosis of neuroinvasive Lyme disease. Positive (Lyme CNS AI >1.5): Results indicate the presence of intrathecal antibody synthesis to Lyme disease associated Borrelia species, suggesting neuroinvasive Lyme disease. Results should be correlated with exposure history and clinical presentation to establish the diagnosis. Invalid (Lyme CNS AI <0.6): Result is due to abnormally elevated total IgG levels in CSF. This may be due to passive diffusion through the blood-brain barrier or contamination of the CSF with blood during a traumatic lumbar puncture. Repeat testing may be considered

Reference Values:
Only orderable as part of a profile. For more information see LNBAB / Lyme Central Nervous System Infection IgG with Antibody Index Reflex, Serum and Spinal Fluid.

0.6-1.2

Clinical References: 1. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006;43(9):1089-1134 2. Halperin JJ, Shapiro ED, Logigian E, et al. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2007;69(1):91-102 3. Halperin JJ. Neuroborreliosis: J Neurol. 2017;264(6):1292-1297 4. Theel ES. The Past, present and (possible) future of serologic testing for Lyme disease. J Clin Microbiol. 2016;54(5):1191-1196 5. Theel ES, Aguero-Rosenfeld ME, Pritt B, Adem PV, Wormser GP. Limitations and confusing aspects of diagnostic testing for neurologic Lyme disease in the United States. J Clin Microbiol. 2019;57(1): e01406-18. doi:10.1128/JCM.01406-18

LYWB
9535

Lyme Disease Antibody, Immunoblot, Serum

Clinical Information: Lyme disease is caused by the spirochete Borrelia burgdorferi. The spirochete is transmitted to humans through the bite of Ixodes species ticks. Endemic areas for Lyme disease in the United States correspond with the distribution of 2 tick species, Ixodes dammini (Northeastern and upper Midwestern US) and Ixodes pacificus (West Coast US). In Europe, Ixodes ricinus transmits the spirochete. Lyme disease exhibits a variety of symptoms that may be confused with immune and inflammatory disorders. Inflammation around the tick bite causes skin lesions. Erythema chronicum migrans (ECM), a unique expanding skin lesion with central clearing, which results in a ring-like appearance, is the first stage of the disease. Any of the following clinical manifestations may be present in patients with Lyme disease: arthritis, neurological or cardiac disease, or skin lesions. Neurologic and cardiac symptoms may appear with stage 2 and arthritic symptoms with stage 3 of

Lyme disease. In some cases, a definitive distinction between stages is not always seen. Further, secondary symptoms may occur even though the patient does not recall having a tick bite or a rash. The Second National Conference on the Serologic Diagnosis of Lyme Disease (1994) recommended that laboratories use a 2-test approach for the serologic diagnosis of Lyme disease. Accordingly, specimens are first tested by the more sensitive enzyme immunoassay (EIA). An immunoblot assay is used to supplement positive or equivocal Lyme EIA results. An immunoblot identifies the specific proteins to which the patient's antibodies bind. Although there are no proteins that specifically diagnose B burgdorferi infection, the number of proteins recognized in the immunoblot assay is correlated with diagnosis. Recently, the Centers for Disease Control and Prevention and US Food and Drug Administration approved the use of a modified two-tiered testing algorithm for diagnosis of Lyme disease (see SLYME / Lyme Antibody Modified 2-Tier with Reflex, Serum). Culture or polymerase chain reaction (PCR) of skin biopsies obtained near the margins of ECM are frequently positive. In late (chronic) stages of the disease, serology is often positive and the diagnostic method of choice. PCR testing also may be useful in these late stages if performed on synovial or cerebrospinal fluid. Diagnosis of neuroinvasive Lyme disease (ie, neuroborreliosis) can be achieved by determining the Lyme antibody index value using paired serum and cerebrospinal fluid samples (LNBAB / Lyme Central Nervous System Infection IgG with Antibody Index Reflex, Serum and Spinal Fluid).

Useful For: Aiding in the diagnosis of systemic Lyme disease This test should not be used as a screening assay.

Interpretation: Per Centers for Disease Control and Prevention criteria, the Lyme IgG Immunoblot is interpreted as positive if IgG-class antibodies are detected to greater than or equal to 5 Borrelia burgdorferi proteins, and the Lyme IgM Immunoblot is interpreted as positive if IgM-class antibodies are detected to greater than or equal to 2 B burgdorferi proteins. Immunoblot patterns not meeting these criteria should not be interpreted as positive. Epitopes from certain B burgdorferi proteins (eg, p41) are conserved across other bacteria, which may lead to the detection of IgM- and/or IgG-class antibodies on the Lyme disease immunoblots in patients without Lyme disease. Immunoblot should only be ordered on specimens that are positive or equivocal by a US Food and Drug Administration-licensed Lyme disease antibody screening test (eg, enzyme immunoassay). Results of the Lyme IgM immunoblot should not be considered in patients with greater than or equal to 30 days of symptoms. Result Interpretation IgG and IgM negative Specific serologic response to B burgdorferi infection is not detected but cannot rule out early infection during which low or undetectable antibody levels to B burgdorferi may be present. If clinically indicated, a new serum specimen should be submitted in 7-14 days. IgG positive and IgM negative Consistent with infection with B burgdorferi at some time in the past IgG and IgM positive Consistent with active or previous infection for B burgdorferi. IgM blot criteria is of diagnostic utility only during the first 4 weeks of early Lyme disease. IgG negative and IgM positive IgM-class antibodies to B burgdorferi (Lyme disease) detected. Results are consistent with acute or recent infection with B burgdorferi. Testing of a new specimen collected in 7-14 days to demonstrate IgG seroconversion may be considered to confirm infection if the diagnosis is in doubt. IgM immunoblot results should only be considered as indicative of recent infection in patients presenting within 30 days of symptom onset. Consideration of IgM immunoblot results in patients with symptoms lasting >30 days is discouraged due to the risk of false positive IgM immunoblot results and/or prolonged IgM seropositivity following disease resolution. IgG and/or IgM uninterpretable Immunoblot invalid due to blurring or indistinct reactivity. Due to an invalid Lyme IgG immunoblot, an interpretation cannot be provided. Please submit a new specimen.

Reference Values:

IgG: Negative
IgM: Negative
Reference values apply to all ages

Clinical References: Theel ES. The past, present and (possible) future of serologic testing for Lyme disease. J Clin Microbiol. 2016;54(5):1191-1196

LYME
9129

Lyme Disease Serology, Serum

Clinical Information: Lyme disease (LD) is caused by infection with a member of the Borrelia burgdorferi sensu lato complex, which includes B burgdorferi sensu stricto (herein referred to as B burgdorferi), Borrelia afzelii, and Borrelia garinii. Among these species, B burgdorferi is the most frequent cause of LD in North America. These tick-borne spirochetes are transmitted to humans through the bite of Ixodes species ticks. Endemic areas for Lyme disease in the United States correspond with the distribution of 2 tick species, Ixodes scapularis (Northeastern and upper Midwestern US) and Ixodes pacificus (West Coast US). Transmission of LD-associated Borrelia requires at least 36 hours of tick attachment. Approximately 80% of infected individuals will develop a unique expanding skin lesion with a central zone of clearing, referred to as erythema migrans (EM; stage 1). In the absence of treatment, patients may progress to early disseminated disease (stage 2), which is characterized by neurologic manifestations (eg, meningitis, cranial neuropathy, radiculoneuropathy) and is often associated with B garinii infection. Patients with late LD often present with intermittent or persistent arthralgia, most often associated with B burgdorferi infection, or with acrodermatitis chronica atrophicans, typically due to infection with B afzelii. Diagnosis of LD is currently based on a 2-tiered serologic testing algorithm, as recommended by the Centers for Disease Control and Prevention, and involves an initial screening assay for detection of antibodies to LD-causing Borrelia species. Samples that are screen positive or equivocal are subsequently reflexed for supplemental assessment using a B burgdorferi immunoblot for detection of IgM- and IgG-class antibodies to specific B burgdorferi antigens. Importantly, while serologic assessment for LD may be negative in the early weeks following infection, over 90% of patients with later stages of infection are seropositive by serology, which remains the diagnostic method of choice for this disease.

Useful For: Diagnosing Lyme disease This test should not be used as a screening procedure for the general population. This test should not be used for treatment monitoring.

Interpretation: Negative: No evidence of antibodies to Borrelia burgdorferi detected. False-negative results may occur in recently infected patients (< or =2 weeks) due to low or undetectable antibody levels to B burgdorferi. If recent exposure is suspected, a second specimen should be collected and tested in 2 to 4 weeks. Equivocal: Not diagnostic. Supplemental testing by immunoblot has been ordered by reflex. Positive: Not diagnostic. Supplemental testing by immunoblot has been ordered by reflex.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Theel ES. The past, present and (possible) future of serologic testing for Lyme disease. J Clin Microbiol. 2016;54(5):1191-1196. doi:10.1128/JCM.03394-15 2. Dattwyler RJ. Lyme borreliosis: an overview of clinical manifestations. Lab Med. 1990;21:290-292 3. Schwan TG, Burgdorfer W, Rosa PA. Borrelia. In: Murray PR, eds. Manual of Clinical Microbiology. 7th ed. ASM Press; 1999:746-758 4. Center for Disease Control and Prevention: Recommendation for test performance and interpretation from second national conference on serological diagnosis of Lyme disease. MMWR Morb Mortal Wkly Rep. 1996;45:481-484

PBORB
87973

Lyme Disease, Molecular Detection, PCR, Blood

Clinical Information: Lyme disease is a multisystem and multistage tick-transmitted infection caused by spirochetal bacteria in the Borrelia burgdorferi sensu lato (Bbsl) complex.(1) Nearly all human infections are caused by 3 Bbsl species; B burgdorferi sensu stricto (hereafter referred to as B burgdorferi) is the primary cause of Lyme disease in North America, while Borrelia afzelii and Borrelia

garinii are the primary causes of Lyme disease in Europe. In 2012, Borrelia mayonii was identified as a less common cause of Lyme disease in the upper Midwestern United States.(2,3) This organism has only been detected in patients with exposure to ticks in Minnesota and Wisconsin and has not been detected in over 10,000 specimens from patients in other states, including regions of the northeast where Lyme disease is endemic. Lyme disease is the most commonly reported tick-borne infection in Europe and North America, causing an estimated 300,000 cases in the United States each year and 85,000 cases in Europe.(4,5) The clinical features of Lyme disease are broad and may be confused with various immune and inflammatory disorders. The classic presenting sign of early localized Lyme disease caused by B burgdorferi is erythema migrans (EM), which occurs in approximately 80% of individuals. Other early signs and symptoms include malaise, headache, fever, lymphadenopathy, and myalgia. Arthritis, neurological disease, and cardiac disease may be later stage manifestations. EM has also been seen in patients with B mayonii infection, but diffuse rashes are more commonly reported.(2) The chronic skin condition, acrodermatitis chronicum atrophicans, is also associated with B afzelii infection. The presence of EM in the appropriate clinical setting is considered diagnostic for Lyme disease; no confirmatory laboratory testing is needed. In the absence of a characteristic EM lesion, serologic testing is the diagnostic method of choice for Lyme disease.(6) However, serology may not be positive until 1 to 2 weeks after onset of symptoms and may show decreased sensitivity for detection of infection with B mayonii. Therefore, detection of Bbsl DNA using polymerase chain reaction (PCR) may be a useful adjunct to serologic testing for detection of acute disease. PCR has shown utility for detection of Borrelia DNA from skin biopsies of Lyme-associated rashes and can be used to detect Borrelia DNA from synovial fluid and synovium biopsies. Less commonly, Borrelia DNA can be detected in cerebrospinal fluid and blood.(7) In general, blood is not the preferred source for detection of Bbsl DNA by PCR, although it may have increased utility for detection of B mayonii, due to the higher levels of observed peripheral spirochetemia with this organism.(2) Lyme PCR should always be performed in conjunction with US Food and Drug Administration approved serologic tests, and results should be correlated with serologic and epidemiologic data and clinical presentation of the patient.(8) The Mayo Clinic Lyme PCR test detects and differentiates the main causes of Lyme disease in North America (B burgdorferi and B mayonii) and Europe (B afzelii and B garinii).(2,7)

Useful For: Supporting the diagnosis of Lyme disease in conjunction with serologic testing This test should not be used to screen asymptomatic patients.

Interpretation: A positive result indicates the presence of DNA from Borrelia burgdorferi, Borrelia mayonii, Borrelia afzelii, or Borrelia garinii, the main agents of Lyme disease. A negative result indicates the absence of detectable target DNA in the specimen. Due to the diagnostic sensitivity limitations of the polymerase chain reaction assay, a negative result does not preclude the presence of the organism or active Lyme disease.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. Lancet. 2012;379(9814):461-473 2. Pritt BS, Mead PS, Johnson, DK, et al. Identification of a novel pathogenic Borrelia species causing Lyme borreliosis with unusually high levels of spirochetemia: a descriptive study. Lancet Infect Dis. 2016;16(5):556-564 3. Pritt BS, Respicio-Kingry LB, Sloan LM, et al. Borrelia mayonii sp. nov., a member of the Borrelia burgdorferi sensu lato complex, detected in patients and ticks in the upper midwestern United States. Int J Sys Evol Microbiol. 2016;66(11):4878-4880 4. Hinckley AF, Connally NP, Meek JI, et al. Lyme disease testing by large commercial laboratories in the United States. Clin Infect Dis. 2014;59(5):676-681 5. Lindgren E, Jaenson TGT. Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation measures. World Health Organization; 2006 6. Centers for Disease Control and Prevention. Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep. 1995 Aug;44(31):590-591 7. Babady NE, Sloan LM, Vetter

EA, et al. Percent positive rate of Lyme real-time polymerase chain reaction in blood, cerebrospinal fluid, synovial fluid, and tissue. Diagn Microbiol Infect Dis. 2008;62(4):464-466 8. Centers for Disease Control and Prevention (CDC). Lyme disease-United States, 1995. MMWR Morb Mortal Wkly Rep. 1996;45(23):481-484

LYMPV
618310

Lyme Disease, Molecular Detection, PCR, Varies

Clinical Information: Lyme disease is a multisystem and multistage tick-transmitted infection caused by spirochetal bacteria in the Borrelia burgdorferi sensu lato (Bbsl) complex.(1) Nearly all human infections are caused by 3 Bbsl species; B burgdorferi sensu stricto (hereafter referred to as B burgdorferi) is the primary cause of Lyme disease in North America, while Borrelia afzelii and Borrelia garinii are the primary causes of Lyme disease in Europe. In 2012, Borrelia mayonii was identified as a less common cause of Lyme disease in the upper Midwestern United States.(2,3) This organism has only been detected in patients with exposure to ticks in Minnesota and Wisconsin and has not been detected in over 10,000 specimens from patients in other states, including regions of northeast where Lyme disease is endemic. Lyme disease is the most commonly reported tick-borne infection in Europe and North America, causing an estimated 300,000 cases in the United States each year and 85,000 cases in Europe.(4,5) The clinical features of Lyme disease are broad and may be confused with various immune and inflammatory disorders. The classic presenting sign of early localized Lyme disease caused by B burgdorferi is erythema migrans (EM), which occurs in approximately 80% of individuals. Other early signs and symptoms include malaise, headache, fever, lymphadenopathy, and myalgia. Arthritis, neurological disease, and cardiac disease may be later stage manifestations. EM has also been seen in patients with B mayonii infection, but diffuse rashes are more commonly reported.(2) The chronic skin condition, acrodermatitis chronicum atrophicans, is also associated with B afzelii infection. The presence of EM in the appropriate clinical setting is considered diagnostic for Lyme disease; no confirmatory laboratory testing is needed. In the absence of a characteristic EM lesion, serologic testing is the diagnostic method of choice for Lyme disease.(6) However, serology may not be positive until 1 to 2 weeks after onset of symptoms and may show decreased sensitivity for detection of infection with B mayonii. Therefore, detection of Bbsl DNA using polymerase chain reaction (PCR) may be a useful adjunct to serologic testing for detection of acute disease. PCR has shown utility for detection of Borrelia DNA from skin biopsies of Lyme-associated rashes and can be used to detect Borrelia DNA from synovial fluid and synovium biopsies. Less commonly, Borrelia DNA can be detected in cerebrospinal fluid.(7) Lyme PCR should always be performed in conjunction with US Food and Drug Administration-approved serologic tests, and the results should be correlated with serologic and epidemiologic data and clinical presentation of the patient.(8) The Mayo Clinic Lyme PCR test detects and differentiates the main causes of Lyme disease in North America (B burgdorferi and B mayonii) and Europe (B afzelii and B garinii).(2,7)

Useful For: Supporting the diagnosis of Lyme disease in conjunction with serologic testing Specific indications including testing skin biopsies when a rash lesion is not characteristic of erythema migrans and testing synovial fluid or synovium to support the diagnosis of Lyme arthritis This test should not be used to screen asymptomatic patients.

Interpretation: A positive result indicates the presence of DNA from Borrelia burgdorferi, Borrelia mayonii, Borrelia afzelii, or Borrelia garinii, the main agents of Lyme disease. A negative result indicates the absence of detectable target DNA in the specimen. Due to the clinical sensitivity limitations of the polymerase chain reaction assay, a negative result does not preclude the presence of the organism or active Lyme disease.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. Lancet. 2012;379(9814):461-473 2. Pritt BS, Mead PS, Johnson DKH, et al. Identification of a novel pathogenic Borrelia species causing Lyme borreliosis with unusually high levels of spirochetaemia: a descriptive study. Lancet Infect Dis. 2016;16(5):556-564 3. Pritt BS, Respicio-Kingry LB, Sloan LM, et al. Borrelia mayonii sp. nov., a member of the Borrelia burgdorferi sensu lato complex, detected in patients and ticks in the upper midwestern United States. Int J Sys Evol Microbiol. 2016;66(11):4878-4880 4. Hinckley AF, Connally NP, Meek JI, et al. Lyme disease testing by large commercial laboratories in the United States. Clin Infect Dis. 2014;59(5):676-681 5. Lindgren E, Jaenson TGT. Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation measures. World Health Organization; 2006 6. Centers for Disease Control and Prevention (CDC). Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep. 1995;44(31):590-591 7. Babady NE, Sloan LM, Vetter EA, Patel R, Binnicker MJ. Percent positive rate of Lyme real-time polymerase chain reaction in blood, cerebrospinal fluid, synovial fluid, and tissue. Diagn Microbiol Infect Dis. 2008;62(4):464-466 8. Centers for Disease Control and Prevention (CDC). Lyme disease--United States, 1995. MMWR Morb Mortal Wkly Rep. 1996;45(23):481-484

TLYME
608104

Lyme IgM and IgG, Whole Cell Sonicate, ELISA, Serum

Clinical Information: Lyme disease (LD) is caused by infection with a member of the Borrelia burgdorferi sensu lato complex, which includes B burgdorferi sensu stricto (herein referred to as B burgdorferi), Borrelia afzelii, and Borrelia garinii. Among these species, B burgdorferi is the most frequent cause of LD in North America. These tick-borne spirochetes are transmitted to humans through the bite of Ixodes species ticks. Endemic areas for LD in the United States correspond with the distribution of 2 tick species, Ixodes scapularis (Northeastern and Upper Midwestern US) and Ixodes pacificus (West Coast US). Transmission of LD-associated Borrelia requires at least 36 hours of tick attachment. Approximately 80% of infected individuals will develop a unique expanding skin lesion with a central zone of clearing, referred to as erythema migrans (EM; stage 1). In the absence of treatment, patients may progress to early disseminated disease (stage 2), which is characterized by neurologic manifestations (eg, meningitis, cranial neuropathy, radiculoneuropathy) and is often associated with B garinii infection. Patients with late LD often present with intermittent or persistent arthralgia, most often associated with B burgdorferi infection, or with acrodermatitis chronica atrophicans), typically due to infection with B afzelii. Diagnosis of LD is currently based on either the standard or modified 2-tiered serologic testing algorithm (STTTA or MTTTA, respectively). For the STTTA, see LYME / Lyme Disease Serology, Serum. The MTTTA starts with an initial enzyme immunoassay (EIA) screen for detection of total antibodies against the Borrelia Vlse/pepC10 proteins. Samples that screen positive or equivocal by this first tier EIA are subsequently reflexed for supplemental assessment using 2 separate EIAs for detection of IgM and IgG antibodies against B burgdorferi whole cell sonicate material. Importantly, while serologic assessment for LD may be negative in the early weeks following infection, over 90% of patients with later stages of infection are seropositive by serology, which remains the diagnostic method of choice for this disease.

Useful For: Supplemental testing for samples with positive or equivocal first-tier test results for antibodies to Lyme disease causing Borrelia species This test should not be used as a screening procedure for the general population.

Interpretation: Tier 1 Tier 2 IgM result Tier 2 IgG result Interpretation Positive/equivocal Negative Negative Negative for antibodies to the Borrelia (Borreliella) species causing Lyme disease. Antibodies detected by the first-tier test were not confirmed. Negative results may occur in recently infected (< or =14 days) patients. If recent infection is suspected, repeat testing on a new sample collected in 7 to 14 days is recommended. Positive/equivocal Positive/equivocal Negative IgM-class antibodies to the Borrelia (Borreliella) species causing Lyme disease were detected, suggesting acute or recent infection. IgM enzyme immunoassay (EIA) results should only be considered as indicative of recent infections in

patients presenting within 30 days of symptom onset. Consideration of IgM EIA results in patients with symptoms lasting more than 30 days is discouraged due to the risk of false-positive IgM results and/or prolonged IgM seropositivity following disease resolution. If both first and second tier IgM results are equivocal consider repeat testing in 7 to 14 days if clinically warranted. Positive/equivocal Negative Positive/equivocal IgG-class antibodies to the Borrelia (Borreliella) species causing Lyme disease were detected, suggesting infection in the recent or remote past. IgG-class antibodies may remain detectable for months to years following resolution of infection. Results should not be used to monitor or establish adequate response to therapy. Response to therapy is confirmed through resolution of clinical symptoms; additional laboratory testing should not be performed. Positive/equivocal Positive/equivocal Positive/equivocal IgM and IgG-class antibodies to the Borrelia (Borreliella) species causing Lyme disease were detected, suggesting infection in the recent or remote past. Antibodies may remain detectable for months to years following resolution of infection. Results should not be used to monitor or establish adequate response to therapy. Response to therapy is confirmed through resolution of clinical symptoms; additional laboratory testing should not be performed. If both first and second tests are equivocal consider repeat testing in 7 to 14 days if clinically warranted. For specimens that did not have first tier testing performed at Mayo Clinic Laboratories, the results will also include the comment: "Interpretation assumes first tier Lyme disease causing Borrelia species antibody test was performed and resulted as positive or equivocal."

Reference Values:

Negative
Reference values apply to all ages.

Clinical References: 1. Theel ES: The past, present and (possible) future of serologic testing for Lyme disease. J Clin Microbiol. 2016 May;54(5):1191-1196. doi: 10.1128/JCM.03394-15 2. Dattwyler RJ: Lyme borreliosis: an overview of clinical manifestations. Lab Med. 1990 May;21(5):290-292. doi: 10.1093/labmed/21.5.290 3. Schwan TG, Burgdorfer W, Rosa PA: Borrelia. In: Murray PR, ed: Manual of Clinical Microbiology. 7th ed. ASM Press; 1999:746-758 4. Centers for Disease Control and Prevention (CDC): Recommendation for test performance and interpretation from second national conference on serological diagnosis of lyme disease. MMWR Morb Mortal Wkly Rep. 1996;45:481-484

PM3CX
606164

Lymph3Cx Assay, Primary Mediastinal Large B-cell Lymphoma and Diffuse Large B-cell Lymphoma, mRNA Gene Expression, NanoString, Tissue

Clinical Information: Primary mediastinal large B-cell lymphoma (PMBCL) is recognized as a distinct entity in the World Health Organization (WHO) classification and accounts for approximately 2% to 3% of all non-Hodgkin lymphomas (NHL).(1) Currently, diagnosis relies on consensus of histopathology, clinical variables, and presentation (as it can present outside the mediastinum), giving rise to diagnostic inaccuracy in routine practice. This is complicated by recent studies that identified lymphomas sharing molecular and morphological features with PMBCL, yet without involvement in the mediastinum.(2) Since classification can impact therapeutic approach, the need has arisen for a more robust method to identify PMBCL vs diffuse large B-cell lymphoma (DLBCL). Gene expression profiling studies have demonstrated that PMBCL can be distinguished from subtypes of DLBCL based on gene expression signatures in fresh/frozen tissues,(3,4) which are often difficult to obtain in conventional clinic settings. Members of the Lymphoma/Leukemia Molecular Profiling Project have developed a robust and accurate molecular classification assay (Lymph3Cx) for the distinction of PMBCL from DLBCL subtypes based on gene expression measurements in clinically-available FFPE tissue,(5) which has been subsequently validated against this published data in the Molecular Diagnostics Arizona Lab. Research suggests that novel therapeutic approaches might have preferential benefit in PMBCL as compared to DLBCL.(6,7,8,9) The Lymph3Cx assay builds upon the previously described and validated Lymph2Cx assay.(4,10) The Lymph3Cx assay is a qualitative assay utilizing a

58-gene signature (45 endogenous targets and 13 housekeeping genes), reporting calculated scores to distinguish PMBCL from DLBCL.(5) After determination of PMBCL vs DLBCL status, the built-in Lymph2Cx assay then provides the cell-of-origin (COO) for samples determined to be DLBCL as previously described. DLBCL is the most common form of NHL, accounting for up to 30% of newly diagnosed cases in the United States. DLBCL is an aggressive (fast-growing) lymphoma caused by the uncontrollable growth and proliferation of B lymphocytes. It can arise in lymph nodes or outside of the lymphatic system in the gastrointestinal tract, testes, thyroid, skin, breast, bone, or brain. Although DLBCL is the most common form of NHL, there are distinct subtypes that may affect prognosis (how well patients will do with standard treatment) and treatment options. Since 2008, WHO classification of lymphoid neoplasms has recognized 2 distinct molecular subgroups of DLBCL: a germinal center B-cell (GCB) type, an activated B-cell (ABC) type, as well as a third group of cases that do not belong to either (unclassifiable). These were all originally grouped together based on shared morphology but can be distinctly separated based on their biology, particularly their gene expression pattern. According to a review of the 2016 revision of the WHO guidelines,(1) a better understanding of the molecular pathogenesis of these 2 subgroups has led to the investigation of more specific therapeutic strategies based on COO classification. Current data suggests that the ABC subtype of DLBCL has a poorer prognosis compared to the GCB subtype or unclassifiable cases; and that the ABC subtype may differentially respond to specific therapies.(11,12,13)

Useful For: Only indicated for formalin-fixed paraffin-embedded specimens from patients diagnosed with large B-cell lymphoma

Interpretation: Results of the consultation are reported in a formal pathology report that includes a description of ancillary test results and an interpretive comment.

Reference Values:
Not applicable

Clinical References: 1. Swerdlow SH, Campo E, Jaffe ES, et al. The 2016 Revision to the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-2390 2. Yuan J, Wright G, Rosenwald A, et al. Identification of primary mediastinal large B-cell lymphoma at nonmediastinal sites by gene expression profiling. Am J Surg Pathol. 2015;39(10):1322-1330 3. Savage KJ, Monti S, Kutok JL, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. Blood. 2003;102(12):3871-3879 4. Rosenwald A, Wright G, Leroy K, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med. 2003;198(6):851-862 5. Mottok A, Wright G, Rimsza L, et al. Molecular classification of primary mediastinal large B-cell lymphoma using routinely available tissue specimens. Blood. 2018;132(22):2401-2405 6. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med. 2013;368(15):1408-1416 7. Xu-Monette ZY, Zhou J, Young KH. PD-1 expression and clinical PD-1 blockade in B-cell lymphomas. Blood. 2018;131(1):68-83 8. Zinzani PL, Ribrag V, Moskowitz CH, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Blood. 2017;130(3):267-270 9. Scott DW, Wright GW, Williams PM, et al. Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. Blood. 2014;123(8):1214-1217 10. Robetorye RS, Ramsower CA, Rimsza LM, et al. Incorporation of digital gene expression profiling for cell-of-origin determination (Lymph2Cx testing) into the routine work-up of diffuse large B cell lymphoma. J Hematop. 2019;12(1):3-10. doi:10.1007/s12308-019-00344-0 11. Nowakowski GS, Chiappella A, Witzig TE, et al. Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-cell lymphoma: a phase II study. J Clin Oncol. 2015;33(3):251-257 12. Dunleavy K, Pittaluga S, Czuczman MS, et al. Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma. Blood. 2009;113(24):6069-6076 13. Thieblemont C, Briere J, Mounier N, et al. The germinal center/activated B-cell subclassification has a

prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. J Clin Oncol. 2011;29(31):4079-4087

LPA3P 62205 Lymphocyte Proliferation to Anti-CD3/Anti-CD28 and Anti-CD3/Interleukin-2 (IL-2), Flow Cytometry, Blood

Clinical Information: T-cell stimulation in vitro is used extensively in the diagnostic immunology arena for facilitating T-cell proliferation and evaluation of T-cell function in a variety of clinical contexts.(1,2) A widely used method for assessing lymphocyte proliferation has hitherto been the measurement of (3)H-thymidine incorporated into the DNA of proliferating cells. The disadvantages of the (3)H-thymidine method of lymphocyte proliferation are as follows: 1. The technique is cumbersome due to the use of radioactivity. 2. It does not distinguish between different cell populations responding to stimulation. 3. It does not provide any information on the contribution of apoptosis or cell death to the interpretation of the final result. Further, decreased lymphocyte proliferation could be due to several factors, including overall diminution of T-cell proliferation, or an apparent decrease in total lymphocyte proliferation due to T-cell lymphopenia and under-representation of T cells in the peripheral blood mononuclear cell pool. None of these can be distinguished by the thymidine uptake assay but can be assessed by flow cytometry, which uses antibodies to identify specific responder cell populations. Cell viability can also be measured within the same assay without requiring additional cell manipulation or specimen. While mitogens such as phytohemagglutinin activate T cells by binding to cell membrane glycoproteins, including the T-cell receptor (TCR)-CD3 complex, there are mitogenic or co-mitogenic antibodies, including those directed against the CD3 coreceptor that can stimulate T-cell proliferation. Typically, anti-CD3 antibodies provide an initial activation signal but do not induce significant proliferation, and the addition of a costimulatory antibody (anti-CD28) provides the stimulus for robust proliferation.(3) An exogenous T-cell growth factor, such as interleukin-2 (IL-2), may also be used as an alternate to anti-CD28 costimulation, and in patients with suspected IL-2 receptor-associated signaling defects, it may be more helpful than the use of anti-CD28. IL-2, an autocrine cytokine, has been demonstrated to be critical in T-cell proliferation.(4,5) The interaction of IL-2 with the IL-2 receptor (IL-2R) plays a central role in regulation of T-cell proliferation.(4) Triggering of the TCR leads to synthesis of IL-2 in certain T-cell subsets and induction of high-affinity IL-2Rs in antigen- or mitogen-activated T cells, and the binding of IL-2 to IL-2R ultimately leads to T-cell proliferation. The use of exogenous IL-2 in association with anti-CD3 allows discrimination of whether T cells, which cannot proliferate to other mitogenic signals, can respond to a potent growth factor such as IL-2. Stimulation of T cells with soluble antibodies to anti-CD3 (and the associated TCR complex) causes mobilization of cytoplasmic calcium and translocation of protein kinase C from the cytoplasm to the cell membrane. This stimulation also causes induction of phosphatidylinositol metabolism and subsequent IL-2 production for proliferation.(6) T-cell activation induced by anti-CD3 antibody requires prolonged stimulation of protein kinase C, which apparently can be achieved by the concomitant use of the anti-CD28 antibody for costimulation without addition of other mitogenic stimuli, such as phorbol myristate acetate.(7) This assay uses a method that directly measures the S-phase proliferation of lymphocytes through the use of click chemistry. In the Invitrogen Click-iT-EdU assay, the click chemistry has been adapted to measure cell proliferation through direct detection of nucleotide incorporation. The Click-iT-EdU assay has been shown to be an acceptable alternative to the (3)H-thymidine assay for measuring lymphocyte/T-cell proliferation.(8,9) In the assay, an alkyne-modified nucleoside is supplied in cell-growth media for a defined period and is incorporated within cells. The cells are subsequently fixed, permeabilized, and reacted with a dye-labeled azide, catalyzed by copper. A covalent bond is formed between the dye and the incorporated nucleotide, and the fluorescent signal is then measured by flow cytometry.(10) Specific proliferating cell populations can be visualized by the addition of cell-specific antibodies. Cell viability, apoptosis, and death can also be measured by flow cytometry using 7-aminoactinomycin D and annexin V. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells

increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer-cell counts, on the other hand, is constant throughout the day. Circadian variations in circulating T-cell counts negatively correlate with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, the numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening(11) and during summer compared to winter.(12) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: A second-level test after lymphocyte proliferation to mitogens (specifically phytohemagglutinin) has been assessed Evaluating patients suspected of having impairment in cellular immunity Evaluation of T-cell function in patients with primary immunodeficiencies, either cellular (DiGeorge syndrome, T-negative severe combined immunodeficiency [SCID], etc) or combined T- and B-cell immunodeficiencies (T- and B-negative SCID, Wiskott-Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency, among others) where T-cell function may be impaired Evaluation of T-cell function in patients with secondary immunodeficiency, either disease related or iatrogenic Evaluation of recovery of T-cell function and competence following bone marrow transplantation or hematopoietic stem cell transplantation Evaluation of T-cell function in patients receiving immunosuppressive or immunomodulatory therapy Evaluation of T-cell function in the context of identifying neutralizing antibodies in patients receiving therapeutic anti-CD3 antibody immunosuppression for solid organ transplantation or autoimmune diseases, such as type 1 diabetes This panel is not useful as a first-level test for assessing lymphocyte (T-cell) function.

Interpretation: Abnormal anti-CD3/anti-CD28/interleukin-2 (IL-2) stimulation test results are indicative of impaired T-cell function if T-cell counts are normal or only modestly decreased. If there is profound T-cell lymphopenia, it must be kept in mind that there could be a "dilution" effect with underrepresentation of T cells within the peripheral blood mononuclear cells population that could result in lower T-cell proliferative responses. However, this is not a significant concern in the flow cytometry assay, since acquisition of additional cellular events during analysis can compensate for artificial reduction in proliferation due to lower T-cell counts. The evaluation of T-cell proliferation to anti-CD3/IL-2 is likely to be helpful in assessing T-cell function in patients with refractory responses to other mitogenic and antigenic stimuli, specifically in the context of IL-2-receptor signaling defects, enabling greater mechanistic insight into the origins of T-cell dysfunction. There is no absolute correlation between T-cell proliferation in vitro and a clinically significant immunodeficiency, whether primary or secondary, since T-cell proliferation in response to activation is necessary, but not sufficient, for an effective immune response. Therefore, the proliferative response to any mitogenic stimulus, including anti-CD3/anti-CD28, can be regarded as a more specific but less sensitive test for the diagnosis of infection susceptibility. No single laboratory test can identify or define impaired cellular immunity on its own. Controls in this laboratory and most clinical laboratories are healthy adults. Since this test is used for screening and evaluating cellular immune dysfunction in infants and children, it is reasonable to question the comparability of proliferative responses between healthy infants, children, and adults. One study has reported that the highest mitogen responses are seen in newborn infants with subsequent decline to 6 months of age, and a continuing decline through adolescence to half the neonatal response.(13) In our evaluation of 43 pediatric samples (of all ages) with adult normal controls, only 21% and 14% were below the tenth percentile of the adult reference range for the mitogens, pokeweed mitogen and phytohemagglutinin, respectively. Comparisons between pediatric and adult data have not been performed for anti-CD3/anti-CD28 due to unavailability of prospective blood samples from healthy or patient pediatric donors for purposes of analytical validation. Without obtaining formal pediatric reference values, it remains a possibility that the response in infants and children can be underestimated. However, the practical challenges of generating a pediatric range for this assay necessitate comparison of pediatric data with adult reference values or controls. Lymphocyte proliferation responses to mitogens (including anti-CD3 stimulation) and antigens are significantly affected by time elapsed since blood collection. Results have been shown to be variable for specimens assessed between 24- and 48-hours post blood collection; therefore, lymphocyte proliferation results must be interpreted with due caution and results should be correlated with clinical context.

Reference Values:
Viability of lymphocytes at day 0: > or =75.0%
Maximum proliferation of anti-CD3 as % CD45: > or =19.4%
Maximum proliferation of anti-CD3 as % CD3: > or =20.3%
Maximum proliferation of anti-CD3 + anti-CD28 as % CD45: > or =37.5%
Maximum proliferation of anti-CD3 + anti-CD28 as % CD3: > or =44.6%
Maximum proliferation of anti-CD3 + IL-2 as % CD45: > or =41.7%
Maximum proliferation of anti-CD3 + IL-2 as % CD3: > or =46.2%

Clinical References: 1. Dupont B, Good RA. Lymphocyte transformation in vitro in patients with immunodeficiency diseases: use in diagnosis, histocompatability testing and monitoring treatment. Birth Defects Orig Artic Ser. 1975;11(1):477-485 2. Stone KD, Feldman HA, Huisman C, Howlett C, Jabara HH, Bonilla FA. Analysis of in vitro lymphocyte proliferation as a screening tool for cellular immunodeficiency. Clin Immunol. 2009;131(1):41-49. doi:10.1016/j.clim.2008.11.003 3. Frauwirth KA, Thompson CB. Activation and inhibition of lymphocytes by costimulation. J Clin Invest. 2002;109(3):295-299. doi:10.1172/JCI14941 4. Smith KA, Gillis S, Baker PE, et al. T-cell growth factor-mediated T cell proliferation. Ann N Y Acad Sci. 1979;332:423. doi:10.1111/j.1749-6632.1979.tb47136.x 5. Cantrell DA, Smith KA. The interleukin-2 T cell system: a new cell growth model. Science. 1984;224(4655):1312-1316. doi:10.1126/science.6427923 6. Ledbetter JA, Gentry LE, June CH, et al. Stimulation of T cells through the CD3/T cell receptor complex: role of cytoplasmic calcium, protein kinase C translocation, and phosphorylation of pp60c-src in the activation pathway. Mol Cell Biol. 1987;7(2):650-656. doi:10.1128/mcb.7.2.650-656.1987 7. Davis LS, Lipsky PE. T cell activation induced by anti-CD3 antibodies requires prolonged stimulation of protein kinase C. Cell Immunol. 1989;118(1):208-221. doi:10.1016/0008-8749(89)90370-5 8. Yu Y, Arora A, Min W, et al. EdU-Click iT flow cytometry assay as an alternative to [3H]thymidine for measuring proliferation of human and mice T lymphocytes. J Allergy Clin Immunol. 2009;123(2):S87. doi:10.1016/j.jaci.2008.12.307 9. Clarke ST, Calderon V, Bradford JA. Click chemistry for analysis of cell proliferation in flow cytometry. Curr Protoc Cytom. 2017;82:7.49.1-7.49.30. doi:10.1002/cpcy.24 10. Salic A, Mitchison TJ. A chemical method for fast and sensitive detection of DNA synthesis in vivo. Proc Natl Acad Sci USA. 2008;105(7):2415-2420. doi:10.1073/pnas.0712168105 11. Malone JL, Simms TE, Gray GC, et al. Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J AIDS. 1990;(3):144-151 12. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994;34(6):512-516 13. Hicks MJ, Jones JK, Thies AC, et al. Age-related changes in mitogen-induced lymphocyte function from birth to old age. Am J Clin Pathol. 1983;80(2):159-163. doi:10.1093/ajcp/80.2.159 14. Fletcher MA, Urban RG, Asthana D, et al. Lymphocyte proliferation. In: Rose NR, de Macario EC, Folds JD, et al: Manual of Clinical Laboratory Immunology. 5th ed.ASM Press; 1997:313-319 15. Knight V, Heimall JR, Chong H, et al. A toolkit and framework for optimal laboratory evaluation of individuals with suspected primary immunodeficiency. J Allergy Clin Immunol Pract. 2021;9(9):3293-3307.e6. doi:10.1016/j.jaip.2021.05.004

LPAGF
60592

Lymphocyte Proliferation to Antigens, Blood

Clinical Information: Determining impaired T-cell function by culturing human peripheral blood mononuclear cells (PBMC) in vitro with recall antigens, including Candida albicans (CA) and tetanus toxoid (TT), has been part of the diagnostic immunology repertoire for many years.(1,2) A widely used method for assessing lymphocyte proliferation to antigens has hitherto been the measurement of (3)H-thymidine incorporated into the DNA of proliferating cells. The disadvantages with the (3)H-thymidine method of lymphocyte proliferation are: 1. The technique is cumbersome due to the use of radioactivity. 2. It does not distinguish between different cell populations responding to stimulation. 3. It does not provide any information on contribution of activation-induced cell death to the interpretation of the final result. Further, decreased lymphocyte proliferation could be due to several factors, including overall diminution of T-cell proliferation, or an apparent decrease in total lymphocyte proliferation due to T-

cell lymphopenia and under representation of T cells in the PBMC pool. None of these can be distinguished by the thymidine uptake assay but can be assessed by flow cytometry, which uses antibodies to identify specific responder cell populations. Cell viability can also be measured within the same assay without requiring additional cell manipulation or specimen. Antigens, like CA and TT, have been widely used to measure antigen-specific recall (anamnestic) T-cell responses when assessing cellular immunity. In fact, it may be more revealing about cellular immune compromise than assessing the response of lymphocytes to mitogens because the latter can induce T-cell proliferative responses even if those T cells are incapable of responding adequately to antigenic (physiologic) stimuli. Therefore, abnormal T-cell responses to antigens are considered a diagnostically more sensitive, but less specific, test of aberrant T-cell function.(2) Antigens used in recall assays measure the ability of T cells bearing specific T-cell receptors to respond to such antigens when processed and presented by antigen-presenting cells. The antigens used for assessment of the cellular immune response are selected to represent antigens, seen by a majority of the population, either through natural exposure (CA) or as a result of vaccination (TT). This assay uses a method that directly measures the S-phase proliferation of lymphocytes through the use of Click chemistry. Cell viability, apoptosis, and death can also be measured by flow cytometry using 7-aminoactinomycin D (7-AAD) and annexin V. The Click-iT-EdU assay has shown to be an acceptable alternative to the (3)H-thymidine assay for measuring lymphocyte/T-cell proliferation.(3,4) The degree of impairment of antigen-specific T-cell responses can vary depending on the nature of the cellular immune compromise. For example, some, but not all, patients with partial DiGeorge syndrome, a primary cellular immunodeficiency, have been reported to have either decreased or absent T-cell responses to CA and TT.(5) Similarly, relative immune compromise, especially to TT, has been reported in children with vitamin A deficiency, but the measurements have been largely of the humoral immune response. Since this requires participation of the cellular immune compartment, it can be postulated that there could be a potential impairment of antigen-specific T-cell responses as well.(6)

Useful For: Assessing T-cell function in patients on immunosuppressive therapy, including solid-organ transplant patients Evaluating patients suspected of having impairment in cellular immunity Evaluation of T-cell function in patients with primary immunodeficiencies, either cellular (DiGeorge syndrome, T-negative severe combined immunodeficiency [SCID], etc) or combined T- and B-cell immunodeficiencies (T- and B-negative SCID, Wiskott-Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency, among others) where T-cell function may be impaired Evaluation of T-cell function in patients with secondary immunodeficiency, either disease related or iatrogenic Evaluation of recovery of T-cell function and competence following bone marrow transplantation or hematopoietic stem cell transplantation This test is not intended for assessment of maternal engraftment.

Interpretation: Abnormal antigen stimulation test results are indicative of impaired T-cell function if T-cell counts are normal or only modestly decreased. If there is profound T-cell lymphopenia, there could be a dilution effect with underrepresentation of T cells within the peripheral blood mononuclear cell population that could result in lower T-cell proliferative responses. However, this is not a significant concern in the flow cytometry assay, since acquisition of additional cellular events during analysis can compensate for artificial reduction in proliferation due to lower T-cell counts. In the case of antigen-specific T-cell responses to tetanus toxoid (TT), there can be absent responses due to natural waning of cellular immunity, if the interval between vaccinations has exceeded the recommended period, especially in adults. In such circumstances, it would be appropriate to measure TT-specific T-cell responses 4 to 6 weeks after a booster vaccination. There is no absolute correlation between T-cell proliferation in vitro and a clinically significant immunodeficiency, whether primary or secondary, since T-cell proliferation in response to activation is necessary, but not sufficient, for an effective immune response. Therefore, the proliferative response to antigens can be regarded as a more sensitive, but less specific, test for the diagnosis of infection susceptibility. No single laboratory test can identify or define impaired cellular immunity on its own. Controls in this laboratory and most clinical laboratories are healthy adults. Since this test is used for screening and evaluating cellular immune dysfunction in infants and children, it is reasonable to question the comparability of proliferative responses between healthy infants, children, and adults. It is reasonable to expect robust T-cell-specific responses to TT in children without cellular immune compromise, as a result of repeated childhood vaccinations. The response to Candida albicans

can be more variable depending on the extent of exposure and age of exposure. A comment will be provided in the report documenting the comparison of pediatric results with an adult reference range and correlation with clinical context for appropriate interpretation. Without obtaining formal pediatric reference values, it remains a possibility that the response in infants and children can be underestimated. However, the practical challenges of generating a pediatric range for this assay necessitate comparison of pediatric data with adult reference values or controls.

Reference Values:

Viability of lymphocytes at day 0: > or =75.0%
Maximum proliferation of Candida albicans as % CD45: > or =5.7%
Maximum proliferation of Candida albicans as % CD3: > or =3.0%
Maximum proliferation of tetanus toxoid as % CD45: > or =5.2%
Maximum proliferation of tetanus toxoid as % CD3: > or =3.3%

Clinical References: 1. Dupont B, Good RA. Lymphocyte transformation in vitro in patients with immunodeficiency diseases: use in diagnosis, histocompatability testing and monitoring treatment. Birth Defects Orig Artic Ser. 1975;11(1):477-485 2. Stone KD, Feldman HA, Huisman C, Howlett C, Jabara HH, Bonilla FA. Analysis of in vitro lymphocyte proliferation as a screening tool for cellular immunodeficiency. Clin Immunol. 2009;131(1):41-49. doi:10.1016/j.clim.2008.11.003 3. Yu Y, Arora A, Min W, et al. EdU-Click iT flow cytometry assay as an alternative to [3H]thymidine for measuring proliferation of human and mice T lymphocytes. J Allergy Clin Immunol. 2009;123(2):S87. doi:10.1016/j.jaci.2008.12.307 4. Clarke ST, Calderon V, Bradford JA. Click chemistry for analysis of cell proliferation in flow cytometry. Curr Protoc Cytom. 2017;82:7.49.1-7.49.30. doi:10.1002/cpcy.24 5. Davis CM, Kancheria VS, Reddy A, et al. Development of specific T cell responses to Candida and tetanus antigens in partial DiGeorge syndrome. J Allergy Clin Immunol. 2008;122(6):1194-1199. doi:10.1016/j.jaci.2008.06.039 6. Semba RD, Muhilal, Scott AL, et al. Depressed immune response to tetanus in children with vitamin A deficiency. J Nutr. 1992;122(1):101-107. doi:10.1093/jn/122.1.101 7. Fletcher MA, Urban RG, Asthana D, et al. Lymphocyte proliferation. In: Rose NR, de Macario EC, Folds JD, et al, eds. Manual of Clinical Laboratory Immunology. 5th ed. ASM Press; 1997:313-319 8. Malone JL, Simms TE, Gray GC, et al. Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J AIDS. 1990;(3):144-151 9. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994;34(6):512-516 10. Lis H, Sharon N. Lectins: Carbohydrate-specific proteins that mediate cellular recognition. Chem Rev. 1998;98(2):637-674. doi:10.1021/cr940413g 11. Salic A, Mitchison TJ. A chemical method for fast and sensitive detection of DNA synthesis in vivo. Proc Natl Acad Sci USA. 2008;105(7):2415-2420. doi:10.1073/pnas.0712168105 12. Knight V, Heimall JR, Chong H, et al. A toolkit and framework for optimal laboratory evaluation of individuals with suspected primary immunodeficiency. J Allergy Clin Immunol Pract. 2021;9(9):3293-3307.e6. doi:10.1016/j.jaip.2021.05.004

LPMGF
60591

Lymphocyte Proliferation to Mitogens, Blood

Clinical Information: The method of determining impaired T-cell function by culturing human peripheral blood mononuclear cells (PBMC) in vitro with mitogenic plant lectins (mitogens), such as phytohemagglutinin (PHA) and pokeweed mitogen (PWM) has been part of the diagnostic immunology repertoire for many years.(1,2) A widely used method for assessing lymphocyte proliferation has hitherto been the measurement of (3)H-thymidine incorporated into the DNA of proliferating cells. The disadvantages with the (3)H-thymidine method of lymphocyte proliferation are as follows: 1. The technique is cumbersome due to the use of radioactivity. 2. It does not distinguish between different cell populations responding to stimulation. 3. It does not provide any information on contribution of activation-induced cell death to the interpretation of the final result. Further, decreased lymphocyte proliferation could be due to several factors, including overall diminution of T-cell proliferation, or an apparent decrease in total lymphocyte proliferation due to T-cell lymphopenia and under-representation

of T cells in the PBMC pool. None of these can be distinguished by the thymidine uptake assay but can be assessed by flow cytometry, which uses antibodies to identify specific responder cell populations. Cell viability can also be measured within the same assay without requiring additional cell manipulation or specimen. Mitogens are very potent stimulators of T-cell activation and proliferation independent of their antigenic specificity.(3) It has been suggested that mitogens can induce T-cell proliferative responses even if they are incapable of responding adequately to antigenic (physiologic) stimuli. Therefore, abnormal T-cell responses to mitogens are considered a diagnostically less sensitive, but more specific, test of aberrant T-cell function. Lectin mitogens have been shown to bind the T-cell receptor, which is glycosylated through its carbohydrate moiety, thereby activating quiescent T cells. Mitogenic stimulation has been shown to increase intracellular calcium (Ca[2+]) in T cells, which is essential for T-cell proliferation. While PHA is a strong T-cell mitogen, PWM is a weak T-cell mitogen but induces B-cell activation and proliferation as well. This assay uses a method that directly measures the S-phase proliferation of lymphocytes through the use of Click chemistry. In the Invitrogen Click-iT-EdU assay, the Click chemistry has been adapted to measure cell proliferation through direct detection of nucleotide incorporation. In the assay, an alkyne-modified nucleoside is supplied in cell-growth media for a defined period and is incorporated within cells. The cells are subsequently fixed, permeabilized, and reacted with a dye-labeled azide, catalyzed by copper. A covalent bond is formed between the dye and the incorporated nucleotide, and the fluorescent signal is then measured by flow cytometry.(4) Specific proliferating cell populations can be visualized by the addition of cell-specific antibodies. Cell viability, apoptosis, and death can also be measured by flow cytometry using 7-aminoactinomycin D (7-AAD) and annexin V. The Click-iT-EdU assay has shown to be an acceptable alternative to the (3)H-thymidine assay for measuring lymphocyte/T-cell proliferation.(5,6) The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer-cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts negatively correlate with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening(7) and during summer compared to winter.(8) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Assessing T-cell function in patients on immunosuppressive therapy, including solid-organ transplant patients Evaluating patients suspected of having impairment in cellular immunity Evaluation of T-cell function in patients with primary immunodeficiencies, either cellular (DiGeorge syndrome, T-negative severe combined immunodeficiency: SCID, etc) or combined T- and B-cell immunodeficiencies (T- and B-negative SCID, Wiskott-Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency, among others) where T-cell function may be impaired Evaluation of T-cell function in patients with secondary immunodeficiency, either disease related or iatrogenic Evaluation of recovery of T-cell function and competence following bone marrow transplantation or hematopoietic stem cell transplantation

Interpretation: Abnormal mitogen stimulation test results are indicative of impaired T-cell function if T-cell counts are normal or only modestly decreased. If there is profound T-cell lymphopenia, there could be a dilution effect with under-representation of T cells within the peripheral blood mononuclear cell population that could result in lower T-cell proliferative responses. However, this is not a significant concern in the flow cytometry assay since acquisition of additional cellular events during analysis can compensate for artificial reduction in proliferation due to lower T-cell counts. There is no absolute correlation between T-cell proliferation in vitro and a clinically significant immunodeficiency, whether primary or secondary, since T-cell proliferation in response to activation is necessary, but not sufficient, for an effective immune response. Therefore, the proliferative response to mitogens can be regarded as a more specific, but less sensitive, test for the diagnosis of infection susceptibility. No single laboratory test can identify or define impaired cellular immunity on its own. Controls in this laboratory and most clinical

laboratories are healthy adults. Since this test is used for screening and evaluating cellular immune dysfunction in infants and children, it is reasonable to question the comparability of proliferative responses between healthy infants, children, and adults. One study has reported that the highest mitogen responses are seen in newborn infants with subsequent decline to 6 months of age and a continuing decline through adolescence to half the neonatal response.(9) In an in-house evaluation of 43 pediatric specimens (of all ages) with adult normal controls, only 21% and 14% were below the tenth percentile of the adult reference range for pokeweed and phytohemagglutinin, respectively. A comment will be provided in the report documenting the comparison of pediatric results with an adult reference range and correlation with clinical context for appropriate interpretation. Without obtaining formal pediatric reference values, it remains a possibility that the response in infants and children can be underestimated. However, the practical challenges of generating a pediatric range for this assay necessitate comparison of pediatric data with adult reference values or controls. Lymphocyte proliferation responses to mitogens and antigens are significantly affected by time elapsed since blood collection. Results have been shown to be variable for specimens assessed between 24- and 48-hours post blood collection; therefore, lymphocyte proliferation results must be interpreted with due caution and results should be correlated with clinical context.

Reference Values:

Viability of lymphocytes at day 0: > or =75.0%
Maximum proliferation of phytohemagglutinin as % CD45: > or =49.9%
Maximum proliferation of phytohemagglutinin as % CD3: > or =58.5%
Maximum proliferation of pokeweed mitogen as % CD45: > or =4.5%
Maximum proliferation of pokeweed mitogen as % CD3: > or =3.5%
Maximum proliferation of pokeweed mitogen as % CD19: > or =3.9%

Clinical References: 1. Dupont B, Good RA. Lymphocyte transformation in vitro in patients with immunodeficiency diseases: use in diagnosis, histocompatibility testing and monitoring treatment. Birth Defects Orig Artic Ser. 1975;11(1):477-485 2. Stone KD, Feldman HA, Huisman C, Howlett C, Jabara HH, Bonilla FA. Analysis of in vitro lymphocyte proliferation as a screening tool for cellular immunodeficiency. Clin Immunol. 2009;131(1):41-49. doi:10.1016/j.clim.2008.11.003 3. Lis H, Sharon N. Lectins: Carbohydrate-specific proteins that mediate cellular recognition. Chem Rev. 1998;98(2):637-674. doi:10.1021/cr940413g 4. Salic A, Mitchison TJ. A chemical method for fast and sensitive detection of DNA synthesis in vivo. Proc Natl Acad Sci USA. 2008;105(7):2415-2420. doi:10.1073/pnas.0712168105 5. Yu Y, Arora A, Min W, Roifman CM, Grunebaum E. EdU-Click iT flow cytometry assay as an alternative to 3H-thymidine for measuring proliferation of human and mice lymphocytes. J Allergy Clin Immunol. 2009;123(2):S87. doi:10.1016/j.jaci.2008.12.307 6. Clarke ST, Calderon V, Bradford JA. Click chemistry for analysis of cell proliferation in flow cytometry. Curr Protoc Cytom. 2017;82:7.49.1-7.49.30. doi:10.1002/cpcy.24 7. Malone JL, Simms TE, Gray GC, et al. Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J AIDS. 1990;(3):144-151 8. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994;34(6):512-516 9. Hicks MJ, Jones JK, Thies AC, Weigle KA, Minnich LL. Age-related changes in mitogen-induced lymphocyte function from birth to old age. Am J Clin Pathol. 1983;80(2):159-163. doi:10.1093/ajcp/80.2.159 10. Fletcher MA, Urban RG, Asthana D, et al. Lymphocyte proliferation. In: Rose NR, de Macario EC, Folds JD, et al, eds. Manual of Clinical Laboratory Immunology. 5th ed. ASM Press; 1997:313-319 11. Knight V, Heimall JR, Chong H, et al. A toolkit and framework for optimal laboratory evaluation of individuals with suspected primary immunodeficiency. J Allergy Clin Immunol Pract. 2021;9(9):3293-3307.e6. doi:10.1016/j.jaip.2021.05.004

LEF1
71356

Lymphoid Enhancer-Binding Factor 1(LEF1) Immunostain, Technical Component Only

Clinical Information: Lymphoid enhancer-binding factor 1 (LEF1) is a transcription factor that participates in the activation of genes within the Wnt signaling pathway. LEF1 is expressed by inactive T-cells and a subset of B-cells.

Useful For: Differentiating cancers of B-cell origin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Ghamlouch H, Darwiche W, Hodroge A, et al. Factors involved in CLL pathogenesis and cell survival are disrupted by differentiation of CLL B-cells into antibody-secreting cells. Oncotarget. 2015;6(21):18484-18503 2. Menter T, Dirnhofer S, Tzankov A. LEF1: a highly specific marker for the diagnosis of chronic lymphocytic B cell leukaemia/small lymphocytic B cell lymphoma. J Clin Pathol. 2015;68(6):473-478 3. Gutierrez A Jr, Tschumper RC, Wu X, et al. LEF-1 is a prosurvival factor in chronic lymphocytic leukemia and is expressed in the preleukemic state of monoclonal B-cell lymphocytosis. Blood. 2010;116(16):2975-2983 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

LPLFX
61114

Lymphoplasmacytic Lymphoma/Waldenstrom Macroglobulinemia, MYD88 L265P with Reflex to CXCR4, Varies

Clinical Information: The MYD88 L265P abnormality is highly associated (>90%) with the pathologic diagnosis of lymphoplasmacytic lymphoma and the clinical syndrome of Waldenstrom macroglobulinemia (LPL/WM), particularly in the setting of an elevated IgM serum monoclonal paraprotein. CXCR4 mutations are identified in approximately 30% to 40% of LPL/WM patients and are almost always in association with MYD88 L265P, which is highly prevalent in this neoplasm. The status of CXCR4 mutations in the context of MYD88 L265P is clinically relevant as important determinants of clinical presentation, overall survival and therapeutic response to ibrutinib. A MYD88-L265P/CXCR4-WHIM (C-terminus nonsense/frameshift variants) molecular signature is associated with intermediate to high bone marrow disease burden and serum IgM levels, less adenopathy, and intermediate response to ibrutinib in previously treated patients. A MYD88-L265P/CXCR4-WT (wildtype) molecular signature is associated with intermediated bone marrow disease burden and serum IgM levels, more adenopathy, and highest response to ibrutinib in previously treated patients. A MYD88-WT/CXCR4-WT molecular signature is associated with inferior overall survival, lower response to ibrutinib therapy in previously treated patients, and lower bone marrow disease burden in comparison to those harboring a MYD88-L265 variant.

Useful For: Establishing a diagnosis of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) Helping distinguish LPL/WM low-grade B-cell lymphoma from other subtypes Aiding in the prognosis and clinical management of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia

Interpretation: Mutation present or not detected; an interpretive report will be issued.

Reference Values:
MYD88 L265P: Mutation present or absent based on expected variant polymerase chain reaction product size for the MYD88 gene (NCBI accession NM_002468.4).

CXCR4: Mutation present or absent in the test region c. 898-1059 (amino acids 300-353) of the CXCR4 gene (NCBI NM_003467.2, GRCh37).

Clinical References: 1. Treon SP, Xu L, Yang G, et al: MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. N Engl J Med. 2012 Aug 30;367(9):826-833. doi: 10.1056/NEJMoa1200710 2. Varettoni M, Arcaini L, Zibellini S, et al: Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in Waldenstrom's macroglobulinemia and related lymphoid neoplasms. Blood. 2013 Mar 28;121(13):2522-2528. doi: 10.1182/blood-2012-09-457101 3. Xu L, Hunter ZR, Yang G, et al: MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. Blood. 2013 Mar 14;121(11):2051-2058. doi: 10.1182/blood-2012-09-454355 4. Poulain S, Roumier C, Decambron A, et al: MYD88 L265P mutation in Waldenstrom macroglobulinemia. Blood. 2013 May 30;121(22):4504-4511. doi: 10.1182/blood-2012-06-436329 5. Gachard N, Parrens M, Soubeyran I, et al: IGHV gene features and MYD88 L265P mutation separate the three marginal zone lymphoma entities and Waldenstrom macroglobulinemia/lymphoplasmacytic lymphomas. Leukemia. 2013 Jan;27(1):183-189. doi: 10.1038/leu.2012.257 6. Ondrejka SL, Lin JJ, Warden DW, et al: MYD88 L265P somatic mutation: its usefulness in the differential diagnosis of bone marrow involvement by B-cell lymphoproliferative disorders. Am J Clin Pathol. 2013 Sept;140(3):387-394. doi: 10.1309/AJCP10ZCLFZGYZIP 7. Hunter Z, Xu L, Yang G, et al: The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood. 2014 Mar 13;123(11):1637-1646. doi: 10.1182/blood-2013-09-525808 9. Poulain S, Roumier C, Venet-Caillault A, et al: Genomic landscape of CXCR4 mutations in Waldenstrom macroglobulinemia. Clin Cancer Res. 2016 Mar 15;22(6):1480-1488. doi: 10.1158/1078-0432.CCR-15-0646 10. Roccaro A, Sacco A, Jimenez C, et al: C1013G/CXCR4 acts as a driver mutation of tumor progression and modulator of drug resistance in lymphoplasmacytic lymphoma. Blood. 2014 Jun 26;123(26):4120-4131. doi: 10.1182/blood-2014-03-564583 11. Schmidt J, Federmann B, Schindler N, et al: MYD88 L265P and CXCR4 mutations in lymphoplasmacytic lymphoma identify cases with high disease activity. Br J Haematol. 2015 Jun;169(6):795-803. doi: 10.1111/bjh.13361 12. Treon SP, Cao Y, Xu L, et al: Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. Blood. 2014 May 1;123(18):2791-2796. doi: 10.1182/blood-2014-01-550905 13. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med. 2015 Apr 9;372(15):1430-1440. doi: 10.1056/NEJMoa1501548

LYNCP
614572

Lynch Syndrome Panel, Varies

Clinical Information: The lifetime risk of colorectal cancer in the general population is 4% to 6%.(1) Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer) is an autosomal dominant hereditary cancer syndrome accounting for 2% to 4% of all colorectal cancer cases.(2,3) Lynch syndrome is associated with germline variants in the mismatch repair genes, MLH1, MSH2, MSH6, PMS2, or deletions of the EPCAM gene. It is predominantly characterized by significantly increased risks for colorectal and endometrial cancer.(2,3) The lifetime risk for cancer is highly variable and dependent on the gene involved. Other malignancies within the tumor spectrum include gastric, ovarian, and small bowel cancers and hepatobiliary and upper urinary tract carcinomas.(2,3) Individuals with biallelic disease-causing variants in the same mismatch repair gene are at risk for constitutional mismatch repair deficiency, an autosomal recessive childhood-onset hereditary cancer syndrome.(3) The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with Lynch syndrome.(2,4)

Useful For: Establishing a diagnosis of Lynch syndrome or constitutional mismatch repair deficiency

allowing for targeted cancer surveillance based on associated risks Identifying MLH1, MSH2, MSH6, PMS2, or EPCAM variants to allow for predictive testing in family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review. 1975-2018. National Cancer Institute. Updated April 2021. Accessed June 28, 2023. Available at: https://seer.cancer.gov/csr/1975_2018 2. Gupta S, Provenzale D, Llor X, et al. NCCN Guidelines Insights: Genetic/familial high-risk assessment: colorectal, version 2.2019. J Natl Compr Canc Netw. 2019;17(9):1032-1041 3. Idos G, Valle L. Lynch syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews (Internet). University of Washington, Seattle; 2004. Updated February 2, 2021. Accessed June 28, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1211/ 4. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2019;69(3):184-210 5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

LPCBS
61766

Lysophosphatidylcholines, LC MS/MS, Blood Spot

Clinical Information: This assay measures C20, C22, C24, and C26 lysophosphatidylcholine (LPC) species in dried blood spots by liquid chromatography tandem mass spectrometry. Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions, including beta-oxidation of very long-chain fatty acids, alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include 2 major subgroups: disorders of peroxisomal biogenesis and single peroxisomal enzyme/transporter defects. Peroxisome biogenesis defects, such as Zellweger spectrum disorder (ZSD), are characterized by defective assembly of the entire organelle, whereas in single enzyme/transporter defects, such as X-linked adrenoleukodystrophy (XALD), the organelle is intact but a specific function is disrupted. These disorders are clinically diverse and range in severity from neonatal lethal to later onset milder variants. X-linked adrenoleukodystrophy is an X-linked disorder affecting the nervous system, adrenal cortex, and testis. It is the most common of the peroxisomal disorders. XALD is caused by a disease-causing variant in the ABCD1 gene. XALD shows a wide range of phenotypic expressions. The clinical phenotypes occurring in male patients can be subdivided in 4 main categories: cerebral inflammatory, adrenomyeloneuropathy (AMN), Addison only, and asymptomatic. The first 2 phenotypes account for almost 80% of the patients, while the frequency of the asymptomatic category diminishes with age and is very rare after age 40. It is estimated that approximately 65% to 80% of heterozygous individuals develop symptoms of an AMN-like phenotype. Treatment options include hormone replacement therapy, hematopoietic stem cell transplantation, gene therapy, or symptom management. Elevations of C24 LPC and C26 LPC may be indicative of XALD. In 2016, XALD was added to the US Recommended Uniform Screening Panel, a list of conditions that are nationally recommended for newborn screening by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. Therefore, measurement of LPCs is a useful second-tier test for newborn screening for XALD. Zellweger spectrum disorders are a continuum of severe disorders affecting the nervous system, vision, hearing, and liver function. Most affected individuals present in childhood, but adult patients have been identified. Most ZSD are inherited in an autosomal recessive pattern. At least 13 different genes have been implicated in ZSD, with approximately 60% to 70% of

variants occurring in PEX1. The clinical phenotypes include Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease. The phenotypic spectrum and disease severity is broad. There is no specific treatment for ZSD. Although ZSD are not a primary disease target for testing, this test can detect individuals with ZSD.

Useful For: Second-tier newborn screen for X-linked adrenoleukodystrophy This test is not intended for metabolic screening of symptomatic patients. This test is supplemental and not intended to replace state mandated newborn screening.

Interpretation: In female patients: Elevations of C24 lysophosphatidylcholine (LPC) or C26 LPC may be indicative of heterozygosity for X-linked adrenoleukodystrophy (XALD) or other forms of peroxisomal disorders. In male patients: Elevations of C24 LPC or C26 LPC may be indicative of XALD or other forms of peroxisomal disorders. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required.

Reference Values:

Analyte	Normal Range (nmol/mL)
C20 Lysophosphatidylcholine	Not applicable
C22 Lysophosphatidylcholine	Not applicable
C24 Lysophosphatidylcholine	< or =0.41
C26 Lysophosphatidylcholine	< or =0.31

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Accessed July 14, 2025. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Huffnagel IC, van de Beek MC, Showers AL, et al. Comparison of C26:0-carnitine and C26:0-lysophosphatidylcholine as diagnostic markers in dried blood spots from newborns and patients with adrenoleukodystrophy. Mol Genet Metab. 2017;122(4):209-215. doi:10.1016/j.ymgme.2017.10.012 3. Klouwer FCC, Ferdinandusse S, van Lenthe H, et al. Evaluation of C26:0-lysophosphatidylcholine and C26:0-carnitine as diagnostic markers for Zellweger spectrum disorders. J Inherit Metab Dis. 2017;40(6):875-881. doi:10.1007/s10545-017-0064-0 4. Sandlers Y, Moser AB, Hubbard WC, Kratz LE, Jones RO, Raymond GV. Combined extraction of acyl carnitines and 26:0 lysophosphatidylcholine from dried blood spots: prospective newborn screening for X-linked adrenoleukodystrophy. Mol Genet Metab. 2012;105(3):416-420

LALB
62954

Lysosomal Acid Lipase, Blood

Clinical Information: Deficiency of lysosomal acid lipase (LAL) results in 2 clinically distinct phenotypes, Wolman disease (WD) and cholesteryl ester storage disease (CESD). Both phenotypes follow an autosomal recessive inheritance pattern and are caused by variant in the LIPA gene. WD, the

early-onset phenotype of LAL deficiency, is a lipid storage disorder characterized by vomiting, diarrhea, failure to thrive, abdominal distension, hepatosplenomegaly, and liver failure. Enlarged adrenal glands with calcification, a classic finding in WD, can lead to adrenal cortical insufficiency. Unless successfully treated, survival is rare beyond infancy. CESD, the late-onset phenotype of LAL deficiency, is clinically variable with patients presenting at any age with progressive hepatomegaly and often splenomegaly, serum lipid abnormalities, and elevated liver enzymes. In childhood, patients can also present with failure to thrive and delayed milestones. Common features include premature atherosclerosis leading to coronary artery disease and strokes, liver disease of varying severity, and organomegaly. Lipid deposition in the intestinal tract can lead to diarrhea and weight loss. CESD is likely underdiagnosed and frequently diagnosed incidentally after liver pathology reveals findings similar to nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. Birefringent cholesteryl ester crystals in hepatocytes or Kupffer cells in fresh-frozen tissues are visualized under polarized light and pathognomonic. Enzyme replacement therapy (sebelipase alfa) was recently approved for both WD and CESD and is now clinically available.

Useful For: Evaluation of patients with a clinical presentation suggestive of lysosomal acid lipase deficiency using blood specimens This test is not useful to determine carrier status for cholesteryl ester storage disease or Wolman disease.

Interpretation: Enzyme activity below 1.5 nmol/h/mL in properly submitted samples is consistent with lysosomal acid lipase deficiency: Wolman disease or cholesteryl ester storage disease. Normal results (> or =21.0 nmol/h/mL) are not consistent with lysosomal acid lipase deficiency.

Reference Values:
> or =21.0 nmol/h/mL

Clinical References: 1. Bernstein DL, Hulkova H, Bialer MG, Desnick RJ. Cholesteryl ester storage disease: review of the findings in 135 reported patients with an underdiagnosed disease. J Hepatol. 2013;58(6):1230-1243 2. Reynolds T. Cholesteryl ester storage disease: a rare and possibly treatable cause of premature vascular disease and cirrhosis. J Clin Pathol. 201366(11):918-923 3. Pericleous M, Kelly C, Wang T, Livingstone C, Ala A. Wolman's disease and cholesteryl ester storage disorder: the phenotypic spectrum of lysosomal acid lipase deficiency. Lancet Gastroenterol Hepatol. 2017;2(9):670-679. doi:10.1016/S2468-1253(17)30052-3 4. Pastores GM, Hughes DA: Lysosomal acid lipase deficiency. Therapeutic options. Drug Des Devel Ther. 2020;14:591-601

LALBS
62955

Lysosomal Acid Lipase, Blood Spot

Clinical Information: Deficiency of lysosomal acid lipase (LAL) results in 2 clinically distinct phenotypes, Wolman disease (WD) and cholesteryl ester storage disease (CESD). Both phenotypes follow an autosomal recessive inheritance pattern and are caused by variant in the LIPA gene. WD, the early-onset phenotype of LAL deficiency, is a lipid storage disorder characterized by vomiting, diarrhea, failure to thrive, abdominal distension, hepatosplenomegaly, and liver failure. Enlarged adrenal glands with calcification, a classic finding in WD, can lead to adrenal cortical insufficiency. Unless successfully treated, survival is rare beyond infancy. CESD, the late-onset phenotype of LAL deficiency, is clinically variable with patients presenting at any age with progressive hepatomegaly and often splenomegaly, serum lipid abnormalities, and elevated liver enzymes. In childhood, patients can also present with failure to thrive and delayed milestones. Common features include premature atherosclerosis leading to coronary artery disease and strokes, liver disease of varying severity, and organomegaly. Lipid deposition in the intestinal tract can lead to diarrhea and weight loss. CESD is likely underdiagnosed and frequently diagnosed incidentally after liver pathology reveals findings similar to nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. Birefringent cholesteryl ester crystals in hepatocytes or Kupffer cells in fresh-frozen tissues are visualized under polarized light and pathognomonic. Enzyme replacement therapy (sebelipase alfa) was recently approved for both WD and CESD and is now clinically available.

Useful For: Evaluation of patients with a clinical presentation suggestive of lysosomal acid lipase deficiency using blood spot specimens This test is not useful to determine carrier status for cholesteryl ester storage disease or Wolman disease.

Interpretation: Enzyme activity below 1.5 nmol/h/mL in properly submitted samples is consistent with lysosomal acid lipase deficiency: Wolman disease or cholesteryl ester storage disease. Normal results (> or =21.0 nmol/h/mL) are not consistent with lysosomal acid lipase deficiency.

Reference Values:
> or =21.0 nmol/h/mL

Clinical References: 1. Bernstein DL, Hulkova H, Bialer MG, Desnick RJ. Cholesteryl ester storage disease: review of the findings in 135 reported patients with an underdiagnosed disease. J Hepatol. 2013;58(6):1230-1243 2. Reynolds T. Cholesteryl ester storage disease: a rare and possibly treatable cause of premature vascular disease and cirrhosis. J Clin Pathol. 2013;66(11):918-923 3. Pericleous M, Kelly C, Wang T, Livingstone C, Ala A. Wolman's disease and cholesteryl ester storage disorder: the phenotypic spectrum of lysosomal acid lipase deficiency. Lancet Gastroenterol Hepatol. 2017;2(9):670-679. doi:10.1016/S2468-1253(17)30052-3 4. Pastores GM, Hughes DA. Lysosomal acid lipase deficiency: Therapeutic options. Drug Des Devel Ther. 2020;14:591-601

LDALD
64907

Lysosomal and Peroxisomal Disorders Newborn Screen, Blood Spot

Clinical Information:

Useful For: First-tier newborn screen for the lysosomal disorders: Fabry, Gaucher, Krabbe, mucopolysaccharidosis I (MPS I) and II (MPS II), infantile neurovisceral or chronic visceral acid sphingomyelinase deficiency, and Pompe (glycogen storage disorder type II) First-tier newborn screen for the peroxisomal disorder, X-linked adrenoleukodystrophy and may also detect Zellweger spectrum disorders This test is supplemental and not intended to replace state-mandated newborn screening. Test is not intended for metabolic screening of symptomatic patients.

Interpretation: The quantitative measurements of informative metabolites and related ratios and their bioinformatic evaluation using the Collaborative Laboratory Integrated Reports (CLIR) system support the initial interpretation of the complete profile and may suggest the need to perform the measurement of more specific biomarkers using the original newborn screen specimen (second-tier test). Nevertheless, abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic's Division of Laboratory Genetics and Genomics. The reports are in text form only. In a case with a completely normal profile, where the interpretation is reported as negative for all listed groups of conditions, no values are provided. A report for an abnormal screening result includes a quantitative result for the relevant abnormal biomarkers, including those of a second-tier test when applicable, the CLIR score indicating the similarity of the newborn's results to those derived from known patients with the relevant disease, a detailed interpretation of the results, and recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis).

Reference Values:
An interpretive report will be provided.

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Accessed July 14, 2025.

Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Klouwer FCC, Ferdinandusse S, van Lenthe H, et al. Evaluation of C26:0-lysophosphatidylcholine and C26:0-carnitine as diagnostic markers for Zellweger spectrum disorders. J Inherit Metab Dis. 2017;40(6):875-881. doi:10.1007/s10545-017-0064-0 3. Huffnagel IC, van de Beek MC, Showers AL, et al. Comparison of C26:0-carnitine and C26:0-lysophosphatidylcholine as diagnostic markers in dried blood spots from newborns and patients with adrenoleukodystrophy. Mol Genet Metab. 2017;122(4):209-215. doi:10.1016/j.ymgme.2017.10.012 4. Part 16: Lysosomal disorders. In: Valle D, Beaudet AL, Vogelstein B, Antonarakis SE, et al, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill Education; 2019. Accessed April 17, 2025. Available at https://ommbid.mhmedical.com/book.aspx?bookid=2709#225069419 5. Part 15: Peroxisomes. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed April 17, 2025. Available at https://ommbid.mhmedical.com/book.aspx?bookid=2709#225069419 6. Minter Baerg MM, Stoway SD, Hart J, et al. Precision newborn screening for lysosomal disorders. Genet Med. 2018;20(8):847-854. doi:10.1038/gim.2017.194 7. Ream MA, Lam WKK, Grosse SD, et al. Evidence and recommendation for mucopolysaccharidosis type II newborn screening in the United States. Genet Med. 2023;25(2):100330. doi:10.1016/j.gim.2022.10.012

PLSD
89678

Lysosomal and Peroxisomal Disorders Screen, Blood Spot

Clinical Information: Lysosomes are intracellular organelles that contain hydrolytic enzymes to degrade a variety of macromolecules. Lysosomal disorders are a diverse group of inherited diseases where macromolecules accumulate due to either defects in their transport mechanisms across the lysosomal membrane or defective lysosomal enzyme function. Accumulation of these macromolecules in the lysosomes leads to cell damage and, eventually, organ dysfunction. More than 50 lysosomal disorders have been described with a wide phenotypic spectrum. Gaucher disease results from a deficiency of the enzyme, beta-glucosidase, due to disease-causing variants in the GBA1 gene. Beta-glucosidase facilitates the lysosomal degradation of glucosylceramide (glucocerebroside) and glucopsychosine (glucosylsphingosine). There are 3 described types of Gaucher disease with varying clinical presentations and age of onset, from a perinatal lethal disorder to milder, later onset variants. Features of all types of Gaucher disease include hepatosplenomegaly and hematological abnormalities. Treatment is available in the form of enzyme replacement therapy (ERT), substrate reduction therapy, and chaperone therapy for types 1 and 3. Currently, only supportive therapy is available for type 2. Acid sphingomyelinase deficiency (ASMD) is an autosomal recessive disorder caused by disease-causing variants in the SMPD1 gene. This results in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. An early-onset form, infantile neurovisceral ASMD (historically known as Niemann-Pick type A) is characterized by early onset feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness leading to death by 3 years of age. A later-onset, chronic visceral form of ASMD (historically known as Niemann-Pick type B) is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells. Approximately 50% of cases have cherry-red spots in the macula. Treatment is available in the form of ERT to help reduce the accumulation of sphingomyelin in the lung, liver, spleen, and other non-central nervous system organs. ERT does not impact the central nervous system. Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to disease-causing variants in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and, eventually, organ dysfunction. The clinical presentation of Pompe disease ranges from a rapidly progressive infantile form, which is lethal if untreated, to a more slowly progressive late-onset form. All disease variants are eventually associated with progressive muscle weakness and respiratory insufficiency.

Cardiomyopathy is associated almost exclusively with the infantile form. Enzyme replacement therapy is available for all forms and should be started as soon as possible for patients with the infantile form and at the first signs of muscle disease in the later onset forms. Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by disease-causing variants in the GALC gene resulting in a deficiency of galactocerebrosidase (GALC; galactosylceramide beta-galactosidase). Galactosylceramide (as with sulfated galactosylceramide) is a lipid component of myelin. The absence of GALC results in globular, distended, multinucleated bodies in the basal ganglia, pontine nuclei, and cerebral white matter. There is severe demyelination throughout the brain with progressive cerebral degenerative disease affecting primarily the white matter. Severely affected individuals typically present between 3 to 6 months with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration, including white matter disease, follows with death usually occurring within 2 to 5 years. A subset of individuals have later onset forms of the disease, which are characterized by ataxia, vision loss, weakness, and psychomotor regression. They can present anywhere from age 6 months to the seventh decade of life and, based on newborn screening experience in New York, appear to be more common than the earlier onset variants. Psychosine has been shown to be elevated in patients with clinical signs and symptoms of disease and, therefore, may be a useful biomarker for the presence of disease or disease progression. The only available therapy is hematopoietic stem cell transplantation (HSCT), which is best performed prior to the onset of clinical symptoms. Infantile Krabbe disease must, therefore, be considered a critical, time-sensitive newborn screening condition. Fabry disease is an X-linked disorder caused by disease-causing variants in the GLA gene resulting in a deficiency of the alpha-galactosidase A (GLA) enzyme.. Reduced GLA activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual GLA activity. Male patients with (near) absent GLA activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. Renal insufficiency, leading to end-stage kidney disease and cardiac and cerebrovascular disease, generally occurs in middle age. Male patients with residual GLA activity may present with a variant form of Fabry disease with onset of symptoms later in life. The renal variant generally has onset of symptoms in the third decade. The most prominent feature is renal insufficiency and, ultimately, end stage kidney disease. Individuals with the renal variant may or may not share other symptoms with the classic form of Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiomyopathy or mitral insufficiency in the fourth decade. The cardiac variant is not associated with kidney failure. Female patients with Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. ERT is a treatment option for all patients with Fabry disease. Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase (IDUA) enzyme. Reduced IDUA activity results in accumulation of glycosaminoglycans (mucopolysaccharides) within the lysosome. The clinical presentation and severity of symptoms of MPS I are variable, ranging from severe disease to attenuated variants (historically known as Hurler-Scheie disease and Scheie disease) that generally present with a later onset and a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, intellectual disability or learning difficulties, and cardiac valvular disease. MPS I is caused by disease-causing variants in the IDUA gene. Treatment options include HSCT and ERT. Mucopolysaccharidosis II (MPS II; Hunter syndrome) is an X-linked disorder caused by the deficiency of iduronate 2-sulfatase (I2S) enzyme due to disease-causing variants in the IDS gene. Reduced I2S activity results in accumulation of glycosaminoglycans (mucopolysaccharides) within the lysosome. Clinical features and severity of symptoms are widely variable ranging from severe infantile onset disease to an attenuated form, which generally has a later onset with a milder clinical presentation. Symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. As an X-linked disorder, MPS II occurs primarily in male patients with an estimated incidence of 1 in 120,000 male births, although symptomatic carrier females have been reported. Treatment options include HSCT and ERT. Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions, including beta-oxidation of very long-chain fatty acids, alpha-oxidation of

phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include 2 major subgroups: disorders of peroxisomal biogenesis and single peroxisomal enzyme/transporter defects. Peroxisome biogenesis defects, such as Zellweger spectrum disorders (ZSD) are characterized by defective assembly of the entire organelle, whereas in single enzyme/transporter defects such as X-linked adrenoleukodystrophy (XALD), the organelle is intact, but a specific function is disrupted. These disorders are clinically diverse and range in severity from neonatal lethal to milder, later onset variants. X-linked adrenoleukodystrophy is an X-linked disorder affecting the nervous system, adrenal cortex, and testis. It is the most common of the peroxisomal disorders. XALD is caused by a disease-causing variant in the ABCD1 gene. XALD shows a wide range of phenotypic expressions. The clinical phenotypes occurring in male patients can be subdivided in 4 main categories: cerebral inflammatory, adrenomyeloneuropathy (AMN), Addison only, and asymptomatic. The first 2 phenotypes account for almost 80% of the patients, while the frequency of the asymptomatic category diminishes with age and is very rare after age 40. It is estimated that approximately 65% to 80% of heterozygous individuals develop symptoms of an AMN-like phenotype. Treatment options include hormone replacement therapy, HSCT, gene therapy, or symptom management. Zellweger spectrum disorders are a continuum of severe disorders affecting the nervous system, vision, hearing, and liver function. Most affected individuals present in childhood, but adult patients have been identified. Most ZSD are inherited in an autosomal recessive pattern. At least 13 different genes have been implicated in ZSD, with approximately 60% to 70% of variants occurring in PEX1. The clinical phenotypes include Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease. The phenotypic spectrum and disease severity is broad. There is no specific treatment for ZSD.

Useful For: Evaluation of patients with a clinical presentation suggestive of a lysosomal disorder, specifically Gaucher, infantile neurovisceral or chronic visceral acid sphingomyelinase deficiency, Pompe, Krabbe, or Fabry disease, or mucopolysaccharidosis I or II; or a peroxisomal disorder, either X-linked adrenoleukodystrophy or Zellweger spectrum disorders

Interpretation: When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required.

Reference Values:

Disease	Marker	Normal range
Gaucher	Acid beta-glucosidase	> or =1.75 nmol/mL/hr
Niemann-Pick A/B	Sphingomyelinase	> or =2.5 nmol/mL/hr
Pompe	Acid alpha-glucosidase	> or =3.0 nmol/mL/hr
Krabbe	Galactocerebrosidase	> or =0.4 nmol/mL/hr
Fabry	Alpha-galactosidase	> or =2.00 nmol/mL/hr
MPS I	Alpha-L-iduronidase	> or =1.5 nmol/mL/hr
MPS II	Iduronate 2-sulfatase	> or =4.0 nmol/mL/hr
NA	C20 Lysophosphatidylcholine	< or =1.81 nmol/mL
NA	C22 Lysophosphatidylcholine	< or =0.43 nmol/mL

ALD/PBD/ALDH	C24 Lysophosphatidylcholine	< or =0.49 nmol/mL
ALD/PBD/ALDH	C26 Lysophosphatidylcholine	< or =0.47 nmol/mL

Clinical References: 1. Newborn Screening ACT Sheets. American College of Medical Genetics and Genomics. Accessed April 17, 2025. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Reuser AJ, Verheijen FW, Bali D, et al. The use of dried blood spot samples in the diagnosis of lysosomal storage disorders--current status and perspectives. Mol Genet Metab. 2011;104(1-2):144-148. doi:10.1016/j.ymgme.2011.07.014 3. Klouwer FCC, Ferdinandusse S, van Lenthe H, et al. Evaluation of C26:0-lysophosphatidylcholine and C26:0-carnitine as diagnostic markers for Zellweger spectrum disorders. J Inherit Metab Dis. 2017;40(6):875-881. doi:10.1007/s10545-017-0064-0 4. Huffnagel IC, van de Beek MC, Showers AL, et al. Comparison of C26:0-carnitine and C26:0-lysophosphatidylcholine as diagnostic markers in dried blood spots from newborns and patients with adrenoleukodystrophy. Mol Genet Metab. 2017;122(4):209-215 5. Part 15: Peroxisomes. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed April 17, 2025. Available at https://ommbid.mhmedical.com/book.aspx?bookid=2709#225069419 6. Part 16: Lysosomal disorders. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed April 17, 2025. Available at https://ommbid.mhmedical.com/book.aspx?bookid=2709#225069419

LSDS
606771

Lysosomal Disorders Screen, Random, Urine

Clinical Information: Lysosomal disorders (LD) are a diverse group of inherited diseases characterized by the intracellular accumulation of macromolecules leading to cell damage and organ dysfunction. Approximately 50 LD have been described with a wide phenotypic spectrum and ranging in severity from neonatal lethal to later onset variants. Although classification is not always straightforward, LD are generally categorized according to the type of storage material that accumulates in the cells and tissues. Major categories include mucopolysaccharidoses, oligosaccharidoses, mucolipidoses, and sphingolipidoses. In many cases, accumulating analytes can be detected in urine. Screening for these disorders typically begins with an analysis to detect disease-specific metabolite patterns or profiles indicative of a LD. The combined analysis of disease-specific markers for LD in multiple tests can allow for the identification of additional disorders that may not be characterized using any of the single tests alone. Disorders detectable by this approach include the oligosaccharidoses: alpha-mannosidosis, aspartylglucosaminuria, beta-mannosidosis, fucosidosis, Schindler disease, and sialidosis; the sphingolipidoses: GM1 gangliosidosis, Sandhoff disease, galactosialidosis, saposin B deficiency, metachromatic leukodystrophy, multiple sulfatase deficiency, Fabry disease, and Gaucher disease; the mucopolysaccharidoses (MPS) excluding MPS IX (hyaluronidase deficiency); the glycogen storage disorder Pompe disease, free sialic storage disorder, and the mucolipidoses types II and III. Additionally, other disorders such as congenital disorder of glycosylation (CDG) type IIb and deglycosylation disorders such as NGLY1-CDG may also be detected. The MPS are a subset of lysosomal disorders caused by the deficiency of any one of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, and/or chondroitin sulfate (glycosaminoglycans: GAG). Undegraded or partially degraded GAG (also called mucopolysaccharides) are stored in lysosomes and excreted in the urine. Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. There are 11 known enzyme deficiencies that result in MPS. In addition, abnormal GAG storage is observed in multiple sulfatase deficiency and in I-cell disease. Finally, an abnormal excretion of GAG in urine is observed occasionally in other disorders including

active bone diseases, connective tissue disease, hypothyroidism, urinary dysfunction, and oligosaccharidoses. The oligosaccharidoses are a subset of lysosomal disorders caused by the deficiency of any one of the lysosomal enzymes involved in the degradation of complex oligosaccharide chains. They are characterized by the abnormal accumulation of incompletely degraded oligosaccharides in cells and tissues and the corresponding increase of related free oligosaccharides in the urine. Clinical features can include bone abnormalities, coarse facial features, corneal cloudiness, organomegaly, muscle weakness, hypotonia, developmental delay, and ataxia. Age of onset ranges from early infancy to adult and can even present prenatally. The sphingolipidoses are a subset of lysosomal disorders caused by a defect in any one of the enzymes that degrade complex ceramide containing lipids. They are characterized by the excessive accumulation of sphingolipids in the tissues, particularly in the central nervous system, resulting in progressive neurodegeneration and developmental regression. In 2 conditions, Fabry disease and Gaucher disease type I, there is only systemic involvement. In many cases, sphingolipidoses can be detected by through oligosaccharide analysis in urine. Sialic acid (SA), or N-acetyl-neuraminic acid, is a component of carbohydrates, glycoproteins, and gangliosides, which are important for the human nervous system. SA can be measured in urine as free sialic acid or in a conjugated form bound to oligosaccharides. Sialic acid disorders are a subset of lysosomal disorders caused by defective protein transport or enzyme deficiency that result in multisystem organ disease. Analysis of free and total sialic acid and their ratio in urine can detect the following conditions: free sialic acid storage disorder, sialuria, N-acetylneuraminate pyruvate lyase deficiency, sialidosis, and galactosialidosis. Because of the similarity of features across disorders and their phenotypic variability, clinical diagnosis of LD can be challenging; therefore, the combined analysis of multiple urine screening tests is an important tool for the initial workup of an individual suspected of having a lysosomal disorder. Abnormal results can be followed up with the appropriate enzyme or molecular analysis.

Useful For: Screening patients suspected of having a lysosomal disorder

Interpretation: When abnormal results are detected with characteristic patterns, a detailed interpretation is given, including an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay and molecular test). Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. Specific enzymatic or molecular assays is recommended to confirm positive results.

Reference Values:

Dermatan Sulfate:
< or =1.00 mg/mmol creatinine

Heparan Sulfate:
< or =4 years: < or =0.50 mg/mmol creatinine
> or =5 years: < or =0.25 mg/mmol creatinine

Chondroitin-6 Sulfate:
< or =24 months: < or =10.00 mg/mmol creatinine
25 months-10 years: < or =2.50 mg/mmol creatinine
> or =11 years: < or =1.50 mg/mmol creatinine

Keratan Sulfate:
< or =12 months: < or =2.00 mg/mmol creatinine
13-24 months: < or =1.50 mg/mmol creatinine
25 months-4 years: < or =1.00 mg/mmol creatinine
5-18 years: < or =0.50 mg/mmol creatinine
> or =19 years: < or =0.30 mg/mmol creatinine

Free Sialic Acid:

< or =4 weeks: < or =208 mmol/mol creatinine
5 weeks-12 months: < or =104 mmol/mol creatinine
13 months-18 years: < or =100 mmol/mol creatinine
> or =19 years: < or =38 mmol/mol creatinine

Total Sialic Acid:
< or =4 weeks: < or =852 mmol/mol creatinine
5 weeks-12 months: < or =656 mmol/mol creatinine
13 months-18 years: < or =335 mmol/mol creatinine
> or =19 years: < or =262 mmol/mol creatinine

Total/Free Ratio:
< or =4 weeks: 1.94-18.68
5 weeks-12 months: 2.34-13.85
13 months-18 years: 2.63-9.18
> or =19 years: 3.35-15.81

Ceramide Trihexosides:
Negative

Sulfatides:
Negative

Oligosaccharides:
Negative
An interpretive report will be provided.

Clinical References: 1. Lysosomal Disorders. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019:part 16. Accessed June 9, 2025. Available at https://ommbid.mhmedical.com/book.aspx?bookID=2709#225069419 2. Pino G, Conboy E, Tortorelli S, et al. Multiplex testing for the screening of lysosomal storage disease in urine: Sulfatides and glycosaminoglycan profiles in 40 cases of sulfatiduria. Mol Genet Metab. 2020;129(2):106-110. doi:10.1016/j.ymgme.2019.10.009 3. Kingma SDA, Bodamer OA, Wijburg FA. Epidemiology and diagnosis of lysosomal storage disorders; challenges of screening. Best Pract Res Clin Endocrinol Metab. 2015;29(2):145-157. doi:10.1016/j.beem.2014.08.004

LSDGP
608011

Lysosomal Storage Disease Gene Panel, Varies

Clinical Information: Lysosomal storage diseases (LSD) encompass a group of over 40 inherited biochemical diseases in which genetic variants cause defective lysosomal functioning. Lysosomes perform catabolic functions for cells, which is accomplished through activity of various proteins such as lysosomal enzymes, transport proteins, and other proteins. Functional deficits in these proteins cause an accumulation of substrates in cells leading to progressive organ dysfunction. This leads to variable clinical features that can affect the cardiovascular, neurological, ocular, and skeletal systems, among others. Clinical features are dependent on the amount and location of the substrate accumulation but may include the following: characteristic facial features (coarse features), hepatomegaly, deafness, vision loss, abnormal skeletal findings, hydrops fetalis, ataxia, hypotonia, developmental delay/regression, and intellectual disability. Age of onset is variable, with symptoms presenting from the prenatal period to adulthood, but generally LSD are progressive and cause significant morbidity and mortality with a decreased lifespan. Enzyme replacement therapy and oral substrate inhibitors are therapeutic options for some LSD. LSD are inherited in an autosomal recessive manner with the exception of Hunter, Fabry, and Danon diseases, which are X-linked. There are founder variants

associated with LSD in the Ashkenazi Jewish and Finnish populations, leading to an increased carrier frequency for some. Overall, the prevalence of LSD is estimated at 1 in 7000 to 1 in 8000. Neuronal ceroid lipofuscinoses (NCL) are a subset of LSD that involve defective cellular processing of lipids. NCL are clinically characterized by epilepsy, intellectual and motor decline, and blindness. Electron microscopy typically shows a characteristic accumulation of granular osmophilic deposits (GROD), curvilinear profiles (CVB), or fingerprint profiles (FP). Enzymatic testing may show deficiency in palmitoyl-protein thioesterase 1 (PPT1), tripeptidyl-peptidase 1 (TPP1), or cathepsin D (CTSD). Currently there are at least 14 genetically distinct forms. Age of onset and clinical features can be variable, from congenital to adult onset. NCL is typically inherited in an autosomal recessive manner, although one adult-onset form (ANCL; DNAJC5 gene) has been shown to be autosomal dominant. This panel includes sequencing of 43 genes related to various LSD, as well as 15 genes specific to NCL. Alterations in various genes on this panel have also been associated with Parkinson disease or Lewy body disease. These alterations are not reported for individuals younger than 18 years of age but are available upon request.

Useful For: Follow up for abnormal biochemical results and confirmation of suspected lysosomal storage disease (LSD) Establishing a molecular diagnosis for patients with LSD Identifying variants within genes known to be associated with LSD, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Wang RY, Bodamer OA, Watson MS, Wilcox WR; ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases. Lysosomal storage diseases: Diagnostic confirmation and management of presymptomatic individuals. Genet Med. 2011;13(5):457-484 3. Parenti G, Andria G, Ballabio A. Lysosomal storage diseases: from pathophysiology to therapy. Ann Rev Med. 2015;66:471-486 4. Filocamo, M. Morrone A. Lysosomal storage disorders: Molecular basis and laboratory testing. Hum Genomics. 2011;5:156-169 5. Coutinho MF, Alves S. From rare to common and back again: 60 years of lysosomal dysfunction. Mol Genet Metab. 2016;117(2):53-65 6. Robak LA, Jansen IE, van Rooij J, et al. Excessive burden of lysosomal storage disorder gene variants in Parkinson's disease. Brain. 2017;140(12):3191-3203

G158
605191

Lysosomal Storage Disease Panel (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

LSD6W
606171

Lysosomal Storage Disorders, Six-Enzyme Panel, Leukocytes

Clinical Information:

Useful For: Diagnosis of the lysosomal storage disorders: Fabry (in male patients), Gaucher, Krabbe, mucopolysaccharidosis I (MPS I), acid sphingomyelinase deficiency (Niemann-Pick types A and B), and Pompe (glycogen storage disorder type II) This test is not intended for carrier detection.

Interpretation: Values below the reference ranges are consistent with a diagnosis of lysosomal storage disorders. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

Beta-Glucosidase: > or =3.53 nmol/hour/mg protein
Acid Sphingomyelinase: > or =0.32 nmol/hour/mg protein
Acid Alpha-Glucosidase: > or =5.00 nmol/hour/mg protein
Galactocerebrosidase: > or =1.88 nmol/hour/mg protein
Alpha-Galactosidase: > or =10.32 nmol/hour/mg protein
Alpha-L-Iduronidase: > or =2.06 nmol/hour/mg protein
Acid Alpha-Glucosidase (Reflex): > or =1.50 nmol/hour/mg protein
Galactocerebrosidase (Reflex): > or =0.300 nmol/hour/mg protein

An interpretative report will be provided.

Clinical References: 1. Newborn Screening ACT Sheets. American College of Medical Genetics and Genomics; Accessed October 30, 2023. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Elliott S, Buroker N, Cournoyer JJ, et al: Pilot study of newborn screening for six lysosomal storage diseases using Tandem Mass Spectrometry. Mol Genet Metab. 2016 Aug;118(4):304-309 3. Matern D, Gavrilov D, Oglesbee D, Raymond K, Rinaldo P, Tortorelli S: Newborn screening for lysosomal storage disorders. Semin Perinatol. 2015 Apr;39(3):206-216 4. Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds.: Lysosomal disorders. In: The Online Metabolic and Molecular Bases of Inherited Disease (OMMBID). Part 16. McGraw-Hill; 2019. Accessed March 3, 2022. Available at https://ommbid.mhmedical.com/book.aspx?bookID=2709#2250694196 5. Liao HC, Spacil Z, Ghomashchi F, et al: Lymphocyte galactocerebrosidase activity by LC-MS/MS for post-newborn screening evaluation of Krabbe disease. Clin Chem. 2017 Aug;63(8):1363-1369 6. Lin N, Huang J, Violante S, et al: Liquid chromatography-tandem mass spectrometry assay of leukocyte acid alpha-glucosidase for post-newborn screening evaluation of Pompe disease. Clin Chem. 2017 Apr;63(4):842-851

MURA
607462

Lysozyme (Muramidase), Plasma

Clinical Information: Lysozyme is a bacteriolytic enzyme that is found in some hematopoietic cells. It is primarily present in granulocytes, monocytes, and histiocytes. The enzyme is present in only minute amounts in lymphocytes; and is not present in myeloblasts, eosinophils, and basophils. Lysozyme in the plasma comes chiefly from the degradation of granulocytes and monocytes and its concentration reflects the turnover of these cells. Increases are seen in benign (eg, infection, inflammation) and malignant processes (eg, some leukemias). Plasma lysozyme is elevated in patients with acute or chronic granulocytic or monocytic leukemias and falls with successful treatment. Conversely, patients with lymphocytic leukemia may have depressed plasma lysozyme levels. Patients with kidney disorders (including rejection of transplanted kidneys) or Crohn disease (regional enteritis)

also tend to have elevated levels of plasma lysozyme.

Useful For: As a screening test for ocular sarcoidosis Confirming marked increases in the granulocyte or monocyte pools as in granulocytic or monocytic leukemias, myeloproliferative disorders, and malignant histiocytosis Following the course of therapy in cases of chronic granulocytic or chronic monocytic leukemias

Interpretation: Levels above 200 mcg/mL may be seen in acute nonlymphocytic leukemia (M2, M4, M5) or chronic granulocytic leukemias.

Reference Values:
> or =12 months: 2.6-6.0 mcg/mL
Reference values have not been established for patients who are less than12 months of age.

Clinical References: 1. Catovsky D, Galton DA, Griffin C. The significance of lysozyme estimations in acute myeloid and chronic monocytic leukaemia. Br J Haematol. 1971;21(5):565-580 2. Herbort CP, Roa NA, Mochizuki M, members of Scientific Committee of First International Workshop on Ocular Sarcoidosis. International criteria for the diagnosis of ocular sarcoidosis: Results of the first International Workshop on Ocular Sarcoidosis (IWOS). Ocul Immunol Inflamm. 2009;17(3):160-169 3. Bergantini L, Bianchi F, Cameli P, et al. Prognostic biomarkers of sarcoidosis: a comparative study of serum chitotriosidase, ACE, lysozyme, and KL-6. Dis Markers. 2019;2019:8565423 doi:10.1155/2019/8565423

LYSOZ
70503

Lysozyme Immunostain, Technical Component Only

Clinical Information: Lysozyme is an intracellular enzyme found in the primary granules of myeloid cells, monocytes, and histiocytes. Diagnostically, antibodies to lysozyme can help confirm monocytic and histiocytic differentiation in acute myeloid leukemia or histiocytic sarcoma.

Useful For: Aiding in confirmation of monocytic and histiocytic differentiation

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Burgdorf WH, Duray P, Rosai J. Immunohistochemical Identification of Lysozyme in Cutaneous Lesions of Alleged Histiocytic Nature. Am J Clin Pathol. 1981;75(2):162-167 2. Kurec AS, Cruz VE, Barrett D, et al. Immunophenotyping of Acute Leukemias Using Paraffin-Embedded Tissue Sections. Am J Clin Pathol. 1990;93(4):502-509 3. Li WV, Kapadia SB, Sonmez-Alpan E, Swerdlow SH. Immunohistochemical Characterization of Mast Cell Disease in Paraffin Sections Using Tryptase, CD68, Myeloperoxidase, Lysozyme, and CD20 Antibodies. Mod Pathol. 1996;9(10):982-988 4. Miettinen M, Fetsch JF. Reticulohistiocytoma (Solitary Epithelioid Histiocytoma). A Clinicopathologic and Immunohistochemical Study of 44 Cases. Am J Surg Pathol. 2006;30:521-528 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

LYSO
82398

Lysozyme, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to lysozyme Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MA2ES
605970

Ma2 Antibody by ELISA, Serum

Clinical Information: Ma2 antibodies are IgG biomarkers found in patients with paraneoplastic encephalitis (limbic encephalitis or brainstem encephalitis) or cerebellar ataxia. Antibodies (Ab) to Ma antigens can be found directed at Ma2 alone, or both Ma1 and Ma2, but never Ma1 alone. The

accompanying neurological disorders (encephalitis, dementia, brainstem encephalitis, cerebellar ataxia) are usually severe. The cancer associations are either testicular germinoma (Ma2 Ab positive only) or diverse (Ma1 and Ma2 Ab positive). Neurological improvement upon treatment of cancer or immunotherapy is more commonly encountered in those seropositive for Ma2 only than when compared to Ma1 and Ma2 together.

Useful For: Evaluating patients with suspected paraneoplastic encephalitides using serum specimens

Interpretation: Seropositivity for Ma2 antibody is consistent with a diagnosis of an autoimmune central nervous system disorder (encephalopathy, dementia, seizure disorder, brainstem encephalitis or cerebellar ataxia). A paraneoplastic basis should be considered and include seminoma (testicular or extra-testicular).

Reference Values:
Negative

Clinical References: 1. Voltz R, Gultekin SH, Rosenfeld MR, et al: A serologic marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. N Engl J Med. 1999 Jun 10;340(23):1788-1795. doi: 10.1056/NEJM199906103402303 2. Rosenfeld MR, Eichen JG, Wade DF, Posner JB, Dalmau J: Molecular and clinical diversity in paraneoplastic immunity to Ma proteins. Ann Neurol. 2001 Sep;50(3):339-348 3. Dalmau J, Graus F, Villarejo A, et al: Clinical analysis of anti-Ma2-associated encephalitis. Brain. 2004 Aug;127(Pt 8):1831-1844. doi: 10.1093/brain/awh203 4. Schuller M, Jenne D, Voltz R. The human PNMA family: novel neuronal proteins implicated in paraneoplastic neurological disease. J Neuroimmunol. 2005 Dec;169(1-2):172-176. doi: 10.1016/j.jneuroim.2005.08.019 5. Hoffmann LA, Jarius S, Pellkofer HL, et al: Anti-Ma and anti-Ta associated paraneoplastic neurological syndromes: 22 newly diagnosed patients and review of previous cases. J Neurol Neurosurg Psychiatry. 2008 Jul;79(7):767-773. doi: 10.1136/jnnp.2007.118588 6. Kunchok A, McKeon A: Opsoclonus in anti-Ma2 brain-stem encephalitis. N Engl J Med. 2020 Sep 24;383(13):e84. doi: 10.1056/NEJMicm1914516 7. Adams C, McKeon A, Silber MH, Kumar R: Narcolepsy, REM sleep behavior disorder, and supranuclear gaze palsy associated with Ma1 and Ma2 antibodies and tonsillar carcinoma. Arch Neurol. 2011 Apr;68(4):521-4. doi: 10.1001/archneurol.2011.56. Erratum in: Arch Neurol. 2011 Sep;68(9):1211

MA2EC
605971

Ma2 Antibody, ELISA, Spinal Fluid

Clinical Information: Ma2 antibodies are IgG biomarkers found in patients with paraneoplastic encephalitis (limbic encephalitis or brainstem encephalitis) or cerebellar ataxia. Antibodies (Ab) to Ma antigens can be found directed at Ma2 alone, or both Ma1 and Ma2, but never Ma1 alone. The accompanying neurological disorders (encephalitis, dementia, brainstem encephalitis, cerebellar ataxia) are usually severe. The cancer associations are either testicular germinoma (Ma2 Ab positive only) or diverse (Ma1 and Ma2 Ab positive). Neurological improvement upon treatment of cancer or immunotherapy is more commonly encountered in those seropositive for Ma2 only than when compared to Ma1 and Ma2 together.

Useful For: Evaluating patients with suspected paraneoplastic encephalitides using spinal fluid specimens

Interpretation: Seropositivity for Ma2 antibody is consistent with a diagnosis of an autoimmune central nervous system disorder (encephalopathy, dementia, seizure disorder, brainstem encephalitis or cerebellar ataxia). A paraneoplastic basis should be considered and include seminoma (testicular or extra-testicular).

Reference Values:
Negative

Clinical References: 1. Voltz R, Gultekin SH, Rosenfeld MR, et al: A serologic marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. N Engl J Med. 1999 Jun 10;340(23):1788-1795. doi: 10.1056/NEJM199906103402303 2. Rosenfeld MR, Eichen JG, Wade DF, Posner JB, Dalmau J: Molecular and clinical diversity in paraneoplastic immunity to Ma proteins. Ann Neurol. 2001 Sep;50(3):339-348 3. Dalmau J, Graus F, Villarejo A, et al: Clinical analysis of anti-Ma2-associated encephalitis. Brain. 2004 Aug;127(Pt 8):1831-1844. doi: 10.1093/brain/awh203 4. Schuller M, Jenne D, Voltz R. The human PNMA family: novel neuronal proteins implicated in paraneoplastic neurological disease. J Neuroimmunol. 2005 Dec;169(1-2):172-176. doi: 10.1016/j.jneuroim.2005.08.019 5. Hoffmann LA, Jarius S, Pellkofer HL, et al: Anti-Ma and anti-Ta associated paraneoplastic neurological syndromes: 22 newly diagnosed patients and review of previous cases. J Neurol Neurosurg Psychiatry. 2008 Jul;79(7):767-773. doi: 10.1136/jnnp.2007.118588 6. Kunchok A, McKeon A: Opsoclonus in anti-Ma2 brain-stem encephalitis. N Engl J Med. 2020 Sep 24;383(13):e84. doi: 10.1056/NEJMicm1914516 7. Adams C, McKeon A, Silber MH, Kumar R: Narcolepsy, REM sleep behavior disorder, and supranuclear gaze palsy associated with Ma1 and Ma2 antibodies and tonsillar carcinoma. Arch Neurol. 2011 Apr;68(4):521-4. doi: 10.1001/archneurol.2011.56. Erratum in: Arch Neurol. 2011 Sep;68(9):1211

MACNT
65405

Macadamia Nut, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to macadamia nut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MACE
82492

Mace, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to mace Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MACK
82342

Mackerel, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to mackerel Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

GNMTC
619313

Macro/Microthrombocytopenia Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Platelets have essential roles in primary hemostasis. Patients with either hereditary or acquired platelet disorders usually have bleeding diathesis, which can potentially be life-threatening. They may also have issues with the development and/or functioning of major organs.(2) Inherited platelet disorders can be syndromic (ie, associated with current or future development of other organ system defects) or non-syndromic (ie, isolated to thrombocytopenia with no other organ system defects). A reliable laboratory diagnosis of a platelet disorder can significantly impact patients' and, potentially, their family members' clinical management and outcome. Identification of an alteration that is known or suspected to cause disease aids in confirmation of the diagnosis and potentially provides prognostic information, especially in syndromic inherited platelet disorders. This panel evaluates 20 genes associated with a variety of hereditary macro- or microthrombocytopenia disorders, including sitosterolemia with macrothrombocytopenia; platelet abnormalities with eosinophilia and immune-mediated inflammatory disease; Takenouchi-Kosaki syndrome with thrombocytopenia; macrothrombocytopenia and sensorineural hearing loss; syndrome with macrothrombocytopenia; thrombocytopenia 3; X-linked thrombocytopenia with dyserythropoiesis; myopathy associated with thrombocytopenia; Bernard-Soulier syndrome; platelet-type von Willebrand disease; thrombocytopenia anemia and myelofibrosis; May-Hegglin disorder/anomaly; Sebastian syndrome; MYH9-related disorders; platelet-type bleeding disorder 19; platelet-type bleeding disorder 20; and Wiskott-Aldrich syndrome. The risk for developing bleeding or other phenotypic features associated with these disorders and syndromes varies. Several of the genes on this panel have established bleeding, thrombocytopenia, or other hematologic or non-hematologic disease associations. Several of the genes on this panel also have expert group guidelines.(1,3-5) It is recommended that genetic testing be offered to all patients suspected of having a heritable platelet disorder since some patients may have normal platelet laboratory testing results.(1,6)

Useful For: Evaluating hereditary macro- or microthrombocytopenia disorders in patients with a personal or family history suggestive of a hereditary macro- or microthrombocytopenia disorder Diagnosing hereditary macro- or microthrombocytopenia disorders for patients in whom phenotypic testing is non-diagnostic but there is a strong clinical suspicion of the hereditary macro- or microthrombocytopenia disorder Confirming a hereditary macro- or microthrombocytopenia disorder

diagnosis with the identification of a known or suspected disease-causing alteration in one or more of 20 genes associated with a variety of hereditary macro- or microthrombocytopenia disorders Determining the disease-causing alterations within one or more of these 20 genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of a macro- or microthrombocytopenia disorder Identifying the causative alteration for genetic counseling purposes Prognosis and risk assessment based on the genotype-phenotype correlations Providing a prognosis in syndromic hereditary macro- or microthrombocytopenia disorders Carrier testing for close family members of an individual with a hereditary macro- or microthrombocytopenia disorder diagnosis This test is not intended for prenatal diagnosis

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Gomez K, Anderson J, Baker P, et al: Clinical and laboratory diagnosis of heritable platelet disorders in adults and children: a British Society for Haematology Guideline. Brit J Haematol. 2021 Oct;195(1):46-72 2. Nurden AT, Freson K, Selifsohn U: Inherited platelet disorders. Haemophilia. 2012 July;18 Suppl 4:154-160 3. International Society on Thrombosis and Haemostasis: Bleeding Thrombotic and Platelet Disorder TIER1 genes. ISTH; 2018. Updated July 2022. Accessed November 23, 2022. Available at: www.isth.org/page/GinTh_GeneLists 4. Megy K, Downes K, Simeoni I, et al: Curated disease-causing genes for bleeding, thrombotic, and platelet disorders: Communication from the SSC of the ISTH. J Thromb Haemost. 2019 Aug;17(8):1253-1260 5. Bolton-Maggs PHB, Chalmers EA, Collins PW, et al: A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. Brit J Haematol. 2006 Dec;135(5):603-633 6. Watson SP, Lowe GC, Lordkipanidze M, Morgan NV, GAPP consortium: Genotyping and phenotyping of platelet function disorders. J Thromb Haemost. 2013 June;11(Suppl. 1):351-363 7. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

FMACR
57817

Macroamylase

Reference Values:
Not Detected

MCRPL
34643

Macroprolactin, Serum

Clinical Information: Prolactin is secreted by the anterior pituitary gland under negative control by dopamine, which is secreted by the hypothalamus. The only physiological function of prolactin is the stimulation of milk production. In normal individuals, the prolactin concentration in blood rises in response to physiologic stimuli such as nipple stimulation, sleep, exercise, sexual intercourse, and hypoglycemia. Certain medications, (eg, phenothiazines, metoclopramide, risperidone, selective serotonin reuptake inhibitors, estrogens, verapamil) may also cause hyperprolactinemia. Pathologic causes of hyperprolactinemia include prolactin-secreting pituitary adenoma (prolactinoma), diseases of the hypothalamus, primary hypothyroidism, section compression of the pituitary stalk, chest wall lesions, renal failure, and ectopic tumors. Hyperprolactinemia may also be caused by the presence of a

high-molecular-mass complex of prolactin called macroprolactin (typically due to prolactin bound to immunoglobulin). In this situation, the patient is asymptomatic. Hyperprolactinemia attributable to macroprolactin is a frequent cause of misdiagnosis and mismanagement of patients. Macroprolactin should be considered if, in the presence of elevated prolactin levels, signs and symptoms of hyperprolactinemia are absent, or pituitary imaging studies are not informative.

Useful For: Determining biologically active levels of prolactin, in asymptomatic patients with elevated prolactin levels Ruling out the presence of macroprolactin

Interpretation: When the fraction (percentage) of polyethylene glycol (PEG)-precipitated (complexed) prolactin is 60% or less of total prolactin, the specimen is considered negative for macroprolactin. When total prolactin exceeds the upper reference limit and macroprolactin is negative, other causes for hyperprolactinemia should be explored. When the fraction (percentage) of polyethylene glycol (PEG)-precipitated (complexed) prolactin is above 60%, the specimen is considered positive for the presence of macroprolactin. Following polyethylene glycol (PEG)-precipitation, a patient whose unprecipitated prolactin concentration is greater than the upper limit of the unprecipitated prolactin reference interval may have hyperprolactinemia. See PRL / Prolactin, Serum for interpretation of prolactin levels.

Reference Values:

PROLACTIN, TOTAL
Males
<18 years: not established
> or =18 years: 4.0-15.2 ng/mL
Females
<18 years: not established
> or =18 years: 4.8-23.3 ng/mL

PROLACTIN, UNPRECIPITATED
Males
<18 years: not established
> or =18 years: 2.7-13.1 ng/mL
Females
<18 years: not established
> or =18 years: 3.4-18.5 ng/mL

When the percent of the precipitated (complexed) prolactin fraction of the total prolactin is 60% or less, the result is considered negative for macroprolactin.

Clinical References: 1. Fahie-Wilson M: In Hyperprolactinemia, Testing for Macroprolactin is Essential. Clin Chem 2003;49(9):1434-1436 2. Gibney J, Smith TP, McKenna TJ: Clinical relevance of macro-prolactin. Clin Endocrinol 2005 Jun;62:633-643

MAGU
610768

Magnesium, 24 Hour, Urine

Clinical Information: Magnesium, along with potassium, is a major intracellular cation. Magnesium is a cofactor of many enzyme systems. All adenosine triphosphate-dependent enzymatic reactions require magnesium as a cofactor. Approximately 70% of magnesium ions are stored in bone. The remainder are involved in intermediary metabolic processes; about 70% are present in free form, while the other 30% are bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The serum magnesium level is kept constant within very narrow limits Renal handling of magnesium is determined by the combination of filtration and reabsorption. Roughly 70% of the magnesium in plasma is filtered by

the glomeruli; 20% to 30% of the filtered magnesium is reabsorbed in the proximal tubule, while less than 5% is reabsorbed in the distal tubule and collecting duct.(1) Numerous causes of renal magnesium wasting have been identified including (but not limited to) congenital defects (including Barter and Gitelman syndrome), various endocrine disorders (including hyperaldosteronism and hyperparathyroidism), exposure to certain drugs (ie, diuretics, cis-platinum, aminoglycoside antibiotics, calcineurin inhibitors), and other miscellaneous causes (including chronic alcohol abuse). Gastrointestinal conditions associated with fat malabsorption and chronic diarrhea can cause fecal magnesium loss and hypomagnesemia. High levels of plasma magnesium are typically only seen in patients with decreased renal function, after administration of a magnesium load large enough to exceed the kidneys' ability to excrete it, or a combination of the 2.(2) Magnesium is an inhibitor of calcium crystal growth and contributes to urinary calcium oxalate and calcium phosphate supersaturation. However, low urinary magnesium in isolation has not been identified as a common cause of kidney stones, nor has magnesium supplementation been proven as an effective therapy for stone prevention.

Useful For: Assessing the cause of abnormal serum magnesium concentrations using a 24-hour urine collection Determining whether nutritional magnesium loads are adequate Calculating urinary calcium oxalate and calcium phosphate supersaturation and assessing kidney stone risk

Interpretation: Urinary magnesium excretion should be interpreted in concert with serum concentrations. In the presence of hypomagnesemia, a 24-hour urine magnesium greater than 24 mg/day or fractional excretion greater than 0.5% suggests renal magnesium wasting. Lower values suggest inadequate magnesium intake and/or gastrointestinal losses. In the presence of hypermagnesemia, urinary magnesium levels provide an indication of current magnesium intake. Lower urinary magnesium excretion increases urinary calcium oxalate and calcium phosphate supersaturation and could contribute to kidney stone risk.

Reference Values:
51-269 mg/24 hours
Reference values have not been established for patients <18 years and >83 years of age.

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. 2018:1309 2. Al Ghamdi SM: Magnesium deficiency: pathophysiologic and clinical overview. Am J Kidney Dis. 1994;24(5):737-752 3. Sutton RA: Abnormal renal magnesium handling. Miner Electrolyte Metab. 1993;19(4-5):232-240

MG_F
606756

Magnesium, Feces

Clinical Information: The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors: -Normal daily dietary intake of electrolytes -Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure -Electrolyte transport into fecal water due to exogenous substances and rare toxins (eg, cholera toxin) Fecal osmolality is normally in equilibrium with vascular osmolality, and sodium is the major effector of this equilibrium. Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or drugs inducing secretions, such as phenolphthalein or bisacodyl (1). Osmotic diarrhea is caused by ingestion of poorly absorbed ions or sugars.(1) There are multiple potential causes of osmotic diarrhea. Measurement of magnesium in liquid stool can assist in identifying intentional or inadvertent use of magnesium and/or phosphate containing laxatives as the cause.(2-4) The other causes of osmotic diarrhea include ingestion of osmotic agents such as sorbitol or polyethylene glycol laxatives, or carbohydrate malabsorption due most commonly to lactose intolerance. Carbohydrate malabsorption can be differentiated from other osmotic causes by a low stool pH (<6).(5,6)

Useful For: Workup of cases of chronic diarrhea Identifying the use of magnesium-containing laxatives contributing to osmotic diarrhea

Interpretation: Magnesium-induced diarrhea should be considered if the osmotic gap is above 75 mOsm/kg and is likely if the magnesium concentration is above 110 mg/dL.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Steffer KJ, Santa Ana CA, Cole JA, Fordtran JS: The practical value of comprehensive stool analysis in detecting the cause of idiopathic chronic diarrhea. Gastroenterol Clin North Am. 2012;41:539-560 2. Ho J, Moyer TP, Phillips SF: Chronic diarrhea: the role of magnesium. Mayo Clin Proc. 1995;70:1091-1092 3. Fine KD, Santa Ana CA, Fordtran JS: Diagnosis of magnesium-induced diarrhea. N Engl J Med. 1991;324:1012-1017 4. Fine KD, Ogunji F, Florio R, Porter J, Ana CS: Investigation and diagnosis of diarrhea caused by sodium phosphate. Dig Dis Sci. 1998;43(12):2708-2714 5. Eherer AJ, Fordtran JS: Fecal osmotic gap and pH in experimental diarrhea of various causes. Gastroenterology. 1992;103:545-551 6. Casprary WF: Diarrhea associated with carbohydrate malabsorption. Clin Gastroenterol. 1986;15:631-655

MGS
8448

Magnesium, Serum

Clinical Information: Magnesium, along with potassium, is a major intracellular cation. Magnesium is a cofactor of many enzyme systems. All adenosine triphosphate (ATP)-dependent enzymatic reactions require magnesium as a cofactor. Approximately 70% of magnesium ions are stored in bone. The remainder is involved in intermediary metabolic processes; about 70% is present in free form while the other 30% is bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The serum magnesium level is kept constant within very narrow limits. Regulation takes place mainly via the kidneys, primarily via the ascending loop of Henle. Conditions that interfere with glomerular filtration result in retention of magnesium and, hence, elevation of serum concentrations. Hypermagnesemia is found in acute and chronic renal failure, magnesium overload, and magnesium release from the intracellular space. Mild-to-moderate hypermagnesemia may prolong atrioventricular conduction time. Magnesium toxicity may result in central nervous system (CNS) depression, cardiac arrest, and respiratory arrest. Numerous studies have shown a correlation between magnesium deficiency and changes in calcium, potassium, and phosphate homeostasis, which are associated with cardiac disorders such as ventricular arrhythmias that cannot be treated by conventional therapy, increased sensitivity to digoxin, coronary artery spasms, and sudden death. Additional concurrent symptoms include neuromuscular and neuropsychiatric disorders. Conditions that have been associated with hypomagnesemia include chronic alcoholism, childhood malnutrition, lactation, malabsorption, acute pancreatitis, hypothyroidism, chronic glomerulonephritis, aldosteronism, and prolonged intravenous feeding.

Useful For: Monitoring preeclampsia patients being treated with magnesium sulfate, although in most cases monitoring clinical signs (respiratory rate and deep tendon reflexes) is adequate and blood magnesium levels are not required

Interpretation: Symptoms of magnesium deficiency do not typically appear until levels are 1.0 mg/dL or lower. Levels of 9.0 mg/dL or higher may be life-threatening.

Reference Values:
0-2 years: 1.6-2.7 mg/dL
3-5 years: 1.6-2.6 mg/dL
6-8 years: 1.6-2.5 mg/dL

9-11 years: 1.6-2.4 mg/dL
12-17 years: 1.6-2.3 mg/dL
>17 years: 1.7-2.3 mg/dL

Clinical References: 1. Tietz Textbook of Clinical Chemistry. Chapter 49: Fourth edition. Edited by CA Burtis, ER Ashwood, DE Bruns. Philadelphia, WB Saunders Company, 2006, pp 1893-1912 2. Ryan MF: The role of magnesium in clinical biochemistry: an overview. Ann Clin Biochem 1991;28:19-26

MAGRU 621396 Magnesium/Creatinine Ratio, Random, Urine

Clinical Information: Magnesium, along with potassium, is a major intracellular cation. Magnesium is a cofactor of many enzyme systems. All adenosine triphosphate-dependent enzymatic reactions require magnesium as a cofactor. Approximately 70% of magnesium ions are stored in bone. The remainder are involved in intermediary metabolic processes; about 70% are present in free form, while the other 30% are bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The serum magnesium level is kept constant within very narrow limits. Renal handling of magnesium is determined by the combination of filtration and reabsorption. Roughly 70% of the magnesium in plasma is filtered by the glomeruli; 20% to 30% of the filtered magnesium is reabsorbed in the proximal tubule, while less than 5% is reabsorbed in the distal tubule and collecting duct.(1) Numerous causes of renal magnesium wasting have been identified including (but not limited to) congenital defects (including Barter and Gitelman syndrome), various endocrine disorders (including hyperaldosteronism and hyperparathyroidism), exposure to certain drugs (ie, diuretics, cis-platinum, aminoglycoside antibiotics, calcineurin inhibitors), and other miscellaneous causes (including chronic alcohol abuse). Gastrointestinal conditions associated with fat malabsorption and chronic diarrhea can cause fecal magnesium loss and hypomagnesemia. High levels of plasma magnesium are typically only seen in patients with decreased renal function, after administration of a magnesium load large enough to exceed the kidneys' ability to excrete it, or a combination of the two.(2) Magnesium is an inhibitor of calcium crystal growth and contributes to urinary calcium oxalate and calcium phosphate supersaturation. However, low urinary magnesium in isolation has not been identified as a common cause of kidney stones, nor has magnesium supplementation been proven as an effective therapy for stone prevention.

Useful For: Assessing the cause of abnormal serum magnesium concentrations Determining whether nutritional magnesium loads are adequate Calculating urinary calcium oxalate and calcium phosphate supersaturation and assessing kidney stone risk.

Interpretation: Urinary magnesium excretion should be interpreted in concert with serum concentrations. In the presence of hypomagnesemia, a 24-hour urine magnesium above 24 mg/day or fractional excretion above 0.5% suggests renal magnesium wasting. Lower values suggest inadequate magnesium intake and/or gastrointestinal losses. In the presence of hypermagnesemia, urinary magnesium levels provide an indication of current magnesium intake. Lower urinary magnesium excretion increases urinary calcium oxalate and calcium phosphate supersaturation and could contribute to kidney stone risk.

Reference Values:
1 month-<12 months: 0.10-0.48 mg/mg creat
12 months-<24 months: 0.09-0.37 mg/mg creat
24 months-<3 years: 0.07-0.34 mg/mg creat
3 years-<5 years: 0.07-0.29 mg/mg creat
5 years-<7 years: 0.06-0.21 mg/mg creat
7 years-<10 years: 0.05-0.18 mg/mg creat

10 years-<14 years: 0.05-0.15 mg/mg creat
14 years-<18 years: 0.05-0.13 mg/mg creat
18 years-83 years: 0.04-0.12 mg/mg creat
Reference values have not been established for patients who are younger than 1 month.
Reference values have not been established for patients who are older than 83 years.

Clinical References: 1. Delaney MP, Lamb EJ. Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1309 2. Al Ghamdi SM. Magnesium deficiency: pathophysiologic and clinical overview. Am J Kidney Dis. 1994;24(5):737-752 3. Sutton RA. Abnormal renal magnesium handling. Miner Electrolyte Metab. 1993;19(4-5):232-240

FMME 57924 Mahi Mahi IgE

Interpretation:

Reference Values:
<0.35 kU/L

MALI 601988 MAL Immunostain, Technical Component Only

Clinical Information: MAL is a nonglycosylated hydrophobic integral membrane protein that forms, stabilizes, and maintains glycosphingolipid-enriched membrane microdomains. MAL is known also as T lymphocyte maturation-associated protein. MAL expression is a specific marker of primary mediastinal large B-cell lymphoma.

Useful For: Diagnosis of primary mediastinal large B-cell lymphoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Gentry M, Bodo J, Durkin L, Hsi ED. Performance of a commercially available MAL antibody in the diagnosis of primary mediastinal large B-cell lymphoma. Am J Surg Pathol. 2017;41(2):189-194 2. Rosenwald A, Wright G, Leroy K, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med. 2003;98(6):851-862 3. Copie-Bergman C, Plonquet A, Alonso MA, et al. MAL expression in lymphoid cells: further evidence for MAL as a distinct molecular marker of primary mediastinal large B-cell lymphomas. Mod Pathol. 2002;15(11):1172-1180 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

MALP 618475 Malabsorption Evaluation Panel, Feces

Clinical Information: Malabsorption is defined as impaired gastrointestinal (GI) absorption of nutrients, including fats, proteins, carbohydrates, vitamins, and minerals. The classic presentation of malabsorption is chronic diarrhea; however, many patients may not display this symptomatology. Instead,

they may present with mild GI symptoms and weight loss or with systemic manifestations associated with a specific nutrient deficiency. Malabsorption can result from different pathologic mechanisms; identification of the specific cause is important for proper treatment. Evaluation for the cause of malabsorption requires a variety of blood and stool tests. Stool testing as a more direct marker of GI function is particularly useful for certain diseases. Fecal calprotectin concentrations are a reflection of the number of neutrophils in the GI tract, with an elevated result consistent with an inflammatory condition such as inflammatory bowel disease. Elastase is an enzyme produced by the pancreas and decreased concentrations in the stool are indicative of pancreatic insufficiency and malabsorption due to a deficiency in digestive enzymes. The reducing substances test is useful in cases of chronic diarrhea; increased concentrations are consistent with osmotic diarrhea caused by disaccharidase deficiency or intestinal monosaccharide malabsorption. In comparison, measurement of alpha-1-antitrypsin in stool is not diagnostic for a specific malabsorption etiology but is useful for determining the extension of protein loss through the GI tract.

Useful For: Evaluation of patients with suspected malabsorption, as suggested by chronic diarrhea, unexplained weight loss, or nutritional deficiencies Differentiation between causes of malabsorption, specifically inflammatory conditions, pancreatic insufficiency, and osmotic diarrhea Detection of protein-losing enteropathy that may be associated with an underlying malabsorption

Interpretation: Calprotectin concentrations above 120 mcg/g are suggestive of an active inflammatory process within the gastrointestinal system; additional diagnostic testing to determine the etiology of the inflammation is suggested. Calprotectin concentrations between 50.0 and 120 mcg/g are borderline and may represent a mild inflammatory process; for patients with clinical symptoms suggestive of an inflammatory process, retesting in 4 to 6 weeks may be indicated. Pancreatic elastase concentrations below 100 mcg/g are consistent with exocrine pancreatic insufficiency; pancreatic elastase concentrations from 100 to 200 mcg/g are suggestive for moderate exocrine pancreatic insufficiency. Reducing substance concentrations above 0.50 g/dL are consistent with grade 2 to 4 osmotic diarrhea; reducing substance concentrations from 0.25 to 0.50 g/dL are consistent with grade 1 osmotic diarrhea. Alpha-1-antitrypsin concentrations above 100 mg/dL are consistent with protein-losing enteropathy

Reference Values:

ALPHA-1-ANTITRYPSIN, RANDOM:
< or =54 mg/dL

CALPROTECTIN:
<50.0 mcg/g (Normal)
50.0-120 mcg/g (Borderline)
>120 mcg/g (Abnormal)
Reference values apply to all ages.

PANCREATIC ELASTASE:
<100 mcg/g (Severe pancreatic insufficiency)
100-200 mcg/g (Moderate pancreatic insufficiency)
>200 mcg/g (Normal)
Reference values apply to all ages.

REDUCING SUBSTANCE:
Negative or trace

Clinical References: 1. Levitt DG, Levitt MD. Protein losing enteropathy: comprehensive review of the mechanistic association with clinical and subclinical disease states. Clin Exp Gastroenterol. 2017;10:147-168 2. Murray FR, Morell B, Biedermann L, Schreiner P. Protein-losing enteropathy as precursor of inflammatory bowel disease: a review of the literature. BMJ Case Rep.

2021;14(1):e238802 3. Gisbert JP, McNicholl AG. Questions and answers on the role of faecal calprotectin as a biological marker in inflammatory bowel disease. Dig Liver Dis. 2009;41(1):56-66 4. Sherwood RA, Walsham NE, Bjarnason I. Gastric, pancreatic, and intestinal function. In: Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1398-1420 5. Capurso G, Traini M, Piciucchi M, Signoretti M, Arcidiacono PG: Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. Clin Exp Gastroenterol. 2019;12:129-139 6. Chowdhury SD, Kurien RT, Ramachandran A, et al. Pancreatic exocrine insufficiency: Comparing fecal elastase 1 with 72-h stool for fecal fat estimation. Indian J Gastroenterol. 2016;35(6):441-444 7. Siddiqui HA, Salwen MJ, Shaikh MF, Bowne WB. Laboratory diagnosis of gastrointestinal and pancreatic disorders. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:306-323 8. Branski D. Disorders of malabsorption. In: Kleigman RM, Stanton BF, St.Geme JW, eds. Nelson Textbook of Pediatrics. Elsevier; 2016:1831-1850 9. Krom FA, Frank CG. Clinitesting neonatal stools. Neonatal Netw. 1989;8(2):37-40 10. Sacks DB. Carbohydrates: Qualitative methods for total reducing substances. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 2nd ed. 1994;968-969

LMALP
37115

Malaria PCR with Parasitemia Reflex, Varies

Clinical Information: Malaria is a mosquito-transmitted disease caused by apicomplexan parasites in the genus Plasmodium. It is an important cause of morbidity and mortality worldwide, with the World Health Organization estimating 219 million cases and 435,000 malaria-related deaths in 2017. Malaria disproportionately affects individuals living in Africa (90% of cases), with individuals living in southeast Asia and the eastern Mediterranean regions next most affected. Malaria is also encountered outside of endemic regions, such as the United States, usually in returning travelers. Malaria is caused primarily by 4 species of the protozoa Plasmodium: Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale. A fifth Plasmodium species, Plasmodium knowlesi, is a simian parasite that may be an important source of human infection in some regions of Southeast Asia. Differentiating P falciparum and P knowlesi from other species is important since both can cause life-threatening infections. In addition, P falciparum is typically resistant to many commonly used antimalarial agents, such as chloroquine. Microscopy of Giemsa-stained thick and thin blood films is the standard laboratory method for diagnosis and species identification of malaria parasites. Under optimal conditions, the sensitivity of the thick film microscopy is estimated to be 10 to 30 parasites per microliter of blood. However, microscopic diagnosis requires considerable expertise and may be insensitive or nonspecific when inadequate training and facilities are available. Furthermore, prolonged exposure to EDTA, transportation conditions, and prior use of antimalarial drugs may alter parasite morphology and negatively impact the ability to perform speciation by microscopy. Finally, Babesia parasites have a similar appearance to P falciparum ring forms (early trophozoites) on peripheral blood films, resulting in potential diagnostic confusion. Polymerase chain reaction (PCR) analysis is an alternative method for malaria diagnosis that allows for sensitive and specific detection of Plasmodium species DNA from peripheral blood. PCR may be more sensitive than conventional microscopy in very low parasitemias and is more specific for species identification. It may be particularly useful when subjective microscopy does not permit certain identification of the species present. Malaria PCR can be used in conjunction with a traditional blood film or Babesia PCR when the clinical or morphologic differential includes both babesiosis and malaria. Examination of the thin film also allows for calculation of percent parasitemia, which can be used to predict prognosis and monitor response to treatment.

Useful For: Detection of Plasmodium DNA and identification of the infecting species, with reflex percent parasitemia calculated using thin blood films for positive cases An adjunct to conventional microscopy of Giemsa-stained films Detection and confirmatory identification of Plasmodium species: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi This test should not be used to screen asymptomatic patients.

Interpretation: A positive result indicates the presence of Plasmodium nucleic acid, and the melting

curve analysis indicates the infecting species.

Reference Values:
Negative

Clinical References: 1. Global Health, Division of Parasitic Diseases and Malaria: Malaria. CDC; Updated March 28, 2023. Accessed March 29, 2023. Available at www.cdc.gov/malaria/ 2. Swan H, Sloan L, Muyombwe A, et al: Evaluation of a real-time polymerase chain reaction assay for the diagnosis of malaria in patients from Thailand. Am J Trop Med Hyg. 2005 Nov;73(5):850-854 3. World Health Organization (WHO). Malaria. WHO; Updated December 8, 2022. Accessed March 29, 2023. Available at www.who.int/news-room/fact-sheets/detail/malaria

LCMAL
87860

Malaria, Molecular Detection, PCR, Varies

Clinical Information: Malaria is a mosquito-transmitted disease caused by apicomplexan parasites in the genus Plasmodium. It is an important cause of morbidity and mortality worldwide, with the World Health Organization (WHO) estimating 219 million cases and 435,000 malaria-related deaths in 2017. Malaria disproportionately affects individuals living in Africa (90% of cases), with individuals living in southeast Asia and the eastern Mediterranean regions next most affected. Malaria is also encountered outside of endemic regions, such as the United States, usually in returning travelers. Malaria is caused primarily by 4 species of the protozoa Plasmodium: Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale. A fifth Plasmodium species, Plasmodium knowlesi, is a simian parasite that may be an important source of human infection in some regions of Southeast Asia. Differentiating P falciparum and P knowlesi from other species is important since both can cause life-threatening infections. In addition, P falciparum is typically resistant to many commonly used antimalarial agents, such as chloroquine. Microscopy of Giemsa-stained thick and thin blood films is the standard laboratory method for diagnosis and differentiation of malaria parasites. Under optimal conditions, the sensitivity of the thick film microscopy is estimated to be 10 to 30 parasites per microliter of blood. However, microscopic diagnosis requires considerable expertise and may be insensitive or nonspecific when inadequate training and facilities are available. Furthermore, prolonged exposure to EDTA, transportation conditions, and prior use of antimalarial drugs may alter parasite morphology and negatively impact the ability to perform species identification by microscopy. Finally, Babesia parasites have a similar appearance to P falciparum ring forms (early trophozoites) on peripheral blood films, resulting in potential diagnostic confusion. Polymerase chain reaction (PCR) analysis is an alternative method of malaria diagnosis that allows for sensitive and specific detection of Plasmodium species DNA from peripheral blood. PCR may be more sensitive than conventional microscopy in very low parasitemias and is more specific for species identification. It may be particularly useful when subjective microscopy does not permit certain identification of the species present. Malaria PCR can be used in conjunction with a traditional blood film or Babesia PCR when the clinical or morphologic differential includes both babesiosis and malaria. Examination of the thin film also allows for calculation of percent parasitemia, which can be used to predict prognosis and monitor response to treatment. This test does not include blood smear examination or calculation of parasitemia.

MCMF
113355

Malignant Cells Cyto/Heme (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MALT
82834

Malt, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to malt Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MAMLF
58105

MAML2 (11q21) Rearrangement, Mucoepidermoid Carcinoma (MEC), FISH, Tissue

Clinical Information: Mucoepidermoid carcinoma is the most common malignant salivary gland neoplasm, representing over 30% of all malignant salivary gland tumors. Mucoepidermoid carcinoma can arise in other locations such as the lung and airways. The diagnosis can be quite challenging due to the degree of histologic overlap with other tumors. MAML2 rearrangements are detectable in 80% to 85% of mucoepidermoid carcinomas but not in morphologic mimics. MAML2 rearrangements can be identified in numerous neoplasms in addition to mucoepidermoid carcinoma including, but not limited to, hidradenoma, poroma, porocarcinoma, and hemangioendothelioma.

Useful For: Supporting the diagnosis of mucoepidermoid carcinoma when used in conjunction with an anatomic pathology consultation

Interpretation: MAML2 will be clinically interpreted as positive, negative, or equivocal. A MAML2 abnormality is detected when the percent of cells with an abnormality exceeds the normal cutoff for the MAML2 probe set. A positive result is consistent with rearrangement of the MAML2 gene and likely reflects MAML2 fusion with a partner gene. The significance of this finding is dependent on the clinical and pathologic features. A negative result suggests a MAML2 gene rearrangement is not present but does not exclude a MAML2 rearrangement.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Seethala RR, Dacic S, Cieply K, Kelly LM, Nikiforova MN. A reappraisal of the MECT1/MAML2 translocation in salivary mucoepidermoid carcinomas. Am J Surg Pathol. 2010;34(8):1106-1121 2. Behboudi A, Enlund F, Winnes M, et al. Molecular classification of mucoepidermoid carcinomas-prognostic significance of the MECT1-MAML2 fusion oncogene. Genes Chromosomes Cancer. 2006;45(5):470-481 3. Salem A, Bell D, Sepesi B, et al. Clinicopathologic and genetic features of primary bronchopulmonary mucoepidermoid carcinoma: the MD Anderson Cancer Center experience and comprehensive review of the literature. Virchows Archiv. 2017;470(6):619-26 4. Kuma Y, Yamada Y, Yamamoto H, et al. A novel fusion gene CRTC3-MAML2 in hidradenoma: histopathological significance. Hum Pathol. 2017;70:55-61 5. Sekine S, Kiyono T, Ryo E, et al. Recurrent YAP1-MAML2 and YAP1-NUTM1 fusions in poroma and porocarcinoma. J Clin Invest. 2019;129(9):3827-3832 6. Antonescu CR, Dickson BC, Sung YS, et al. Recurrent YAP1 and MAML2 gene rearrangements in retiform and composite hemangioendothelioma. Am J Surg Pathol. 2020;44(12):1677-1684

MGB
70507

Mammaglobin (MGB) Immunostain, Technical Component Only

Clinical Information: Mammaglobin, a mammary specific member of the uteroglobin family, is known to be overexpressed in human breast cancer. It may be valuable when used in a panel with GCDFP-15 and ER to evaluate tumors of unknown primary site.

Useful For: Breast-specific marker Aids in evaluating tumors of unknown primary site

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Bernstein JL, Godbold JH, Raptis G, et al. Identification of mammaglobin

as a novel serum marker for breast cancer. Clin Cancer Res. 2005;11(18):6528-35 2. Leygue E, Snell L, Dotzlaw H, et al. Mammaglobin, a potential marker of breast cancer nodal metastasis. J Pathol. 1999;189(1):28-33 3. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

MAND
82352

Mandarin, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to mandarin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier;

MNU
8080

Manganese, 24 Hour, Urine

Clinical Information: Manganese (Mn) is a trace essential element with many industrial uses. Mining as well as iron and steel production have been implicated as occupational sources of exposure. It is principally used in steel production to improve hardness, stiffness, and strength. Mn is a normal constituent of air, soil, water, and food. The primary nonoccupational source of exposure is by eating food or Mn-containing nutritional supplements. Vegetarians who consume foods rich in Mn such as grains, beans, and nuts, as well as heavy tea drinkers, may have a higher intake than the average person. People who smoke tobacco or inhale second-hand smoke are also exposed to Mn at higher levels than nonsmokers. Inhalation is the primary source of entry for Mn but is also partially absorbed (3%-5%) through the gastrointestinal tract. Only very small amounts of Mn are absorbed dermally. Signs of toxicity may appear quickly, and neurological symptoms are rarely reversible. Mn toxicity is generally recognized to progress through 3 stages. Levy describes these stages. "The first stage is a prodrome of malaise, somnolence, apathy, emotional lability, sexual dysfunction, weakness, lethargy, anorexia, and headaches. If there is continued exposure, progression to a second stage may occur, with psychological disturbances, including impaired memory and judgement, anxiety, and sometimes psychotic manifestations such as hallucinations. The third stage consists of progressive bradykinesia, dysarthria, axial and extremity dystonia, paresis, gait disturbances, cogwheel rigidity, intention tremor, impaired coordination, and a mask-like face. Many of those affected may be permanently and completely disabled."(1) Mn is removed from the blood by the liver where it's conjugated with bile and excreted. As listed in the United States National Agriculture Library, Mn adequate intake is 1.6 to 2.3 mg/day for adults. This level of intake is easily achieved without supplementation by a diverse diet including fruits and vegetables, which have higher amounts of Mn than other food types. Patients on a long-term parenteral nutrition should receive Mn supplementation and should be monitored to ensure that circulatory levels of Mn are appropriate.

Useful For: Monitoring manganese exposure using 24 hour urine collections Nutritional monitoring

Interpretation: Manganese (Mn) in urine represents the excretion of excess Mn from the body. Elevated levels may indicate occupational exposure or excessive nutritional intake. Specimens from normal individuals have very low levels of Mn.

Reference Values:
0-17 years: Not established
> or =18 years: <4.0 mcg/24 hr

Clinical References: 1. Levy BS, Nassetta WJ. Neurologic effects of manganese in humans: A review. Int J Occup Environ Health. 2003;9(2):153-163. doi:10.1179/oeh.2003.9.2.153 2. Paschal DC, Ting BG, Morrow JC, et al. Trace metals in urine of United States residents: reference range concentrations. Environ Res. 1998;76(1):53-59. doi:10.1006/enrs.1997.3793 3. Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023

MNB
89120

Manganese, Blood

Clinical Information: Manganese (Mn) is a trace essential element with many industrial uses. Mining as well as iron and steel production have been implicated as occupational sources of exposure. It is principally used in steel production to improve hardness, stiffness, and strength. Mn is a normal constituent of air, soil, water, and food. The primary nonoccupational source of exposure is by eating

food or Mn-containing nutritional supplements. Vegetarians who consume foods rich in Mn such as grains, beans, and nuts, as well as heavy tea drinkers, may have a higher intake than the average person. People who smoke tobacco or inhale second-hand smoke are also exposed to Mn at higher levels than nonsmokers. Inhalation is the primary source of entry for Mn but is also partially absorbed (3%-5%) through the gastrointestinal tract. Only very small amounts of Mn are absorbed dermally. Signs of toxicity may appear quickly, and neurological symptoms are rarely reversible. Mn toxicity is generally recognized to progress through 3 stages. Levy describes these stages. "The first stage is a prodrome of malaise, somnolence, apathy, emotional lability, sexual dysfunction, weakness, lethargy, anorexia, and headaches. If there is continued exposure, progression to a second stage may occur, with psychological disturbances, including impaired memory and judgement, anxiety, and sometimes psychotic manifestations such as hallucinations. The third stage consists of progressive bradykinesia, dysarthria, axial and extremity dystonia, paresis, gait disturbances, cogwheel rigidity, intention tremor, impaired coordination, and a mask-like face. Many of those affected may be permanently and completely disabled."(1) Mn is removed from the blood by the liver where it's conjugated with bile and excreted. The major compartment for circulating Mn is the erythrocytes, bound to hemoglobin, with whole blood concentrations of Mn (in patients with normal levels) being 10 times that of the serum. Mn passes from the blood to the tissues quickly. Concentrations in the liver are highest, with 1 to 1.5 mg Mn/kg (wet weight) in normal individuals. The half-life of Mn in the body is about 40 days, with elimination primarily through the feces. Only small amounts are excreted in the urine. Elevated levels of whole blood Mn have been reported, with and without central nervous system (CNS) symptoms, in patients with hepatitis B virus-induced liver cirrhosis, in patients on total parenteral nutrition (TPN) with Mn supplementation, and in infants born to mothers who were on TPN. The studies in cirrhotic patients with extrapyramidal symptoms indicate a possible correlation between whole blood Mn and that measured by T1-weighted magnetic resonance in the globus pallidus and midbrain, with whole blood Mn levels being 2-fold or more, higher than normal. Increases in whole blood Mn over time may be indicative of future CNS effects. The data on TPN patients is based on anecdotes or small studies and is highly variable, as is that obtained in infants.(2) Behcet disease, a form of chronic systemic vasculitis, has been reported to exhibit 4-fold increase in erythrocyte Mn, and it is suggested that increased activity of superoxide dismutase may contribute to the pathogenesis of the disease. Mn has also been reported as a contaminant in "garage" preparations of the abused drug methcathinone. Continued use of the drug gives rise to CNS toxicity typical of manganism.(3) For monitoring therapy, whether of environmental exposure, TPN, or cirrhosis, whole blood levels have been shown to correlate well with neuropsychological improvement, although whether the laboratory changes precede the CNS or merely track with them remains unclear. It is recommended that both CNS functional testing and laboratory evaluation be used to monitor therapy of these patients. Long-term monitoring of Behcet disease has not been reported, and it is not known if the Mn levels respond to therapy.

Useful For: Evaluation of central nervous system symptoms, similar to Parkinson disease, in manganese (Mn) miners and processors Characterization of liver cirrhosis Therapeutic monitoring in treatment of cirrhosis, parenteral nutrition-related Mn toxicity, and environmental exposure to Mn

Interpretation:

Reference Values:
4.7-18.3 ng/mL

Clinical References: 1. Levy BS, Nassetta WJ. Neurologic effects of manganese in humans: A review. Int J Occup Environ Health. 2003;9(2):153-163. doi:10.1179/oeh.2003.9.2.153 2. Choi Y, Park JK, Park NH, et al. Whole blood and red blood cell manganese reflected signal intensities of T1-weighted magnetic resonance images better than plasma manganese in liver cirrhotics. J Occup Health. 2005;47(1):68-73. doi:10.1539/joh.47.68 3. Sanotsky Y, Lesyk R, Fedoryshyn L, Komnatska I, Matviyenko Y, Fahn S. Manganic encephalopathy due to "ephedrone" abuse. Mov Disord. 2007;22(9):1337-1343. doi:10.1002/mds.21378 4. Jiang Y, Zheng W, Long L, et al. Brain magnetic resonance imaging and manganese concentrations in red blood cells of smelting workers: search for biomarkers of manganese exposure. Neurotoxicology. 2007;28(1):126-135.

doi:10.1016/j.neuro.2006.08.005 5. Guilarte TR, Chen MK, McGlothan JL, et al. Nigrostriatal dopamine system dysfunction and subtle motor deficits in manganese-exposed non-human primates. Exp Neurol. 2006;202(2):381-390. doi:10.1016/j.expneurol.2006.06.015 6. Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 7. O'Neal SL, Zheng W. Manganese toxicity upon overexposure: a decade in review. Curr Environ Health Rep. 2015;2(3):315-328. doi:10.1007/s40572-015-0056-x

FMNRB
57196

Manganese, RBC and Plasma

Interpretation: Manganese is highly concentrated in the cellular elements of blood. Hemolysis of the cellular elements that is unobservable to the naked eye can result in elevated plasma manganese concentrations.

Reference Values:

MNS
8413

Manganese, Serum

Clinical Information: Manganese (Mn) is a trace essential element with many industrial uses. Mining and iron and steel production have been implicated as occupational sources of exposure. It is principally used in steel production to improve hardness, stiffness, and strength. Mn is a normal constituent of air, soil, water, and food. The primary non-occupational source of exposure is by eating food or Mn-containing nutritional supplements. Vegetarians who consume foods rich in Mn such as grains, beans, and nuts, as well as heavy tea drinkers may have a higher intake than the average person. People who smoke tobacco or inhale second-hand smoke are also exposed to Mn at higher levels than nonsmokers. Inhalation is the primary source of entry for Mn, but is also partially absorbed (3%-5%) through the gastrointestinal tract. Only very small amounts of Mn are absorbed dermally. Signs of toxicity may appear quickly, and neurological symptoms are rarely reversible. Mn toxicity is generally recognized to progress through 3 stages. Levy describes these stages. "The first stage is a prodrome of malaise, somnolence, apathy, emotional lability, sexual dysfunction, weakness, lethargy, anorexia, and headaches. If there is continued exposure, progression to a second stage may occur, with psychological disturbances, including impaired memory and judgement, anxiety, and sometimes psychotic manifestations such as hallucinations. The third stage consists of progressive bradykinesia, dysarthria axial and extremity dystonia, paresis, gait disturbances, cogwheel rigidity, intention tremor, impaired coordination, and a mask-like face. Many of those affected may be permanently and completely disabled."(1) Mn is removed from the blood by the liver where it's conjugated with bile and excreted. As listed in the United States National Agriculture Library, Mn adequate intake is 1.6 to 2.3 mg/day for adults. This level of intake is easily achieved without supplementation by a diverse diet including fruits and vegetables, which have higher amounts of Mn than other food types. Patients on a long-term parenteral nutrition should receive Mn supplementation and should be monitored to ensure that circulatory levels of Mn are appropriate.

Useful For: Monitoring manganese exposure using serum specimens Nutritional monitoring

Interpretation: Serum manganese results above the reference values suggest recent exposure. Serum concentrations in combination with brain magnetic resonance imaging scans and neurological assessment may be used to detect excessive exposure.

Reference Values:
0-17 years: Not established
> or =18 years: 0.5-1.2 ng/mL

Clinical References: 1. Levy BS, Nassetta WJ. Neurologic effects of manganese in humans: A review. Int J Occup Environ Health. 2003;9(2):153-163. doi:10.1179/oeh.2003.9.2.153 2. Chiswell B, Johnson D. Manganese: In: Seiler HG, Sigel A, Sigel H, eds. Handbook on Metals in Clinical and Analytical Chemistry. CRC Press; 1994:479-494 3. Finley JW, Davis CD. Manganese deficiency and toxicity: Are high or low dietary amounts of manganese cause for concern? Biofactors. 1999;10(1):15-24. doi:10.1002/biof.5520100102 4. Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 5. O'Neal SL, Zheng W. Manganese toxicity upon overexposure: a decade in review. Curr Environ Health Rep. 2015;2(3):315-328. doi:10.1007/s40572-015-0056-x 6. Glasdam SM, Glasdam S, Peters GH. The importance of magnesium in the human body: A systematic literature review. Adv Clin Chem. 2016;73:169-193. doi:10.1016/bs.acc.2015.10.002

MNRCU
614993

Manganese/Creatinine Ratio, Random, Urine

Clinical Information:

Useful For: Monitoring manganese exposure using random urine specimens Nutritional monitoring Clinical trials

Interpretation: Manganese in urine represents the excretion of excess manganese from the body and may be used to monitor exposure or excessive nutritional intake.

Reference Values:
MANGANESE
0-17 years: Not established
> or =18 years: <4.0 mcg/g creatinine

CREATININE
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Levy BS, Nassetta WJ. Neurologic effects of manganese in humans: A review. Int J Occup Environ Health. 2003;9(2):153-163. doi:10.1179/oeh.2003.9.2.153 2. Paschal DC, Ting BG, Morrow JC, et al. Trace metals in urine of United States residents: reference range concentrations. Environ Res. 1998;76(1):53-59. doi:10.1006/enrs.1997.3793 3. Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 4. O'Neal SL, Zheng W. Manganese toxicity upon overexposure: a decade in review. Curr Environ Health Rep. 2015;2(3):315-328. doi:10.1007/s40572-015-0056-x

MNCU
614994

Manganese/Creatinine Ratio, Urine

Clinical Information:

Useful For: Measurement of manganese as a part of a profile Monitoring manganese exposure Nutritional monitoring Clinical trials

Interpretation: Manganese in urine represents the excretion of excess manganese from the body and may be used to monitor exposure or excessive nutritional intake.

Reference Values:

Only orderable as part of a profile. For further information see MNRCU / Manganese/Creatinine Ratio, Random, Urine.

0-17 years: Not established
> or =18 years: <4.0 mcg/g creatinine

Clinical References: 1. Levy BS, Nassetta WJ: Neurologic effects of manganese in humans: A review. Int J Occup Environ Health. 2003 Apr-Jun;9(2):153-163. doi: 10.1179/oeh.2003.9.2.153 2. Paschal DC, Ting BG, Morrow JC, et al: Trace metals in urine of United States residents: reference range concentrations. Environ Res. 1998 Jan;76(1):53-59. doi: 10.1006/enrs.1997.3793 3. Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 4. O'Neal SL, Zheng W: Manganese toxicity upon overexposure: a decade in review. Curr Environ Health Rep. 2015 Sep;2(3):315-328. doi: 10.1007/s40572-015-0056-x

MANGO
82811

Mango, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mango Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive

4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MBLF
614985

Mannan Binding Lectin Complement Pathway, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: the classical pathway, the alternative (or properdin) pathway, and the lectin (or mannan binding lectin: MBL) pathway. The total complement assay (COM / Complement, Total, Serum) is the best screening assay for complement abnormalities of the classical complement pathway (C1qrs, C4, C2, C3, C5, C6, C7, C8, C9). The COM assay will be abnormal if there are specific hereditary or acquired C1-C9 complement component deficiencies or if there is consumption of complement due to immune (or autoimmune) complexes. Abnormalities in the alternative pathway may be evaluated with the AH50 functional assay (AH50 / Alternative Complement Pathway, Functional, Serum). The alternative pathway shares C3 and C5 through C9 components but has unique early complement components designated factors D, B, and P, as well as regulatory factors H and I. This pathway can be activated by hydrolysis of C3 or by microbial polysaccharides and does not require immune complex formation as a trigger. Patients with deficiencies in the alternative pathway factors (D, B, P, H, and I) or late complement components (C3, C5-C9) are unusually susceptible to recurrent Neisserial meningitis. Dysregulation of the alternative pathway is also observed in cases of atypical hemolytic uremic syndrome and rare kidney diseases such as C3 glomerulopathies.(1) MBL is an acute phase protein, one of several lectins and collectins that initiate lectin pathway complement activity. These proteins play a role in host defense, recognizing pathogen- and damage-associated molecular patterns. MBL associates with MBL-associated serine proteases (MASP-1, -2, and -3) to activate complement components C2 through C9. MBL deficiency is a common finding worldwide due to the broad genetic distribution of deficient MBL2 alleles (5%-30% or higher in isolated populations).(1-3) Seven haplotypes are commonly observed, with a potential for 28 possible combinations.(4) MBL activity of less than 10% may be found in a normal population at frequencies of 20% to 30%, a finding confirmed by Mayo Clinic during validation studies. MBL function assessment is recommended as second-tier testing when total complement and alternative complement analyses are both within reference intervals, and the clinical presentation of recurrent infections, along with suspicion of complement dysregulation, remains in the differential.

Useful For: Investigating recurrent meningococcal disease in young children Investigating recurrent or severe infections in adults Investigating glomerular kidney diseases Additionally, deficiencies or dysregulation within the complement system may be identified in patients when this test is used in combination with related tests.

Interpretation: Low (<10%) mannan-binding lectin (MBL) pathway activity is consistent with very low or absent MBL protein in the context of normal alternative pathway and normal classical pathway activity. Not all individuals with decreased MBL function will manifest with clinical symptoms. MBL pathway function test results must be interpreted with clinical presentation, other comorbidities (autoimmune disease, infection, malignancy), and the overall status of the immune system (primary and secondary immunodeficiencies). In addition, identification of an MBL deficiency does not exclude other

etiologies that would predispose individuals to an increased risk of infection.

Reference Values:
> or =10%

Clinical References: 1. Willrich MAV, Braun KMP, Moyer AM, Jeffrey DH, Frazer-Abel A. Complement testing in the clinical laboratory. Crit Rev Clin Lab Sci. 2021;58(7):447-478. doi:10.1080/10408363.2021.1907297 2. Heitzeneder S, Seidel M, Forster-Waldl E, Heitger A. Mannan-binding lectin deficiency - Good news, bad news, doesn't matter? Clin Immunol. 2012;143(1):22-38. doi:10.1016/j.clim.2011.11.002 3. Kalia N, Singh J, Kaur M. The ambiguous role of mannose-binding lectin (MBL) in human immunity. Open Med (Wars). 2021;16(1):299-310. doi:10.1515/med-2021-0239 4. Eisen DP, Osthoff M. If there is an evolutionary selection pressure for the high frequency of MBL2 polymorphisms, what is it? Clin Exp Immunol. 2014;176(2):165-171. doi:10.1111/cei.12241

FMPRE
57535

Maple Red (Acer rubrum) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >=50 Very Strong Positive

Reference Values:
<0.35 kU/L

MSUDP
608031

Maple Syrup Urine Disease Gene Panel, Varies

Clinical Information: Maple syrup urine disease (MSUD) is an inborn error of metabolism caused by the deficiency of the branched-chain ketoacid dehydrogenase (BCKDH) complex. The BCKDH complex is involved in the metabolism of the branched-chain amino acids (BCAA): isoleucine (Ile), leucine (Leu), and valine (Val). MSUD can be divided into 5 phenotypes: classic, intermediate, intermittent, thiamine-responsive, and dihydrolipoyl dehydrogenase (E3)-deficient, depending on the clinical presentation and response to thiamine administration. Classic MSUD, the most common and most severe form, presents in newborns with feeding intolerance, failure to thrive, vomiting, lethargy, and maple syrup odor in urine and cerumen. If untreated, it progresses to irreversible intellectual disability, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. Age of onset for individuals with non-classical forms of MSUD is variable, with some presenting with symptoms as early as 2 years of age. Symptoms include poor growth and feeding, irritability, and developmental delays. These patients can also experience severe metabolic intoxication and encephalopathy during periods of sufficient catabolic stress. MSUD is a panethnic condition but is most prevalent in the Old Order Mennonite community in Lancaster, Pennsylvania with an incidence there of 1 in 760 live births. The incidence of MSUD is approximately 1 in 185,000 live births in the general population. A comprehensive gene panel is a helpful tool to establish a diagnosis for patients with suggestive clinical and biochemical features given the broad clinical spectrum and genetic heterogeneity of MSUD. The BCKDH complex consists of 4 subunits (E1a, E1b, E2, E3), and this panel includes testing of the genes that encode each subunit (BCKDHA for E1a, BCKDHB for E1b, DBT for E2, and DLD for E3). In addition, BCKDK and PPM1K are also included, both of which impact the activity of the BCKDH complex. Disease-causing variants in both alleles of any of these genes result in disease. The recommended first-tier tests to screen for MSUD is a combination of biochemical tests including quantitative plasma amino acids (AAQP / Amino Acids, Quantitative, Plasma) to measure BCAA levels and alloisoleucine and urine organic acids (OAU / Organic Acids Screen, Urine) to look for presence of toxic urine metabolites including 2-hydroxy-isovaleric acid and 2-oxo-isocaprioic acid. Treatment of MSUD aims to normalize the concentration of BCAA by dietary restriction of these amino acids.

Because BCAA belong to the essential amino acids, the dietary treatment requires frequent adjustment, which is accomplished by regular determination of BCAA and allo-isoleucine concentrations. Orthotopic liver transplantation has been successful and is an effective therapy for MSUD.

Useful For: Follow up for abnormal biochemical results suggestive of maple syrup urine disease (MSUD) Establishing a molecular diagnosis for patients with MSUD Identifying variants within genes known to be associated with MSUD, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. 2. Chuang DT, Shih VE, Wynn RM. Maple syrup urine disease (branched-chain ketoaciduria). In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Accessed March 8, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225084607&bookid=2709#225084691 3. Frazier DM, Allgeier C, Horner C, et al. Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach. Mol Genet Metab. 2014;112(3)210-217 4. Strauss KA, Puffenberger EG, Morton DH. Maple Syrup Urine Disease. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated April 23, 2020. Accessed March 8, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1319 5. Diaz VM, Camarena C, de la Vega A, et al. Liver transplantation for classical maple syrup urine disease: long-term follow-up. J Pediatr Gastroenterol Nutr. 2014;59(5):636-639

MARE
82141

Mare's Milk, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to mare's milk Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of

allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MFRGG
617379

Marfan, Loeys-Dietz, and Aortopathy Gene Panel, Varies

Clinical Information: Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue that occurs in approximately 1 to 2 per 10,000 individuals. It is characterized by the presence of skeletal, ocular, and cardiovascular manifestations and is caused by variants in the FBN1 gene. Skeletal findings may include tall stature, chest wall deformity, scoliosis, and joint hypermobility. Lens dislocation (ectopia lentis) is the cardinal ocular feature, with mitral valve prolapse and aortic root dilatation/dissection the main cardiovascular features.(1) Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with significant overlap with Marfan syndrome but may include involvement of other organ systems and is primarily caused by variants in the TGFBR1 and TGFBR2 genes.(2,3) Features of LDS that are not typical of MFS include craniofacial and neurodevelopmental abnormalities and arterial tortuosity with increased risk for aneurysm and dissection throughout the arterial tree. Variants in the SMAD3 gene have been reported in families with an LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis. Variants in the TGFB3 gene have also been reported in families with an LDS-like phenotype, although these individuals tend to not have arterial tortuosity. Heritable thoracic aortic disease, also known as familial thoracic aortic aneurysm/dissection (FTAAD), is a genetic condition primarily involving dilatation and dissection of the thoracic aorta but may also include aneurysm and dissection of other arteries. This condition has a highly variable age of onset and presentation and may involve additional features such as congenital heart defects and other features of connective tissue disease or smooth muscle abnormalities depending on the causative gene. The gene most commonly involved in FTAAD is ACTA2.(4,5) Vascular Ehlers-Danlos syndrome (also known as vEDS or EDS IV) is an autosomal dominant connective tissue disease caused by variants in the COL3A1 gene. vEDS may present with

characteristic facial features, thin, translucent skin, easy bruising, and arterial, intestinal, and uterine fragility. Arterial rupture may be preceded by aneurysm or dissection or may occur spontaneously.(6) Classic Ehlers-Danlos syndrome types I and II (also known as cEDS) are caused by variants in the COL5A1 and COL5A2 genes. Aortic root dilation and, more rarely, spontaneous vessel rupture have been reported in cEDS.(7) Other genes included on this panel are associated with less common conditions that have significant overlap with Marfan syndrome, Loeys-Dietz syndrome, vEDS, and cEDS.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of Marfan syndrome and related conditions Establishing a diagnosis for Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, classic Ehlers-Danlos syndrome, and heritable thoracic aortic disease/aortopathy

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Loeys BL, Dietz HC, Braverman AC, et al: The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010 Jul;47(7):476-485 2. Loeys BL, Schwarze U, Holm T, et al: Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med. 2006 Aug 24;355(8):788-798 3. Loeys BL, Chen J, Neptune ER, et al: A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet. 2005 Mar;37(3):275-281 4. Milewicz DM, Regalado E: Heritable thoracic aortic disease overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated December 14, 2017. Accessed September 22, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1120/ 5. Guo DC, Pannu H, Tran-Fadulu V, et al: Mutations in smooth muscle a-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. Nat Genet. 2007 Dec;39(12):1488-1493 6. Pepin M, Schwarze U, Superti-Furga A, Byers PH: Clinical and genetic features of Ehlers-Danlos syndrome type IV, The vascular type. N Engl J Med. 2000 Mar 9;342(10):673-680 7. Malfait F, Wenstrup R, Paepe AD: Classic Ehlers-Danlos syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2007. Updated July 26, 2018. Accessed August 1, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1244/ 8. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

MARJ
82605

Marjoram, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to marjoram Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MSPTC
113288

Mass Spectrometry (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MSMNT
621774

Mass Spectrometry, Membranous Nephropathy, Technical Component (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MCM24
608378

Mast Cell Mediators, 24 Hour, Urine

Clinical Information: Primary mast cell activation syndromes (MCAS) have clonal markers, such as the KIT Asp816Val variant or aberrant expression of CD25 or CD2 on MC. The 2 primary groups of MCAS are mastocytosis (cutaneous and systemic) and monoclonal MCAS. Systemic mastocytosis (SM) is a disease in which clonally derived mast cells accumulate in peripheral tissues. Degranulation of these mast cells releases large amounts of histamines, prostaglandins, leukotrienes, and tryptase. Patients with SM should fulfill the World Health Organization diagnostic criteria for this disorder. Diagnosis requires either the major plus one minor criterion or 3 minor criteria.(1-3) The consensus diagnostic criteria for SM include: Major criterion: Imaging of the multifocal infiltrates Minor criteria: 1. Identifying morphological features of above 25% of MC from bone marrow biopsy 2. Detection of the point alteration at codon 816 in the KIT gene 3. CD2, CD25, and/or CD30 expression in MC 4. Persistently elevated serum tryptase (>20 ng/mL) The 2 main nonclonal MCAS categories include secondary MCAS, for which there is a known trigger for MC activation (IgE-dependent and independent allergic reactions, atopic disorders, autoimmune processes), and idiopathic, in which the etiology for MC activation is undefined.(1,3-7) Based on consensus criteria, the diagnosis of MCAS can be established when typical clinical symptoms arising from recurrent (episodic) acute systemic MC activation (typically in the form of recurrent anaphylaxis in at least 2 organ systems) have been documented; MC-derived mediators increase substantially in serum or urine over the individual's baseline; and the symptoms respond to drugs blocking MC activation, MC mediators, mediator production, or mediator effects.(6) A recently proposed diagnostic algorithm for the evaluation of patients with suspected MCAS considers 2 main diagnoses that may underlie severe forms of MC activation (anaphylaxis), namely, IgE-dependent allergies and clonal MC disorders.(1,3-7) A serum tryptase level, which has long been used in diagnosing these disorders, has several drawbacks, including the need to obtain acute and baseline specimens to fulfill diagnostic criteria. Furthermore, an increased baseline tryptase level has been reported in hereditary alpha tryptasemia, complicating the diagnostic possibilities.(1,5) In addition to the limitations of serum tryptase, there are reports of symptomatic patients with features of MC activation who do not meet all the criteria for MCAS but have elevated baseline mediator metabolites.(3,5,7) In these patients, there is evidence that their symptoms respond to drugs that target MC activation, the mediators released by MC, and/or the effects of these mediators. Based on these observations, validated biomarkers suggestive of MC activation, such as an increase in the histamine metabolite (N-methylhistamine) or the prostaglandin D2 metabolite (2,3-dinor 11 beta-prostaglandin F2 alpha), have been recommended for testing when tryptase is not available, or the result is inconclusive.(7) Elevated concentrations of leukotriene E4 are associated with both clonal (primary) and nonclonal (secondary and idiopathic) MCAS.(1,4,5)

Useful For: Evaluating patients at risk for mast cell activation syndrome (eg, systemic mastocytosis) using 24-hour urine collections

Interpretation: Analytical reports within the scope of the individual assays will be provided when testing is complete.

Reference Values:
N-METHYLHISTAMINE:
0-5 years: 120-510 mcg/g creatinine
6-16 years: 70-330 mcg/g creatinine
>16 years: 30-200 mcg/g creatinine

2,3-DINOR 11B-PROSTAGLANDIN F2a:
<1802 pg/mg creatinine

LEUKOTRIENE E4:
< or =104 pg/mg creatinine

CREATININE:

Males: 930-2955 mg/24 h
Females: 603-1783 mg/24 h
Reference values have not been established for patients who are younger than 18 years.

Clinical References: 1. Weiler CR. Mast cell activation syndrome: Tools for diagnosis and differential diagnosis. J Allergy Clin Immunol Pract. 2020;8(2):498-506 2. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017;129(11):1420-1427 3. Valent P, Akin C, Hartmann K., et al. Updated diagnostic criteria and classification of mast cell disorders: A consensus proposal. Hemasphere. 2021;5(11):e646 4. Gulen T, Akin C, Bonadonna P, et al. Selecting the right criteria and proper classification to diagnose mast cell activation syndromes: A critical review. J Allergy Clin Immunol Pract. 2021;9(11):3918-3928 5. Butterfield JH. Nontryptase urinary and hematologic biomarkers of mast cell expansion and mast cell activation: Status 2022. J Allergy Clin Immunol Pract. 2022;10(8):1974-1984 6. Divekar R, Hagan J, Rank M, et al. Diagnostic utility of urinary LTE4 in asthma, allergic rhinitis, chronic rhinosinusitis, nasal polyps, and aspirin sensitivity. J Allergy Clin Immunol Pract. 2016;4(4):665-670 7. Valent P, Hartmann K, Bonadonna P, et al. Global classification of mast cell activation disorders: An ICD-10-CM-adjusted proposal of the ECNM-AIM Consortium. J Allergy Clin Immunol Pract. 2022;10(8):1941-1950

MCMRU 608379 Mast Cell Mediators, Random, Urine

Clinical Information: Primary mast cell activation syndromes (MCAS) have clonal markers, such as the KIT Asp816Val variant or aberrant expression of CD25 or CD2 on MC. The 2 primary groups of MCAS are mastocytosis (cutaneous and systemic) and monoclonal MCAS. Systemic mastocytosis (SM) is a disease in which clonally derived mast cells accumulate in peripheral tissues. Degranulation of these mast cells releases large amounts of histamines, prostaglandins, leukotrienes, and tryptase. Patients with SM should fulfill the World Health Organization diagnostic criteria for this disorder. Diagnosis requires either the major plus one minor criterion or 3 minor criteria.(1-3) The consensus diagnostic criteria for SM include: Major criterion: Imaging of the multifocal infiltrates Minor criteria: 1. Identifying morphological features of above 25% of MC from bone marrow biopsy 2. Detection of the point alteration at codon 816 in the KIT gene 3. CD2, CD25, and/or CD30 expression in MC 4. Persistently elevated serum tryptase (>20 ng/mL) The 2 main nonclonal MCAS categories include secondary MCAS, for which there is a known trigger for MC activation (IgE-dependent and independent allergic reactions, atopic disorders, autoimmune processes), and idiopathic, in which the etiology for MC activation is undefined.(1,3-7) Based on consensus criteria, the diagnosis of MCAS can be established when typical clinical symptoms arising from recurrent (episodic) acute systemic MC activation (typically in the form of recurrent anaphylaxis in at least 2 organ systems) have been documented; MC-derived mediators increase substantially in serum or urine over the individual's baseline; and the symptoms respond to drugs blocking MC activation, MC mediators, mediator production, or mediator effects.(6) A recently proposed diagnostic algorithm for the evaluation of patients with suspected MCAS considers 2 main diagnoses that may underlie severe forms of MC activation (anaphylaxis), namely, IgE-dependent allergies and clonal MC disorders.(1,3-7) A serum tryptase level, which has long been used in diagnosing these disorders, has several drawbacks, including the need to obtain acute and baseline specimens to fulfill diagnostic criteria. Furthermore, an increased baseline tryptase level has been reported in hereditary alpha tryptasemia, complicating the diagnostic possibilities.(1,5) In addition to the limitations of serum tryptase, there are reports of symptomatic patients with features of MC activation who do not meet all the criteria for MCAS but have elevated baseline mediator metabolites.(3,5,7) In these patients, there is evidence that their symptoms respond to drugs that target MC activation, the mediators released by MC, and/or the effects of these mediators. Based on these observations, validated biomarkers suggestive of MC activation, such as an increase in the histamine metabolite (N-methylhistamine) or the prostaglandin D2 metabolite (2,3-dinor 11 beta-prostaglandin F2 alpha), have been recommended for testing when tryptase is not available, or the result is inconclusive.(7) Elevated concentrations of leukotriene E4 are associated with both clonal (primary)

and nonclonal (secondary and idiopathic) MCAS.(1,4,5)

Useful For: Evaluating patients at risk for mast cell activation syndrome (eg, systemic mastocytosis) using random urine collections

Interpretation: Analytical reports within the scope of the individual assays will be provided when testing is complete.

Reference Values:
LEUKOTRIENE E4:
< or =104 pg/mg creatinine

2,3-DINOR 11B-PROSTAGLANDIN F2a:
<1802 pg/mg creatinine

N-METHYLHISTAMINE:
0-5 years: 120-510 mcg/g creatinine
6-16 years: 70-330 mcg/g creatinine
>16 years: 30-200 mcg/g creatinine

CREATININE:
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years.

Clinical References: 1. Weiler CR. Mast cell activation syndrome. Tools for diagnosis and differential diagnosis. J Allergy Clin Immunol Pract. 2020;8(2):498-506 2. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017;129(11):1420-1427 3. Valent, P, Akin, C, Hartmann, K., et.al. Updated diagnostic criteria and classification of mast cell disorders: A consensus proposal. Hemasphere. 2021;5(11): e646 4. Gulen T, Akin C, Bonadonna P, et al. Selecting the right criteria and proper classification to diagnose mast cell activation syndromes: A critical review. J Allergy Clin Immunol Pract. 2021;9(11):3918-3928 5. Butterfield JH. Nontryptase urinary and hematologic biomarkers of mast cell expansion and mast cell activation: Status 2022. J Allergy Clin Immunol Pract. 2022;10(8):1974-1984 6. Divekar R, Hagan J, Rank M, et al. Diagnostic utility of urinary LTE4 in asthma, allergic rhinitis, chronic rhinosinusitis, nasal polyps, and aspirin sensitivity. J Allergy Clin Immunol Pract. 2016;4(4):665-670 7. Valent P, Hartmann K, Bonadonna P, et al. Global classification of mast cell activation disorders: An ICD-10-CM-adjusted proposal of the ECNM-AIM Consortium. J Allergy Clin Immunol Pract. 2022;10(8):1941-1950

MATCC
35479

Maternal Cell Contamination, Molecular Analysis, Varies

Clinical Information: One of the risks associated with prenatal testing is maternal cell contamination (MCC), which can occur when a fetal specimen comes into contact with maternal blood or tissue. The risk of MCC is associated with procedures such as chorionic villus sampling, amniocentesis, or extraction of fetal blood from the umbilical cord (cord blood). If MCC is present, the maternal DNA may mask the results of any genetic testing performed on the fetal DNA. Therefore, the results of prenatal testing may be compromised. To rule out the presence of MCC, a maternal blood specimen is necessary for comparison of maternal and fetal chromosomal markers. The presence of both maternal and nonmaternal alleles for each fetal marker indicates the fetal specimen is not contaminated. MCC is confirmed when both alleles in the fetus are maternal.

Useful For: Ruling out the presence of maternal cell contamination within a fetal specimen Required for all prenatal testing performed in Mayo Clinic Laboratories' Molecular and Biochemical Genetics

laboratories

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretative report will be provided.

Clinical References: Nagan N, Faulkner NE, Curtis C, et al: Laboratory guidelines for detection, interpretation, and reporting of maternal cell contamination in prenatal analyses a report of the association for molecular pathology. J Mol Diagn. 2011 Jan;13(1):7-11, doi: 10.1016/j.jmoldx.2010.11.013

FFMSS 75692 Maternal Serum Screening, Integrated, Specimen #1, PAPP-A, NT

Clinical Information: This test combines a first- and second-trimester specimen to screen low-risk pregnancies for Down syndrome (DS), open neural tube defects (ONTD) and trisomy 18 (T18). Collection of two blood samples is required for this test. A first trimester ultrasound to measure the fetal nuchal translucency (NT) is optional (see special instructions). Patient demographics and analyte/ultrasound measurements are used to calculate multiple of the median (MoM) values for each of the laboratory analytes and the NT. The pattern of the MoM values is used to calculate post-test risks of ONTD, DS and T18. Markers used for assessment of risk include first-trimester PAPP-A with or without NT and second-trimester AFP, hCG, unconjugated estriol (uE3) and dimeric Inhibin A. A DS risk of 1 in 110 or worse is reported as abnormal. This risk cutoff predicts a detection rate of 87 percent at a screen positive rate of 1.0%. A T18 risk of 1 in 100 or worse is reported as abnormal. This risk cutoff predicts a detection rate of 90 percent at a screen positive rate of <0.5%. ARUP uses a singleton AFP MoM cut off of >or= 2.5. If the interpretation is "high AFP," there is an increased risk of an ONTD in the pregnancy. This cutoff value predicts a detection rate of 80% at a screen positive rate of 1.5%. High AFP also occurs in unrecognized twin pregnancies and with underestimated gestational age. Pregnancies at an increased risk for ONTD with an AFP MoM <2.5, but a risk of 1 in 250 or worse, are also reported as abnormal. This is usually due to a family history of ONTD, the use of certain seizure medications by the patient during pregnancy, or the presence of maternal insulin-dependent diabetes, any of which increases a patients risk for ONTD. An increased risk of congenital steroid sulfatase deficiency or Smith-Lemli-Opitz syndrome (uE3 <or= 0.14 MoM) and poor fetal outcome (hCG >or= 3.5 MoM) is reported as "see note".

Useful For: Helpful to identify pregnancies at increased risk of having a child with Down Syndrome (DS), open neural tube defects (ONTD) and trisomy 18 (T18). This test is not diagnostic.

Interpretation: The first specimen of an integrated Maternal Serum Screening is used to measure PAPP-A. A second sample must be submitted for a final interpretive report. Acceptable date ranges to draw the second samples will be provided in the Integrated-1 report. Final interpretive report will be available when the second specimen test results are complete.

Reference Values:
An interpretive report will be provided.

Part 2 must be completed in order to receive an interpretable result.

If the second specimen is not received for sequential screening, the results are uninterpretable and no maternal risk will be provided.

FMSS2
75351

Maternal Serum Screening, Integrated, Specimen #2, Alpha Fetoprotein, Hcg, Estriol, and Inhibin A

Clinical Information: This test combines a first-and second-trimester specimen to screen low-risk pregnancies for Down syndrome (DS), open neural tube defects (ONTD) and trisomy 18 (T18). Collection of two blood samples is required for this test. A first trimester ultrasound to measure the fetal nuchal translucency (NT) is optional (see special instructions). Patient demographics and analyte/ultrasound measurements are used to calculate multiple of the median (MoM) values for each of the laboratory analytes and the NT. The pattern of the MoM values is used to calculate post-test risks for ONTD, DS and T18. Markers used for assessment of risk include first-trimester PAPP-A with or without NT and second-trimester AFP, hCG, unconjugated estriol (uE3), and dimeric Inhibin A. A DS risk of 1 in 110 or worse is reported as abnormal. This risk cutoff predicts a detection rate of 87 percent at a screen positive rate of 1.0%. A T18 risk of 1 in 100 or worse is reported as abnormal. This risk cutoff predicts a detection rate of 90 percent at a screen positive rate of <0.5%. ARUP uses a singleton AFP MoM cutoff of >or=2.5. If the interpretation is "high AFP," there is an increased risk of an ONTD in the pregnancy. This cutoff value predicts a detection rate of 80% at a screen positive rate of 1.5%. High AFP also occurs in unrecognized twin pregnancies and with underestimated gestational age. Pregnancies at an increased risk for ONTD with an AFP MoM <2.5, but a risk of 1 in 250 or worse, are also reported as abnormal. This is usually due to a family history of ONTD, the use of certain seizure medications by the patient during pregnancy, or the presence of maternal insulin-dependent diabetes, any of which increases a patient's priori risk for ONTD. An increased risk of congenital steroid sulfatase deficiency or Smith-Lemli-Opitz syndrome (uE3 <or=0.14 MoM) and poor fetal outcome (hCG >or=3.5 MoM) is reported as "see note."

Useful For: Helpful to identify pregnancies at increased risk of having a child with Down syndrome (trisomy 21), Open Neural Tube Defect (ONTD, spina bifida) and trisomy 18 (T18). This test is not diagnostic. The patient information provided with the Integrated, Specm1 will be used to calculate the risks for this report.

Interpretation:

Reference Values:
An interpretive report will be provided.

FMT21
57852

MaterniT21 Plus

Clinical Information: The MaterniT21 PLUS test analyzes circulating cell-free DNA extracted from a maternal blood sample. The test is indicated for use in pregnant women with increased risk for chromosomal aneuploidy. Validation data on twin pregnancies is limited and the ability of this test to detect aneuploidy in a triplet pregnancy has not yet been validated. DNA test results do not provide a definitive genetic risk in all individuals. Cell-free DNA does not replace the accuracy and precision of prenatal diagnosis with CVS or amniocentesis. These tests are not intended to identify pregnancies at risk for neural tube defects or ventral wall defects. A patient with a positive test result should be referred for genetic counseling and offered invasive prenatal diagnosis for confirmation of test results. A negative test result does not ensure an unaffected pregnancy. While results of this testing are highly accurate, not all chromosomal abnormalities may be detected due to placental, maternal or fetal mosaicism, or other causes. The health care provider is responsible for the use of this information in the management of their patient.

Reference Values:
A final report will be provided

MSMRT 64946 Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy Report, Bone Marrow

Clinical Information: Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options. Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy (MSMRT) classifies patients into either standard or high-risk categories based on the results of 2 assays: plasma cell proliferation and fluorescence in situ hybridization for specific multiple myeloma-associated abnormalities.

Useful For: Risk stratification of patients with treated multiple myeloma, which can assist in determining treatment and management decisions Risk stratification of patients with newly diagnosed multiple myeloma

Interpretation: The interpretation of results includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:

PLASMA CELL CLONALITY:
Normal bone marrow
No monotypic clonal plasma cells detected

DNA INDEX:
Normal polytypic plasma cells
DNA index (G0/G1 cells): Diploid 0.95-1.05

Clinical References: 1. Gonsalves WI, Buadi FK, Ailawadhi S, et al. Utilization of hematopoietic stem cell transplantation for the treatment of multiple myeloma: a Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus statement. Bone Marrow Transplant. 2019;54(3):353-367. doi:10.1038/s41409-018-0264-8 2. Kapoor P, Ansell SM, Fonseca R, et al. Diagnosis and management of waldenstrom macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) guidelines 2016. JAMA Oncol. 2017;3(9):1257-1265. doi:10.1001/jamaoncol.2016.5763 3. Mikhael JR, Dingli D, Roy V, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. Mayo Clin Proc. 2013;88(4):360-376. doi: 10.1016/j.mayocp.2013.01.019 4. Swerdlow S, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours, Vol. 2 5. Kumar SK, Rajkumar SV. The multiple myelomas-current concepts in cytogenetic classification and therapy. Nat Rev Clin Oncol. 2018;15(7):409-421 doi:10.1038/s41571-018-0018-y 6. Rajkumar SV, Landgren O, Mateos MV. Smoldering multiple myeloma. Blood. 2015;125(20):3069-3075. doi:10.1182/blood-2014-09-568899 7. Aljama MA, Sidiqi MH, Lakshman A, et al. Plasma cell proliferative index is an independent predictor of progression in smoldering multiple myeloma. Blood Adv. 2018;2(22):3149-3154 8. Mellors PW, Binder M, Ketterling RP, et al. Metaphase cytogenetics and plasma cell proliferation index for risk stratification in newly diagnosed multiple myeloma. Blood Adv. 2020 May 26;4(10):2236-2244 9. Sidana S, Jevremovic D, Ketterling RP, et al: Rapid assessment of hyperdiploidy in plasma cell disorders using a novel multi-parametric flow cytometry method. Am J Hematol. 2019;94(4):424-430 10. Ghosh T, Gonsalves WI, Jevremovic D, et al. The prognostic significance of polyclonal bone marrow plasma cells in patients with relapsing multiple myeloma. Am J Hematol. 2017;92(9):E507-E512

NGAML
65089

MayoComplete Acute Myeloid Leukemia, 11-Gene Panel, Varies

Clinical Information: Next-generation sequencing is a comprehensive molecular diagnostic methodology that can interrogate multiple regions of genomic tumor DNA in a single assay. Many hematologic neoplasms, including acute myeloid leukemia (AML), are characterized by morphologic or phenotypic similarities but can have characteristic somatic mutations in several genes that enable more specific categorization. In addition, many cases of AML lack a clonal cytogenetic finding at diagnosis (normal karyotype) and can be better classified according to gene mutation profile. The presence and pattern of gene mutations in AML can provide critical prognostic information and may help in guiding therapeutic management decisions by physicians, particularly if targeted therapies are available.

Useful For: Evaluation of acute myeloid leukemia using a focused 11-gene panel at the time of diagnosis, or possibly at the time of relapsed/refractory disease, to help guide classification and possible therapeutic approaches

Interpretation: Detailed variant assessment and interpretive comments will be provided for all reportable genetic alterations.

Reference Values:
An interpretive report will be provided

Clinical References: 1. National Comprehensive Cancer Network (NCCN). NCCN Guidelines: Acute Myeloid Leukemia. NCCN; Version 3.2024. Accessed November 27, 2024. Available at www.nccn.org/guidelines/guidelines-detail?category=1&id=1411 2. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med. 2018;378(25):2386-2398. doi:10.1056/NEJMoa1716984 3. Stein EM, DiNardo CD, Fathi AT, et al. Molecular remission and response patterns in patients with mutant-IDH2 acute myeloid leukemia treated with enasidenib. Blood. 2019;133(7):676-687. doi:10.1182/blood-2018-08-869008 4. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447. doi:10.1182/blood-2016-08-733196 5. Smith CC. The growing landscape of FLT3 inhibition in AML. Hematology Am Soc Hematol Educ Program. 2019;2019(1):539-547. doi:10.1182/hematology.2019000058 6. Daver N, Schlenk RF, Russell NH, Levis MJ. Targeting FLT3 mutations in AML: review of current knowledge and evidence. Leukemia. 2019;33(2):299-312. doi:10.1038/s41375-018-0357-9

NGAMT
65661

MayoComplete Acute Myeloid Leukemia, Therapeutic Gene Mutation Panel (FLT3, IDH1, IDH2, TP53), Next-Generation Sequencing, Varies

Clinical Information: Next-generation sequencing is a comprehensive molecular diagnostic methodology that can interrogate multiple regions of genomic tumor DNA in a single assay. Many hematologic neoplasms, including acute myeloid leukemia (AML), are characterized by morphologic or phenotypic similarities but can have characteristic somatic mutations in several genes that enable a more specific categorization. In addition, many cases of AML lack a clonal cytogenetic finding at diagnosis (normal karyotype) and can be better classified according to gene mutation profile. The presence and pattern of gene mutations in AML can provide critical prognostic information and may help in guiding therapeutic management decisions by physicians, particularly if targeted therapies are available.

Useful For: Evaluation of acute myeloid leukemia using a focused 4-gene panel at the time of diagnosis, or possibly relapsed or refractory disease, to help guide possible therapeutic approaches

Interpretation: Detailed variant assessment and interpretive comments will be provided for all reportable genetic alterations.

Reference Values:
An interpretive report will be provided

Clinical References: 1. National Comprehensive Cancer Network (NCCN): NCCN Guidelines: Acute Myeloid Leukemia. NCCN; Version 3.2024 Accessed November 27, 2024. Available at www.nccn.org/guidelines/guidelines-detail?category=1&id=1411 2. DiNardo CD, Stein EM, de Botton S, et al: Durable remissions with Ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med. 2018;378(25):2386-2398. doi:10.1056/NEJMoa1716984 3. Stein EM, DiNardo CD, Fathi AT, et al. Molecular remission and response patterns in patients with mutant-IDH2 acute myeloid leukemia treated with enasidenib. Blood. 2019;133(7):676-687. doi:10.1182/blood-2018-08-869008 4. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447. doi:10.1182/blood-2016-08-733196 5. Smith CC. The growing landscape of FLT3 inhibition in AML. Hematology Am Soc Hematol Educ Program. 2019;2019(1):539-547. doi:10.1182/hematology.2019000058 6. Daver N, Schlenk RF, Russell NH, Levis MJ. Targeting FLT3 mutations in AML: review of current knowledge and evidence. Leukemia. 2019;33(2):299-312. doi:10.1038/s41375-018-0357-9

NGBCL
618477

MayoComplete B-Cell Lymphoma, Next-Generation Sequencing, Varies

Clinical Information: B-cell lymphomas are a heterogenous group of hematological malignancies characterized by a range of morphological, immunophenotypic, and clinical features. Many entities share overlapping morphologic and immunophenotypic features resulting in challenges for accurate diagnosis and classification. Genomic profiling by next-generation sequencing has revealed many genetic markers that aid in the classification and characterization of mature B-cell neoplasms. In some lymphomas, specific tumor genetic mutations may also have therapeutic implications. This test is intended to interrogate a set of genes with diagnostic, prognostic, and therapeutic value among a diverse group of B-cell lymphomas that include both clinically low grade and aggressive subtypes.

Useful For: Aiding in establishing diagnosis, refining prognosis, and potentially identifying targeted therapies for the optimal management of patients with B-cell lymphomas

Interpretation: Genomic variants detected by this test will be documented in a detailed laboratory-issued report. This report will contain information regarding the detected alterations and their associations with prognosis or possible therapeutic implications in B-cell non-Hodgkin lymphomas. The information in the clinical report may be used by the patient's healthcare professional to help guide decisions concerning management. Final interpretation of next-generation sequencing results requires correlation with all relevant clinical, pathologic, and laboratory findings and is the responsibility of the managing healthcare professional.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow S, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours, Vol 2 2. Onaindia A, Medeiros LJ, Patel KP. Clinical utility of recently identified diagnostic, prognostic, and predictive molecular biomarkers in mature B-cell neoplasms. Mod Pathol. 2017;30(10):1338-1366. doi:10.1038/modpathol.2017.58 3. Jajosky AA, Havens NP, Sadri N, et al.

Clinical utility of targeted next-generation sequencing in the evaluation of low-grade lymphoproliferative disorders. Am J Clin Pathol. 2021;156(3):433-444 4. David AR, Stone SL, Oran AR, et al. Targeted massively parallel sequencing of mature lymphoid neoplasms: assessment of empirical application and diagnostic utility in routine clinical practice. Mod Pathol. 2021;34(5):904-921 5. Stewart JP, Gazdovz J, Darzentas N, et al. Validation of the EuroClonality-NGS DNA capture panel as an integrated genomic tool for lymphoproliferative disorders. Blood Adv. 2021;5(16):3188-3198 6. Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. Blood. 2014;123(18):2791-2796. doi:10.1182/blood-2014-01-550905 7. Morin RD, Arthur SE, Assouline S. Treating lymphoma is now a bit EZ-er. Blood Adv. 2021;5(8):2256-2263 8. Thangavadivel S, Byrd JC. Gly101Val BCL2 mutation: One step closer to understanding Venetoclax resistance in CLL. Cancer Discov. 2019;9(3):320-322. doi:10.1158/2159-8290.CD-19-0029 9. Lee J, Wang YL. Prognostic and predictive molecular biomarkers in chronic lymphocytic leukemia. J Mol Diagn. 2020;22(9):1114-1125 10. Liebers N, Roider T, Bohn J-P, et al. BRAF inhibitor treatment in classic hairy cell leukemia: a long-term follow-up study of patients treated outside clinical trials. Leukemia. 2020;34(5):1454-1457

MCBPP 619604 MayoComplete Bladder and Prostate Cancer Panel, Next-Generation Sequencing, Tumor

Clinical Information: Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Microsatellite instability (MSI) status is an increasingly important biomarker for determining effective immunotherapeutic treatment options for patients with solid tumors. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for somatic mutations involving the following genes known to be associated with bladder/prostate cancer: APC, AR, ARID1A, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CDK12, CDKN2A, CHD1, CHEK1, CHEK2, CTNNB1, EGFR, ERBB2, ERCC2, FANCA, FANCC, FANCL, FGFR1, FGFR2, FGFR3, FOXA1, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, RAD51B, RAD51C, RAD51D, RAD54L, RB1, SPOP, TERT, and TP53. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with bladder/prostate tumors. The data can also be used to help determine clinical trial eligibility for patients with alterations in genes not amenable to current US Food and Drug Administration-approved targeted therapies.

Useful For: Primarily for determining if patients will respond to targeted therapy Assessment of microsatellite instability for immunotherapy decisions

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. Abida W, Armenia J, Gopalan A, et al: Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol. 2017;2017:PO.17.00029 4. Robertson AG, Kim J, Al-Ahmadie H, et al: Comprehensive molecular characterization of muscle-invasive bladder cancer. Cell. 2017;171(3):540-556.e25 5. Siefker-Radtke AO, Necchi A, Park SH, et al: Efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma: long-term follow-up of a phase 2 study. Lancet Oncol. 2022;23(2):248-258 6. Marcus L, Lemery SJ, Keegan P, Pazdur R: FDA

Approval Summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758

NGCLN 618476 MayoComplete Chronic Lymphoid Neoplasms, Next-Generation Sequencing, Varies

Clinical Information: This test is intended to evaluate a targeted set of genes involved in a heterogeneous group of chronic lymphoid neoplasms that includes chronic lymphocytic leukemia (CLL) and various low-grade B-cell lymphomas. The test includes actionable targets to aid in the differential diagnosis of low-grade B-cell lymphomas (eg, hairy cell leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma), predict prognosis (eg, risk stratification in CLL), and evaluate therapeutic options or efficacy (eg, ibrutinib therapy in CLL, EZH2 [enhancer of zeste homolog 2] inhibitors in follicular lymphoma). Genomic analysis by next-generation sequencing is complementary to the standard evaluation in the classification and management of patients with chronic lymphoid neoplasms.

Useful For: Aiding in establishing diagnosis, refining prognosis, and potentially identifying targeted therapies for the optimal management of patients with chronic or low-grade B-cell lymphoid neoplasms

Interpretation: Genomic variants detected by this test will be documented in a detailed laboratory-issued report. This report will contain information regarding the detected alterations and their associations with prognosis or possible therapeutic implications in chronic lymphoid neoplasms. The information in the clinical report may be used by the patient's healthcare professional to help guide decisions concerning management. Final interpretation of next-generation sequencing results requires correlation with all relevant clinical, pathologic, and laboratory findings and is the responsibility of the managing healthcare professional.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow S, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours, Vol 2 2. Onaindia A, Medeiros LJ, Patel KP. Clinical utility of recently identified diagnostic, prognostic, and predictive molecular biomarkers in mature B-cell neoplasms. Mod Pathol. 2017;30(10):1338-1366. doi:10.1038/modpathol.2017.58 3. Jajosky AA, Havens NP, Sadri N, et al. Clinical utility of targeted next-generation sequencing in the evaluation of low-grade lymphoproliferative disorders. Am J Clin Pathol. 2021;156(3):433-444 4. Davis AR, Stone SL, Oran AR, et al. Targeted massively parallel sequencing of mature lymphoid neoplasms: assessment of empirical application and diagnostic utility in routine clinical practice. Mod Pathol. 2021;34(5):904-921 5. Stewart JP, Gazdova J, Darzentas N, et al. Validation of the EuroClonality-NGS DNA capture panel as an integrated genomic tool for lymphoproliferative disorders. Blood Adv. 2021;5(16):3188-3198 6. Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. Blood. 2014;123(18):2791-2796. doi:10.1182/blood-2014-01-550905 7. Morin RD, Arthur SE, Assouline S. Treating lymphoma is now a bit EZ-er. Blood Adv. 2021;5(8):2256-2263 8. Thangavadivel S, Byrd JC. Gly101Val BCL2 Mutation: One step closer to understanding Venetoclax resistance in CLL. Cancer Discov. 2019;9(3):320-322. doi:10.1158/2159-8290.CD-19-0029 9. Lee J, Wang YL. Prognostic and predictive molecular biomarkers in chronic lymphocytic leukemia. J Mol Diagn. 2020;22(9):1114-1125 10. Liebers N, Roider T, Bohn JP, et al. BRAF inhibitor treatment in classic hairy cell leukemia: a long-term follow-up study of patients treated outside clinical trials. Leukemia. 2020;34(5):1454-1457

MCCRC
616489

MayoComplete Colorectal Cancer Panel, Next-Generation Sequencing, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Microsatellite instability status is an important biomarker for determining effective immunotherapeutic treatment options for patients with solid tumors. Next-generation sequencing is an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. This test is a single assay that uses formalin-fixed paraffin-embedded tissue to assess for common mutations in the following genes known to be associated with colorectal cancer: APC, BRAF, HRAS, KRAS, MLH1, MSH2, MSH6, NRAS, and PMS2. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with colorectal cancer.

Useful For: Primarily for determining patient response to various targeted therapies/immunotherapy
Predicting prognosis from microsatellite instability status

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. U.S. Food and Drug Administration (FDA). Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated August 11, 2022, Accessed July 31, 2023. Available at www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling 4. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA Approval Summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758. doi:10.1158/1078-0432.CCR-18-4070 5. Vogelstein B, Papadopoulos N, Velculescu VE, et al. Cancer genome landscapes. Science. 2013 Mar;339:1546-1558 6. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to Panitumumab or Cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008;26(35):5705-5712 7. Lievre A, Bachet JB, Le Corre D, et al. KRAS mutation status is predictive of response to Cetuximab therapy in colorectal cancer. Cancer Res. 2006;66(8):3992-3995 8. Jones JC, Renfro LA, Kipp BR, et al. Non-V600BRAF mutations define a clinically distinct molecular subtype of metastatic colorectal cancer. J Clin Oncol. 2017;35(23):2624-2630

MCSRC
616492

MayoComplete Comprehensive Sarcoma Panel, Next-Generation Sequencing, Tumor

Clinical Information: Molecular analysis of biomarkers is increasingly being utilized in oncology practices to support and guide diagnosis, prognosis, and therapeutic management of patients. Microsatellite instability status is an increasingly important biomarker for determining effective immunotherapeutic treatment options for patients with solid tumors. This next-generation sequencing assay interrogates targeted regions for the presence of somatic mutations, chromosomal translocations, interstitial deletions, and inversions that lead to gene fusions that are common in various sarcomas.

Useful For: Primarily for identifying mutations that help in the diagnosis of specific soft tissue and bone tumors (sarcoma) Secondarily for identifying mutations that have therapeutic or prognostic significance Assessing microsatellite instability for immunotherapy decisions

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. US Food and Drug Administration (FDA): Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated February 10, 2023, Accessed August 1, 2023. Available at www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling 4. Jia Y, Xie Z, Li H. Intergenically spliced chimeric RNAs in cancer. Trends Cancer. 2016;2(9):475-482. doi:10.1016/j.trecan.2016.07.006 5. Jo VY, Fletcher CDM. WHO classification of soft tissue tumours: an update based on the 2013. 4th ed. Pathology. 2014;46(2):95-104. doi:10.1097/PAT.0000000000000050 6. Fletcher CDM. The evolving classification of soft tissue tumours - an update based on the new 2013 WHO classification. Histopathology. 2014;64(1):2-11. doi:10.1111/his.12267 7. Quesada J, Amato R. The molecular biology of soft-tissue sarcomas and current trends in therapy. Sarcoma. 2012;2012:849456. doi:10.1155/2012/849456 8. Podnar J, Deiderick H, Huerta G, Hunicke-Smith S. Next-generation sequencing RNA-seq library construction. Curr Protoc Mol Biol. 2014;106:4.21.1-19. doi:10.1002/0471142727.mb0421s106 9. Mertens F, Tayebwa J. Evolving techniques for gene fusion detection in soft tissue tumours. Histopathology. 2014;64(1):151-162. doi: 10.1111/his.12272 10. AI-Zaid T, Wang WL, Somaiah N, Lazar AJ. Molecular profiling of sarcomas: new vistas for precision medicine. Virchows Arch. 2017;471(2):243-255 11. Gao Q, Liang WW, Foltz SM, et al. Driver fusions and their implications in the development and treatment of human cancers. Cell Rep. 2018;23(1):227-238e3. doi:10.1016/j.celrep.2018.03.050 12. Lam SW, Cleton-Jansen AM, Cleven AHG, et al. Molecular analysis of gene fusions in bone and soft tissue tumors by anchored multiplex PCR-based targeted next-generation sequencing. J Mol Diagn. 2018;20(5):653-663. doi:10.1016/j.jmoldx.2018.05.007 13. Roy A, Kumar V, Zorman B, et al. Recurrent internal tandem duplications of BCOR in clear cell sarcoma of the kidney. Nat Commun. 2015;6:8891. doi:10.1038/ncomms9891 14. Marino-Enriquez A, Lauria A, Przybyl J, et al. BCOR internal tandem duplication in high-grade uterine sarcomas. Am J Surg Pathol. 2018;42(3):335-341. doi:10.1097/PAS.0000000000000993 15. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA Approval Summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758. doi:10.1158/1078-0432.CCR-18-4070

MCECP 619631 MayoComplete Endometrial Carcinoma Panel, Next-Generation Sequencing, Tumor

Clinical Information: This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for somatic mutations involving the following genes, known to be associated with endometrial cancer: ATM, ATR, BRCA1, BRCA2, CDK12, CTNNB1, EPCAM, ERBB2, FBXW7, L1CAM, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, POLE, PPP2R1A, and TP53. The testing also includes microsatellite instability status, a biomarker for determining efficacy of immunotherapy in solid tumors. The results of this test can be useful for molecular tumor classification, assessing prognosis and guiding treatment of individuals with endometrial tumors. The data can also be useful in determining clinical trial eligibility.

Useful For: Primarily for determining if patients will respond to targeted therapy Assessment of microsatellite instability for immunotherapy decisions Molecular-based classification of endometrial carcinoma

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board, eds. Female genital tumours. 5th ed. World Health Organization; 2020. WHO Classification of Tumours. Vol 4 2. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 3. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 4. Marcus L, Lemery SJ, Keegan P, Pazdur R: FDA Approval Summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019 Jul 1;25(13):3753-3758 5. Leon-Castillo A, Britton H, McConechy MK, et al: Interpretation of somatic POLE mutations in endometrial carcinoma. J Pathol. 2020 Mar;250(3):323-335 6. Cancer Genome Atlas Research Network; Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013 May 2;497(7447):67-73

MCGST 616490 MayoComplete Gastrointestinal Stromal Tumor (GIST) Panel, Next-Generation Sequencing, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Microsatellite instability status is an important biomarker for determining effective immunotherapeutic treatment options for patients with solid tumors. Next-generation sequencing is an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. This test is a single assay that uses formalin-fixed paraffin-embedded tissue to assess for common mutations in the following genes known to be associated with gastrointestinal stromal tumors (GIST): APC, BRAF, HRAS, KIT, KRAS, NF1, NRAS, PDGFRA, PIK3CA, SETD2, and TP53. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with GIST.

Useful For: Establishing diagnosis and identifying targeted therapies for patients with gastrointestinal stromal tumors Assessing microsatellite instability

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer

analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. US Food and Drug Administration (FDA). Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated August 11, 2022. Accessed July 31, 2023. Available at www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling 4. El-Menyar A, Mekkodathil A, Al-Thani H. Diagnosis and management of gastrointestinal stromal tumors: an up-to-date literature review. J Can Res Ther. 2017;13(6):889-900. doi:10.4103/0973-1482.177499 5. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA Approval Summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758. doi:10.1158/1078-0432.CCR-18-4070

MCGYN 619622 MayoComplete Gynecological Cancer Panel, Next-Generation Sequencing, Tumor

Clinical Information: Molecular genetic profiling identifies targets amenable to targeted therapies, minimizing treatment costs and therapy-associated risks. Microsatellite instability (MSI) status is an increasingly important biomarker for determining effective immunotherapeutic treatment options for patients with solid tumors. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for somatic mutations in the following genes known to be associated with gynecologic cancer: AKT1, APC, ARID1A, ARID1B, ATM, ATR, ATRX, BAP1, BARD1, BRAF, BRCA1, BRCA2, BRIP1, CDC42, CDK12, CDKN2A, CTNNB1, DICER1, EIF1AX, EPCAM, ERBB2, FBXW7, FOXL2, GNAS, KRAS, L1CAM, MED12, MLH1, MSH2, MSH6, NBN, NF2, NRAS, PALB2, PIK3CA, PIK3R1, PMS2, POLE, PPP2R1A, PTEN, RAD51C, RAD51D, RB1, SMARCA2, SMARCA4, SMARCB1, STK11, TP53, and TRAF7, as well as MSI status. The results of this test can be useful for molecular classification, assessing prognosis, and guiding treatment of individuals with gynecologic tumors, including endometrial, ovarian, and sex-cord stromal tumors. The data can also be used to help determine clinical trial eligibility.

Useful For: Predicting patients' prognosis and response to targeted therapy Assessment of microsatellite instability for immunotherapy decisions

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board, eds. Female genital tumours. 5th ed. World Health Organization; 2020. WHO Classification of Tumours. Vol 4 2. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 3. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 Marcus L, Lemery SJ, Keegan P, Pazdur R: FDA Approval Summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758 4. Cancer Genome Atlas Research Network; Kandoth C, Schultz N, et al: Integrated genomic characterization of endometrial carcinoma [published correction appears in Nature. 2013 Aug 8;500(7461):242]. Nature. 2013;497(7447):67-73. doi:10.1038/nature12113 5. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma [published correction appears in Nature. 2012 Oct 11;490(7419):298]. Nature. 2011;474(7353):609-615

NGHIS
618480

MayoComplete Histiocytic Neoplasms, Next-Generation Sequencing, Varies

Clinical Information: Histiocytic neoplasms are a diverse group of disorders characterized by the infiltration of neoplastic histiocytes within various tissues. Traditionally classification has been based on histopathology and limited immunohistochemical markers, as well as specific clinical presentations. Distinction between entities can be diagnostically difficult. Recently, genomic profiling by next-generation sequencing has revealed recurrent mutations in several genes that can be used to better subclassify entities in this challenging group of neoplasms. Furthermore, mutations involving the mitogen-activated protein kinase (MAPK) pathway (eg, BRAF, MAP2K1) have potential therapeutic implications for the use of targeted BRAF and MEK inhibitors.

Useful For: Aiding in establishing diagnosis, refining prognosis, and potentially identifying targeted therapies for the optimal management of patients with histiocytic neoplasms

Interpretation: Genomic variants detected by this test will be documented in a detailed laboratory-issued report. This report will contain information regarding the detected alterations and their associations with prognosis or possible therapeutic implications in histiocytic neoplasms. The information in the clinical report may be used by the patient's healthcare professional to help guide decisions concerning management. Final interpretation of next-generation sequencing results requires correlation with all relevant clinical, pathologic, and laboratory findings and is the responsibility of the managing healthcare professional.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow S, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours, Vol 2 2. Badalian-Very G, Vergilio JA, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010;116(11):1919-1923. doi:10.1182/blood-2010-04-279083 3. Haroche J, Charlotte F, Arnaud L, et al. High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. Blood. 2012;120(13):2700-2703. doi:10.1182/blood-2012-05-430140 4. Diamond EL, Durham BH, Haroche J, et al. Diverse and targetable kinase alterations drive histiocytic neoplasms. Cancer Discov. 2016;6(2):154-165. doi:10.1158/2159-8290.CD-15-0913 5. Durham BH, Lopez Rodrigo E, Picarsic J, et al. Activating mutations in CSF1R and additional receptor tyrosine kinases in histiocytic neoplasms. Nat Med. 2019;25(12):1839-1842. doi:10.1038/s41591-019-0653-6

MCKCP
619595

MayoComplete Kidney Cancer Panel, Next-Generation Sequencing, Tumor

Clinical Information: Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Microsatellite instability (MSI) status is an increasingly important biomarker for determining effective immunotherapeutic treatment options for patients with solid tumors. Renal cell carcinoma is being increasingly subtyped based on underlying molecular alterations. Some kidney tumor types are defined by molecular alterations based on the recent World Health Organization classification of tumors.(1) In addition, the identification of pathognomonic alterations may help classify poorly differentiated tumors, and those associated with hereditary predisposition syndromes. It is important to note that this assay does not distinguish between germline and somatic alterations. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for somatic mutations involving the following genes known to be associated with kidney

cancer: ATRX, BAP1, BRAF, CDKN2A, FH, FLCN, KRAS, MET, MITF, MLH1, MSH2, MSH6, MTOR, NF2, PBRM1, PMS2, PTEN, RB1, SDHA, SDHB, SDHC, SDHD, SETD2, SMARCB1, ELOC (TCEB1), TERT, TP53, TSC1, TSC2, and VHL, as well as MSI status. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with kidney tumors. These data can also be used to help determine clinical trial eligibility for patients with alterations in genes not amenable to current US Food and Drug Administration-approved targeted therapies.

Useful For: Identifying specific mutations to assist in tumor diagnosis/classification Assisting in the clinical management of patients with renal cell carcinoma Assessment of microsatellite instability for immunotherapy decisions

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board, eds. Urinary and male genital tumors. 5th ed. World Health Organization; 2022. WHO Classification of Tumours. Vol 8 2. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 3. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 4. Trpkov K, Hes O, Williamson SR, et al: New developments in existing WHO entities and evolving molecular concepts: The Genitourinary Pathology Society (GUPS) update on renal neoplasia. Mod Pathol. 2021;34(7):1392-1424 5. Trpkov K, Williamson SR, Gill AJ, et al. Novel, emerging and provisional renal entities: The Genitourinary Pathology Society (GUPS) update on renal neoplasia. Mod Pathol. 2021;34(6):1167-1184 6. Marcus L, Lemery SJ, Keegan P, Pazdur R: FDA Approval Summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758

MCLBP
614939

MayoComplete Liquid Biopsy Panel, Next-Generation Sequencing, Cell-Free DNA

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration for treatment of solid tumor malignancies. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Microsatellite instability status is an increasingly important biomarker for determining effective immunotherapeutic treatment options for patients with solid tumors. In addition to providing therapeutic insight, molecular profiling of tumors often provides prognostic and diagnostic information. Next-generation sequencing is an accurate, cost-effective method to identify variants across numerous genes known to be associated with response or resistance to specific targeted therapies. This test is intended for the use of cell-free DNA to access genetic mutations of somatic tumors without a tissue biopsy.

Useful For: As an alternative to invasive tissue biopsies to assist in tumor profiling for diagnosis, predicting prognosis, and identifying targeted therapies for the treatment and management of patients with solid tumors As an alternative to invasive tissue biopsies for assessment of microsatellite instability status

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the

results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Schwaederle M, Husain H, Fanta PT, et al. Use of liquid biopsies in clinical oncology: Pilot experience in 168 patients. Clin Cancer Res. 2016;22(22):5497-5505 2. Kilgour E, Rothwell DG, Brady G, Dive C. Liquid biopsy-based biomarkers of treatment response and resistance. Cancer Cell. 2020;37(4):485-495 3. Leighl NB, Page RD, Raymond VM, et al. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. Clin Cancer Res. 2019;25(15):4691-4700 4. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA approval summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758 5. Wan JCM, Massie C, Garcia-Corbacho J, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. Nat Rev Cancer. 2017;17(4):223-238 6. Aggarwal C, Thompson JC, Black TA, et al. Clinical implications of plasma-based genotyping with the delivery of personalized therapy in metastatic non-small cell lung cancer. JAMA Oncol. 2019;5(2):173-180

MCLNM 616487 MayoComplete Lung Cancer Mutations, Next-Generation Sequencing, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Microsatellite instability status is an increasingly important biomarker for determining effective immunotherapeutic treatment options for patients with solid tumors. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. This test is a single assay that uses formalin-fixed paraffin-embedded tissue to assess for common mutations in the following genes known to be associated with lung cancer: ALK, BRAF, EGFR, ERBB2, HRAS, KRAS, MDM2, MET, NRAS, RET, ROS1, and STK11. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with lung cancer. Current data suggests that: -The efficacy of EGFR-targeted therapies in patients with non-small cell lung cancer is limited to tumors with mutations in the EGFR gene -Metastatic non-small cell lung cancer with BRAF V600E mutations may be sensitive to targeted therapy -Metastatic non-small cell lung cancer with KRAS G12C mutations may be sensitive to targeted therapy -Advanced or metastatic non-small cell lung cancer with MET exon 14 skipping mutations may be sensitive to MET inhibitors

Useful For: Diagnosis and management of patients with lung cancer Assessing microsatellite instability

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11.

doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. U.S. Food and Drug Administration (FDA). Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated August 11, 2022, Accessed July 31, 2023. Available at: www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling 4. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer. 2007;7(3):169-181 5. Mok TS. Personalized medicine in lung cancer: What we need to know. Nat Rev Clin Oncol. 2011;8(11):661-668 6. Cheng L, Alexander RE, Maclennan GT, et al, Molecular pathology of lung cancer: key to personalized medicine. Mod Path. 2012;25(3):347-369 7. Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. 2006;118(2):257-262 8. Gao G, Ren S, Li A, et al. Epidermal growth factor receptor-tyrosine kinase inhibitor therapy is effective as first-line treatment of advanced non-small-cell lung cancer with mutated EGFR: A meta-analysis from six phase III randomized controlled trials. Int J Cancer. 2012;131(5):E822-829. doi:10.1002/ijc.27396 9. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol. 2005;23(25):5900-5909 10. Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET Inhibitors. Cancer Discov. 2015;5(8):850-859. doi:10.1158/2159-8290 11. Marcus L, Lemery SJ, Keegan P, Pazdur R: FDA Approval Summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758. doi:10.1158/1078-0432.CCR-18-4070 12. Clay R, Kipp BR, Jenkins S, et al. Computer-aided nodule assessment and risk yield (CANARY) may facilitate non-invasive prediction of EGFR mutation status in lung adenocarcinomas. Sci Rep. 2017;7(1):17620. doi:10.1038/s41598-017-17659-6

MCLNG
616486

MayoComplete Lung Cancer-Targeted Gene Panel with Rearrangement, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration (FDA) for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Microsatellite instability status is an increasingly important biomarker for determining effective immunotherapeutic treatment options for patients with solid tumors. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for somatic mutations within the ALK, BRAF, EGFR, ERBB2, HRAS, KRAS, MDM2, MET, NRAS, RET, ROS1, and STK11 genes; identifies gene fusions involving ALK, ROS1, RET, NTRK1, NTRK2, and NTRK3 genes by specific rearrangements (fusions) within the ALK, ROS1, and RET genes; and expression imbalance for the ALK, ROS1, RET, NTRK1, NTRK2, and NTRK3 genes, as well as MET exon 14 skipping alterations. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with lung tumors. These data can also be used to help determine clinical trial eligibility for patients with alterations in genes not amenable to current FDA-approved targeted therapies. Current data suggests that: -The efficacy of EGFR-targeted therapies in patients with non-small cell lung cancer is limited to tumors with mutations in the EGFR gene -Metastatic non-small cell lung cancer with BRAF V600E mutations may be sensitive to targeted therapy -Metastatic non-small cell lung cancer with KRAS G12C mutations may be sensitive to targeted therapy -Advanced or metastatic non-small cell lung cancer with MET exon 14 skipping mutations may be sensitive to MET inhibitors -Lung carcinomas with ALK rearrangements may be sensitive to ALK inhibitors -Lung carcinomas with ROS1 rearrangements may be sensitive to ROS1 inhibitors -Lung carcinomas with RET rearrangements may be sensitive to RET inhibitors -Solid tumors with NTRK rearrangements may be sensitive to multikinase inhibitors

Useful For: Diagnosis and management of patients with lung cancer Assessing microsatellite instability

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. US Food and Drug Administration (FDA). Table of Pharmacogenomic Biomarkers in Drug Labeling. Updated August 11, 2022, Accessed July 31, 2023. Available at www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling 4. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer. 2007;7(3):169-181 5. Mok TS: Personalized medicine in lung cancer: What we need to know. Nat Rev Clin Oncol. 2011 Aug 23;8:661-668 6. Cheng L, Alexander RE, Maclennan GT, et al. Molecular pathology of lung cancer: key to personalized medicine. Mod Path. 2012;25(3):346-369 7. Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. Int J Cancer. 2006;118(2):257-262 8. Gao G, Ren S, Li A, et al. Epidermal growth factor receptor tyrosine kinase inhibitor therapy is effective as first-line treatment of advanced non-small-cell lung cancer with mutated EGFR: A meta-analysis from six phase III randomized controlled trials. Int J Cancer. 2012;131(5):E822-829. doi:10.1002/ijc.27396 9. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol. 2005;23(25):5900-5909 10. Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov. 2015;5(8):850-859 11. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA Approval Summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758. doi:10.1158/1078-0432.CCR-18-4070 12. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013;368(25):2385-94. doi:10.1056/NEJMoa1214886 13. Sehgal K, Patell R, Rangachari D, Costa DB. Targeting ROS1 rearrangements in non-small cell lung cancer with crizotinib and other kinase inhibitors. Transl Cancer Res. 2018;7(Suppl 7):S779-S86. doi:10.21037/tcr.2018.08.11 14. Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of Selpercatinib in RET fusion-positive non-small-cell lung cancer. N Engl J Med. 2020;383(9):813-24. doi:10.1056/NEJMoa2005653 15. Vaishnavi A, Capelletti M, Le AT, et al. Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer.Nat Med. 2013;19(11):1469-1472 16. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol. 2018;15(12):731-747 doi:10.1038/s41571-018-0113-0 17. Clay R, Kipp BR, Jenkins S, et al. Computer-aided nodule assessment and risk yield (CANARY) may facilitate non-invasive prediction of EGFR mutation status in lung adenocarcinomas. Sci Rep. 2017;7(1):17620. doi:10.1038/s41598-017-17659-6

MCLNR
616488

MayoComplete Lung Rearrangements, Rapid Test, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration for treatment of specific cancers. Molecular genetic profiling is often needed to identify

targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Fusions involving the NTRK1, NTRK2, or NTRK3 genes (ie, NTRK gene fusions) form through intra- and interchromosomal rearrangements. NTRK gene fusions lead to activation of downstream MAPK, PIK, and STAT3 signaling pathways and act as oncogenic drivers of multiple types of pediatric and adult solid tumors. In solid tumors, the presence of an NTRK gene fusion is a biomarker for response to tropomyosin receptor kinase inhibitor therapy. Lung cancers harboring ALK rearrangements are resistant to epidermal growth factor receptor tyrosine kinase inhibitors but may be highly sensitive to ALK inhibitors, like Xalkori (crizotinib). The drug Xalkori works by blocking certain kinases, including those produced by the abnormal ALK gene. Clinical studies have demonstrated that Xalkori treatment of patients with tumors exhibiting ALK rearrangements can halt tumor progression or result in tumor regression. RET rearrangements occur in approximately 2.5% to 10% of sporadic papillary thyroid cancer(1) and 1% to 3% of non-small cell lung cancer. The most prevalent fusions are KIF5B exon 15 - RET exon 12 and KIF5B exon 16 - RET exon 12, which represent over 75% of RET fusions. ROS1 (c-ros oncogene 1), originally described in glioblastomas, has been identified as a potential relevant therapeutic target in lung adenocarcinoma. Crizotinib has shown in vitro activity and early evidence of clinical activity in ROS1-rearranged tumors. Many cases of METex14 alterations are found in lung adenocarcinomas, these events have a much higher incidence in pulmonary sarcomatoid carcinomas. Approximately 20% to 30% of sarcomatoid carcinomas harbor METex14 alterations.

Useful For: Identifying lung tumors that may respond to targeted therapies by simultaneously assessing multiple genes involved in rearrangements resulting in fusion transcripts Diagnosing and managing patients with lung cancer

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Vaishnavi A, Capelletti M, Le AT, et al: Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer.Nat Med. 2013 Nov;19(11):1469-1472 2. US Food and Drug Administration (FDA): Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated August 11, 2022, Accessed February 3, 2023. Available at www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling 3. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013;368(25):2385-94. doi: 10.1056/NEJMoa1214886 4. Sehgal K, Patell R, Rangachari D, Costa DB. Targeting ROS1 rearrangements in non-small cell lung cancer with crizotinib and other kinase inhibitors. Transl Cancer Res. 2018;7(Suppl 7):S779-S86. doi: 10.21037/tcr.2018.08.11 5. Drilon A, Oxnard GR, Tan DSW, Loong HHF, Johnson M, Gainor J, et al. Efficacy of Selpercatinib in RET fusion-positive non-small-cell lung cancer. N Engl J Med. 2020;383(9):813-24. doi: 10.1056/NEJMoa2005653 6. Cocco E, Scaltriti M, Drilon A: NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol 2018 Dec;15(12):731-747. doi: 10.1038/s41571-018-0113-0 7. Frampton GM, Ali SM, Rosenzweig M, Chmielecki J, Lu X, Bauer TM, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov. 2015;5(8):850-9. doi: 10.1158/2159-8290.CD-15-0285

MCMLN 616491 MayoComplete Melanoma Panel, Next-Generation Sequencing, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug

Administration for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Microsatellite instability status is an important biomarker for determining effective immunotherapeutic treatment options for patients with solid tumors. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. This test is a single assay that uses formalin-fixed paraffin-embedded tissue or cytology specimens to assess for common mutations in the following genes known to be associated with melanoma: BAP1, BRAF, CDKN2A, CTNNB1, EIF1AX, GNA11, GNAQ, HRAS, KIT, KRAS, MAP2K1, MAP2K2, NF1, NRAS, SF3B1, TERT promoter, and TP53. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with melanoma.

Useful For: Determining if patients will respond to targeted therapy Assessing microsatellite instability for immunotherapy decisions

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. US Food and Drug Administration (FDA): Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated August 11, 2022, Accessed July 31, 2023. Available at www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling 4. Guo W, Wang H, Li Chunying. Signal pathways of melanoma and targeted therapy. Signal Transduct Target Ther. 2021:6(1):424 5. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA approval summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758. doi:10.1158/1078-0432.CCR-18-4070 6. Seedor RS, Orloff M, Sato T. Genetic landscape and emerging therapies in uveal melanoma, Cancers (Basel). 2021;13(21):5503

NGSHM 63367 MayoComplete Myeloid Neoplasms, Comprehensive OncoHeme Next-Generation Sequencing, Varies

Clinical Information: Next-generation sequencing is a comprehensive molecular diagnostic methodology that can interrogate multiple regions of genomic tumor DNA in a single assay. Many hematologic neoplasms are characterized by morphologic or phenotypic similarities but can have characteristic somatic mutations in many genes that enable more specific categorization. In addition, many myeloid neoplasms lack a clonal cytogenetic finding at diagnosis (normal karyotype) but can be diagnosed or confirmed and classified according to the gene mutation profile. Patients with unexplained cytopenias may harbor acquired genetic alterations in hematopoietic cells (clonal cytopenias of uncertain significance), which may carry risk of developing overt myeloid malignancies. The presence and pattern of gene mutations in known or suspected myeloid neoplasm can provide critical diagnostic, prognostic, and therapeutic information to help guide management for the patient's physician. Patients presenting with severe inflammatory features, often with cytopenias, may have VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome and can be identified by the presence of somatic UBA1 gene mutation.

Useful For: Evaluation of known or suspected hematologic neoplasms, specifically of myeloid origin (eg, acute myeloid leukemia, myelodysplastic syndrome, myeloproliferative neoplasm,

myelodysplastic/myeloproliferative neoplasm, unexplained cytopenias) at the time of diagnosis or possibly disease relapse Aiding in determining diagnostic classification Providing prognostic or therapeutic information for helping guide clinical management Evaluating patients with suspected VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome Determining the presence of new clinically important gene mutation changes at relapse

Interpretation: Detailed variant assessment and interpretive comments will be provided for all reportable genetic alterations. If this test is ordered in the setting of erythrocytosis and suspicion of polycythemia vera, interpretation requires correlation with a concurrent or recent prior bone marrow evaluation.

Reference Values:
An interpretive report will be provided.

Clinical References:

MCOCP 619640 MayoComplete Ovarian, Fallopian Tube, and Peritoneal Cancer Panel, Next-Generation Sequencing, Tumor

Clinical Information: Molecular genetic profiling identifies biomarkers amenable to targeted therapies, minimizing treatment costs and therapy-associated risks. Microsatellite instability (MSI) status is an increasingly important biomarker for determining effective immunotherapeutic treatment options for patients with solid tumors. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for somatic mutations involving the following genes known to be associated with ovarian cancer: ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CDK12, MLH1, MSH2, MSH6, PALB2, PMS2, RAD51C, and RAD51D. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with ovarian tumors. The data can also be used to help determine clinical trial eligibility for patients with genetic alterations.

Useful For: Primarily for determining if patients will respond to targeted therapy Assessment of microsatellite instability for immunotherapy decisions

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. Marcus L, Lemery SJ, Keegan P, Pazdur R: FDA Approval Summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758 4. Fong PC, Boss DS, Yap TA, et al: Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med. 2009;361(2):123-134 5. AlHilli MM, Becker MA, Weroha SJ, et al: In vivo anti-tumor activity of the PARP inhibitor niraparib in homologous recombination deficient and proficient ovarian carcinoma. Gynecol Oncol. 2016;143(2):379-388

NGPCM
618479

MayoComplete Plasma Cell Myeloma, Next-Generation Sequencing, Varies

Clinical Information: Multiple myeloma (MM) is a malignancy of bone marrow plasma cells with an annual global incidence of nearly 200,000. Comprehensive clinical, radiologic, and laboratory evaluation can initially stratify patients by disease phase and burden. Cytogenetic and fluorescence in situ hybridization studies are important to help classify MM into standard, intermediate, and high-risk groups. Advances in nontargeted therapies, including autologous bone marrow transplantation, have significantly improved the outcome of many patients; however, most patients with myeloma suffer relapse after initial treatment. Clinical next-generation sequencing (NGS) technology has enabled a deeper and more detailed evaluation of MM genetics. Testing allows for further risk categorization of the disease through the identification of additional genetic abnormalities of prognostic and potentially therapeutic value. Application of targeted NGS-based analysis is a useful adjunct to the standard evaluation of MM patients at diagnosis and relapse. This test comprises a DNA-based multigene panel that includes preanalytic plasma cell enrichment, NGS, and detailed analysis, resulting in a clinical report.

Useful For: Evaluating multiple myeloma at the time of diagnosis and at disease relapse or when changing clinical management to provide prognostic information and determine potential therapeutic implications

Interpretation:

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow S, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours, Vol 2 2. Onaindia A, Medeiros LJ, Patel KP. Clinical utility of recently identified diagnostic, prognostic, and predictive molecular biomarkers in mature B-cell neoplasms. Mod Pathol. 2017;30(10):1338-1366. doi:10.1038/modpathol.2017.58 3. Walker BA, Mavrommatis K, Wardell CP, et al. Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma. Blood. 2018;132(6):587-597. doi:10.1182/blood-2018-03-840132 4. Walker BA, Boyle EM, Wardell CP, et al. Mutational spectrum, copy number changes, and outcome: Results of a sequencing study of patients with newly diagnosed myeloma. J Clin Oncol. 2015;33(33):3911-20. doi:10.1200/JCO.2014.59.1503 5. Kortuem KM, Braggio E, Bruins L, et al. Panel sequencing for clinically oriented variant screening and copy number detection in 142 untreated multiple myeloma patients. Blood Cancer J. 2016;6(2):e397. doi:10.1038/bcj.2016.1 6. Jimenez C, Jara-Acevedo M, Corchete LA, et al. A next-generation sequencing strategy for evaluating the most common genetic abnormalities in multiple myeloma. J Mol Diagn. 2017;19(1):99-106 7. Yellapantula V, Hultcrantz M, Rustad EH, et al. Comprehensive detection of recurring genomic abnormalities: a targeted sequencing approach for multiple myeloma. Blood Cancer J. 2019;9(12):101. doi:10.1038/s41408-019-0264-y 8. Cutler SD, Knopf P, Campbell CJV, et al. DMG26 A targeted sequencing panel for mutation profiling to address gaps in the prognostication of multiple myeloma. J Mol Diagn. 2021;23(12):1699-1714

MCFRC
619613

MayoComplete Renal Cell Carcinoma with Fibromyomatous Stroma Panel, Next-Generation Sequencing, Tumor

Clinical Information: A subset of renal cell carcinoma commonly referred to as "renal cell carcinoma with fibromyomatous stroma" frequently shows overlapping morphologic and immunophenotypic features. These tumors are thought to arise secondary to alterations of ELOC (also referred to as TCEB1) and other MTOR (mechanistic target of rapamycin) pathway genes, such as TSC1

and TSC2. Furthermore, these tumors are unrelated to clear cell renal cell carcinoma that typically show alterations of the VHL gene (including epigenetic silencing, truncating alterations, and deletions). The 5th edition of the World Health Organization classification of tumors recognizes ELOC (TCEB1)-mutated renal cell carcinoma as a molecularly defined entity.(1) This assay, performed using formalin-fixed paraffin-embedded tissue or cytology material, is therefore helpful for establishing an accurate diagnosis and to define prognosis. It is important to note that this assay does not distinguish between germline and somatic alterations.

Useful For: Identifying specific mutations within the ELOC (TCEB1), TSC1, TSC2, and VHL genes to assist in tumor diagnosis/classification Assisting in the clinical management of patients with renal cell carcinoma

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board. Urinary and male genital tumors. 5th ed, World Health Organization; 2022. WHO Classification of Tumours. Vol 8 2. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 3. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 4. Shah RB. Renal cell carcinoma with fibromyomatous stroma-The whole story. Adv Anat Pathol. 2022;29(3):168-177 5. Trpkov K, Williamson SR, Gill AJ, et al: Novel, emerging and provisional renal entities: The genitourinary pathology society (GUPS) update on renal neoplasia. Mod Pathol. 2021;34(6):1167-1184 6. DiNatale RG, Gorelick AN, Makarov V, et al: Putative drivers of aggressiveness in TCEB1-mutant renal cell carcinoma: An emerging entity with variable clinical course. Eur Urol Focus. 2021;7(2):381-389 7. Shah RB, Stohr BA, Tu ZJ, et al: "Renal Cell carcinoma with leiomyomatous stroma" Harbor somatic mutations of TSC1, TSC2, MTOR, and/or ELOC (TCEB1): clinicopathologic and molecular characterization of 18 sporadic tumors supports a distinct entity. Am J Surg Pathol. 2020;44(5):571-581. 8. Gupta S, Stanton ML, Reynolds JP, et al: Reprint of: lessons from histopathologic examination of nephrectomy specimens in patients with tuberous sclerosis complex: cysts, angiomyolipomas & renal cell carcinoma. Hum Pathol. 2023;133:136-152

MCSMP
616493

MayoComplete Sarcoma Mutation Panel, Next-Generation Sequencing, Tumor

Clinical Information: Molecular analysis of biomarkers is increasingly being utilized in oncology practices to support and guide diagnosis, prognosis, and therapeutic management of patients. For example, the identification of MYOD1 mutations can be helpful in establishing a diagnosis of sclerosing rhabdomyosarcoma. In addition, microsatellite instability status is an important biomarker for determining effective immunotherapeutic treatment options for patients with solid tumors. This next-generation sequencing assay interrogates targeted regions to assess for the presence of somatic mutations across 31 genes associated with soft tissue tumors: ALK, APC, BAP1, BCOR, BRAF, CDKN2A, CTNNB1, DICER1, EED, EGFR, FGFR4, GNA11, GNA14, GNAQ, GNAS, H3-3A, H3-3B, KIT, MDM2, MED12, MYOD1, NF1, PDGFRA, PDGFRB, PTPRD, ROS1, SMARCB1, SUZ12, TERT-promoter, TP53, and TSC2 genes. This test also assesses for BCOR internal tandem duplications.

Useful For: Primarily for identifying mutations that help in the diagnosis of specific soft tissue and

bone tumors (sarcoma) Secondarily for identifying mutations that have therapeutic or prognostic significance Assessing microsatellite instability for immunotherapy decisions

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing.Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. Apellaniz-Ruiz M, McCluggage WG, Foulkes WD. DICER1-associated embryonal rhabdomyosarcoma and adenosarcoma of the gynecologic tract: Pathology, molecular genetics, and indications for molecular testing. Genes Chromosomes Cancer. 2021;60(3):217-233 4. Agaram NP, LaQuaglia MP, Alaggio R, et al: MYOD1-mutant spindle cell and sclerosing rhabdomyosarcoma: an aggressive subtype irrespective of age. A reappraisal for molecular classification and risk stratification. Mod Pathol. 2019 Jan;32(1):27-36. doi:10.1038/s41379-018-0120-9 5. WHO Classification of Tumours Editorial Board: Soft tissue and bone tumours. 5th ed. World Health Organization; 2022. WHO Classification of Tumours. Vol 3. 6. Gao P, Seebacher NA, Hornicek F, et al. Advances in sarcoma gene mutations and therapeutic targets. Cancer Treat Rev. 2018;62:98-109 7. Marino-Enriquez A, Lauria A, Przybyl J, et al. BCOR Internal tandem duplication in high-grade uterine sarcomas. Am J Surg Pathol. 2018;42(3):335-341. doi: 10.1097/PAS.0000000000000993 8. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA approval summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758. doi:10.1158/1078-0432.CCR-18-4070

MCSTP
606162

MayoComplete Solid Tumor Panel, Next-Generation Sequencing, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration for the treatment of solid tumor malignancies. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Tumor mutational burden and microsatellite instability status are increasingly important biomarkers for determining effective immunotherapeutic treatment options for patients with solid tumors.(1,2) In addition to providing therapeutic insight, molecular profiling of tumors often provides prognostic and diagnostic information. Next-generation sequencing is an accurate, cost-effective method to identify variants across numerous genes known to be associated with response or resistance to specific targeted therapies. This test is a single assay that uses formalin-fixed paraffin-embedded tissue or cytology specimens to assess for Tier I and Tier II variants in 515 genes known to be associated with solid tumors.(3)

Useful For: Assisting in tumor profiling for diagnosis, predicting prognosis, and identifying targeted therapies for the treatment and management of patients with solid tumors Identifying somatic alterations including single nucleotide variants, small deletions/insertions, gene amplifications, homozygous gene deletions, fusions, and splice variants in genes known to be associated with the tumorigenesis of solid tumors Assessment of microsatellite instability and tumor mutational burden status

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results

and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Subbiah V, Solit DB, Chan TA, Kurzrock R. The FDA approval of pembrolizumab for adult and pediatric patients with tumor mutational burden (TMB) > or =10: a decision centered on empowering patients and their physicians. Ann Oncol. 2020;31(9):1115-1118. doi:10.1016/j.annonc.2020.07.002 2. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA Approval Summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res. 2019;25(13):3753-3758. doi:10.1158/1078-0432.CCR-18-4070 3. Li MM, Datto M, Duncavage EJ, et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer: A joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diag. 2017;19(1):4-23. doi:10.1016/j.jmoldx.2016.10.002 4. Mikhail FM, Biegel JA, Cooley LD, et al. Technical laboratory standards for interpretation and reporting of acquired copy-number abnormalities and copy-neutral loss of heterozygosity in neoplastic disorders: a joint consensus recommendation from the American College of Medical Genetics and Genomics (ACMG) and the Cancer Genomics Consortium (CGC). Genet Med. 2019;21(9):1903-1916. doi:10.1038/s41436-019-0545-7

NGTCL 618478 MayoComplete T-Cell Lymphoma, Next-Generation Sequencing, Varies

Clinical Information: T-cell lymphomas are a heterogenous group of hematological disorders characterized by a range of morphological, immunophenotypic, and clinical features. Many entities share overlapping morphologic and immunophenotypic features resulting in challenges for accurate diagnosis and classification. Genomic profiling by next-generation sequencing has revealed genetic markers that aid in the classification and characterization of mature T-cell neoplasms. This test is intended to interrogate a set of genes with diagnostic, prognostic, and possible therapeutic value in a diverse group of T-cell lymphomas, which includes peripheral T-cell lymphomas and its major subtypes (eg, angioimmunoblastic T-cell lymphomas).

Useful For: Aiding in establishing diagnosis, refining prognosis, and potentially identifying targeted therapies for the optimal management of patients with T-cell lymphomas

Interpretation: Genomic variants detected by this test will be documented in a detailed laboratory-issued report. This report will contain information regarding the detected alterations and their associations with prognosis or possible therapeutic implications in T-cell lymphomas. The information in the clinical report may be used by the patient's healthcare professional to help guide decisions concerning management. Final interpretation of next-generation sequencing results requires correlation with all relevant clinical, pathologic, and laboratory findings and is the responsibility of the managing healthcare professional.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow S, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours, Vol 2 2. Sandell RF, Boddicker RL, Feldman AL. Genetic landscape and classification of peripheral T cell lymphomas. Curr Oncol Rep. 2017;19(4):28. doi:10.1007/s11912-017-0582-9 3. Lemonnier F, Gaulard P, de Leval L. New insights in the pathogenesis of T-cell lymphomas. Curr Opin

Oncol. 2018;30(5):277-284. doi:10.1097/CCO.0000000000000474 4. Vallois D, Dobay MP, Morin RD, et al. Activating mutations in genes related to TCR signaling in angioimmunoblastic and other follicular helper T-cell-derived lymphomas. Blood. 2016;128(11):1490-502. doi:10.1182/blood-2016-02-698977

JMDMF
616053

MDM2 (12q15) Amplification, Well-Differentiated Liposarcoma/Atypical Lipomatous Tumor, FISH, Tissue

Clinical Information: Differential diagnosis of well-differentiated liposarcoma/atypical lipomatous tumor: The histological discrimination of well-differentiated liposarcoma/atypical lipomatous tumor (WDL/ALT) from lipoma can be diagnostically challenging. However, standard cytogenetic identification of ring and giant rod chromosomes strongly support the diagnosis of WDL/ALT. These abnormal chromosomes are mainly composed of amplified sequences derived from chromosome bands 12q13-15 and contain several amplified genes including MDM2, CPM, CDK4, and TSPAN31. MDM2 is amplified in greater than 99% of WDL and up to 30% of other types of sarcomas. Differential diagnosis of osteosarcoma: The histological discrimination of parosteal or low-grade central osteosarcoma from other morphologically similar, but clinically distinct entities, can be difficult. Amplification of genomic material derived from chromosome 12q13-15, which contains several genes including MDM2, has been shown to be a recurrent finding in a large proportion (67-100%) of parosteal and central low-grade osteosarcomas. Therefore, the detection of MDM2 gene amplification by fluorescence in situ hybridization may be a useful adjunct to support a diagnosis of low-grade central or parosteal osteosarcoma in the proper histopathologic context. Amplifications of 12q13-15 (including MDM2) are less common in conventional high-grade osteosarcoma, estimated to occur in approximately 5% to 10% of tumors.

Useful For: Supporting a diagnosis of well-differentiated liposarcoma/atypical lipomatous tumor

Interpretation: Differential diagnosis of well-differentiated liposarcoma/atypical lipomatous tumor: A neoplastic clone is detected when the percentage of cells with an abnormality exceeds the normal reference range for the MDM2 fluorescence in situ hybridization (FISH) probe (positive result). A positive result is consistent with amplification of the MDM2 gene locus (12q15) and supports the diagnosis of well-differentiated liposarcoma/atypical lipomatous tumor (WDL/ALT). A negative result is consistent with absence of amplification of the MDM2 gene locus (12q15). However, negative results do not exclude the diagnosis of WDL/ALT. Amplification varies in individual tumors and among different cells in the same tumor. Differential diagnosis of osteosarcoma: A positive result is consistent with amplification of the MDM2 gene locus (12q15) and supports the diagnosis of parosteal osteosarcoma or low-grade central osteosarcoma. A negative result indicates an absence of amplification of the MDM2 gene locus (12q15). However, negative results do not exclude the diagnosis of low-grade central osteosarcoma or parosteal osteosarcoma.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Erickson-Johnson MR, Seys AR, Roth CW, et al. Carboxypeptidase M: a biomarker for the discrimination of lipoma from liposarcoma. Mod Pathol. 2009;22(12):1541-1547 2. Jacob E, Erickson-Johnson MR, Wang X, et al. Assessment of MDM2 amplification using fluorescence in situ hybridization on paraffin-embedded tissue discriminates atypical lipomatous tumors from lipomas. Mod Pathol. 2006;19:13A 3. He X, Pang Z, Zhang X, et al. Consistent Amplification of FRS2 and MDM2 in Low-grade Osteosarcoma: A genetic study of 22 cases with clinicopathologic analysis. Am J Surg Pathol. 2018;42(9):1143-1155 4. Duhamel LAE, Ye H, Halai, D, et al. Frequency of Mouse Double Minute 2 (MDM2) and Mouse Double Minute 4 (MDM4) amplification in parosteal and conventional osteosarcoma subtypes. Histopathology. 2012;60(2):357-359 5. Dujardin F, Binh MBN, Bourvier C, et al. MDM2 and CDK4 Immunohistochemistry Is a Valuable Tool in the Differential Diagnosis of Low-Grade

Osteosarcomas and Other Primary Fibro-Osseous Lesions of the Bone. Mod Pathol. 2011;24(5):624-637 6. Fletcher DM, Bridge JA, Hogendoorn PCW, Mertens F eds. WHO Classification of Tumours of Soft Tissue and Bone. International Agency for Research on Cancer; 2013

MDM2F 63049 MDM2 (12q15) Amplification, Well-Differentiated Liposarcoma/Atypical Lipomatous Tumor, FISH, Tissue

Clinical Information: Differential Diagnosis of Well-Differentiated Liposarcoma/Atypical Lipomatous Tumor: The histological discrimination of well-differentiated liposarcoma/atypical lipomatous tumor (WDL/ALT) from lipoma can be diagnostically challenging. Amplification of genomic material derived from the chromosome band 12q13-15, which contains several genes, including MDM2, has been shown to be a recurrent finding in most WDL/ALT. Therefore, the detection of MDM2 gene amplification by fluorescence in situ hybridization may be a useful adjunct to support a diagnosis of WDL/ALT in the proper histopathologic context. Differential Diagnosis of Osteosarcoma: The histological discrimination of parosteal or low-grade central osteosarcoma from other morphologically similar, but clinically distinct, entities can be difficult. Amplification of genomic material derived from the chromosome band 12q13-15, which contains several genes, including MDM2, has been shown to be a recurrent finding in a large proportion (67%-100%) of parosteal and central low-grade osteosarcomas. Therefore, the detection of MDM2 gene amplification by fluorescence in situ hybridization may be a useful adjunct to support a diagnosis of low-grade central or parosteal osteosarcoma in the proper histopathologic context. Amplifications of 12q13-15 (including MDM2) are less common in conventional high-grade osteosarcoma, estimated to occur in approximately 5% to 10% of tumors.

Useful For: Identifying MDM2 amplification Supporting the diagnosis of many neoplasms, including, but not limited to, well-differentiated liposarcoma, atypical lipomatous tumor, dedifferentiated liposarcoma, parosteal osteosarcoma and central low-grade osteosarcoma

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for the MDM2 fluorescence in situ hybridization probe set. Differential Diagnosis of Well-Differentiated Liposarcoma/Atypical Lipomatous Tumor: A positive result is consistent with amplification of the MDM2 gene locus (12q15) and, in the proper clinical and pathologic context, may support the diagnosis of well-differentiated liposarcoma/atypical lipomatous tumor (WDL/ALT). MDM2 amplification may be seen in other neoplasms and is not diagnostic in isolation. Clinical and pathologic correlation is required. A negative result is consistent with absence of amplification of the MDM2 gene locus (12q15) but does not exclude the diagnosis of WDL/ALT. Clinical and pathologic correlation is required. Differential Diagnosis of Osteosarcoma: A positive result is consistent with amplification of the MDM2 gene locus (12q15) and, in the proper clinical and pathologic context, may support the diagnosis of parosteal osteosarcoma or low-grade central osteosarcoma. MDM2 amplification may be seen in other neoplasms and is not diagnostic in isolation. Clinical and pathologic correlation is required. A negative result is consistent with absence of amplification of the MDM2 gene locus (12q15) but does not exclude the diagnosis of low-grade central osteosarcoma or parosteal osteosarcoma. Clinical and pathologic correlation is required.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Erickson-Johnson MR, Seys AR, Roth CW, et al. Carboxypeptidase M: a biomarker for the discrimination of lipoma from liposarcoma. Mod Pathol. 2009;22(12):1541-1547 2. Jacob E, Erickson-Johnson MR, Wang X, et al. Assessment of MDM2 amplification using fluorescence in situ hybridization on paraffin-embedded tissue discriminates atypical lipomatous tumors from lipomas. Mod Pathol. 2006;19:13A 3. He X, Pang Z, Zhang X, et al. Consistent amplification of FRS2

and MDM2 in low-grade osteosarcoma: A genetic study of 22 cases with clinicopathologic analysis. Am J Surg Pathol. 2018;42(9):1143-1155 4. Duhamel LAE, Ye H, Halai, D, et al. Frequency of Mouse Double Minute 2 (MDM2) and Mouse Double Minute 4 (MDM4) amplification in parosteal and conventional osteosarcoma subtypes. Histopathology. 2012;60(2):357-359 5. Dujardin F, Binh MBN, Bourvier C, et al. MDM2 and CDK4 immunohistochemistry is a valuable tool in the differential diagnosis of low-grade osteosarcomas and other primary fibro-osseous lesions of the bone. Mod Pathol. 2011;24(5):624-637 6. WHO Classification of Tumours Editorial Board. Soft Tissue and Bone. 5th ed. IARC; 2020. World Health Organization Classification of Tumours. Vol 3

MEAD
82890

Meadow Fescue, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to meadow fescue Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MFOX
82914

Meadow Foxtail, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to meadow foxtail Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ROPG
34941

Measles (Rubeola) Antibodies, IgG, Serum

Clinical Information: The measles virus is a member of the Paramyxoviridae family of viruses, which includes parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is one of the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours.(1,2) Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and spreads centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system involvement.(1,3) Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to fewer than 0.5 cases per 1,000,000 population, and the virus is no longer considered endemic in the United States.(4) Measles outbreaks continue to occur in the United States however, due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs.(5) The diagnosis of measles infection is often based on clinical presentation alone. Screening for IgG-class antibodies to measles virus will aid in identifying nonimmune individuals.

Useful For: Determining immune status of individuals to the measles virus Documenting previous infection with measles virus in an individual without a previous record of immunization to measles virus

Interpretation: The reported antibody index (AI) value is for reference only. This is a qualitative test, and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cutoff for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. Positive: AI value of 1.1 or higher The presence of detectable IgG-class antibodies indicates prior exposure to the measles virus through infection or immunization. Individuals testing positive are considered immune to measles infection. Equivocal: AI value 0.9-1.0 Submit an additional sample for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or otherwise clinically indicated. Negative: AI value of 0.8 or lower The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the measles virus.

Reference Values:
Vaccinated: Positive (> or =1.1 antibody index [AI])
Unvaccinated: Negative (< or =0.8 AI)
Reference values apply to all ages.

Clinical References: 1. Perry RT, Halsey NA. The clinical significance of measles-a review. J Infect Dis. 2004;189 Supp 1:S4-S16. doi:10.1086/377712 2. Babbott FL, Gordon JE: Modern measles. Am J Med Sci. 1954;228(3):334-361 3. Liebert UG. Measles virus infections of the central nervous system. Intervirology. 1997;40(2-3):176-184 4. Centers for Disease Control and Prevention (CDC). Measles-United States, 1999. MMWR Morb Mortal Wkly Rep. 2000;49(25):557-560 5. Centers for Disease Control and Prevention (CDC). Increased transmission and outbreaks of measles-European Region, 2011. MMWR Morb Mortal Wkly Rep. 2011;60(47):1605-1610 6. Theel ES, Sorenson M, Rahman C, Granger D, Vaughn A, Breeher L. Performance characteristics of a multiplex flow immunoassay for detection of IgG-Class antibodies to measles, mumps, rubella, and Varicella-Zoster viruses in presumptively immune health care workers. J Clin Microbiol. 2020;58(4):e00136-20. doi:10.1128/JCM.00136-20

ROM
80979

Measles (Rubeola) Antibodies, IgM, Serum

Clinical Information: The measles virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is one of the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours.(1,2) Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and spreads centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies, are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system involvement.(1,3) Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to below 0.5 cases per 1,000,000 population, and the virus is no longer considered endemic in the United States.(4) Measles outbreaks continue to occur in the United States however, due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs.(5) The diagnosis of measles infection is often based on clinical presentation alone. The presence of IgM-class antibodies suggests recent infection but should not be used alone to diagnose measles infection. Screening for IgG-class antibodies to measles virus aids in identifying nonimmune individuals.

Useful For: Determining acute-phase infection with rubeola (measles) virus using IgM antibody testing Aiding in the identification of nonimmune individuals through IgM antibody testing

Interpretation: The presence of IgM-class antibodies, with or without the presence of IgG-class antibodies, to measles virus may support a clinical diagnosis of recent/acute phase infection with the virus. IgM results alone should not be used to diagnose measles virus infection. The absence of IgM-class antibodies suggests lack of an acute phase infection with measles virus. However, serology may be negative for IgM-class antibodies in early disease, and results should be interpreted in the context of clinical findings. Testing for IgM-class antibodies to measles should be limited to patients with clinically compatible disease. The presence of detectable IgG-class antibodies, in the absence of IgM-class antibodies, indicates prior exposure to the measles virus through infection or immunization. These individuals are considered immune to measles infection. The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the measles virus. These individuals are considered nonimmune to measles virus infection.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Liebert UG. Measles virus infections of the central nervous system. Intervirology. 1997;40:176-184. doi:10.1159/000150544 2. Norrby E, Kristensson K. Measles virus in the brain. Brain Res Bull. 1997;44:213-220 3. Sable CA, Hayden FG. Orthomyxoviral and paramyxoviral infections in transplant patients. Infect Dis Clin North Am. 1995;9:987-1003 4. Matsuzono Y, Narita M, Satake A, et al: Measles encephalomyelitis in a patient with a history of vaccination. Acta Paediatr Jpn 1995;37:374-376 5. Cremer, NE, Devlin VL, Riggs JL, Hagens SJ. Anomalous antibody responses in viral infection: specific stimulation or polyclonal activation? J Clin Microbio. 1984;20:468-472 6. Gershon AA, Krugman S. Measles virus. In: Lennette EH, Schmidt NJ, eds. Diagnostic Procedures for Viral, Rickettsial and Chlamydial Infections. 5th ed. American Public Health Association, Inc., 1979;665-693 7. Theel ES, Sorenson M, Rahman C, Granger D, Vaughn A, Breeher L. Performance characteristics of a multiplex flow immunoassay for detection of IgG-Class antibodies to measles, mumps, rubella, and Varicella-Zoster viruses in presumptively immune health

care workers. J Clin Microbiol. 2020;58(4):e00136-20. doi:10.1128/JCM.00136.20 8. National Center for Immunization and Respiratory Diseases, Division of Viral Diseases; Centers for Disease Control and Prevention (CDC). Measles (Rubeola). CDC; Updated November 5, 2020. Accessed October 25, 2022. Available at www.cdc.gov/measles/hcp/index.html

ROGM
62066

Measles (Rubeola) Virus Antibody, IgM and IgG, Serum

Clinical Information: The measles virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is one of the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours.(1,2) Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and spreads centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies, are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system involvement.(1,3) Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to below 0.5 cases per 1,000,000 population and the virus is no longer considered endemic in the United States.(4) Measles outbreaks continue to occur in the United States however, due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs.(5) The diagnosis of measles infection is often based on clinical presentation alone. The presence of IgM-class antibodies suggests recent infection but should not be used alone to diagnose measles infection. Screening for IgG-class antibodies to measles virus aids in identifying nonimmune individuals.

Useful For: Diagnosing measles virus infection Determination of immune status of individuals to the measles virus using IgG antibody testing Documentation of previous infection with measles virus in an individual without a previous record of immunization to measles virus

Interpretation: This assay tests for both IgM and IgG-class antibodies. The presence of IgM-class antibodies, with or without the presence of IgG-class antibodies, to measles virus may support a clinical diagnosis of recent/acute phase infection with the virus. IgM results alone should not be used to diagnose measles virus infection. The absence of IgM-class antibodies suggests lack of an acute phase infection with measles virus. However, serology may be negative for IgM-class antibodies in early disease, and results should be interpreted in the context of clinical findings. Testing for IgM-class antibodies to measles should be limited to patients with clinically compatible disease. The presence of detectable IgG-class antibodies, in the absence of IgM-class antibodies, indicates prior exposure to the measles virus through infection or immunization. These individuals are considered immune to measles infection. The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the measles virus. These individuals are considered nonimmune to measles virus infection.

Reference Values:
IMMUNOGLOBULIN M
Negative
Reference values apply to all ages.

IMMUNOGLOBULIN G
Vaccinated: Positive (> or =1.1 AI)

Unvaccinated: Negative (< or =0.8 AI)
Reference values apply to all ages.

Clinical References: 1. Perry RT, Halsey NA. The clinical significance of measles-a review. J Infect Dis. 2004;189 Supp 1:S4-S16. doi:10.1086/377712 2. Babbott FL, Gordon JE. Modern measles. Am J Med Sci. 1954 Sep;228(3):334-361 3. Liebert UG: Measles virus infections of the central nervous system. Intervirology. 1997;40:176-184. doi:10.1159/000150544 4. Centers for Disease Control and Prevention (CDC): Measles-United States, 1999. MMWR Morb Mortal Wkly Rep. 2000;49(25):557-560 5. Centers for Disease Control and Prevention (CDC): Increased transmission and outbreaks of Measles-European region. MMWR Morb Mortal Wkly Rep. 2011;60(47):1605-1610 6. Cremer NE, Devlin VL, Riggs JL, Hagens SJ. Anomalous antibody responses in viral infection: specific stimulation or polyclonal activation? J Clin Microbiol. 1984;20:468-472 7. Theel ES, Sorenson M, Rahman C, Granger D, Vaughn A, Breeher L. Performance characteristics of a multiplex flow immunoassay for detection of IgG-Class antibodies to measles, mumps, rubella, and Varicella-Zoster viruses in presumptively immune health care workers. J Clin Microbiol. 2020;58(4):e00136-20. doi:10.1128 /JCM.00136-20 8. National Center for Immunization and Respiratory Diseases, Division of Viral Diseases; Centers for Disease Control and Prevention (CDC). Measles (Rubeola). CDC; Updated July 15, 2024. Accessed December 16, 2024. Available at www.cdc.gov/measles/hcp/index.html

MEASU 617822 Measles Virus, Molecular Detection, PCR, Random, Urine

Clinical Information: Measles virus is a single-stranded, negative-sense RNA paramyxovirus belonging to the genus Morbillivirus that causes acute respiratory illness. Symptoms of infection include fever, malaise, cough, coryza, and conjunctivitis. Following the onset of symptoms, individuals typically develop a pathognomonic enanthema (Koplik spots) followed by a maculopapular rash. Measles virus is transmitted via inhalation of aerosols or respiratory droplets and is highly contagious. Measles virus can also be transmitted by direct contact with infected secretions or contaminated fomites. Laboratory confirmation of measles cases can be through serologic detection of measles-specific IgM antibodies or molecular detection of measles virus RNA. The use of reverse-transcription polymerase chain reaction can provide increased sensitivity and specificity compared to serologic testing if specimens are collected early after rash onset. Collection of both respiratory and urine samples for analysis is recommended to increase the likelihood of detecting the virus.

Useful For: Identifying measles infection using random urine specimens

Interpretation: A positive result indicates the presence of measles virus RNA in the specimen.

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention (CDC) Measles (Rubeola): Clinical Overview of Measles. Updated July 15, 2024. Accessed March 4, 2025 . Available at: www.cdc.gov/measles/hcp/clinical-overview/?CDC_AAref_Val=https://www.cdc.gov/measles/hcp/ 2. Moss WJ. Measles. Lancet. 2017;390(10111):2490-2502 3. Porter A, Goldfarb J. Measles: A dangerous vaccine-preventable disease returns. Cleve Clin J Med. 2019;86(6):393-398

MEASR 617821 Measles Virus, Molecular Detection, PCR, Throat

Clinical Information: Measles virus is a single-stranded, negative-sense RNA paramyxovirus belonging to the genus Morbillivirus that causes acute respiratory illness. Symptoms of infection include fever, malaise, cough, coryza, and conjunctivitis. Following the onset of symptoms, individuals

typically develop a pathognomonic enanthema (Koplik spots) followed by a maculopapular rash. Measles virus is transmitted via inhalation of aerosols or respiratory droplets and is highly contagious. Measles virus can also be transmitted by direct contact with infected secretions or contaminated fomites. Laboratory confirmation of measles cases can be through serologic detection of measles-specific IgM antibodies or molecular detection of measles virus RNA. The use of reverse-transcription polymerase chain reaction can provide increased sensitivity and specificity compared to serologic testing if specimens are collected early after rash onset. Collection of both respiratory and urine samples for analysis is recommended to increase the likelihood of detecting the virus.

Useful For: Identifying measles virus infection using throat swab specimens

Interpretation: A positive result indicates the presence of measles virus RNA in the specimen.

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention (CDC). Measles (Rubeola): Clinical Overview of Measles. Updated July 15, 2024. Accessed March 4, 2025. Available at: www.cdc.gov/measles/hcp/clinical-overview/?CDC_AAref_Val=https://www.cdc.gov/measles/hcp/ 2. Moss WJ. Measles. Lancet. 2017;390(10111):2490-2502 3. Porter A, Goldfarb J. Measles: a dangerous vaccine-preventable disease returns. Cleve Clin J Med. 2019 Jun;86(6):393-398

MMRV
61853

Measles, Mumps, Rubella, and Varicella (MMRV) Immune Status Profile, Serum

Clinical Information: The measles virus is a member of the Paramyxoviridae family of viruses, which includes parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is among the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours.(1) Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead, and spreads centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system (CNS) involvement.(1) Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to fewer than 0.5 cases per 1,000,000 individuals, and the virus is no longer considered endemic in the United States. Measles outbreaks continue to occur in the United States due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs.(2) The diagnosis of measles infection is often based on clinical presentation alone. Screening for IgG-class antibodies to measles virus will aid in identifying nonimmune individuals. Mumps: The mumps virus is a member of the Paramyxoviridae family of viruses, which includes parainfluenza virus serotypes 1-4, measles, RSV, and metapneumovirus. Mumps is highly infectious among unvaccinated individuals and is typically transmitted through inhalation of infected respiratory droplets or secretions. Following an approximately 2-week incubation period, symptom onset is typically acute with a prodrome of low-grade fever, headache, and malaise.(3,4) Painful enlargement of the salivary glands, the hallmark of mumps, occurs in approximately 60% to 70% of infections and in 95% of patients with symptoms. Testicular pain (orchitis) occurs in approximately 15% to 30% of postpubertal men and abdominal pain (oophoritis) is found in 5% of postpubertal women.(3) Other complications include mumps-associated pancreatitis (<5% of cases)

and CNS disease (meningitis <10% and encephalitis <1%). Widespread routine immunization of infants with attenuated mumps virus has dramatically decreased the number of reported mumps cases in the United States. However, outbreaks continue to occur, indicating persistence of the virus in the general population. Laboratory diagnosis of mumps is typically accomplished by detection of IgM- and IgG-class antibodies to the mumps virus. However, due to the widespread mumps vaccination program, in clinically suspected cases of acute mumps infection, serologic testing should be supplemented with virus isolation in culture or detection of viral nucleic acid by polymerase chain reaction in throat, saliva, or urine specimens. Rubella: Rubella (German or 3-day measles) is a member of the Togavirus family, and humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets and the incubation period following exposure can range from 12 to 23 days.(5) Infection is generally mild and self-limited and is characterized by a maculopapular rash beginning on the face and spreading to the trunk and extremities, as well as fever, malaise, and lymphadenopathy.(6) Primary in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of gestation. Congenital rubella syndrome is often associated with hearing loss and cardiovascular and ocular defects.(7) The United States 2-dose measles, mumps, and rubella (MMR) vaccination program, which calls for vaccination of all children, leads to seroconversion in 95% of children following the first dose.(5) A total of 4 cases of rubella were reported to the Centers of Disease Control and Prevention in 2011 without any cases of congenital rubella syndrome.(8) Due to the success of the national vaccination program, rubella is no longer considered endemic in the United States.(9) Immunity may, however, wane with age as approximately 80% to 90% of adults will show serologic evidence of immunity to rubella. Varicella-Zoster Virus: Varicella-Zoster virus (VZV), a herpes virus, causes 2 distinct exanthematous (rash-associated) diseases: chickenpox (varicella) and shingles (herpes zoster). Chickenpox is a highly contagious, though typically benign, disease, usually contracted during childhood. Chickenpox is characterized by a dermal vesiculopustular rash that develops in successive crops approximately 10 to 21 days following exposure.(10) Although primary infection with VZV results in immunity and protection from subsequent infection, VZV remains latent within sensory dorsal root ganglia and upon reactivation, manifests as herpes zoster or shingles. During reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash, usually limited to a single dermatome. Shingles is an extremely painful condition typically occurring in older, nonimmune adults, those with waning immunity to VZV, and in patients with impaired cellular immunity. Individuals at risk for severe complications following primary VZV infection include pregnant women, in whom the virus may spread through the placenta to the fetus, causing congenital disease in the infant. Additionally, immunosuppressed patients are at risk for developing severe VZV-related complications, which include cutaneous disseminated disease and visceral organ involvement. Serologic screening for IgG-class antibodies to VZV aids in identifying nonimmune individuals.

Useful For: Determining immune status of individuals to measles, mumps, rubella, and varicella-zoster viruses (VZV) Documentation of previous infection with measles, mumps, rubella, or VZV in an individual without a previous record of immunization to these viruses

Interpretation: The reported antibody index (AI) value is for reference only. This is a qualitative test, and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cutoff for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. Positive measles, mumps, varicella-zoster viruses: AI value > or =1.1 Positive rubella: AI Value > or =1.0 -The presence of detectable IgG-class antibodies to these viruses indicates prior exposure through infection or immunization. Individuals testing positive for IgG-class antibodies to measles, mumps, rubella, or varicella-zoster viruses (VZV) are considered immune. Equivocal measles, mumps, VZV: AI value 0.9-1.0 Equivocal rubella: AI value 0.8-0.9 -Submit an additional sample for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative measles, mumps, VZV: AI value < or =0.8 Negative rubella: AI value < or =0.7 -The absence of detectable IgG-class antibodies to measles, mumps, rubella, or VZV suggests no prior exposure to these viruses or the lack of a specific immune response to immunization.

Reference Values:

MEASLES, MUMPS and VARICELLA:
Vaccinated: Positive (> or =1.1 AI)
Unvaccinated: Negative (< or =0.8 AI)
Reference values apply to all ages

RUBELLA:
Vaccinated: Positive (> or =1.0 AI)
Unvaccinated: Negative (< or =0.7 AI)
Reference values apply to all ages

Clinical References:

FFMTH 75544 Meconium Methadone Screen with Reflex Confirmation

Reference Values:

MCP2Z 616576 MECP2 Gene, Full Gene Analysis, Varies

Clinical Information: Methyl-CpG-binding protein 2 (MeCP2) is encoded by the MECP2 gene located on the X chromosome and plays an important role in gene regulation. MeCP2 binds methylated DNA and is involved in both transcription activation and repression of other gene targets. As MECP2-related disorders are X-linked, female and male patients with disease-causing variants in the MECP2 gene present with unique variable phenotypes. In female patients, disease-causing variants in MECP2 can be associated with classic Rett syndrome, variant or atypical Rett syndrome, or mild learning disabilities. Distinct phenotypes in male patients with disease-causing MECP2 variants include MECP2-duplication syndrome; MECP2-related severe neonatal encephalopathy; pyramidal signs, parkinsonism, and macroorchidism syndrome (PPM-X); and syndromic/non-syndromic intellectual disability. MECP2 analysis is useful in identifying germline variants in individuals with these clinical presentations. Rett Syndrome: Classic Rett syndrome and other variant MECP2-related disorders result from loss of MeCP2 expression. Rett syndrome is an X-linked, panethnic condition associated with neurologic regression after a 6- to 18-month period of initial normal development. Main clinical findings include stereotypic hand movements such as hand wringing and loss of purposeful hand movements, loss of acquired language, and gait abnormalities. Bruxism, irregular breathing, seizures, acquired microcephaly, and impaired sleep patterns are also common. Greater than 99% of individuals with Rett syndrome are simplex cases due to a de novo variant or inheritance from a parent with germline mosaicism. Asymptomatic or very mildly affected carrier mothers of classically affected daughters have been reported due to nonrandom X chromosome inactivation. MECP2 Duplication Syndrome: MECP2 duplication syndrome involves variably sized duplications of the MECP2 gene (ranging in size from 0.3 to 4 Mb) that result in MeCP2 protein overexpression. It is characterized by severe intellectual disability, hypotonia, feeding difficulties, and progressive spasticity. Seizures and recurrent respiratory infections are commonly reported as well. In contrast to Rett syndrome, most male patients with MECP2 duplication syndrome inherit the duplication from their asymptomatic mothers, although rare de novo variants may occur. Additionally, female patients with an MECP2 duplication that do not demonstrate skewed X-inactivation may present with variable features of MECP2-duplication syndrome.

Useful For: Establishing a molecular diagnosis in individuals with features of Rett syndrome and MECP2-related disorders Identifying pathogenic variants within the MECP2 gene known to be associated with Rett syndrome and MECP2-related disorders, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 2. Sandweiss AJ, Brandt VL, Zoghbi HY: Advances in understanding of Rett syndrome and MECP2 duplication syndrome: prospects for future therapies. Lancet Neurol. 2020 Aug;19(8):689-698 3. Neul JL, Kaufmann WE, Glaze DG, et al: Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol. 2010 Dec; 68(6):944-950

MCADZ
35478

Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency Full Gene Analysis, Varies

Clinical Information: Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is an autosomal recessive inherited defect in the mitochondrial oxidation of fatty acids. The mitochondrial beta-oxidation pathway plays a major role in energy production, especially during periods of fasting and physical exertion. MCAD deficiency is prevalent among individuals of northern European origin, affecting 1 in 4900 to 1 in 17,000 individuals, with a carrier frequency estimated as high as 1 in 40 for some populations. Phenotypic expression of MCAD deficiency is episodic in nature (ie, asymptomatic between attacks). Symptoms are typically precipitated by any stress (eg, fever, infection, vaccination) and mostly occur during the first 2 years of life, although some cases have been diagnosed in adulthood. Characteristic features of MCAD deficiency include: Reye-like syndrome (an acquired encephalopathy characterized by recurrent vomiting, agitation, and lethargy), fasting intolerance with vomiting, recurrent episodes of hypoglycemic coma, hypoketotic dicarboxylic aciduria, low plasma and tissue levels of carnitine, hepatic failure with fat infiltration (fatty liver), encephalopathy, and rapidly progressive deterioration leading to death. MCAD deficiency has also been associated with sudden infant death or sudden unexpected death syndrome. Review of clinical features and biochemical analysis via plasma acylcarnitines (ACRN / Acylcarnitines, Quantitative, Plasma), fatty acid profile (FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture), urine organic acids (OAU / Organic Acids Screen, Random, Urine), and urine acylglycines (ACYLG / Acylglycines, Quantitative, Urine) are always recommended as the initial evaluation for MCAD. If previously performed, the results of these biochemical assays should be included with the specimen as they are necessary for accurate interpretation of the MCAD sequence analysis. The MCAD gene (ACADM) maps to 1p31 and has 12 exons, spanning 44 kb of DNA. Most variants are family-specific with the exception of the recurrent A->G transition at nucleotide 985 (985A->G). Among MCAD-deficient patients, approximately 52% are homozygous for the 985A->G pathogenic variant. The majority of the remaining patients are compound heterozygous for the 985A->G pathogenic variant and a different pathogenic variant.

Useful For: Confirmation of diagnosis of medium-chain acyl-CoA dehydrogenase (MCAD) deficiency (as a follow-up to biochemical analyses) Screening of at-risk carriers of MCAD deficiency when an affected relative has not had molecular testing Diagnosis of MCAD deficiency in autopsy specimens

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Grosse SD, Khoury MJ, Greene CL, et al. The epidemiology of medium chain acyl-CoA dehydrogenase deficiency: An update. Genet Med. 2006:8(4):205-212 2. Ziadeh R, Hoffman EP, Finegold DM, et al. Medium chain acyl-CoA dehydrogenase deficiency in Pennsylvania: neonatal screening shows high incidence and unexpected mutation frequency. Pediatr Res. 1995;37(5):675-678 3. Roe CR, Coates PM: Mitochondrial fatty acid oxidation. In Scriver CR, Beaude AL, Sly WS, eds. The Metabolic and Molecular Bases of Inherited Disease. Vol 1. 7th ed. McGraw-Hill Book Company, 1995:1501-1533

MEGR
82347

Megrim, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to megrim Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive

4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MELAI
82724

Melaleuca leucadendron, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Melaleuca leucadendrony Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive

6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MELAN
70504

Melan A (MART-1) Immunostain, Technical Component Only

Clinical Information: Melanoma antigen recognized by T cells or Melan-A (MART-1), is a protein with unknown function that is associated with endoplasmic reticulum and melanosomes. Melan A is a sensitive and specific marker for the diagnosis of melanoma. Melan A is also found in other tumors of melanocytic origin such as clear cell sarcoma, melanotic neurofibroma, melanotic schwannoma, as well as in perivascular epithelioid cell tumor. The monoclonal antibody A103 for Melan A cross-reacts with steroid hormone producing cells and tumors. Consequently, adrenocortical adenomas/carcinomas and sex cord-stromal tumors of the ovary and testis may exhibit staining.

Useful For: Aids in the identification of melanoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Blessing K, Sanders DSA, Grant JJH. Comparison of immunohistochemical staining of the novel antibody melan-A with S-100 protein and HMB-45 in malignant melanoma and melanoma variants. Histopathol. 1998;32:139-1462 2. Clarkson KS, Sturdgess IC, Molyneux AJ. The usefulness of tyrosinase in the immunohistochemical assessment of melanocytic lesions: a comparison of the novel T311 antibody (anti-tyrosinase) with S-100, HMB45 and A103 (anti-melan-A). J Clin Pathol. 2001;54:196-2003 3. Kaufmann O, Koch S, Gurghardt J, et al. Tyrosinase, melan-A, and KBA62 as markers for the immunohistochemical identification of metastatic amelanotic melanomas on paraffin sections. Mod Pathol. 1998;11(8):740-7464 4. Torres-Mora J, Dry S, Li X, et al. Malignant Melanotic Schwannian Tumor: a clinicopathologic, immunohistochemical, and gene expression profiling study of 40 cases, with a proposal for the reclassification of "melanotic schwannoma". Am J Surg Pathol. 2014;38(1):94-1055 5. Xu X, Chu AY, Pasha T, et al. Immunoprofile of MITF, tyrosinase, melan-A, and MAGE-1 in HMB-45 negative melanomas. Am J Surg Pathol. 2002; 26(1):82-87 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FMARP
75449

Melanoma Associated Retinopathy MAR Panel by Immunoblot and IHC

Reference Values:
A final report will be provided.

FMELA
75386

Melatonin, Plasma

Interpretation:

Reference Values:
Reporting limit determined each analysis.

Units: ng/mL

FMELG
57652

Melons IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

MELN
82762

Melons, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to melons Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MSMN
620788

Membranous Nephropathy Target Antigen Identification, Mass Spectrometry, Tissue

Clinical Information: Membranous nephropathy (MN) is an autoimmune disease and a common cause of nephrotic syndrome in adults. MN results from glomerular accumulation of antigen-antibody complexes along the subepithelial region of the glomerular basement membranes. A series of novel antigens have recently been identified, and many of these antigen-associated MN have distinct clinical and pathologic findings as well as outcomes. This assay is intended to identify the antigens associated with MN using laser microdissection of MN glomeruli followed by mass spectrometry. The panel of MN antigens includes CNTN1, EXT1, EXT2, FAT1, HTRA1, NCAM1, NDNF, NELL1, PCDH7, PCSK6, PLA2R, SEMA3B, and THSD7A.

Useful For: Identification of antigen in membranous nephropathy

Interpretation: For results with a detected peptide profile, a description will be provided. The interpretation will include a diagnosis supported by the findings and a clinical reference. A simple description will be given for results that have no peptides detected or insufficient glomeruli.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Sethi S, Madden B. Mapping antigens of membranous nephropathy: almost there. Kidney Int. 2023;103(3):469-472 2. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4):753-779 3. Sethi S. Membranous nephropathy: a single disease or a pattern of injury resulting from different diseases. Clin Kidney J. 2021;14(10):2166-2169 4. Bobart SA, Tehranian S, Sethi S, et al. A target antigen-based approach to the classification of membranous nephropathy. Mayo Clin Proc. 2021;96(3):577-591 5. Ravindran A, Casal Moura M, Fervenza FC, et al. In patients with membranous lupus nephritis, exostosin-positivity and exostosin-negativity represent two different phenotypes. J Am Soc Nephrol. 2021;32(3):695-706

CSFME
67846

Meningitis/Encephalitis Pathogen Panel, PCR, Spinal Fluid

Clinical Information: Bacteria: Escherichia coli K1 strains account for nearly 80% of E coli isolated from cerebrospinal fluid (CSF). While most E coli are harmless enteric organisms residing in the intestines of humans and animals, some cause gastrointestinal illness and extraintestinal infections (eg, urinary tract infections, bacteremia, and meningitis). E coli associated with meningitis contain virulence factors that contribute to their pathogenesis by allowing them to spread through the blood, hijack normal host cell functions, infiltrate endothelial cells, and gain access to the tissues of the central nervous system (CNS). The K1 antigen is a capsule that protects the bacteria from the immune system. These infections are of particular concern for preterm babies and neonates, and they are responsible for nearly 45% and 30% of meningitis cases in these age groups with a mortality rate of 13% and 25%, respectively. Infections in adults are less common and generally opportunistic in nature, following exposure of sterile organs to contents of the gastrointestinal tract following trauma or surgical procedures; the mortality rate for adults is reported to be 28% to 36%. Haemophilus influenzae is a gram-negative coccobacillus that is isolated exclusively from humans. Strains of H influenzae are divided into 2 groups based on the presence or absence of a polysaccharide capsule. Encapsulated strains are further divided into 6 serotypes (a through f). Prior to widespread use of the H influenzae type b (Hib) conjugate vaccines, Hib caused more than 80% of invasive H influenzae infections, predominantly in children younger than 5, with a mortality rate of 3% to 6% and a further 20% to 30% developing permanent sequelae ranging from mild hearing loss to intellectual disability. In areas with routine vaccination, the majority of invasive H influenzae infections are caused by nontypeable strains and remain an important cause of meningitis, particularly for persons with predisposing conditions such as otitis or sinusitis, diabetes, immune deficiency, or head trauma with CSF leakage. Meningitis due to H influenzae occurs at an estimated rate of 0.08 cases per 100,000 in the United States, and it has been reported as the etiologic agent of bacterial meningitis in 20% to 50% of cases worldwide over the last several decades. Listeria monocytogenes, the causative agent of listeriosis, is a gram-positive bacillus that is ubiquitous in soil and water and can be found in the gastrointestinal tract of up to 5% of healthy human adults. Listeriosis is considered one of the most severe bacterial foodborne infections due to its high mortality rate, even with early antibiotic treatment (11%-60%). Invasive listeriosis can result in abortion, sepsis, meningitis, and meningoencephalitis. Populations at risk for developing invasive listeriosis include individuals who are immunosuppressed, pregnant women, neonates, fetuses, and older adults. Meningitis due to L monocytogenes is reported to be approximately 0.05 cases per 100,000 persons in the United States per year, and causes from 0.5% to 2.0% of bacterial meningitis cases in non-United States countries.(1) Neisseria meningitidis (encapsulated) is a fastidious, aerobic, gram-negative diplococcus that is transmitted by contact with mucus or respiratory droplets, often from asymptomatic carriers. There are at least 12 different serogroups of N meningitidis, 6 of which are associated with epidemics (groups A, B, C, W135, X, and Y). The serogroup refers to types of capsular antigens, generally only encapsulated N meningitidis are considered pathogenic. Meningococcal disease (meningitis and meningococcemia) is rare in developed countries, but it can occur in outbreaks and is a public health issue in developing countries. It is most common in infants, children, and young adults, and appears in places with crowded living conditions (eg, college dormitories and military barracks). Seasonal incidence peaks in late winter and early spring with an annual incidence of about 0.2 cases per 100,000 in the United States. The disease can progress extremely quickly (<24 hours), with hypotension, multiorgan dysfunction, shock, peripheral ischemia, and limb loss, and has a mortality rate of approximately 5% to 10%. There are licensed meningococcal vaccines available in United States that may be used in persons of all ages, depending on the vaccine. Despite extensive vaccination efforts worldwide, several serogroups of N meningitidis still cause seasonal outbreaks, particularly in sub-Saharan Africa. Extreme reductions in serogroup C meningococcal meningitis have been observed in countries where vaccines providing protection for this serogroup have been introduced. Streptococcus agalactiae (group B Streptococcus or GBS) is an important cause of meningitis in neonates, particularly those that are preterm, and is often coincident with neonatal sepsis. The most important risk factor for neonatal disease is maternal colonization with GBS. Since 1996, the Centers for Disease Control and Prevention guidelines (updated in 2010) have called for prophylactic antibiotic treatment several hours before delivery in at-risk deliveries, resulting in declining rates of neonatal GBS. In adult patients, GBS

is associated with advanced age or severe underlying health conditions. Overall incidence in the United States is estimated to be 0.25 infections per 100,000 and neonatal GBS disease has ranged from 0.2 to 2.4 per 1000 births in Europe over the last few decades. Mortality rates range from 10% for neonates to 25% to 30% in adults. Streptococcus pneumoniae colonizes the upper respiratory tract and is the most frequently isolated respiratory pathogen in community-acquired pneumonia. It is also a major cause of meningitis, particularly in pediatric and older adult patients, and especially in those with underlying medical conditions, with an incidence rate of approximately 0.8 infections per 100,000 in the United States and causes 20% to 31% of bacterial meningitis cases in non-United States countries. The mortality rate is also high: 8% to 15% for children and 20% to 37% for adults. Mortality approaches 50% in resource-poor countries, especially where HIV coinfection is a factor. Neurological sequelae (cognitive impairment, deafness, epilepsy) are reported in up to 40% of survivors. Vaccines have helped reduce the risk of both invasive disease and pneumococcal pneumonia by 50% to 80%. Viruses: Human cytomegalovirus (CMV) is a double-stranded DNA virus of the Herpesviridae family. Seroprevalence data show that infection is nearly ubiquitous in the population worldwide, with rates approaching 100% in developing countries and 36% to 90% in the United States depending on age and race/ethnicity. While severe illness in immunocompetent patients is rare, CMV is an opportunistic pathogen in individuals who are immunocompromised or immunosuppressed, either as an initial infection or activation of a latent infection. In some patients (eg, transplant recipients), CMV may infect the central nervous system and cause meningoencephalitis. Enteroviruses (EV) are small RNA viruses that are members of the Picornaviridae family and associated with human illnesses ranging from asymptomatic or mild infections to serious CNS illnesses requiring hospitalization. Infection rates are highest in children, with the majority of infections occurring during summer months. The most common EV serotypes are coxsackie viruses A9 and B1, and echoviruses 6, 9, and 18, which account for over 50% of serotyped detections. Infections are spread via fecal-oral and respiratory routes and can spread quickly in community settings, particularly in areas with poor sanitation. EV is one of the commonly identified causes of infectious encephalitis/meningitis, with prevalence rates reported between 5.5% and 30% depending on location and patient demographics. Herpes simplex viruses 1 and 2 (HSV-1 and HSV-2) are DNA viruses of the Herpesviridae family named for the spreading skin ulcerations caused by infection with these viruses. HSV-1 infections usually occur early in childhood and manifest primarily as oral lesions. However HSV-2 is primarily associated with genital lesions, and infections are acquired later in life and are associated with sexual activity. HSV establishes residency in nerve cells following initial infection, which is asymptomatic in most cases. Viral activation resulting in lesions or other severe disease outcomes (such as CNS infection) may occur throughout life and are associated with fever, injury, exposure to ultraviolet irradiation (sunlight), emotional stress, hormone irregularities, and changes in immune status. In the United States, overall seroprevalence for HSV-1 is around 60%. The overall seroprevalence for HSV-2 is around 16% but varies with age, sex, and ethnicity. Worldwide, approximately 90% of people are infected with HSV-1; HSV-2 is less common with 15% to 80% of people infected. HSV is one of the most common causes of viral encephalitis and is a significant cause of meningitis. In a large study of over 1600 CSF specimens in the United Kingdom, HSV-1 was found in 25 (1.5%) patients (almost all of whom had encephalitis), and HSV-2 was found in 33 (1.9%) patients (almost all of whom had meningitis). This overall prevalence of approximately 3% in CSF is similar to that seen in a recent study of CSF patients in New York state. This study also saw a similar distribution of HSV-1 and HSV-2 in encephalitis versus meningitis. Human herpesvirus 6 (HHV-6) was discovered in the mid-1980s, when the rise of patients who are immunocompromised led to an increase in the population susceptible to severe disease outcome. There are 2 species: HHV-6A and HHV-6B. Studies have shown that over 95% of persons aged 2 or older are positive for 1 or both variants, and the infection establishes latency due to viral integration into host cells. While primary infection with HHV-6B causes roseola in infants, the clinical manifestations of primary infection with HHV-6A remain somewhat undefined; however, some studies have suggested that HHV-6A infection may be linked to inflammatory or neurological disease, and HHV-6A may have an increased neurotropism compared to HHV-6B. This hypothesis is supported by the finding that HHV-6 inhabits CNS tissues, including the brain, where it may cause tissue damage leading to encephalitis or meningitis. Furthermore, HHV-6 was identified in CSF of 1.8% of patients with encephalitis or meningitis in a recent study. CNS disease associated with HHV-6 is found in both children and adults, suggesting CNS invasion during primary infection is possible. While immunocompetent patients may

experience CNS infection, it is much more common in individuals who are severely immunosuppressed. However, HHV-6 is known to reactivate in asymptomatic patients and can be detected by polymerase chain reaction (PCR) analysis in otherwise healthy individuals without signs of active HHV-6 infection. Studies of HHV-6 in normal brain tissue have identified HHV-6 DNA via PCR in up to 85% of patients without signs of active infection, and HHV-6 DNA may persist in the CSF after acute infection. In a study of 56 allogeneic stem cell transplant patients, HHV-6 DNA was detected in the CSF of 14 (27%) patients without CNS symptoms. Given the prevalence of latent infection and potential for asymptomatic reactivation, positive HHV-6 results should be carefully interpreted in association with clinical symptoms and supplemental laboratory testing. Human parechoviruses (HPeV) comprise another genus of the Picornaviridae family. HPeV were originally classified as enterovirus upon their discovery in the 1950s, and at least a dozen serotypes have been identified. Seroprevalence for HPeV-1 approaches 100% in adult populations, with most infections occurring during early childhood. As with EV, infections are spread via fecal-oral and respiratory routes, with the most common symptoms being mild respiratory or gastrointestinal illness. CNS disease from HPeV-1 is rare, but HPeV-3 is associated with severe disease outcomes, such as sepsis, encephalitis, meningitis, and hepatitis in children younger than 3 months of age. Recent studies of CSF from infants with suspected CNS illness or sepsis have demonstrated HPeV at a prevalence of 3% to 17%, nearly all of which were HPeV-3. Magnetic resonance imaging studies of infants who survive HPeV CNS disease show damage to the white matter of the brain and developmental disabilities later in life. Varicella zoster virus (VZV) is a double-stranded DNA virus of the Herpesviridae family that usually causes infections in childhood (chicken pox) and establishes latent presence in cells that can reactivate later in life (zoster or shingles). VZV is primarily spread through respiratory secretions or direct contact with lesions of an infected individual, and infection of new hosts begins within the epithelial cells of the respiratory tract. Following primary infection (fever and malaise accompanied with a maculopapular rash), VZV establishes itself in the sensory ganglia of the nervous system where it remains latent. In the United States, nearly 90% of the population had been infected with VZV before the advent of vaccines. Similar rates have been reported in European countries. Of those infected, between 10% and 30% develop zoster (a painful rash along the dorsal ganglia), primarily later in life. It is estimated that the median global incidence of zoster is 4.0 to 4.5 per 1000 person-years, which highlights the frequency of VZV reactivation worldwide. Studies have shown that VZV is transiently detectable by PCR in the blood of older, asymptomatic individuals (both immunocompetent and immunocompromised), suggesting reactivation occurs throughout life but is usually managed by the immune system. Encephalitis and meningitis are complications of both varicella and zoster infections. In 1 study, VZV was the third most detected virus among patients with signs and symptoms of encephalitis or meningitis, with a reported prevalence of 1.9% in the study population. There are live, attenuated VZV vaccines licensed for use in the United States for the vaccination of children against varicella and adults against zoster. Yeast: Cryptococcus neoformans and Cryptococcus gattii are pathogenic fungi that are acquired by inhalation and can spread to other organ systems (particularly the brain and meninges). C neoformans is considered an opportunistic pathogen of individuals who are immunocompromised. It is the AIDS-defining illness in up to 50% of patients with AIDS. C gattii infections are relatively rare but appear to be increasing. While typically associated with tropical and subtropical climates, since the 1990s, C gattii infections have been reported in British Columbia, Canada, the United States Pacific Northwest region, the Northeastern United States, and in Europe. In addition to those with reduced immune function, C gattii can also cause disease in the immunocompetent, particularly in persons with underlying health conditions. Mortality from cryptococcal meningitis is high, ranging from 10% to nearly 50% in immunocompromised patients.(1)

Useful For: Rapid detection of meningitis and encephalitis caused by: -Escherichia coli K1 (K1 serotype only) -Haemophilus influenzae -Listeria monocytogenes -Neisseria meningitidis (encapsulated strains only) -Streptococcus agalactiae (Group B Strep) -Streptococcus pneumoniae -Cytomegalovirus (CMV) -Enterovirus -Herpes simplex virus 1 (HSV-1) -Herpes simplex virus 2 (HSV-2) -Herpes simplex virus 6 (HHV-6) -Human parechovirus -Varicella zoster virus (VZV) -Cryptococcus neoformans/gattii This test is not intended for use with cerebrospinal fluid (CSF) collected from indwelling medical devices (eg, CSF shunts). This test is not recommended as a test of cure.

Interpretation: A positive result for 1 or more of the organisms suggests that nucleic acid from the organism was present in the sample. A negative result suggests that the nucleic acid of 14 common pathogens of the central nervous system (CNS) was not present in the sample. A negative result should not rule-out central CNS infection in patients with a high pretest probability for meningitis or encephalitis. The assay does not test for all potential infectious agents of CNS disease. Negative results should be considered in the context of a patient's clinical course and treatment history, if applicable. False-negative results may occur when the concentration of nucleic acid in the specimen is below the limit of detection for the test. Detection of multiple viruses or bacteria or viruses and bacteria may be observed with this test. In these situations, the clinical history and presentation should be reviewed thoroughly to determine the clinical significance of multiple pathogens in the same specimen. Results are intended to aid in the diagnosis of illness and are meant to be used in conjunction with other clinical and epidemiological findings.

Reference Values:
Negative (for all targets)

Clinical References: 1. FilmArray Meningitis/Encephalitis [ME] Panel CE IVD Instruction Booklet. BioFire Diagnostics, LLC; RFIT-PRT-0276-03, 06/2017 2. Liesman R, Strasburg A, Heitman A, Theel ES, Patel R, Binnicker MJ. Evaluation of a commercial multiplex molecular panel for the diagnosis of infectious meningitis and encephalitis. J Clin Microbiol. 2018;56(4):e012927-17. doi:10.1128/JCM.01927-17 3. Ramanan P, Bryson A, Binnicker MJ, Pritt BS, Patel R. Syndromic panel-based testing in clinical microbiology. Clin Microbiol Rev. 2017;31(1):e00024-17. doi:10.1128/CMR.00024-17 4. Rhein J, Bahr NC, Hemmert AC, et al. Diagnostic performance of a multiplex PCR assay for meningitis in an HIV-infected population in Uganda. 2016;84(3):268-273. doi:10.1016/j.diagmicrobio.2015.11.017 5. Wootton SH, Aguilera E, Salazar L, et al. Enhancing pathogen identification in patients with meningitis and a negative Gram stain using the BioFire FilmArray(R) Meningitis/Encephalitis panel. Ann Clin Microbiol Antimicrob 2016;15:26. doi:10.1186/s12941-016-0137-1

FMEP
90090

Meperidine (Demerol) and Normeperidine, serum

Clinical Information: Category: Narcotic Analgesic

Reference Values:
Meperidine:
Reference Range: 400 - 700 ng/ml

Normeperidine: No reference range provided

FMMM
57766

Mephedrone, MDPV and Methylone, Urine

Reference Values:

Drug	Units	Reference Range
Mephedrone		Negative
MDPV		Negative
Methylone		Negative

Qualitative analysis for Mephedrone, Methylenedioxypyrovalerone (MDPV) and Methylone
Screening threshold: 1.0 ng/mL

MEPHS
83778

Mephobarbital and Phenobarbital, Serum

Clinical Information: Mephobarbital is an orally administered, methylated barbiturate used for the treatment of epilepsy.(1,2) It is demethylated by hepatic microsomal enzymes to generate its major metabolite, phenobarbital. During long-term use, most of the mephobarbital activity can be attributed to the accumulation of phenobarbital. Consequently, the pharmacological properties, toxicity, and clinical uses of mephobarbital are the same as phenobarbital.(1,2) The use of mephobarbital is uncommon as it offers no significant advantage over phenobarbital alone.(1,2)

Useful For: Monitoring of mephobarbital and phenobarbital therapy

Interpretation: Mephobarbital concentrations above 15 mcg/mL have been associated with toxicity. Phenobarbital concentrations between 35 and 80 mcg/mL have been associated with slowness, ataxia, and nystagmus, while concentrations above 100 mcg/mL have been associated with coma without reflexes.

Reference Values:
MEPHOBARBITAL
Therapeutic range: 1.0-7.0 mcg/mL
Toxic concentration: > or =15.0 mcg/mL

PHENOBARBITAL
Therapeutic range
Children: 15.0-30.0 mcg/mL
Adults: 20.0-40.0 mcg/mL
Toxic concentration: > or =60.0 mcg/mL

Clinical References:

FMERC
91120

Mercaptopurine (6-MP, Purinethol)

Reference Values:
Units: ng/mL

Mercaptopurine may be administered as an antineoplastic or may be present as a metabolite of the immunosuppressant drug azathioprine. Therapeutic and toxic ranges have not been established. Usual therapeutic doses of either mercaptopurine or azathioprine produce 6-mercaptopurine serum concentrations of less than 1000 ng/mL.

HGOU
608893

Mercury Occupational Exposure, Random, Urine

Clinical Information: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. However, urinary Hg is the most reliable way to assess exposure to inorganic Hg. For more information, see HG / Mercury, Blood.

Useful For: Detecting mercury toxicity due to occupational exposure in random urine specimens

Reference Values:
Only orderable as part of a profile. For more information see:
-HGUOE/ Mercury Occupational Exposure, Random, Urine

-HMUOE / Heavy Metal Occupational Exposure, with Reflex, Random, Urine

Biological Exposure Index (BEI): <35 mcg/g creatinine prior to shift

Clinical References: 1. Snoj Tratniid J, Falnoga I, Mazej D, et al. Results of the first national human biomonitoring in Slovenia: Trace elements in men and lactating women, predictors of exposure and reference values. Int J Hyg Environ Health. 2019222(3):563-582 2. Sherman LS, Blum JD, Franzblau A, Basu N. New insights into biomarkers of human mercury exposure using naturally occurring mercury stable isotopes. Envrn Sci Technol. 2013;47(7):3403-3409 3. Lee R, Middleton D, Caldwell K, et al. A review of events that expose children to elemental mercury in the United States. Environ Health Perspect. 2009;117(6):871-878 4. Bjorkman L, Lundekvam BF, Laegreid T, et al. Mercury in human brain, blood, muscle and toenails in relation to exposure: an autopsy study. Environ Health. 2007 11;6:30 5. Strathmann FG, Blum LM: Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

HGUOE
608897

Mercury Occupational Exposure, Random, Urine

Clinical Information: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. Previous thought indicated urine as a more appropriate marker of inorganic mercury because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury levels (up to 30%),(1) which is consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood.(2) For more information see HG / Mercury, Blood.

Useful For: Detecting mercury toxicity due to occupational exposure

Interpretation: Daily urine excretion of mercury greater than 50 mcg/day indicates significant exposure (per World Health Organization standard).

Reference Values:

Clinical References: 1. Snoj Tratniid J, Falnoga I, Mazej D, et al. Results of the first national human biomonitoring in Slovenia: Trace elements in men and lactating women, predictors of exposure and reference values. Int J Hyg Environ Heatlh. 2019;222(3):563-582 2. Sherman LS, Blum JD, Franzblau A, Basu N. New insights into biomarkers of human mercury exposure using naturally occurring mercury stable isotopes. Environ Sci Technol. 2013 2;47(7):3403-3409 3. Lee R, Middleton D, Caldwell K, et al. A review of events that expose children to elemental mercury in the United States. Environ Health Perspect. 2009;117(6):871-878 4. Bjorkman L, Lundekvam BF, Laegreid T, et al. Mercury in human brain, blood, muscle and toenails in relation to exposure: an autopsy study. Environ Health. 2007 11;6:30 5. Strathmann FG, Blum LM: Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

HGU
8592

Mercury, 24 Hour, Urine

Clinical Information: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. Previous thought indicated urine as a more appropriate marker of inorganic mercury because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury

levels (up to 30%),(1) which is consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood.(2) For more information see HG / Mercury, Blood.

Useful For: Detecting mercury toxicity using 24-hour urine specimens

Interpretation: Daily urine excretion of mercury above 50 mcg/day indicates significant exposure (per World Health Organization standard).

Reference Values:
0-17 years: Not established
> or =18 years: <2 mcg/24 h
Toxic concentration: >50 mcg/24 h
The concentration at which toxicity is expressed is widely variable between patients. The lowest concentration at which toxicity is usually apparent is 50 mcg/24 h.

Clinical References: 1. Snoj Tratniid J, Falnoga I, Mazej D, et al. Results of the first national human biomonitoring in Slovenia: Trace elements in men and lactating women, predictors of exposure and reference values. Int J Hyg Environ Heatlh. 2019;222(3):563-582 2. Sherman LS, Blum JD, Franzblau A, Basu N. New insights into biomarkers of human mercury exposure using naturally occurring mercury stable isotopes. Envrn Sci Technol. 2013;47(7):3403-3409 3. Lee R, Middleton D, Caldwell K, et al. A review of events that expose children to elemental mercury in the United States. Environ Health Perspect. 2009;117(6):871-878 4. Bjorkman L, Lundekvam BF, Laegreid T, et al. Mercury in human brain, blood, muscle and toenails in relation to exposure: an autopsy study. Environ Health. 2007;6:30 5. Bernhoft RA. Mercury toxicity and treatment: a review of the literature. J Environ Public Health. 2012;2012:460508. doi:10.1155/2012/460508 6. Strathmann FG, Blum LM: Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

HG
8618

Mercury, Blood

Clinical Information: Mercury (Hg) is relatively non-toxic in its elemental form. If Hg(0) is chemically modified to the ionized, inorganic species, Hg(2+), it becomes toxic. Further bioconversion to an alkyl Hg, such as methyl Hg (CH3Hg[+]), yields a species of mercury that is highly selective for lipid-rich tissue, such as neurons, and is very toxic. The relative order of toxicity is: Least Toxic - Hg(0) < Hg(2+) << CH3Hg(+) -- Very Toxic Mercury can be chemically converted from the elemental state to the ionized state. In industry, this is frequently done by exposing Hg(0) to strong oxidizing agents, such as chlorine. Hg(0) can be bioconverted to both Hg(2+) and alkyl Hg by microorganisms that exist both in the normal human gut and in the bottom sediment of lakes, rivers, and oceans. When Hg(0) enters bottom sediment, it is absorbed by bacteria, fungi, and small microorganisms; they metabolically convert it to Hg(2+), CH3Hg(+), and C2H6Hg. Should these microorganisms be consumed by larger marine animals and fish, the mercury passes up the food chain in rather toxic form. Mercury expresses its toxicity in 3 ways: -Hg(2+) is readily absorbed and reacts with sulfhydryl groups of protein, causing a change in the tertiary structure of the protein-a stereoisomeric change-with subsequent loss of the unique activity associated with that protein. Because Hg(2+) becomes concentrated in the kidney during the regular clearance processes, this target organ experiences the greatest toxicity. -With the tertiary change noted previously, some proteins become immunogenic, eliciting a proliferation of T lymphocytes that generate immunoglobulins to bind the new antigen; collagen tissues are particularly sensitive to this. -Alkyl Hg species, such as CH3Hg(+), are lipophilic and avidly bind to lipid-rich tissues such as neurons. Myelin is particularly susceptible to disruption by this mechanism. Members of the public will occasionally become concerned about exposure to mercury from dental amalgams. Restorative dentistry has used a mercury-silver amalgam for approximately 90 years as a filling

material. A small amount of mercury (2-20 mcg/day) is released from a dental amalgam when it was mechanically manipulated, such as by chewing. The habit of gum chewing can cause release of mercury from dental amalgams greatly above normal. The normal bacterial microbiota present in the mouth converts a fraction of this to Hg(2+) and CH3Hg(+), which was shown to be incorporated into body tissues. The World Health Organization safety standard for daily exposure to mercury is 45 mcg/day. Thus, if one had no other source of exposure, the amount of mercury released from dental amalgams is not significant.(1) Many foods contain mercury. For example, commercial fish considered safe for consumption contain less than 0.3 mcg/g of mercury, but some game fish contain more than 2.0 mcg/g and, if consumed on a regular basis, contribute to significant body burdens. Therapy is usually monitored by following urine output; therapy may be terminated after urine excretion is below 50 mcg/day.

Useful For: Detecting mercury toxicity

Interpretation: The quantity of mercury (Hg) found in blood and urine correlates with degree of toxicity. Hair analysis can be used to document the time of peak exposure if the event was in the past. Normal whole blood mercury is usually below 10 ng/mL. Individuals who have mild exposure during work, such as dentists, may routinely have whole blood mercury levels up to 15 ng/mL. Significant exposure is indicated when the whole blood mercury is above 50 ng/mL if exposure is due to alkyl Hg, or above 200 ng/mL if exposure is due to Hg(2+).

Reference Values:
<10 ng/mL
Reference values apply to all ages.

Clinical References: 1. Lee R, Middleton D, Calwell K, et al. A review of events that expose children to elemental mercury in the United States. Environ Health Perspect. 2009;117(6):871-878 2. Bjorkman L, Lundekvam B, Laegreid T, et al. Mercury in human brain, blood, muscle and toenails in relation to exposure: an autopsy study. Environ Health. 2007;6:30. Published 2007 Oct 11. doi:10.1186/1476-069X-6-30 3. deBurbure C, Buchet JP, Leroyer A, et al. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect. 2006;114(4):584-590 4. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

HGHAR
8498

Mercury, Hair

Clinical Information: Once absorbed and circulating, mercury becomes bound to numerous proteins, including keratin. The concentration of mercury in hair correlates with the severity of clinical symptoms. If hair can be segregated by length, such an exercise may be useful in identifying the time of exposure.

HGNA
89856

Mercury, Nails

Clinical Information: Once absorbed and circulating, mercury becomes bound to numerous proteins, including keratin. The concentration of mercury in nails correlates with the severity of clinical symptoms.

HGCU
608903

Mercury/Creatinine Ratio, Random, Urine

Clinical Information: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. Previous thought indicated urine as a more appropriate marker of inorganic mercury because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury levels (up to 30%),(1) which is consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood.(2). For more information see HG / Mercury, Blood.

Useful For: Detecting mercury toxicity using random urine specimens

Interpretation: Daily urine excretion of mercury above 50 mcg/day indicates significant exposure (per World Health Organization standard).

Reference Values:
Only orderable as part of profile. For more information see:
-HGUCR / Mercury/Creatinine Ratio, Random, Urine
-HMUCR / Heavy Metal/Creatinine Ratio, with Reflex, Random Urine.

0-17 years: Not established
> or =18 years: <2 mcg/g creatinine

Clinical References: 1. Snoj Tratniid J, Falnoga I, Mazej D, et al. Results of the first national human biomonitoring in Slovenia: Trace elements in men and lactating women, predictors of exposure and reference values. Int J Hyg Environ Health. 2019;222(3):563-582. doi:10.1016/j.ijheh.2019.02.008 2. Sherman LS, Blum JD, Franzblau A, Basu N. New insights into biomarkers of human mercury exposure using naturally occurring mercury stable isotopes. Environ Sci Technol. 2013;47(7):3403-3409. doi:10.1021/es305250z 3. Lee R, Middleton D, Caldwell K, et al. A review of events that expose children to elemental mercury in the United States. Environ Health Perspect. 2009;117(6):871-878. doi:10.1289/ehp.0800337 4. Bjorkman L, Lundekvam BF, Laegreid T, et al. Mercury in human brain, blood, muscle and toenails in relation to exposure: an autopsy study. Environ Health. 2007;6:30. doi: 10.1186/1476-069X-6-30 5. Bernhoft RA. Mercury toxicity and treatment: a review of the literature. J Environ Public Health. 2012;2012:460508. doi:10.1155/2012/460508 6. Strathmann FG, Blum LM: Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

HGUCR
608907

Mercury/Creatinine Ratio, Random, Urine

Clinical Information: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. Previous thought indicated urine as a more appropriate marker of inorganic mercury because organic mercury represented only a small fraction of urinary mercury. Based on possible demethylation of methylmercury within the body, urine may represent a mixture of dietary methylmercury and inorganic mercury. Seafood consumption can contribute to urinary mercury levels (up to 30%),(1) which is consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood.(2) Small amounts of mercury are often present in urine, often stemming from environmental exposure or from dental amalgam. The amount of mercury in urine depends upon the form of mercury, the level and duration of mercury exposure, and the elapsed time between exposure and urine sample collection. For potential mercury vapor exposure: urine mercury levels are unlikely to be useful for assessing potential health effects from short-term, low-level exposures to mercury vapor because such exposures are unlikely to result in mercury urine levels elevated above typical values. High level mercury vapor exposure or long-term, low-level vapor exposures may result in elevated urine mercury levels, which can indicate potential for health effects. Random urine mercury level is adjusted to concentration of creatinine. Urine mercury concentrations in unexposed individuals are typically less than 10 mcg/L (50 nmol/L) or 2 mcg/g creatinine. Twenty-four-hour urine concentrations of 30 mcg/L to 100 mcg/L (150-499 nmol/L) may be associated with subclinical neuropsychiatric symptoms and tremor, while concentrations greater than 100 mcg/L (499 nmol/L) can be associated with overt neuropsychiatric disturbances and tremors.(4) Mercury concentrations of greater than 10 mcg/g creatinine may associate with subtle effects on visual memory, attention, manual coordination, mood, increased levels of fatigue and confusion. Higher level of urine mercury is associated with increasing frequent and severe nervous system changes in personality, cognition, and

coordination.(3) Mercury concentrations of 20 mcg/g to 35 mcg/g creatinine may be associated with hand tremors and potential kidney damage.(3)

Useful For: Detecting mercury toxicity, a toxic heavy metal, using random urine specimens

Interpretation: Daily urine excretion of mercury above 50 mcg/day indicates significant exposure (per World Health Organization standard).

Reference Values:

Clinical References: 1. Snoj Tratniid J, Falnoga I, Mazej D, et al. Results of the first national human biomonitoring in Slovenia: Trace elements in men and lactating women, predictors of exposure and reference values Int. J. Hyg Environ Health. 2019;222(3):563-582 2. Sherman LS, Blum JD, Franzblau A, Basu N. New insights into biomarkers of human mercury exposure using naturally occurring mercury stable isotopes. Environ Sci and Tech. 2013;47(7):3403-3409 3. McKelvey W, Alex B, Chernov C, et al. Tracking Declines in Mercury Exposure in the New York City Adult Population, 2004-2014. J Urban Health. 2018;95(6):813-825 4. Agency for Toxic Substances and Disease Registry. Atsdr - addendum to the toxicological profile: Mercury. 2022. 5. Lee R, Middleton D, Caldwell K, et al. A review of events that expose children to elemental mercury in the United States. Environ Health Perspect. 2009;117(6):871-878 6. Bjorkman L, Lundekvam BF, Laegreid T, et al. Mercury in human brain, blood, muscle and toenails in relation to exposure: an autopsy study. Environ Health. 2007 11;6:30 7. Bernhoft RA. Mercury toxicity and treatment: a review of the literature. J Environ Public Health. 2012;2012:460508. doi:10.1155/2012/460508 8. Strathmann FG, Blum LM: Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

MERKC 71538 Merkel CC (MCPyV) Immunostain, Technical Component Only

Clinical Information: Merkel cell polyomavirus (MCPyV) infections are common and typically benign. In rare instances, these infections lead to neoplastic transformations known as Merkel cell carcinoma (MCC) through the expression (nuclear) of MCPyV large T-antigen. MCPyV-positive MCC have been reported to behave less aggressively than MCPyV-negative MCC.

Useful For: Identification of Merkel cell polyomavirus infected cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Leroux-Kozal V, Leveque N, Brodard V, et al. Merkel cell carcinoma: histopathologic and prognostic features according to the immunohistochemical expression of Merkel cell polyomavirus large T antigen correlated with viral load. Hum Pathol. 2015;46(3):443-453 2. Samimi M, Molet L, Fleury M, et al. Prognostic value of antibodies to Merkel cell polyomavirus T antigens and VP1 protein in patients with Merkel cell carcinoma. Br J Dermatol. 2016;174(4):813-822 3. Richards KF, Guastafierro A, Shuda M, Toptan T, Moore PS, Change Y. Merkel cell polyomavirus T antigens promote cell proliferation and inflammatory cytokine gene expression. J Gen Virol. 2015;96(12):3532-3544 4. Jung HS, Choi YL, Choi JS, et al. Detection of Merkel cell polyomavirus in Merkel cell carcinomas and small cell carcinomas by PCR and immunohistochemistry. Histol Histopathol. 2011;26(10):1231-1241 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HBME
70452

Mesothelial Cell (HBME-1) Immunostain, Technical Component Only

Clinical Information: This mesothelial cell (HBME-1) antibody stains an unknown antigen in the microvillous processes of mesothelial cells with a "thick membrane" staining pattern. The antibody also reacts with a wide variety of normal and neoplastic tissues. This stain is diagnostically useful in distinguishing thyroid carcinoma (papillary and follicular types) from thyroid follicular adenomas, which usually lack staining.

Useful For: Classification of thyroid carcinomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. de Matos LL, Del Giglio AB, Matsubayashi CO, de Lima Farah M, Del Giglio A, da Silva Pinhal MA: Expression of CK-19, galectin-3 and HBME-1 in the differentiation of thyroid lesions: systematic review and diagnostic meta-analysis. Diagn Pathol. 2012;7:97 2. Rossi ED, Straccia P, Palumbo M, et al. Diagnostic and prognostic role of HBME-1, galectin-3, and beta-catenin in poorly differentiated and anaplastic thyroid carcinomas. Appl Immunohistochem Mol Morphol. 2013;21(3):237-241 3. Liu Z, Li X, Shi L, et al. Cytokeratin 19, thyroperoxidase, HBME-1 and galectin-3 in evaluation of aggressive behavior of papillary thyroid carcinoma. Int J Clin Exp Med. 2014 15;7(8):2304-2308 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

MESOP
620227

Mesothelioma Panel (WT1/KRT5/TTF1/pCEA) Immunostain, Technical Component Only

Clinical Information: The Mesothelioma Panel assay consists of 4 antibodies WT-1, KRT5, TTF1 (clone SPT24) and P-CEA. This multiplex immunohistochemistry assay is used in the differential diagnosis of mesothelioma and non-small cell lung cancer (NSCLC). WT-1 (nuclear; detected with green chromogen) and KRT5 (cytoplasmic; detected with purple chromogen) are biomarkers expressed in mesothelioma. TTF1 (nuclear; detected with red chromogen) and P-CEA (membranous/cytoplasmic; detected with teal chromogen) are biomarkers expressed in NSCLC.

Useful For:

Interpretation: This test does not include pathologist interpretation only technical performance of the stain. If interpretation is required order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

MESOF
609714

Mesothelioma, CDKN2A FISH, Tissue

Clinical Information: The histologic distinction of malignant mesothelioma from benign mesothelial proliferations can be challenging. Loss of both copies of CDKN2A has been described as a recurrent abnormality in 59% to 80% of pleural malignant mesotheliomas depending on histologic features.(1-3) Homozygous deletion of CDKN2A is less common in peritoneal mesothelioma, reported to occur in 25% to 35% of cases.(2,4,5) The detection of homozygous deletion of CDKN2A by fluorescence in situ hybridization has been suggested as a useful adjunct to histologic examination in the differentiation of malignant mesothelioma from other processes.(6,7)

Useful For: Supporting the diagnosis of mesothelioma when used in conjunction with an anatomic pathology consultation

Interpretation: CDKN2A will be clinically interpreted as positive or negative. A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the CDKN2A/D9Z1 probe set. In the proper clinical and histologic context, a positive result may support a diagnosis of mesothelioma. However, homozygous loss of CDKN2A can be identified in many neoplasms. Therefore, clinical and pathologic correlation are required. A negative result suggests no deletion of the CDKN2A gene region at 9p21. However, as homozygous deletion is not present in all mesotheliomas, this result does not exclude the diagnosis of malignant mesothelioma. In addition, due to limitations of the technology, fluorescence in situ hybridization cannot detect all CDKN2A deletions.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Illel P, Ladanyl M, Rusch V, Zakowski MF. The use of CDKN2A deletion as a diagnostic marker for malignant mesothelioma in body cavity effusions. Cancer. 2003;99:51-56 2. Chiosea C, Krasinkas A, Cagle P, Mitchell KA, Zander DS, Dacic S. Diagnostic importance of 9p21 homozygous deletion in malignant mesotheliomas. Mod Pathol. 2008;21:742-747 3. Hwang H, Pyott S, Rodriguez S, et al. BAP1 immunohistochemistry and p16 FISH in the diagnosis of sarcomatous and desmoplastic mesotheliomas. Am J Surg Pathol. 2016;40:714-718 4. Krasinskas A, Bartlett D, Cieply K, Dacic S. CDKN2A and MTAP deletions in peritoneal mesotheliomas are correlated with loss of p16 protein expression and poor survival. Mod Pathol. 2010;23:531-538 5. Singhi A, Krasinskas A, Choudry H, et al. The prognostic significance of BAP1, NF2, and CDKN2A in malignant peritoneal mesothelioma. Mod Pathol. 2016;29:14-24 6. Monaco S, Shuai Y, Bansal M, Krasinskas AM, Dacic S. The diagnostic utility of p16 FISH and GLUT-1 immunohistochemical analysis in mesothelial proliferations. Am J Clin Pathol. 2011;135:619-627 7. Wu D, Hiroshima K, Yusa T, et al. Usefulness of p16/CDKN2A Fluorescence in situ hybridization and BAP1 immunohistochemistry for the diagnosis of biphasic mesothelioma. Ann Diagn Pathol. 2017;26:31-37

MESQ
82776

Mesquite, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant

allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mesquite Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

METF
58123

MET (7q31), FISH, Tissue

Clinical Information: MET is a proto-oncogene and its overexpression is associated with disease progression. Recent studies have shown MET amplification to be a major mechanism of acquired resistance to epidermal growth factor receptor tyrosine kinase domain inhibitor (EGFR-TKI). MET amplification has been reported in approximately 5% of patients not treated with EGFR-TKI and up to 20% of patients with acquired resistance to gefitinib or erlotinib. MET amplification has also been identified in several other cancers including colorectal adenocarcinoma, gastric adenocarcinoma, and gastroesophageal adenocarcinoma.

Useful For: Providing prognostic information and guiding treatment primarily for patients with lung, gastric, and colorectal tumors as well as other tumor types

Interpretation: MET will be clinically interpreted as positive, negative or equivocal. Establishment

of a clear definition of MET amplification has been challenging with the evolution of criteria, as the need to differentiate between true MET amplification and chromosome 7 polysomy has become clear. For this assay, MET will be reported as amplified (positive) when there is a MET:D7Z1 ratio greater than 2.0 and an average of greater or equal to 5 MET signals/nucleus based on current scientific literature. Because various other definitions have been proposed, results indicating a greater or equal to 5 MET signals/nucleus with a MET:D7Z1 ratio less than 2.0 will be reported as an equivocal result as this finding likely reflects chromosome 7 polysomy but may represent an unusual mechanism of MET amplification. Similarly, results indicating a MET:D7Z1 ratio greater than 2.0 and less than 5 MET signals/nucleus will be reported as equivocal. Chromosomal microarray studies (TEST: CMAPT) may be considered in these instances to clarify the FISH results. A result with a MET:D7Z1 ratio less than or equal to 2.0 and an average of less than 5 MET signals/nucleus will be considered negative for amplification of MET. Patients with 5 or more copies of MET have a poor prognosis. A negative result does not exclude the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References:

MT
619972

Metallothionein Immunostain, Technical Component Only

Clinical Information: This test is intended to identify the presence of metallothionein (MT). MT is useful to support a diagnosis of Wilson disease (WD). MT plays a role in binding the accumulated copper in WD disorder. MT can detect even early-stage cases of WD before the development of cirrhosis. The MT assay has been shown to have higher sensitivity and specificity compared to the use of the Leipzig criteria and rhodanine. MT expression by IHC is a more cost effective and practical approach compared to quantitative liver copper assays.

Useful For: Supporting the diagnosis of Wilson disease

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Rowan D, Mangalaparthi KK, Singh S, et al. Metallothionein immunohistochemistry has high sensitivity and specificity for detection of Wilson disease. Mod Pathol. 2022;35(7):946-955 2. Poujois A, Woimant F. Wilson's disease: A 2017 update. Clin Res Hepatol Gastroenterol. 2018;42(6):512-520 3. Mulder TP, Janssens AR, Verspaget HW, et al. Metallothionein concentration in the liver of patients with wilson's disease, primary biliary cirrhosis, and liver metastasis of colorectal cancer. J Hepatol. 1992;16(3):346-350 4. Petering DH, Fowler BA. Roles of metallothionein and related proteins in metal metabolism and toxicity: problems and perspectives. Environ Health Perspect. 1986;65:217-224

MHBRP
65129

Metamycoplasma hominis, Molecular Detection, PCR, Blood

Clinical Information: Metamycoplasma hominis, previously Mycoplasma hominis, has been associated with a number of clinically significant infections, although it is also part of the normal urogenital microbiota. M hominis may be found in the respiratory specimens and spinal fluid of neonates. Although the clinical significance of such findings is often unclear, as spontaneous clinical recovery may

occur without specific treatment. In premature infants, clinical manifestations of meningoencephalitis have been reported. M hominis may play a role in some cases of pelvic inflammatory disease, usually in combination with other organisms. M hominis may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis; there is evidence that it may be involved in postpartum fever or fever following abortion, usually as a complication of endometritis. M hominis has rarely been associated with septic arthritis (including prosthetic joint infection), pyelonephritis, intraabdominal infection, wound infection, endocarditis, central nervous system infection (including meningoencephalitis, brain abscess, central nervous system shunt infection and subdural empyema), pneumonia, and infected pleural and pericardial effusions. Extragenital infection typically occurs in those with hypogammaglobulinemia or depressed cell-mediated immunity; in lung transplant recipients in particular, M hominis has been associated with pleuritis and mediastinitis. Recent evidence implicates donor transmission in some cases of M hominis infection in lung transplant recipients. Polymerase chain reaction (PCR) detection of M hominis is sensitive, specific, and provides same-day results. Although this organism can occasionally be detected in routine plate cultures, this is neither a rapid nor a sensitive approach to detection. Specialized cultures are more time consuming than the described PCR assay. The described PCR assay has replaced conventional culture for M hominis at Mayo Clinic Laboratories due to its speed and equivalent performance to culture.

Useful For: Rapid, sensitive, and specific identification of Metamycoplasma hominis from whole blood This test is not intended for medicolegal use.

Interpretation: A positive polymerase chain reaction (PCR) result for the presence of a specific sequence found within the Metamycoplasma hominis tuf gene indicates the presence of M hominis DNA in the specimen. A negative PCR result indicates the absence of detectable M hominis DNA in the specimen, but it does not rule-out infection as falsely negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of M hominis in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References:

MHPRP 65134 Metamycoplasma hominis, Molecular Detection, PCR, Plasma

Clinical Information: Metamycoplasma hominis, previously Mycoplasma hominis, has been associated with a number of clinically significant infections, although it is also part of the normal urogenital microbiota. M hominis may be found in the respiratory specimens and spinal fluid of neonates. Although the clinical significance of such findings is often unclear, as spontaneous clinical recovery may occur without specific treatment. In premature infants, clinical manifestations of meningoencephalitis have been reported. M hominis may play a role in some cases of pelvic inflammatory disease, usually in combination with other organisms. M hominis may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis; there is evidence that it may be involved in postpartum fever or fever following abortion, usually as a complication of endometritis. M hominis has rarely been associated with septic arthritis (including prosthetic joint infection), pyelonephritis, intraabdominal infection, wound infection, endocarditis, central nervous system infection (including meningoencephalitis, brain abscess, central nervous system shunt infection and subdural empyema), pneumonia, and infected pleural and pericardial effusions. Extragenital infection typically occurs in those with hypogammaglobulinemia or depressed cell-mediated immunity. In lung transplant recipients in particular, M hominis has been associated with pleuritis and mediastinitis. Recent evidence implicates donor transmission in some cases

of M hominis infection in lung transplant recipients. Polymerase chain reaction (PCR) detection of M hominis is sensitive, specific, and provides same-day results. Although this organism can occasionally be detected in routine plate cultures, this is neither a rapid nor a sensitive approach to detection. Specialized cultures are more time consuming than the described PCR assay. The described PCR assay has replaced conventional culture for M hominis at Mayo Clinic Laboratories due to its speed and equivalent performance to culture.

Useful For: Rapid, sensitive, and specific identification of Metamycoplasma hominis from plasma This test is not intended for medicolegal use.

Interpretation: A positive polymerase chain reaction (PCR) result for the presence of a specific sequence found within the Metamycoplasma hominis tuf gene indicates the presence of M hominis DNA in the specimen. A negative PCR result indicates the absence of detectable M hominis DNA in the specimen, but it does not rule-out infection as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of M hominis in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. Sampath R, Patel R, Cunningham SA, et al: Cardiothoracic transplant recipient Mycoplasma hominis: An uncommon infection with probable donor transmission, EBioMedicine 2017 May;19:84-90 2. Waites KB, Taylor-Robinson D: Mycoplasma and Ureaplasma. In: Jorgensen JH, ed. Manual of Clinical Microbiology. 11th ed. ASM Press; 2015:1088-1105

MHRP 60756 Metamycoplasma hominis, Molecular Detection, PCR, Varies

Clinical Information: Metamycoplasma hominis, formerly Mycoplasma hominis, has been associated with a number of clinically significant infections, although it is also part of the normal genital microbiota. M hominis may be found in the respiratory specimens and spinal fluid of neonates. Although the clinical significance of such findings is often unclear as spontaneous clinical recovery may occur without specific treatment, clinical manifestations of meningoencephalitis in premature infants have been reported. M hominis may play a role in some cases of pelvic inflammatory disease, usually in combination with other organisms. M hominis may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis; there is evidence that it may be involved in postpartum fever or fever following abortion, usually as a complication of endometritis. M hominis has rarely been associated with septic arthritis (including prosthetic joint infection), pyelonephritis, intraabdominal infection, wound infection, endocarditis, central nervous system infection (including meningoencephalitis, brain abscess, central nervous system shunt infection, and subdural empyema), pneumonia, and infected pleural and pericardial effusions. Extragenital infection typically occurs in those with hypogammaglobulinemia or depressed cell-mediated immunity; in lung transplant recipients in particular, M hominis has been associated with pleuritis and mediastinitis. Recent evidence implicates donor transmission in some cases of M hominis infection in lung transplant recipients. Polymerase chain reaction (PCR) detection of M hominis is sensitive, specific, and provides same-day results. Although this organism can occasionally be detected in routine plate cultures, this is neither a rapid nor a sensitive approach to detection. Specialized cultures are more time consuming than the described PCR assay. The described PCR assay has replaced conventional culture for M hominis at Mayo Clinic Laboratories due to its speed and equivalent performance to culture.

Useful For: Rapid, sensitive, and specific identification of Metamycoplasma hominis from synovial fluid, genitourinary, reproductive, lower respiratory sources, pleural/chest fluid, pericardial fluid, and wound specimens This test is not intended for medicolegal use.

Interpretation: A positive polymerase chain reaction (PCR) result for the presence of a specific sequence found within the Metamycoplasma hominis tuf gene indicates the presence of M hominis DNA in the specimen. A negative PCR result indicates the absence of detectable M hominis DNA in the specimen but does not rule out infection, as falsely negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of M hominis in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. Sampath R, Patel R, Cunningham SA, et al. Cardiothoracic transplant recipient Mycoplasma hominis: An uncommon infection with probable donor transmission. EBioMedicine. 2017;19:84-90 2. Waites KB, Bebear C. Mycoplasma and Ureaplasma. In: Carroll KC, Pfaller MA, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:1117-1136

META3
65158

Metanephrines with 3-Methoxytyramine, 24 Hour, Urine

Clinical Information: Pheochromocytomas and paragangliomas (Pheo/PGL) are rare, usually benign, tumors of chromaffin cells in the adrenal medulla or paragangliomas (estimated population prevalence rates of 1 in 200,000 with a yearly incidence rate of 1-2/1000), that are potentially lethal, because they secrete excessive, uncontrolled amounts of catecholamines (dopamine, epinephrine, and norepinephrine) resulting in often severe hypertension and many cardiac abnormalities. A subgroup of these patients will also suffer tumor recurrence and sometimes malignant behavior. Untreated, these tumors have substantial morbidity and mortality. Key symptoms are episodes of hypertension with palpitations, severe headaches, and sweating (spells). However, some patients might be asymptomatic, have mild symptoms that might be missed, or have sustained hypertension, which is frequently observed in these patients. Finally, due to the high frequency of medical imaging for unrelated ailments, increasing numbers of occult small adrenal tumors are often incidentally discovered, some of which might be Pheo/PGLs. 3-Methoxytyramine (3MT), metanephrine, and normetanephrine are the metabolites of dopamine, epinephrine, and norepinephrine, respectively. These metabolites are further metabolized to vanillylmandelic acid. Pheochromocytoma cells also have the ability to oxymethylate catecholamines into metanephrines, which are secreted into circulation and urine. 3MT is only elevated in a small proportion of patients with Pheo/PGL. Because of its low levels testing is performed using only 24-hour urine specimens at this time, while epinephrine, and norepinephrine can be measured in plasma or 24-hour urine specimens. An early childhood malignancy that arises from immature neuroendocrines in the adrenals, called neuroblastoma, shares many features of Pheo/PGL but has the added threat of a high malignancy rate; however, there are also frequent spontaneous remissions, particular in very young infants. Biochemical testing for neuroblastoma differs from Pheo/PGL because of many specific issues in testing infants and young children, using urine tests rather than blood tests. For all Pheo/PGL, the preferred initial testing is by plasma metanephrine testing, as it has the highest clinical sensitivity thus facilitating ruling out Pheo/PGL, if the test results are within the healthy population reference range. However, in potentially familial cases, or monitoring of treated patients some additional and repeated testing may be required. Testing for 24-hour urine metanephrine plus urinary catecholamine levels may be used as a confirmatory study in patients with less than a 2-fold elevation in plasma free fractionated catecholamines. This is highly desirable, as the very low population incidence rate of Pheo/PGL (<1:200,000 population per year) will otherwise result in large numbers of unnecessary, costly, and sometimes risky imaging procedures. Finally, familial Pheo/PGL probably accounts for a higher proportion of cases than previously thought; at least 30% are now believed to be familial. The corollary of this is that about 20 to 30 seemingly sporadic cases are likely familial. Given these statistics, genetic testing for index cases and family members should be considered. Treatment consists of surgical tumor removal after pharmaceutical alpha-adrenergic blockade, which may be supplemented with beta blockade once the alpha blockade has been established. This preparation is aimed to prevent massive catecholamine surges during surgery.

Useful For: A first- and second-tier screening test for the presumptive diagnosis of catecholamine-secreting pheochromocytomas and paragangliomas

Interpretation: Further clinical investigation (eg, radiographic studies) and genetic studies might be warranted in patients whose 3-methoxytyramine (3MT), metanephrine, or normetanephrine are elevated or when there is a very high clinical index of suspicion. Increased 3MT levels are found in patients with pheochromocytoma and dopamine-secreting tumors. 3MT levels of 306 mcg/24 h or less in male patients and 242 mcg/24 h or less in female patients can be detected in non-pheochromocytoma hypertensive patients.

Reference Values:

3-Methoxytyramine:
Males: < or =306 mcg/24 h
Females: < or =242 mcg/24 h

METANEPHRINE
Males
Normotensives
3-8 years: 29-92 mcg/24 h
9-12 years: 59-188 mcg/24 h
13-17 years: 69-221 mcg/24 h
> or =18 years: 44-261 mcg/24 h
Reference values have not been established for patients that are younger than 36 months.

Hypertensives: <400 mcg/24 h

Females
Normotensives
3-8 years: 18-144 mcg/24 h
9-12 years: 43-122 mcg/24 h
13-17 years: 33-185 mcg/24 h
> or =18 years: 30-180 mcg/24 h
Reference values have not been established for patients that are younger than 36 months.

Hypertensives: <400 mcg/24 h

NORMETANEPHRINE
Males
Normotensives
3-8 years: 34-169 mcg/24 h
9-12 years: 84-422 mcg/24 h
13-17 years: 91-456 mcg/24 h
18-29 years: 103-390 mcg/24 h
30-39 years: 111-419 mcg/24 h
40-49 years: 119-451 mcg/24 h
50-59 years: 128-484 mcg/24 h
60-69 years: 138-521 mcg/24 h
> or =70 years: 148-560 mcg/24 h
Reference values have not been established for patients that are younger than 36 months.

Hypertensives: <900 mcg/24 h

Females
Normotensives

3-8 years: 29-145 mcg/24 h
9-12 years: 55-277 mcg/24 h
13-17 years: 57-286 mcg/24 h
18-29 years: 103-390 mcg/24 h
30-39 years: 111-419 mcg/24 h
40-49 years: 119-451 mcg/24 h
50-59 years: 128-484 mcg/24 h
60-69 years: 138-521 mcg/24 h
> or =70 years: 148-560 mcg/24 h
Reference values have not been established for patients that are younger than 36 months.

Hypertensives: <900 mcg/24 h

TOTAL METANEPHRINE
Males
Normotensives
3-8 years: 47-223 mcg/24 h
9-12 years: 201-528 mcg/24 h
13-17 years: 120-603 mcg/24 h
18-29 years: 190-583 mcg/24 h
30-39 years: 200-614 mcg/24 h
40-49 years: 211-646 mcg/24 h
50-59 years: 222-680 mcg/24 h
60-69 years: 233-716 mcg/24 h
> or =70 years: 246-753 mcg/24 h
Reference values have not been established for patients that are younger than 36 months.

Hypertensives: <1300 mcg/24 h

Females
Normotensives
3-8 years: 57-210 mcg/24 h
9-12 years: 107-394 mcg/24 h
13-17 years: 113-414 mcg/24 h
18-29 years: 142-510 mcg/24 h
30-39 years: 149-535 mcg/24 h
40-49 years: 156-561 mcg/24 h
50-59 years: 164-555 mcg/24 h
60-69 years: 171-616 mcg/24 h
> or =70 years: 180-646 mcg/24 h
Reference values have not been established for patients that are younger than 36 months.

Hypertensives: <1300 mcg/24 h

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Muskiet FA, Thomasson CG, Gerding AM, Fremouw-Ottevangers DC, Nagel GT, Wolthers BG. Determination of catecholamines and their 3-O-methylated metabolites in urine by mass fragmentography with use of deuterated internal standards. Clin Chem. 1979;25(3):453-460 2. Taylor RL, Singh RJ. Validation of liquid chromatography-tandem mass spectrometry method for analysis of urinary conjugated metanephrine and normetanephrine for screening of pheochromocytoma. Clin Chem. 2002;48(3):533-539. 3. Roden M, Raffesberg W, Raber W, et al. Quantification of unconjugated metanephrines in human plasma without interference by

acetaminophen. Clin Chem. 2001;47(6):1061-1067 4. Sawka AM, Singh RJ, Young WF Jr. False positive biochemical testing for pheochromocytoma caused by surreptitious catecholamine addition to urine. The Endocrinologist. 2001;11(5):421-423 5. van Duinen N, Steenvoorden D, Kema IP, et al. Increased urinary excretion of 3-methoxytyramine in patients with head and neck paragangliomas. J Clin Endocrinol Metab. 2010;95(1):209-214 6. Le Jacques A, Abalain JH, Le Saos F, Carre JL. Interet du dosage urinaire de la 3-methoxytyramine dans le diagnostic des pheochromocytomes et paragangliomes: a propos de 28 cas [Significance of 3-methoxytyramine urine measurement in the diagnosis of pheochromocytomas and paragangliomas: about 28 patients]. Ann Biol Clin (Paris). 2011;69(5):555-559. doi:10.1684/abc.2011.0612 7. Lam L, Woollard GA, Teague L, Davidson JS. Clinical validation of urine 3-methoxytyramine as a biomarker of neuroblastoma and comparison with other catecholamine-related biomarkers. Ann Clin Biochem. 2017;54(2):264-272 8. Hirsch D, Grossman A, Nadler V, Alboim S, Tsvetov G. Pheochromocytoma: Positive predictive values of mildly elevated urinary fractionated metanephrines in a large cohort of community-dwelling patients. J Clin Hypertens (Greenwich). 2019;21(10):1527-1533. doi:10.1111/jch.13657 9. Gupta PK, Marwaha B. Pheochromocytoma. In: StatPearls [Internet]. StatPearls Publishing; 2024. Updated March 5, 2023. Accessed April 22, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK589700

METAF
83006

Metanephrines, Fractionated, 24 Hour, Urine

Clinical Information:

Useful For: A first- and second-order screening test for the presumptive diagnosis of catecholamine-secreting pheochromocytomas and paragangliomas Confirming positive plasma metanephrine results

Interpretation: Increased metanephrine and normetanephrine levels are found in patients with pheochromocytoma and tumors derived from neural crest cells. Total urine metanephrine levels of 1300 mcg/24 h and lower can be detected in non-pheochromocytoma hypertensive patients. Further clinical investigation (eg, radiographic studies) is warranted in patients whose total urinary metanephrine levels are above 1300 mcg/24 h (approximately 2 times the upper limit of normal). For patients with total urinary metanephrine levels below 1300 mcg/24 h, further investigations may also be indicated if either the normetanephrine or the metanephrine fraction of the total metanephrines exceed their respective upper limit for hypertensive patients. Finally, repeat testing or further investigations may occasionally be indicated in patients with urinary metanephrine levels below the hypertensive cutoff, or even normal levels, if there is a very high clinical index of suspicion.

Reference Values:

METANEPHRINE
Males
Normotensives
3-8 years: 29-92 mcg/24 h
9-12 years: 59-188 mcg/24 h
13-17 years: 69-221 mcg/24 h
> or =18 years: 44-261 mcg/24 h
Reference values have not been established for patients that are younger than 36 months.

Hypertensives: <400 mcg/24 h
Females
Normotensives
3-8 years: 18-144 mcg/24 h
9-12 years: 43-122 mcg/24 h
13-17 years: 33-185 mcg/24 h
> or =18 years: 30-180 mcg/24 h

Reference values have not been established for patients that are younger than 36 months.

Hypertensives: <400 mcg/24 h

NORMETANEPHRINE
Males
Normotensives
3-8 years: 34-169 mcg/24 h
9-12 years: 84-422 mcg/24 h
13-17 years: 91-456 mcg/24 h
18-29 years: 103-390 mcg/24 h
30-39 years: 111-419 mcg/24 h
40-49 years: 119-451 mcg/24 h
50-59 years: 128-484 mcg/24 h
60-69 years: 138-521 mcg/24 h
> or =70 years: 148-560 mcg/24 h
Reference values have not been established for patients that are younger than 36 months.

Hypertensives: <900 mcg/24 h

Females
Normotensives
3-8 years: 29-145 mcg/24 h
9-12 years: 55-277 mcg/24 h
13-17 years: 57-286 mcg/24 h
18-29 years: 103-390 mcg/24 h
30-39 years: 111-419 mcg/24 h
40-49 years: 119-451 mcg/24 h
50-59 years: 128-484 mcg/24 h
60-69 years: 138-521 mcg/24 h
> or =70 years: 148-560 mcg/24 h
Reference values have not been established for patients that are younger than 36 months.

Hypertensives: <900 mcg/24 h

TOTAL METANEPHRINE
Males
Normotensives
3-8 years: 47-223 mcg/24 h
9-12 years: 201-528 mcg/24 h
13-17 years: 120-603 mcg/24 h
18-29 years: 190-583 mcg/24 h
30-39 years: 200-614 mcg/24 h
40-49 years: 211-646 mcg/24 h
50-59 years: 222-680 mcg/24 h
60-69 years: 233-716 mcg/24 h
> or =70 years: 246-753 mcg/24 h
Reference values have not been established for patients that are younger than 36 months.

Hypertensives: <1,300 mcg/24 h

Females
Normotensives
3-8 years: 57-210 mcg/24 h

9-12 years: 107-394 mcg/24 h
13-17 years: 113-414 mcg/24 h
18-29 years: 142-510 mcg/24 h
30-39 years: 149-535 mcg/24 h
40-49 years: 156-561 mcg/24 h
50-59 years: 164-555 mcg/24 h
60-69 years: 171-616 mcg/24 h
> or =70 years: 180-646 mcg/24 h
Reference values have not been established for patients that are younger than 36 months.

Hypertensives: <1,300 mcg/24 h

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. van Duinen N, Corssmit EPM, de Jong WHA, Brookman D, Kema IP, Romijn JA. Plasma levels of free metanephrines and 3-methoxytyramine indicate a higher number of biochemically active HNPGL than 24-h urinary excretion rates of catecholamines and metabolites. Eur J Endocrinol. 2013;169(3):377-382. doi:10.1530/EJE-13-0529 2. Pacak K, Linehan WM, Eisenhofer G, Walther MM, Goldstein DS. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med. 2001;134(4):315-329 3. Sawka AM, Singh RJ, Young WF Jr. False positive biochemical testing for pheochromocytoma caused by surreptitious catecholamine addition to urine. Endocrinologist. 2001;11:421-423 4. Eisenhofer G, Grebe S, Cheung NKV. Monoamine-producing tumors. In: Rafai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1421 5. Shen Y, Cheng L. Biochemical diagnosis of pheochromocytoma and paraganglioma. In: Mariani-Costantini R, ed. Paraganglioma: A Multidisciplinary Approach. Codon Publications; 2019. doi:10.15586/paraganglioma.2019.ch2. Accessed: April 22, 2024. Available at: www.ncbi.nlm.nih.gov/books/NBK543224/

PMET
81609

Metanephrines, Fractionated, Free, Plasma

Clinical Information: Pheochromocytoma is a rare, though potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating ("spells"). Patients with pheochromocytoma may also be asymptomatic and present with sustained hypertension or an incidentally discovered adrenal mass. Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine, norepinephrine, and dopamine). Metanephrine and normetanephrine (collectively referred to as metanephrines) are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively. The metanephrines are stable metabolites and are cosecreted directly with catecholamines by pheochromocytomas and other neural crest tumors. This results in sustained elevations in plasma free metanephrine levels, making them more sensitive and specific than plasma catecholamines in the identification of pheochromocytoma patients.(1) Metanephrine and normetanephrine are both further metabolized to conjugated metanephrines and vanillylmandelic acid.

Useful For: Screening test for presumptive diagnosis of catecholamine-secreting pheochromocytomas or paragangliomas

Interpretation: In the normal population, plasma metanephrine and normetanephrine levels are low, but in patients with pheochromocytoma or paragangliomas, the concentrations may be significantly elevated. This is due to the relatively long half-life of these compounds, ongoing secretion by the tumors and, to a lesser degree, peripheral conversion of tumor-secreted catecholamines into metanephrines. Measurement of plasma free metanephrines appears to be the best test for excluding pheochromocytoma.

The test's sensitivity approaches 100%, making it extremely unlikely that individuals with normal plasma metanephrine and normetanephrine levels suffer from pheochromocytoma or paraganglioma.(1,2) Due to the low prevalence of pheochromocytomas and related tumors (<1:100,000), it is recommended to confirm elevated plasma free metanephrines with a second, different testing strategy in order to avoid large numbers of false-positive test results.(3) The recommended second-line test is measurement of fractionated 24-hour urinary metanephrines (METAF / Metanephrines, Fractionated, 24 Hour, Urine). In most cases this strategy will suffice in confirming or excluding the diagnosis. Occasionally, it will be necessary to extend this approach if there is a very high clinical index of suspicion or if test results are nonconclusive. In these cases, repeat plasma and urinary metanephrines testing, additional measurement of plasma or urinary catecholamines, or imaging procedures might be indicated. Elevated results are reported with appropriate comments.

Reference Values:

METANEPHRINE, FREE
<0.50 nmol/L

NORMETANEPHRINE, FREE
<0.90 nmol/L

Clinical References: 1. Eisenhofer G. Free or total metanephrines for diagnosis of pheochromocytoma: what is the difference? Clin Chem. 2001;47(6):988-989 2. Lenders JW, Pacek K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA. 2002;287(11):1427-1434 3. Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared to the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab. 2003;88(2):553-558 4. Algeciras-Schimnich A, Preissner CM, Young WF Jr, et al. Plasma chromogranin A or urine fractionated metanephrines follow-up testing improves the diagnostic accuracy of plasma fractionated metanephrines for pheochromocytoma. J Clin Endocrinol Metab. 2008;93(1):91-95. doi:10.1210/jc.2007-1354 5. Eisenhofer G, Deutschbein T, Constantinescu G, et al. Plasma metanephrines and prospective prediction of tumor location, size and mutation type in patients with pheochromocytoma and paraganglioma. Clin Chem Lab Med. 2020;59(2):353-363. doi:10.1515/cclm-2020-0904 6. Taylor RL, Singh RJ. Validation of liquid chromatography-tandem mass spectrometry method for analysis of urinary conjugated metanephrine and normetanephrine for screening of pheochromocytoma. Clin Chem 2002;48(3):533-539

METRN
609696

Metanephrines, Fractionated, Random, Urine

Clinical Information: Pheochromocytoma is a rare, potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating ("spells"). Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine and norepinephrine). Metanephrine and normetanephrine are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively. Both are further metabolized to vanillylmandelic acid. Pheochromocytoma cells are also able to oxymethylate catecholamines into metanephrines that are secreted into circulation.

Useful For: A second-order screening test for the presumptive diagnosis of pheochromocytoma in patients with non-episodic hypertension Confirming positive plasma metanephrine results in patients with non-episodic hypertension

Interpretation: Increased metanephrine and normetanephrine levels are found in patients with pheochromocytoma and tumors derived from neural crest cells. Increased urine metanephrines can be detected in non-pheochromocytoma hypertensive patients; quantification may help distinguish these

patients from those with tumor-induced symptoms.

Reference Values:

METANEPHRINE/CREATININE
Normotensives
0-2 years: 82-418 mcg/g creatinine
3-8 years: 65-332 mcg/g creatinine
9-12 years: 41-209 mcg/g creatinine
13-17 years: 30-154 mcg/g creatinine
> or =18 years: 29-158 mcg/g creatinine

NORMETANEPHRINE/CREATININE
Males
Normotensives
0-2 years: 121-946 mcg/g creatinine
3-8 years: 92-718 mcg/g creatinine
9-12 years: 53-413 mcg/g creatinine
13-17 years: 37-286 mcg/g creatinine
18-29 years: 53-190 mcg/g creatinine
30-39 years: 60-216 mcg/g creatinine
40-49 years: 69-247 mcg/g creatinine
50-59 years: 78-282 mcg/g creatinine
60-69 years: 89-322 mcg/g creatinine
> or =70 years: 102-367 mcg/g creatinine

Females
Normotensives
0-2 years: 121-946 mcg/g creatinine
3-8 years: 92-718 mcg/g creatinine
9-12 years: 53-413 mcg/g creatinine
13-17 years: 37-286 mcg/g creatinine
18-29 years: 81-330 mcg/g creatinine
30-39 years: 93-379 mcg/g creatinine
40-49 years: 107-436 mcg/g creatinine
50-59 years: 122-500 mcg/g creatinine
60-69 years: 141-574 mcg/g creatinine
> or =70 years: 161-659 mcg/g creatinine

TOTAL METANEPHRINE/CREATININE
Males
Normotensives
0-2 years: 241-1,272 mcg/g creatinine
3-8 years: 186-980 mcg/g creatinine
9-12 years: 110-582 mcg/g creatinine
13-17 years: 78-412 mcg/g creatinine
18-29 years: 96-286 mcg/g creatinine
30-39 years: 106-316 mcg/g creatinine
40-49 years: 117-349 mcg/g creatinine
50-59 years: 130-386 mcg/g creatinine
60-69 years: 143-427 mcg/g creatinine
> or =70 years: 159-472 mcg/g creatinine

Females
Normotensives

0-2 years: 241-1,272 mcg/g creatinine
3-8 years: 186-980 mcg/g creatinine
9-12 years: 110-582 mcg/g creatinine
13-17 years: 78-412 mcg/g creatinine
18-29 years: 131-467 mcg/g creatinine
30-39 years: 147-523 mcg/g creatinine
40-49 years: 164-585 mcg/g creatinine
50-59 years: 184-655 mcg/g creatinine
60-69 years: 206-733 mcg/g creatinine
> or =70 years: 230-821 mcg/g creatinine

Clinical References: 1. van Duinen N, Corssmit EPM, de Jong WHA, Brookman D, Kema P, Romijn JA. Plasma levels of free metanephrines and 3-methoxytyramine indicate a higher number of biochemically active HNPGL than 24-h urinary excretion rates of catecholamines and metabolites. Eur J Endocrinol. 2013;169(3):377-382 doi:10.1530/EJE-13-0529 2. Pacak K, Linehan WM, Eisenhofer G, Walther MM, Goldstein DS. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med. 2001;134(4):315-329 3. Sawka AM, Singh RJ, Young WF Jr. False positive biochemical testing for pheochromocytoma caused by surreptitious catecholamine addition to urine. Endocrinologist. 2001;11:421-423 4. Eisenhofer G, Grebe S, Cheung NKV. Monoamine-producing tumors. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1421 5. Shen Y, Cheng L. Biochemical diagnosis of pheochromocytoma and paraganglioma. In: Mariani-Costantini R, ed. Paraganglioma: A Multidisciplinary Approach. Codon Publications; 2019. Accessed May 2, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK543224/ 6. Hernandez FC, Sanchez M, Alvarez A, et al. A five-year report on experience in the detection of pheochromocytoma. Clin Biochem. 2000;33(8):649-55. doi:10.1016/s0009-9120(00)00172-7 7. van Duinen N, Steenvoorden D, Kema IP, et al. Increased urinary excretion of 3-methoxytyramine in patients with head and neck paragangliomas. J Clin Endocrinol Metab. 2010;95(1):209-14. doi:10.1210/jc.2009-1632 8. Le Jacques A, Abalain JH, Le Saos F, Carre JL. Significance of 3-methoxytyramine urine measurement in the diagnosis of pheochromocytomas and paragangliomas: about 28 patients. Ann Biol Clin (Paris). 2011;69(5):555-9. French. doi:10.1684/abc.2011.0612 9. Muskiet FA, Thomasson CG, Gerding AM, Fremouw-Ottevangers DC, Nagel GT, Wolthers BG. Determination of catecholamines and their 3-O-methylated metabolites in urine by mass fragmentography with use of deuterated internal standards. Clin Chem. 1979;25(3):453-60 10. Hirsch D, Grossman A, Nadler V, Alboim S, Tsvetov G. Pheochromocytoma: Positive predictive values of mildly elevated urinary fractionated metanephrines in a large cohort of community-dwelling patients. J Clin Hypertens (Greenwich). 2019;21(10):1527-1533. doi:10.1111/jch.13657

FMETN
75389

Metformin, Plasma

Reference Values:
Reporting limit determined each analysis.

Units: mcg/mL

Therapeutic range: Approximately 1-2 mcg/mL.
Metformin associated lactic acidosis generally has been associated with Metformin plasma concentrations exceeding 5 mcg/mL.

MDNS
36309

Methadone and Metabolites, Serum

Clinical Information: Methadone, a long-acting synthetic opioid analgesic, is an agonist at the mu receptor. It has several actions qualitatively similar to those of morphine, primarily involving the central nervous system and organs composed of smooth muscles. Analgesia, sedation, and detoxification or maintenance in opioid addiction can be achieved with therapeutic use of methadone hydrochloride. Methadone acts by binding to the mu-opioid receptor but also has some affinity for the N-methyl-D-aspartate receptor (NMDA) ionotropic glutamate receptor. Methadone undergoes extensive biotransformation in the liver. Methadone is metabolized by cytochrome P450 (CYP) 3A4, CYP2B6, CYP2C19, and CYP2D6 enzymes. It is also a substrate for the P-glycoprotein efflux protein. The major inactive metabolite is a result of N-demethylation and cyclization, and forms 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Substantial interindividual and intraindividual variabilities in metabolism and elimination have been noted. The half-life of methadone is highly variable and typically ranges from 7 to 59 hours; however, longer half-lives have been reported.

Useful For: Compliance monitoring of methadone Assessment of methadone toxicity

Interpretation: There is a significant overlap between the reported therapeutic and toxic concentrations of methadone in blood specimens.

Reference Values:
Methadone:
Therapeutic: 100-400 ng/mL
Toxic: >2000 ng/mL

EDDP:
Not established

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Methadone: 10 ng/mL
EDDP: 5.0 ng/mL

Clinical References: 1. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 2. Yaksh TL, Wallace MS. Opioids, analgesia, and pain management. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th ed. McGraw-Hill Book Company; 2011:chap 18 3. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 9th ed. Biomedical Publications; 2011:1021-1025

MTDNX
62734

Methadone Confirmation, Chain of Custody, Random, Urine

Clinical Information: Methadone (Dolophine) is a synthetic opioid, a compound that is structurally unrelated to natural opiates but is capable of binding to opioid receptors. These receptor interactions create many of the same effects seen with natural opiates, including analgesia and sedation. However, methadone does not produce feelings of euphoria and has substantially fewer withdrawal symptoms than opiates such as heroin.(1) Methadone is used clinically to relieve pain, treat opioid abstinence syndrome, and treat heroin addiction in an attempt to wean patients from illicit drug use. Metabolism of methadone to inactive forms is the main form of elimination. Oral delivery of methadone makes it subject to first-pass metabolism by the liver and creates interindividual variability in its bioavailability, which ranges from 80% to 95%. The most important enzymes in methadone metabolism are cytochrome P450 (CYP) 3A4 and CYP2B6.(1-4) CYP2D6 appears to have a minor role, and CYP1A2 may possibly be involved.(1-5) Methadone is metabolized to a variety of metabolites, the primary metabolite is 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP).(1-4) The efficiency of this process is prone to wide inter- and intraindividual variability due to inherent differences in enzymatic activity as well as

enzyme induction or inhibition by numerous drugs. Excretion of methadone and its metabolites (including EDDP) occurs primarily through the kidneys.(1,4) Patients who are taking methadone for therapeutic purposes excrete both parent methadone and EDDP in their urine. Clinically, it is important to measure levels of both methadone and EDDP. Methadone levels in urine vary widely depending on factors such as dose, metabolism, and urine pH.(5) EDDP levels, in contrast, are relatively unaffected by the influence of pH and are, therefore, preferable for assessing compliance with therapy.(5) Some patients undergoing treatment with methadone have attempted to pass compliance testing by adding a portion of the supplied methadone to the urine.(6) This is commonly referred to as "spiking." In these situations, the specimen will contain large amounts of methadone and no or very small amounts of EDDP.(6) The absence of EDDP in the presence of methadone in urine strongly suggests adulteration of the urine specimen by direct addition of methadone to the specimen. Chain of custody is a record of the disposition of a specimen to document the personnel who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Monitoring for compliance of methadone treatment for analgesia or drug rehabilitation Assessing compliance with rehabilitation programs Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The absolute concentration of methadone and its metabolites found in patient urine specimens can be highly variable and does not correlate with dose. However, the medical literature and our experience show that patients who are known to be compliant with their methadone therapy have ratios of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP):methadone of greater than 0.60.(7) An EDDP:methadone ratio less than

Reference Values:

Negative

Positive results are reported with a quantitative result.

Cutoff concentrations:

Immunoassay screen: 300 ng/mL

Gas chromatography mass spectrometry:
Methadone: 100 ng/mL
2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine: 100 ng/mL

Clinical References: 1. Gutstein HB, Akil H. Opioid analgesics. In: Hardman JG, Limbird LE, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 10th ed. McGraw-Hill; 2001:569-619 2. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. Clin Pharmacokinet. 2002;41(14):1153-1193 3. Ferrari A, Coccia CP, Bertolini A, Sternieri E. Methadone-metabolism, pharmacokinetics and interactions. Pharmacol Res. 2004;50(6):551-559 4. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 7th ed. Chemical Toxicology Institute; 2005 5. Levine B. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:385 6. Galloway FR, Bellet NF. Methadone conversion to EDDP during GC-MS analysis of urine samples. J Anal Toxicol. 1999;23(7):615-619 7. George S, Braithwaite RA. A pilot study to determine the usefulness of the urinary excretion of methadone and its primary metabolite (EDDP) as potential markers of compliance in methadone detoxification programs. J Anal Toxicol. 1999;23:81-85 8. Jutkiewicz EM, Traynor JR. Opioid analgesics. In: Brunton LL, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 14th Ed. McGraw-Hill Education; 2023 9. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz

MTDNU
83129

Methadone Confirmation, Random, Urine

Clinical Information: Methadone (Dolophine) is a synthetic opioid, a compound that is structurally unrelated to natural opiates but is capable of binding to opioid receptors. These receptor interactions create many of the same effects seen with natural opiates including analgesia and sedation. However, methadone does not produce feelings of euphoria and has substantially fewer withdrawal symptoms than opiates such as heroin.(1) Methadone is used clinically to relieve pain, treat opioid abstinence syndrome, and treat heroin addiction in an attempt to wean patients from illicit drug use. Metabolism of methadone to inactive forms is the main form of elimination. Oral delivery of methadone makes it subject to first-pass metabolism by the liver and creates interindividual variability in its bioavailability, which ranges from 80% to 95%. The most important enzymes in methadone metabolism are cytochrome P450 (CYP) 3A4 and CYP2B6.(1-4) CYP2D6 appears to have a minor role, and CYP1A2 may possibly be involved.(1-5) Methadone is metabolized to a variety of metabolites with the primary metabolite being 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP).(1-4) The efficiency of this process is prone to wide inter- and intraindividual variability, due to inherent differences in enzymatic activity as well as enzyme induction or inhibition by numerous drugs. Excretion of methadone and its metabolites (including EDDP) occurs primarily through the kidneys.(1,4) Patients who are taking methadone for therapeutic purposes excrete both parent methadone and EDDP in their urine. Clinically, it is important to measure levels of both methadone and EDDP. Methadone levels in urine vary widely depending on factors such as dose, metabolism, and urine pH.(5) EDDP levels, in contrast, are relatively unaffected by the influence of pH and are, therefore, preferable for assessing compliance with therapy.(5) Some patients undergoing treatment with methadone have attempted to pass compliance testing by adding a portion of the supplied methadone to the urine.(6) This is commonly referred to as "spiking." In these situations, the specimen will contain large amounts of methadone and no or very small amounts of EDDP.(6) The absence of EDDP in the presence of methadone in urine strongly suggests adulteration of the urine specimen by direct addition of methadone to the specimen.

Useful For: Monitoring for compliance of methadone treatment for analgesia or drug rehabilitation
Assessing compliance with rehabilitation programs by urine measurement of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine

Interpretation: The absolute concentration of methadone and its metabolites found in patient urine specimens can be highly variable and does not correlate with dose. However, the medical literature and our experience show that patients who are known to be compliant with their methadone therapy have ratios of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP):methadone of greater than 0.60.(7) An EDDP:methadone ratio less than 0.090 strongly suggests manipulation of the urine specimen by direct addition of methadone to the specimen.(6)

Reference Values:
Negative (Positive results are reported with a quantitative result.)

Cutoff concentrations by gas chromatography mass spectrometry:
METHADONE: 100 ng/mL
2-ETHYLIDENE-1,5-DIMETHYL-3,3-DIPHENYLPYRROLIDINE (EDDP): 100 ng/mL

Clinical References: 1. Gutstein HB, Akil H. Opioid analgesics. In: Hardman JG, Limbird LE, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 10th ed. McGraw-Hill; 2001:569-619 2. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. Clin Pharmacokinet. 2002;41(14):1153-1193 3. Ferrari A, Coccia CP, Bertolini A, Sternieri E. Methadone-

metabolism, pharmacokinetics and interactions. Pharmacol Res. 2004;50(6):551-559 4. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 10th ed. Biomedical Publications; 2014 5. Levine B. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:385 6. Galloway FR, Bellet NF. Methadone conversion to EDDP during GC-MS analysis of urine samples. J Anal Toxicol. 1999;23(7):615-619 7. George S, Braithwaite RA. A pilot study to determine the usefulness of the urinary excretion of methadone and its primary metabolite (EDDP) as potential markers of compliance in methadone detoxification programs. J Anal Toxicol. 1999;23(2):81-85 8. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

FMETH
57996

Methaqualone Confirmation, urine

Interpretation: Methaqualone, ng/mL Report Limit 50 ng/mL Reference Range 500-80000 ng/mL Critical Value – High 160000 ng/mL

Reference Values:
ng/mL

Results are reported to the limit of quantitation for the analysis.

MET
81032

Methemoglobin and Sulfhemoglobin, Blood

Clinical Information: Methemoglobin: When iron in hemoglobin is oxidized from the normal divalent state to a trivalent state, the resulting brownish pigment is methemoglobin. Methemoglobin cannot combine reversibly with oxygen and is associated with cyanosis. Methemoglobinemia, with or without sulfhemoglobinemia, is most frequently encountered as a result of administration of medications such as phenacetin, phenazopyridine, sulfonamides, local anesthetics, dapsone, or following ingestion of nitrites or nitrates. Congenital methemoglobinemias are rare. They are due to either: -Deficiency of methemoglobin reductase (also called cytochrome B5 reductase or diaphorase) in erythrocytes, an autosomal recessive disorder -One of several intrinsic structural disorders of hemoglobin, called methemoglobin-M; all autosomal dominant in inheritance Methemoglobinemia responds to treatment with methylene blue or ascorbic acid. Sulfhemoglobin: Sulfhemoglobin cannot combine with oxygen. Sulfhemoglobinemia is associated with cyanosis and often accompanies drug-induced methemoglobinemia. Sulfhemoglobinemia can be due to exposure to trinitrotoluene or zinc ethylene bisdithiocarbamate (a fungicide), or by ingestion of therapeutic doses of flutamide. In contrast to methemoglobinemia, sulfhemoglobinemia persists until the erythrocytes containing it are destroyed. Therefore, the blood level of sulfhemoglobin declines gradually over a period of weeks. Patients with sulfhemoglobinemia often also have methemoglobinemia. There is no specific treatment for sulfhemoglobinemia. Therapy is directed at reversing the methemoglobinemia if present.

Useful For: Diagnosing methemoglobinemia and sulfhemoglobinemia Identifying cyanosis due to other causes, such as congenital heart disease

Interpretation: In congenital methemoglobinemia, the methemoglobinemia concentration in blood is about 15% to 20% of total hemoglobin. Such patients are mildly cyanotic and asymptomatic. In acquired (toxic) methemoglobinemia, the concentration may be much higher. Symptoms may be severe when methemoglobin is greater than 40% of hemoglobin. Very high concentrations (>70%) may be fatal.

Reference Values:
METHEMOGLOBIN

0-11 months: Not established
> or =1 year: 0.0-1.5% of total hemoglobin

SULFHEMOGLOBIN
0-11 months: Not established
> or =1 year: 0.0-0.4% of total hemoglobin

Clinical References: Prchal JT. Methemoglobinemia and other dyshemoglobinemias. In: In: Kaushansky K, Prchal JT, Burns LJ, Lichtman MA, Levi M, Linch DC, eds. Williams Hematology, 10 ed. McGraw-Hill Education; 2021:chap 51

MEV0 608089 Methemoglobin Summary Interpretation

Clinical Information: Hemoglobin variants can be associated with increased measured levels of methemoglobin and sulfhemoglobin. Some hemoglobin disorders can be very complex and involve abnormalities of the alpha, beta, delta, and gamma genes. These abnormalities can be due to, not only point alterations, but also deletions within 1 or more globin genes. Multiple genetic variants can be seen in the same patient, and molecular testing is necessary to fully evaluate such cases. A summary interpretation that incorporates all testing performed is beneficial to the ordering physician.

Useful For: Incorporating and summarizing subsequent results into an overall interpretation for the MEV1 / Methemoglobinemia Evaluation, Blood

Interpretation: An interpretive report will be provided that summarizes all testing as well as any pertinent clinical information.

Reference Values:
Only orderable as a reflex. For more information see MEV1 / Methemoglobinemia Evaluation, Blood.

An interpretive report will be provided.

Clinical References: 1. Beutler E. Methemoglobinemia and sulfhemoglobinemia. In: Beutler E, Lichtman MA, Caller BS, Kipps TJ, eds. Hematology. 5th ed. McGraw-Hill Book Company; 1995:654-663 2. Harteveld CL, Higgs DR. Alpha-thalassemia. Orphanet J Rare Dis. 2010;5:13 3. Thein SL. The molecular basis of beta-thalassemia. Cold Spring Harb Persepct Med. 2013;1;3(5):a011700 4. Crowley MA, Mollan TL, Abdulmalik OY, et al. A hemoglobin variant associated with neonatal cyanosis and anemia. N Engl J Med. 2011;364(19):1837-1843 5. Harteveld CL, Voskamp A, Phylipsen M, et al. Nine unknown rearrangements in 16p13.3 and 11p15.4 causing alpha- and beta-thalassaemia characterized by high resolution multiplex ligation-dependent probe amplification. J Med Genet. 2005;42:922-931 6. Hein MS, Oliveira JL, Swanson KC, et al. Large deletions involving the beta globin gene complex: genotype-phenotype correlation of 119 cases. Blood. 2015;126:3374

MEV1 607495 Methemoglobinemia Evaluation, Blood

Clinical Information: Methemoglobin: Methemoglobin forms when the hemoglobin (Hb) molecule iron is in the ferric (Fe3[+]) form instead of the functional ferrous (Fe2[+]) form. Methemoglobinemia can be hereditary or acquired and is present by definition when methemoglobin levels are greater than the normal range. Acquired methemoglobinemia results after toxic exposure to nitrates and nitrites/nitrates (fertilizer, nitric oxide), topical anesthetics ("caines"), dapsone, naphthalene (moth balls/toilet deodorant cakes), and industrial use of aromatic compounds (aniline dyes). Congenital methemoglobinemias are rare. They are due either to: -A deficiency of cytochrome b5 reductase (methemoglobin reductase) in

erythrocytes, an autosomal recessive disorder resulting from genetic variants in either CYB5R3 or CYB5A.(1,2) Type IV is thought to be extraordinarily rare. Type III is no longer a category. -One of several intrinsic structural disorders of Hb, called M-Hbs; all of which are inherited in an autosomal dominant manner.(3,4) Classically, M-Hbs result from histidine-to tyrosine substitutions at the proximal or distal histidine important in coordinating the oxygen molecule. These include alpha-, beta- and gamma-chain variants. Rarely, other substitutions outside the proximal and distal histidine location can cause Hb variants that increase methemoglobin or sulfhemoglobin levels. Most M-Hb variants are readily identified by high performance liquid chromatography (HPLC) or mass spectrometry methods with characteristic electrophoresis patterns; however, some require more specialized techniques. Most are associated with increased methemoglobin with or without an increase in sulfhemoglobin. Alpha chain M-Hb variants can be associated with increased sulfhemoglobin without an increase in methemoglobin. Sulfhemoglobin: Sulfhemoglobin cannot combine with oxygen. When acquired, sulfhemoglobinemia can be associated with cyanosis and often accompanies methemoglobinemia. Sulfhemoglobinemia has been associated with exposure to sumatriptan, sulfonamides, metoclopramide, paint or varnish vapors, dimethyl sulfoxide, acetanilide, phenacetin, trinitroluene, zinc ethylene bisdithiocarbamate (a fungicide), and flutamide. It is important to note that some Hb variants are known to interfere with this test (especially M-Hbs) and sulfhemoglobin absorbance can be increased due to the Hb variant. Hb evaluation that includes the HPLC method is recommended to exclude this possibility. In contrast to methemoglobinemia, sulfhemoglobinemia persists until the erythrocytes containing it are destroyed. Therefore, blood level of sulfhemoglobin declines gradually over a period of weeks.

Useful For: Diagnosis of methemoglobinemia and sulfhemoglobinemia and possible hereditary (congenital) causes Differentiation of methemoglobinemia and sulfhemoglobinemia from other causes of cyanosis (eg, congenital heart disease)

Interpretation: This is a consultative evaluation in which the history and previous laboratory values are reviewed by a hematologist who is an expert on these disorders. Appropriate tests are performed, and an interpretive report is issued.

Reference Values:
Definitive results and an interpretive report will be provided.

Clinical References: 1. OMIM: 250800 Methemoglobinemia due to deficiency of methemoglobin reductase. Updated May 20, 2019. Accessed January 23, 2024. Available at www.omim.org/entry/250800?search=250800&highlight=250800 2. OMIM: 250790 Methemoglobinemia and ambiguous genitalia. Updated December 9, 2022. Accessed January 23, 2024. Available at www.omim.org/entry/250790?search=250790&highlight=250790 3. OMIM: 141800 Hemoglobin alpha locus 1; HBA1. Updated September 15, 2023. Accessed January 23, 2024. Available at www.omim.org/entry/141800?search=141800&highlight=141800 4. OMIM: 141900 Hemoglobin beta locus; HBB. Updated September 15, 2023. Accessed January 23, 2024. Available at www.omim.org/entry/141900?search=141900&highlight=141900 5. Haymond S, Cariappa R, Eby CS, Scott MG. Laboratory assessment of oxygenation in methemoglobinemia. Clin Chem. 2005;51(2):434-444 6. Noor M, Beutler E. Acquired sulfhemoglobinemia. An underreported diagnosis? West J Med. 1998;169(6):386-389 7. Thom CS, Dickson CF, Gell DA, Weiss MJ. Hemoglobin variants: biochemical properties and clinical correlates. Cold Spring Harb Perspect Med. 2013;3(3):a011858 8. Percy MJ, McFerran NV, Lappin TR. Disorders of oxidized haemoglobin. Blood Rev. 2005;19(2):61-68 9. Agarwal AM, Prchal JT. Methemoglobinemia and Other Dyshemoglobinemias. In: Kaushansky K, Lichtman MA, Prchal JT, Levi MM, Press OW, Burns LJ, Caligiuri M, eds. Williams Hematology. 9th ed. McGraw-Hill; 2016: 789-800

MEVI
608086

Methemoglobinemia Interpretation

Clinical Information:

Useful For: Interpretation of the methemoglobinemia evaluation results Diagnosis of methemoglobinemia and sulfhemoglobinemia and possible hereditary (congenital) causes Differentiation of methemoglobinemia and sulfhemoglobinemia from other causes of cyanosis (eg, congenital heart disease)

Interpretation: This is a consultative evaluation in which the history and previous laboratory values are reviewed by a hematologist who is an expert on these disorders. Appropriate tests are performed and an interpretive report is issued.

Reference Values:
Only orderable as part of a profile. For more information see MEV1 / Methemoglobinemia Evaluation.

Definitive results and an interpretive report will be provided.

Clinical References: 1. OMIM: 250800 Methemoglobinemia due to deficiency of methemoglobin reductase. Updated May 20, 2019. Accessed January 22, 2024. Available at www.omim.org/entry/250800?search=250800&highlight=250800 2. OMIM: 250790 Methemoglobinemia and ambiguous genitalia. Updated December 9, 2022. Accessed January 22, 2024. Available at www.omim.org/entry/250790?search=250790&highlight=250790 3. OMIM: 141800 Hemoglobin alpha locus 1; HBA1. Updated September 15, 2023. Accessed January 22, 2024. Available at www.omim.org/entry/141800?search=141800&highlight=141800 4. OMIM: 141900 Hemoglobin beta locus; HBB. Updated September 15, 2023. Accessed January 22, 2024. Available at www.omim.org/entry/141900?search=141900&highlight=141900 5. Haymond S, Cariappa R, Eby CS, Scott MG. Laboratory assessment of oxygenation in methemoglobinemia. Clin Chem. 2005;51(2):434-444 6. Noor M, Beutler E. Acquired sulfhemoglobinemia. An underreported diagnosis?. West J Med. 1998;169(6):386-389 7. Thom CS, Dickson CF, Gell DA, Weiss MJ. Hemoglobin variants: biochemical properties and clinical correlates. Cold Spring Harb Perspect Med. 2013;3(3):a011858 8. Percy MJ, McFerran NV, Lappin TR. Disorders of oxidized haemoglobin. Blood Rev. 2005;19(2):61-68 9. Agarwal AM, Prchal JT. Methemoglobinemia and other dyshemoglobinemias. In: Kaushansky K, Lichtman MA, Prchal JT, et al. eds. Williams Hematology. 9th ed. McGraw-Hill Book Company; 2016:789-800

MECPI
621419

Methicillin Resistance Gene, Molecular Detection, PCR, Varies

Clinical Information: The presence of mecA has been associated with methicillin resistance in staphylococcal isolates. Rapid identification of mecA in staphylococcal isolates will help in determining which antimicrobial therapy to use when treating infections due to methicillin-resistant Staphylococcus aureus or methicillin-resistant Staphylococcus species other than S aureus. Bacteria can acquire resistance to certain beta-lactam antibiotics through a variety of mechanisms. One such mechanism is the mecA gene. The mecA gene encodes penicillin-binding protein 2a (PBP2a), which has a low affinity for beta-lactam antibiotics. Bacteria expressing this gene can maintain cell wall synthesis even in the presence of beta-lactam antibiotics. Testing of bacterial isolates by molecular methods may be needed when oxacillin or cefoxitin breakpoints are unavailable (eg, certain Staphylococcus species other than S aureus) or when discrepancies exist among cefoxitin and oxacillin phenotypic antimicrobial susceptibility testing results or PBP2a results. Use of this assay may also be helpful when isolates do not grow adequately for phenotypic antimicrobial susceptibility testing (eg, staphylococcal small colony variants).

Useful For: Detecting mecA in staphylococcal bacterial isolates Evaluating treatment options when oxacillin or cefoxitin breakpoints are unavailable (eg, certain Staphylococcus species other than Staphylococcus aureus) Predicting antimicrobial resistance when bacterial growth is inadequate for

phenotypic antimicrobial susceptibility testing (eg, staphylococcal small colony variants) Assessing discrepancies amongst cefoxitin and oxacillin phenotypic testing results or penicillin-binding protein 2a test results

Interpretation: A positive result indicates the presence of the methicillin resistance gene (mecA) in the bacterial isolate. A negative result indicates the absence of detectable DNA in the bacterial isolate.

Reference Values:
Not detected

Clinical References: 1. Xpert SA Nasal Complete 300-8799. Package insert: Cepheid; Rev H, 09/2019 2. Ali GH, Seiffein N. Association of some virulence genes in methicillin resistant and methicillin sensitive Staphylococcus aureus infections isolated in community with special emphasis on pvl/mecA genes profiles in Alexandria, Egypt. Gene Reports. 2021;25:101334. doi:10.1016/j.genrep.2021.101334 3. Seker E, Ozenc E, Turedi OK, Yilmaz M. Prevalence of mecA and pvl genes in coagulase negative staphylococci isolated from bovine mastitis in smallholder dairy farms in Turkey. Anim Biotechnol. 2022;34(7):2427-2432. doi:10.1080/10495398.2022.2094802 4. Palavecino E. Rapid methods for detection of MRSA in clinical specimens. Methods Mol Biol. 2020:2069:29-45. doi:10.1007/978-1-4939-9849-4_2

MRSAP
609735

Methicillin Resistant Staphylococcus aureus, PCR, Nasal

Clinical Information: Staphylococcus aureus causes a variety of human infections and is a major cause of hospital acquired infection of surgical wounds and infections associated with indwelling medical devices. Mayo Clinic has established a program to reduce the number of S aureus surgical infections, which involves surgical patients being tested for S aureus and treated, if positive, prior to surgery. This assay not only detects S aureus, but, if positive, indicates whether S aureus is methicillin susceptible or resistant.

Useful For: Rapid screening test for Staphylococcus aureus nasal carriage that, if positive, indicates whether the S aureus is methicillin susceptible or resistant This test should not be used to guide or monitor treatment for methicillin-resistant S aureus or S aureus infections.

Interpretation: A positive result indicates presence of DNA from Staphylococcus aureus. The assay also detects the gene for methicillin resistance (mecA). A negative result indicates the absence of detectable S aureus DNA in the specimen.

Reference Values:
Negative for Staphylococcus aureus
Negative for methicillin-resistant S aureus

Clinical References: 1. Xpert SA Nasal Complete 300-8799. Package insert: Cepheid; Rev H, 09/2019 2. Muto C, Jernigan J, Ostrowsky BE, et al: SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of Staphylococcus aureus and Enterococcus. Infect Control Hosp Epidemiol. 2003 May;24(5):362-386 3. Carr AL, Daley MJ, Givens Merkel K, Rose DT. Clinical utility of methicillin-resistant Staphylococcus aureus nasal screening for antimicrobial stewardship: A review of current literature. Pharmacotherapy. 2018 Dec;38(12):1216-1228. doi: 10.1002/phar.2188 4. Saraswat MK, Magruder JT, Crawford TC, et al: Preoperative Staphylococcus aureus screening and targeted decolonization in cardiac surgery. Ann Thorac Surg. 2017 Oct;104(4):1349-1356. doi: 10.1016/j.athoracsur.2017.03.018 5. Chen AF, Wessel CB, Rao N. Staphylococcus aureus screening and decolonization in orthopaedic surgery and reduction of surgical site infections. Clin Orthop Relat Res. 2013;471(7):2383-2399. doi: 10.1007/s11999-013-2875-0

MTXSG
62580

Methotrexate Post Glucarpidase, Serum

Clinical Information: Methotrexate (MTX) is a folate antimetabolite that reversibly inhibits dihydrofolate reductase. MTX is used alone or in combination with other agents to treat a variety of cancers (ie, breast, leukemia, lymphoma, head and neck, lung, and sarcomas). Administration of intravenous high-dose MTX (ie, 1-15 g/m[2]) occurs at different intervals in treatments and depends on the regimen being used. Therapy is guided by measurement of serum concentration: 24 hours after dosage, the serum concentration should be less than 10 mcmol/L; 48 hours after therapy, concentration should be less than 1 mcmol/L; and 72 hours after dosage, the concentration should be less than 0.1 mcmol/L or less than 0.05 mcmol/L, depending on clinical protocol. MTX can also be used at lower doses (ie, a single dose of 5-15 mg/wk) to treat patients with rheumatoid arthritis and severe psoriasis. In adults, oral absorption appears to be dose dependent. Peak serum concentrations are reached within 1 to 3 hours after oral dosing and 0.5 to 1 hour after intramuscular injection. Protein binding is approximately 50%. Volume of distribution is 0.4 to 0.8 L/kg. Elimination is concentration dependent with an apparent elimination half-life of 3 to 10 hours for patients on low dose therapy (<30 mg/m[2]) compared to 8 to 15 hours for patients on high doses of MTX.

Useful For: Monitoring methotrexate concentrations post-glucarpidase therapy Documenting failure to respond that may be due to noncompliance Guiding dosage adjustments in patients with kidney failure

Interpretation: Following a 4- to 6-hour intravenous infusion of methotrexate, postinfusion concentrations greater than the following indicate an increased risk of toxicity if conventional low-dose leucovorin rescue is given: -24-hour postinfusion concentration: 5.0 to 10.0 mcmol/L -48-hour postinfusion concentration: 0.5 to 1.0 mcmol/L -72-hour postinfusion concentration: 0.1 mcmol/L

Reference Values:
Nontoxic drug concentration after 72 hours: <0.1 mcmol/L

Clinical References: 1. Cadman EC, Durivage HJ. Cancer chemotherapy: alkylating agents. In: Wilson JD, Braunwald E, Isselbacher KJ, eds. Harrison's Principles of Internal Medicine. 12th ed. McGraw-Hill Book Company; 1991: 1592-1594 2. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. McGraw-Hill Education; 2018

MTHX
37047

Methotrexate, Serum

Clinical Information: Methotrexate is an antineoplastic agent that inhibits DNA synthesis. The medication exerts its effects through competitive inhibition of the enzyme dihydrofolate reductase thus decreasing the concentrations of tetrahydrofolate essential to the methylation of pyrimidine nucleotides and consequently the rate of pyrimidine nucleotide and ultimately DNA synthesis. Methotrexate is used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis. Methotrexate is effective against malignancies characterized by rapid cell proliferation. Intermediate to high doses of methotrexate with leucovorin (citrovorum-factor or folinic acid) rescue to salvage nontumor cells have been used with favorable results in the treatment of osteogenic sarcoma, leukemia, non-Hodgkin lymphoma, lung, and breast cancer. Methotrexate has the potential for serious toxicity. Patients undergoing methotrexate therapy are closely monitored so that toxic effects are detected promptly.

Useful For: Determining whether methotrexate is being cleared appropriately and verifying that a nontoxic concentration has been attained following therapy

Interpretation: Serum concentrations of methotrexate are commonly monitored during high-dose therapy (>50 mg/m[2]) to identify the time at which active intervention by leucovorin rescue should be initiated. Criteria for serum concentrations indicative of a potential for toxicity after single-bolus, high-

dose therapy are as follows: -Methotrexate >10 mcmol/L 24 hours after dose -Methotrexate >1 mcmol/L 48 hours after dose -Methotrexate >0.1 mcmol/L 72 hours after dose

Reference Values:
Nontoxic drug concentration after 72 hours: <0.1 mcmol/L

Clinical References: 1. Snozek CLH, McMillin GA, Moyer TP. Therapeutic drugs and their management. In: Burtis CA, Ashwood ER, Bruns D. Tietz Textbook of Clinical Chemistry. 5th ed. WB Saunders Company; 2012:1057-1108 2. Cadman EC, Durivage HJ: Cancer chemotherapy: alkylating agents. In: Wilson JD, Braunwald E, Isselbacher KJ, et al. Harrison's Principles of Internal Medicine. 12th ed. McGraw-Hill Book Company; 1991:1592-1594 3. LaCasce AS. Therapeutic use and toxicity of high-dose methotrexate. UpToDate; Updated August 1, 2024. Accessed February 18, 2025. Available at www.uptodate.com/contents/therapeutic-use-and-toxicity-of-high-dose-methotrexate

FMETX
91822

Methsuximide (Celontin) as Desmethylmethsuximide

Reference Values:
10.0 - 40.0 ug/mL

Methsuximide measured as desmethylmethsuximide.

MMAP
31927

Methylmalonic Acid, Quantitative, Plasma

Clinical Information: Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 (cobalamin) or its downstream metabolites. Acquired deficiencies of vitamin B12 are much more common and can be due to intestinal malabsorption, impaired digestion, or poor diet. Older adult patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as kidney insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, thousands of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a lifelong risk unless treatment is closely monitored, including plasma and urine MMA levels. Several studies have suggested that the determination of plasma or urinary methylmalonic acid could be a more reliable marker of vitamin B12 deficiency than direct vitamin B12 determination.

Useful For: Evaluating children with signs and symptoms of methylmalonic acidemia using plasma specimens Evaluating individuals with signs and symptoms associated with a variety of causes of vitamin B12 (cobalamin) deficiency

Interpretation: In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed. In

adults, moderately elevated values indicate a likely vitamin B12 (cobalamin) deficiency.

Reference Values:
< or =0.40 nmol/mL

Clinical References: 1. Fenton WA, Gravel RA, Rosenblatt DS. Disorders of propionate and methylmalonate metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill; 2019. Accessed November 27, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225086103&bookid=2709 2. Klee GG. Cobalamin and folate evaluation: measurement of methylmalonic acid and homocysteine vs vitamin B(12) and folate. Clin Chem. 2000:46(8 Pt 2):1277-1283 3. Watkins D, Rosenblatt DS. Inherited disorders of folate and cobalamin transport and metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill; 2019. Accessed November 27, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225548307&bookid=2709 4. Vashi P, Edwin P, Popiel B, Lammersfeld C, Gupta D. Methylmalonic acid and homocysteine as indicators of vitamin B-12 deficiency in cancer. PLoS One. 2016;11(1):e0147843

MMAS
80289

Methylmalonic Acid, Quantitative, Serum

Clinical Information: Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 (cobalamin) or its downstream metabolites. Acquired deficiencies of vitamin B12 are much more common and can be due to intestinal malabsorption, impaired digestion, or poor diet. Older adult patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as kidney insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, thousands of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a lifelong risk unless treatment is closely monitored, including serum and urine MMA levels. Several studies have suggested that the determination of serum or urinary methylmalonic acid could be a more reliable marker of vitamin B12 deficiency than direct vitamin B12 determination.

Useful For: Evaluating children with signs and symptoms of methylmalonic acidemia using serum specimens Evaluating individuals with signs and symptoms associated with a variety of causes of vitamin B12 (cobalamin) deficiency

Interpretation: In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed. In adults, moderately elevated values indicate a likely vitamin B12 (cobalamin) deficiency.

Reference Values:
< or =0.40 nmol/mL

Clinical References: 1. Fenton WA, Gravel RA, Rosenblatt DS. Disorders of propionate and methylmalonate metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill; 2019. Accessed November 27, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225086103&bookid=2709 2. Klee GG. Cobalamin and folate evaluation: measurement of methylmalonic acid and homocysteine vs vitamin B(12) and folate. Clin Chem. 2000;46(8):1277-1283 3. Watkins D, Rosenblatt DS. Inherited disorders of folate and cobalamin transport and metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill; 2019. Accessed November 27, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225548307&bookid=2709 4. Vashi P, Edwin P, Popiel B, Lammersfeld C, Gupta D. Methylmalonic acid and homocysteine as indicators of vitamin B-12 deficiency in cancer. PLoS One. 2016;11(1):e0147843

MMAU
80290

Methylmalonic Acid, Quantitative, Urine

Clinical Information: Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 (cobalamin) or its downstream metabolites. Acquired deficiencies of vitamin B12 are much more common and can be due to intestinal malabsorption, impaired digestion, or poor diet. Older adult patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as kidney insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, thousands of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a lifelong risk unless treatment is closely monitored, which includes serum and urine MMA levels. Several studies have suggested that the determination of serum or urinary methylmalonic acid could be a more reliable marker of vitamin B12 deficiency than direct vitamin B12 determination.

Useful For: Evaluating children with signs and symptoms of methylmalonic acidemia using urine specimens Evaluating individuals with signs and symptoms associated with a variety of causes of vitamin B12 (cobalamin) deficiency

Interpretation: In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed. In adults, moderately elevated values indicate a likely vitamin B12 (cobalamin) deficiency.

Reference Values:
<3.60 mmol/mol creatinine

Clinical References: 1. Fenton WA, Gravel RA, Rosenblatt DS. Disorders of propionate and methylmalonate metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed

November 27, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225086103&bookid=2709 2. Klee GG. Cobalamin and folate evaluation: Measurement of methylmalonic acid and homocysteine vs vitamin B(12) and folate. Clin Chem. 2000;46(8 Pt 2):1277-1283 3. Watkins D, Rosenblatt DS. Inherited disorders of folate and cobalamin transport and metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill; 2014. Accessed November 27, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225548307&bookid=2709 4. Vashi P, Edwin P, Popiel B, Lammersfeld C, Gupta D. Methylmalonic acid and homocysteine as indicators of vitamin B-12 deficiency in cancer. PLoS One. 2016;11(1):e0147843

MMAGP
608021

Methylmalonic Aciduria Gene Panel, Varies

Clinical Information: Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism. MMA is a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase caused by pathogenic variants in the mutase gene (MUT). Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin (Cbl) synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, hundreds of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a life-long risk unless treatment is closely monitored, including plasma and urine MMA levels (MMAP / Methylmalonic Acid, Quantitative, Plasma and MMAU / Methylmalonic Acid, Quantitative, Urine). Plasma acylcarnitine profile (ACRN / Acylcarnitines, Quantitative, Plasma), quantitative plasma amino acids (AAQP / Amino Acids, Quantitative, Plasma), urine organic acids (OAU / Organic Acids Screen, Random, Urine), and homocysteine (HCYSP / Homocysteine, Total, Plasma or HCYSS / Homocysteine, Total, Serum) are recommended first-tier biochemical tests to screen patients for methylmalonic acidemia. A comprehensive gene panel is a helpful tool to establish a targeted diagnosis for patients with suggestive clinical and biochemical features of methylmalonic acidemia. Treatment is most effective when tailored to the specific type of methylmalonic acidemia. For example, intramuscular injections of hydroxocobalamin are critical in the treatment of CblC, whereas oral cyanocobalamin is effective for methylmalonic acidemia mutase subtypes as well as other cobalamin subtypes. Acute treatment for methylmalonic acidemia consists of dialysis and administration of nitrogen scavenger drugs to reduce ammonia concentration. Chronic management typically involves restriction of dietary protein with essential amino acid supplementation. More recently, liver transplantation has been successful in treating some patients.

Useful For: Follow up for abnormal biochemical results suggestive of a methylmalonic acidemia (MMA) Establishing a molecular diagnosis for patients with MMA Identifying variants within genes known to be associated with MMA, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

MPAGP
608022

Methylmalonic Aciduria-Propionic Aciduria Combined Gene Panel, Varies

Clinical Information: Methylmalonic acidemia (MMA) and propionic acidemia (PA) are defects of propionate metabolism caused by deficiencies in methylmalonyl-CoA mutase and propionyl-CoA carboxylase, respectively. The clinical phenotype includes vomiting, hypotonia, lethargy, apnea, hypothermia, and coma. The biochemical phenotype for MMA includes elevations of propionyl carnitine, methylmalonic acid, and methylcitric acid. Patients with PA will have elevations of propionyl carnitine and methylcitric acid with normal methylmalonic acid concentrations as the enzymatic defect is upstream of methylmalonic-CoA mutase. All known disorders of MMA and PA metabolism are inherited in an autosomal recessive manner. Newborn screening for inborn errors of propionic acid metabolism relies on elevations of methionine and propionyl carnitine, which are reported as an elevation of C3. These analytes are not specific for this condition and are prone to false-positive results, leading to increased cost, stress, and anxiety for families who are subjected to follow-up testing. Homocysteine, methylmalonic acid, and methylcitric acid are more specific markers for inborn errors of propionic acid metabolism (HCMM / Homocysteine [Total], Methylmalonic Acid, and Methylcitric Acid, Blood Spot). For MMA, the preferred biochemical screening tests include plasma acylcarnitine profile (ACRN / Acylcarnitines, Quantitative, Plasma), quantitative plasma amino acids (AAQP / Amino Acids, Quantitative, Plasma), urine organic acids (OAU / Organic Acids Screen, Urine), and homocysteine (HCYSP / Homocysteine, Total, Plasma or HCYSS / Homocysteine, Total, Serum). Molecular genetic testing can be used to confirm a biochemical diagnosis for MMA or PA. Treatment is most effective when tailored to the specific type of MMA or PA. For example, intramuscular injections of hydroxocobalamin are critical in the treatment of Cbl C, whereas oral cyanocobalamin is effective for MMA mutase subtypes as well as other cobalamin subtypes. Acute treatment for MMA and PA is similar, consisting of dialysis and administration of nitrogen scavenger drugs to reduce ammonia concentration. Chronic management typically involves restriction of dietary protein with essential amino acid supplementation. More recently, liver transplantation has been used with success in treating some patients with MMA or PA.

Useful For: Follow up for abnormal biochemical results suggestive of methylmalonic acidemia or propionic acidemia Establishing a molecular diagnosis for patients with methylmalonic acidemia or propionic acidemia Identifying variants within genes known to be associated with methylmalonic acidemia or propionic acidemia, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Fenton WA, Gravel RA, Rosenblatt DS et al. Disorders of propionate and methylmalonate metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Accessed March 8, 2024. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225086103

MPHNU
608882

Methylphenidate and Metabolite, Random, Urine

Clinical Information: Methylphenidate (MPH) is utilized for the treatment of attention-deficit hyperactivity disorder and narcolepsy. MPH has two chiral centers and is marketed as a racemic mixture and as the active d-enantiomer of racemic MPH. Although the exact mechanism of its action has not been fully defined, it blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron thus increasing the concentrations of these monoamines in the extraneural space.

Useful For: Monitoring urine methylphenidate and ritalinic acid concentrations to assess compliance in patients

Interpretation: Methylphenidate (MPH) has an oral bioavailability of 22% to 100% with peak concentrations occurring around 2 hours for instant release and approximately 5 to 6 hours for extended-release formulations. The half-life of MPH is 2 to 4 hours. MPH is extensively metabolized to ritalinic acid, which is an inactive metabolite. The half-life of ritalinic acid is about 3 to 4 hours. Only small quantities (<1%) of unchanged MPH appear in the urine as most of the dose (60%-86%) is excreted in the urine as ritalinic acid. The presence of MPH or ritalinic acid in the urine indicates the patient has taken MPH in the past 1 to 2 days.

Reference Values:
Negative (Positive results are reported with a quantitative result.)

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Methylphenidate: 10 ng/mL
Ritalinic Acid: 50 ng/mL

Clinical References: 1 .Kimko HC, Cross JT, Abernethy DR. Pharmacokinetics and clinical effectiveness of methylphenidate. Clin Pharmacokinetics. 1999;37(6):457-470. doi:10.2165/00003088-199937060-00002 2. Ramos L, Bakhtiar R, Tse FL. Liquid-liquid extraction using 96-well plate format in conjunction with liquid chromatography/tandem mass spectrometry for quantitative determination of methylphenidate (Ritalin1) in human plasma. Rapid Commun Mass Spectrom. 2000;14(9):740-745. doi:10.1002/(SICI)1097-0231(20000515)14:9<740:AID-RCM938>3.0.CO;2-C 3. Paterson SM, Moore GA, Florkowski CM, George PM. Determination of methylphenidate and its metabolite in urine by liquid chromatography/tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2012;881-881:20-26. doi:10.1016/j.jchromb.2011.11.007 4. Mulet CT, Arroyo-Moro LE, Leon LA, Gnagy E, DeCaprio AP. Rapid quantitative analysis of methylphenidate and ritalinic acid in oral fluid by liquid chromatography triple quadrupole mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2018;1092:313-319. doi:10.1016/j.jchromb.2018.06.025 5. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

RIT
80456

Methylphenidate, Serum

Reference Values:
Reference Range: 5.0 - 20.0 ng/mL

MTAP
605177

Methylthioadenosine Phosphorylase (MTAP) Immunostain, Tech Only

Clinical Information: Methylthioadenosine phosphorylase (MTAP) is a 9p21.3 related protein involved in purine metabolism that plays a role in salvage of adenosine and methionine and is expressed in mesothelial cells. Deletion of the 9p21.3 chromosome region and loss of MTAP (or BCRA1 associated protein 1: BAP1) protein expression is a reliable marker for malignant mesothelioma diagnosis.

Useful For: Aiding in the diagnosis of malignant mesothelioma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Berg K, Dacic S, Miller C, et al. Utility of methylthioadenosine phosphorylase compared With BAP1 immunohistochemistry, and CDKN2A and NF2 fluorescence in situ hybridization in separating reactive mesothelian proliferations from epithelioid malignant mesotheliomas. Arch Pathol Lab Med. 2018;1-5 2. Hida T, Hamasaki M, Matsumoto S, et al. Immunohistochemical detection of MTAP and BAP1 protein loss for mesothelioma diagnosis: Comparison with 9p21 FISH and BAP1 immunohistochemistry. Lung Cancer. 2017;104(12):98-105 3. Su C, Chang Y, Chan Y, et al. MTAP is an independent prognosis marker and the concordant loss of MTAP and p16 expression predicts short survival in non-small cell lung cancer patients. EJSO. 2014;40(6):1143-1150 4. Watanabe F, Takao M, Inoue K, et al: Immunohistochemical diagnosis of methylthiodenosine phosphorylase (MTAP) deficiency in non-small cell lung carcinoma. Lung Cancer. 2009;63(4):39-44 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

MEX
9245

Mexiletine, Serum

Clinical Information: Mexiletine is a class I B antiarrhythmic with electrophysiologic properties similar to lidocaine and is useful in suppression of ventricular arrhythmias. The drug exhibits a high degree of oral bioavailability, is approximately 60% protein bound, and undergoes renal clearance. Mexiletine has a volume of distribution of approximately 6 L/kg and a half-life of approximately 11 hours. Myocardial infarction and uremia reduce the rate of clearance and increase the half-life of mexiletine, requiring dosage adjustment guided by drug monitoring. Mexiletine toxicity can occur at concentrations above 2.0 mcg/mL (trough value) and is characterized by symptoms of nausea, hypotension, sinus bradycardia, paresthesia, seizures, intermittent left bundle branch block, and temporary asystole.

Useful For: Assessing achievement of optimal therapeutic mexiletine concentrations Assessing potential mexiletine toxicity

Interpretation: Optimal response to mexiletine occurs when the serum concentration is within the range of 0.5 to 2.0 mcg/mL (trough value).

Reference Values:
Trough Value
0.5-2.0 mcg/mL: Therapeutic concentration
>2.0 mcg/mL: Toxic concentration

Clinical References: 1. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th

ed. Elsevier; 2023:420-453 2. Josephson ME, Buxton AE, Marchlinski FE. The tachyarrhythmias: tachycardias. In: Wilson JD, Braunwald E, Isselbacher KJ, et al, eds. Harrison's Principles of Internal Medicine. 12th ed. McGraw-Hill Book Company; 1991:915 3. Valdes R Jr, Jortani SA, Gheorghiade M. Standards of laboratory practice: cardiac drug monitoring. National Academy of Clinical Biochemistry. Clin Chem. 1998;44(5):1096-1099 4. Joseph SP, Holt DW: Electrophysiological properties of mexiletine assessed with respect to plasma concentrations. Eur J Cardiol. 1980;11(2):115-121

MGMT
36733

MGMT Promoter Methylation, Tumor

Clinical Information: Glioblastoma is the most frequent malignant primary central nervous system (CNS) tumor in adults as originally defined based on morphology. Based on the 2021 World Health Organization (WHO) classification of CNS tumors, the original glioblastoma is now divided in "glioblastoma, IDH-wildtype, CNS WHO grade 4" (most cases) and "astrocytoma, IDH-mutant, CNS WHO grade 4." Current standard of care in both tumor types consists of surgical resection followed by radiotherapy in addition to alkylating chemotherapy with temozolomide. MGMT (O[6]-methylguanine-DNA methyltransferase) encodes a DNA repair enzyme. This enzyme rescues tumor cells from alkylating agent-induced damage and confers tumor resistance to chemotherapy with alkylating agents. Epigenetic silencing of MGMT by promoter methylation of upstream and downstream CpG sites within differentially methylated regions results in decreased MGMT expression and presumably reduces MGMT-mediated DNA repair of alkylating agent-induced DNA damage in tumor cells. In newly diagnosed original glioblastoma patients, MGMT promoter methylation has been shown to be a favorable prognostic biomarker and a strong predictor of responsiveness to alkylating chemotherapy. This is particularly relevant for older patients (>60-65 years), who may have decreased tolerance for combined chemoradiation. For this group of patients, MGMT promoter methylation status guides therapy decision making, as MGMT promoter methylation identifies patients who would benefit from monotherapy with the alkylating agent temozolomide instead of radiotherapy alone. In IDH-mutant diffuse gliomas, MGMT promoter methylation is very frequent and occurs as part of the IDH mutation-induced glioma CpG island methylation phenotype; in infratentorial IDH-mutant astrocytomas, however, MGMT promoter methylation is less common. The prognostic and predictive significance of MGMT promoter methylation status in the context of IDH-mutant tumors is unclear. MGMT promoter methylation is also frequent in "diffuse hemispheric glioma, H3 G34-mutant" and limited data suggest that it is also a favorable prognostic marker in this tumor context. MGMT promoter methylation status may be evaluated by multiple methods, and the testing platform with most prospective clinical trial validation is methylation-specific polymerase chain reaction evaluating downstream CpG sites.

Useful For: Prognostication of newly diagnosed patients with glioblastoma, IDH-wildtype Identifying newly diagnosed glioblastoma, IDH-wildtype patients that may respond to alkylating chemotherapy (ie, temozolomide) Guiding therapy decision making for newly diagnosed glioblastoma, IDH-wildtype in older patients (>60-65 years)

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005;352(10):997-1003 2. Weller M, Stupp R, Reifenberger G, et al. MGMT promoter methylation in malignant gliomas: ready for personalized medicine? Nat Rev Neurol. 2010;6(1):39-51 3. Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: The NOA-08 randomised, phase 3 trial. Lancet Oncol. 2012;13(7):707-715 4. Malmstrom A, Gronberg BH, Marosi C,

et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol. 2012;13(9):916-926 5. Korshunov A, Capper D, Reuss D, et al. Histologically distinct neuroepithelial tumors with histone 3 G34 mutation are molecularly similar and comprise a single nosologic entity. Acta Neuropathol. 2016;131(1):137-146 6. Korshunov A, Casalini B, Chavez L, et al. Integrated molecular characterization of IDH-mutant glioblastomas. Neuropathol Appl Neurobiol. 2019;45(2):108-118 7. Mansouri A, Hachem LD, Mansouri S, et al. MGMT promoter methylation status testing to guide therapy for glioblastoma: refining the approach based on emerging evidence and current challenges. Neuro Oncol. 2019;21(2):167-178 8. Banan R, Stichel D, Bleck A, et al. Infratentorial IDH-mutant astrocytoma is a distinct subtype. Acta Neuropathol. 2020;140(4):569-581 9. Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. Neuro Oncol. 2020;22(8):1073-1113 10. WHO Classification of Tumours Editorial Board. Central Nervous System Tumours. 5th ed. IARC Press; 2021. WHO Classification of Tumours, Vol 6 11. Brat DJ, Aldape K, Bridge JA, et al. Molecular biomarker testing for the diagnosis of diffuse gliomas. Arch Pathol Lab Med. 2022;146(5):547-574

CERAM
606777

MI-Heart Ceramides, Plasma

Clinical Information: MI-Heart Ceramides is a blood test that measures risk for adverse cardiovascular events and quantifies plasma ceramides. Plasma ceramides are predictors of adverse cardiovascular events resulting from unstable atherosclerotic plaque. Ceramides are complex lipids that play a central role in cell membrane integrity, cellular stress response, inflammatory signaling, and apoptosis. Synthesis of ceramides from saturated fats and sphingosine occurs in all tissues. Metabolic dysfunction and dyslipidemia results in accumulation of ceramides in tissues not suited for lipid storage. Elevated concentrations of circulating ceramides are associated with atherosclerotic plaque formation, ischemic heart disease, myocardial infarction, hypertension, stroke, type 2 diabetes mellitus, insulin resistance, and obesity. Three specific ceramides have been identified as highly linked to cardiovascular disease and insulin resistance: N-palmitoyl-sphingosine (Cer16:0), N-stearoyl-sphingosine (Cer18:0), and N-nervonoyl-sphingosine(Cer24:1). A fourth ceramide, N-lignoceroyl-sphingosine (Cer24:0), is highly abundant in all individuals and is useful as a normalization factor for intra-individual variability of ceramide concentrations. Individuals with elevated plasma ceramides are at higher risk of major adverse cardiovascular events even after adjusting for age, gender, smoking status, and serum biomarkers such as low-density lipoprotein and high-density lipoprotein cholesterol, C-reactive protein and lipoprotein-associated phospholipase A2. Ceramide concentrations are reduced by current cardiovascular therapies including diet, exercise, statins, and proprotein convertase subtilisin/kexin type inhibitors.

Useful For: Evaluating the risk of major adverse cardiovascular events within the next 1 to 5 years

Interpretation: Elevated plasma ceramides are associated with increased risk of myocardial infarction, acute coronary syndromes, and mortality within 1 to 5 years. Ceramide Score Relative Risk Risk Category 0-2 1.0 Lower 3-6 1.5 Moderate 7-9 2.2 Increased 10-12 3.5 Higher Score is based on trial data including >4000 subjects.

Reference Values:
MI-Heart Ceramide Risk Score:
0-2 Lower risk
3-6 Moderate risk
7-9 Increased risk
10-12 Higher risk
Ceramide (16:0): 0.19-0.36 mcmol/L

Ceramide (18:0): 0.05-0.14 mcmol/L
Ceramide (24:1): 0.65-1.65 mcmol/L
Ceramide (16:0)/(24:0): <0.11
Ceramide (18:0)/(24:0): <0.05
Ceramide (24:1)/(24:0): <0.45

Reference values have not been established for patients who are less than 18 years of age.

Note: Ceramide (24:0) alone has not been independently associated with disease and will not be reported.

Clinical References: 1 Laaksonen R, Ekroos K, Sysi-Aho M, et al. Plasma ceramides predict cardiovascular death in patients with stable coronary artery disease and acute coronary syndromes beyond LDL-cholesterol. Eur Heart J. 2016;37(25):1967-1976 2. Havulinna AS, Sysi-Aho M, Hilvo M, et al. Circulating ceramides predict cardiovascular outcomes in the population-based FINRISK 2002 cohort. Arterioscler Thromb Vasc Biol. 2016;36(12):2424-2430 3. Wang DD, Toledo E, Hruby A, et al. Plasma ceramides, Mediterranean diet, and incident cardiovascular disease in the PREDIMED trial (Prevenci on con Dieta Mediterranea). Circulation. 2017;135(21):2028-2040. doi:10.1161/CIRCULATIONAHA.116.024261 4. Meeusen JW, Donato LJ, Bryant SC, et al: Plasma Ceramides. Arterioscler Thromb Vasc Biol. 2018;38(8):1933-1939. doi:10.1161/ATVBAHA.118.311199 5. Peterson LR, Xanthakis V, Duncan MS, et al. Ceramide remodeling and risk of cardiovascular events and mortality. J Am Heart Assoc. 2018;7(10). doi:10.1161/JAHA.117.007931 6. Hilvo M, Meikle PJ, Pedersen ER, et al. Development and validation of a ceramide- and phospholipid-based cardiovascular risk estimation score for coronary artery disease patients. Eur Heart J. 2020;41(3):371-380. doi:10.1093/eurheartj/ehz387 7. Alshehry ZH, Mundra PA, Barlow CK, et al. Plasma lipidomic profiles improve on traditional risk factors for the prediction of cardiovascular events in type 2 diabetes mellitus. Circulation. 2016;134(21):1637-1650 8. Anroedh S, Hilvo M, Akkerhuis KM, et al. Plasma concentrations of molecular lipid species predict long-term clinical outcome in coronary artery disease patients. J Lipid Res. 2018;59(9):1729-1737. doi:10.1194/jlr.P081281 9. Lemaitre RN, Jensen PN, Hoofnagle A, et al. Plasma ceramides and sphingomyelins in relation to heart failure risk. Circ Heart Fail. 2019;12(7):e005708. doi:10.1161/CIRCHEARTFAILURE.118.005708

MADON 622523 Microbiology Add-On

Reference Values:
See Individual Components

MLCPC 113370 Microdissection, Laser Capture (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MNLCP 621773 Microdissection, Laser Capture, Membranous Nephropathy (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

TMSI
609364

Microsatellite Instability, Tumor

Clinical Information: Somatic (tumor-specific) microsatellite instability (MSI) is assessed by this test. MSI is characterized by numerous alterations in a type of repetitive DNA called microsatellites and occurs as the result of an impaired DNA mismatch repair process. Impaired DNA mismatch repair is a key factor in tumorigenesis and can occur sporadically or as the result of a hereditary cancer predisposition called Lynch syndrome. Evaluation for MSI may be valuable for clinical decision making. Current data suggest that advanced stage solid tumors with defective DNA mismatch repair (MSI-high: MSI-H) are more likely to respond to treatment with immunotherapies, such as anti-PD-1 therapies. Colon cancers that demonstrate defective DNA mismatch repair (MSI-H) have a significantly better prognosis compared to those with intact mismatch repair (microsatellite stable/MSI- low: MSS/MSI-L). Additionally, current data indicate that stage II and stage III patients with colon cancers characterized by the presence of defective mismatch repair (MSI-H) may not benefit from treatment with fluorouracil alone or in combination with leucovorin. These findings are most likely to impact the management of patients with stage II disease. MSI analysis, usually in combination with immunohistochemistry staining of the mismatch repair proteins, can also provide helpful diagnostic information in the context of evaluation for Lynch syndrome. See Lynch Syndrome Testing Algorithm.

Useful For: Evaluation of tumor tissue to identify patients at high risk for having Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer Evaluation of tumor tissue for clinical decision-making purposes given the prognostic and therapeutic implications associated with microsatellite instability phenotypes

Interpretation: The report will include specimen information, assay information, and interpretation of test results. Microsatellite stable (MSS) is reported as MSS (0 or 1 of 7 markers demonstrating instability) or microsatellite instability-high (MSI-H) (2 or more of 7 markers demonstrating instability).

LCMSP
63097

Microsporidia species, Molecular Detection, PCR, Varies

Clinical Information: Microsporidia are highly specialized fungi that cause a wide variety of clinical syndromes in humans. The most common microsporidia are Enterocytozoon bieneusi and Encephalitozoon intestinalis, which infect the gastrointestinal tract and cause a diarrheal illness, and Encephalitozoon cuniculi and Encephalitozoon hellem, which can infect the conjunctiva, respiratory tract, and genitourinary system. Human infections have been reported most frequently in patients with AIDS but can also occur in other patients who are immunocompromised, including solid organ allograft recipients and, sporadically, immunocompetent hosts. Less commonly, other microsporidia, such as Vittaforma corneae and Brachiola species, can cause disseminated or organ-specific disease. This assay detects only the most common microsporidia, E bieneusi and Encephalitozoon species, and not microsporidiosis due to other species. For other diagnostic tests that may be of value in evaluating patients with diarrhea, see Parasitic Investigation of Stool Specimens Algorithm and Laboratory Testing for Infectious Causes of Diarrhea.

Useful For: Detecting Enterocytozoon bieneusi and Encephalitozoon species in fecal and urine specimens to support the clinical diagnosis of microsporidiosis

Interpretation: A positive result indicates the presence of Enterocytozoon bieneusi and Encephalitozoon species DNA and is consistent with an active or recent infection. Since microsporidia DNA may be present in feces or urine in the absence of clinical symptoms, results should be correlated with clinical presentation. A negative result indicates absence of detectable DNA from E bieneusi and Encephalitozoon species in the specimen. Still, this does not always rule out ongoing microsporidiosis since the organism may be present at very low levels or may be sporadic. Other tests to consider in the evaluation of a patient presenting with acute or chronic watery diarrhea include cultures or specific

assays for bacterial, viral, and parasitic pathogens.

Reference Values:
Negative

Clinical References: 1. Didier ES, Weiss LM: Microsporidiosis: Not just in AIDS patients. Curr Opin Infect Dis. 2011 Oct;24(5):490-495 2. Nagpal A, Pritt BS, Lorenz EC, et al: Disseminated microsporidiosis in a renal transplant recipient: case report and review of the literature. Transpl Infect Dis. 2013 Oct;15(5):526-532 3. Verweij JJ, Stensvold CR: Molecular testing for clinical diagnosis and epidemiological investigations of intestinal parasitic infections. Clin Microbiol Rev. 2014 Apr;27(2):371-418 4. Wolk DM, Schneider SK, Wengenack NL, Sloan LM, Rosenblatt JE: Real-time PCR method for detection of Encephalitozoon intestinalis from stool specimens. J Clin Microbio. 2002 Nov;40(11):3922-3928

MTBS
81507

Microsporidia Stain, Varies

Clinical Information: Microsporidia are highly specialized fungi that cause a wide variety of clinical syndromes in humans. The most common microsporidia are Enterocytozoon bieneusi and Encephalitozoon intestinalis, which infect the gastrointestinal tract and cause a diarrheal illness, and Encephalitozoon cuniculi and Encephalitozoon hellem, which can infect the conjunctiva, respiratory tract, and genitourinary system. Human infections have been reported most frequently in patients with AIDS, but also can occur in other immunocompromised patients, including solid organ allograft recipients and, sporadically, immunocompetent hosts. Less commonly, other microsporidia such as Vittaforma corneae and Brachiola species can cause disseminated or organ-specific disease. Diagnosis of microsporidiosis is traditionally performed by light microscopic examination of stool, urine, and other specimens using a strong trichrome (chromotrope 2R) stain for detection of the characteristic spores. Unfortunately, microscopic identification can be challenging due to the small size of the spores (1-4 micrometer) and their resemblance to yeast. Molecular detection using species-specific polymerase chain reaction offers improved sensitivity and specificity and is available for the microsporidia that cause the majority of intestinal and renal infections (ie, Encephalitozoon species and Enterocytozoon bieneusi). The microsporidia stain is reserved for use with other (nonstool and nonurine) specimen sources due to the variety of other species that may be detected outside of the intestinal tract and kidney. The antihelmintic drug, albendazole has been found effective in some infections due to Enterocytozoon bieneusi and Encephalitozoon (Septata) intestinalis.

Useful For: Diagnosis of extra-intestinal microsporidiosis involving the lung, skin, and other organs, particularly in immunocompromised hosts Diagnosis of ocular microsporidiosis

Interpretation: A positive result suggests an active or recent infection. Results should be correlated with the patient's clinical presentation and immune status. A negative result indicates absence of detectable microsporidial spores in the specimen but does not always rule out ongoing microsporidiosis since the organism may be present at very low levels or shed sporadically.

Reference Values:
Negative
If positive, reported as Microsporidia detected

Clinical References: 1. Weber R, Bryan RT, Schwartz DA, Owen RL. Human microsporidial infections. Clin Microbiol Rev. 1994;7:426-461 2. Goodgame RW. Understanding intestinal spore-forming protozoa: cryptosporidia, microsporidia, isospora, and cyclospora. Ann Intern Med. 1996;124:429-441 3. Wanke CA, DeGirolami P, Federman M. Enterocytozoon bieneusi infection and diarrheal disease in patients who were not infected with human immunodeficiency virus: case report and

review. Clin Infect Dis. 1996;23:816-818 4. Special Stains for Microsporidia: Modified Trichrome-Ryan Blue. American Society of Microbiology. Updated December 19, 2022. Accessed August 31, 2023. Available at www.clinmicronow.org/doi/10.1128/9781683670438.CMPH.ch9.4-4 5. Special Stains for Microsporidia: Modified Trichrome-Ryan Blue. Center for Disease Control and Prevention. Updated May 29, 2019. Accessed August 31, 2023. Available at www.cdc.gov/dpdx/microsporidiosis/index.html

FMIDZ
90112

Midazolam (Versed), serum

Reference Values:
Reference Range: 50 - 600 ng/mL

FMCG4
57536

Milk Cow IgG4

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

MILK
82871

Milk, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to milk Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with

the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PMLK
82827

Milk, Processed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to processed milk Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FMINT
57885

Mint (Mentha Piperita) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

FMIRT
57749

Mirtazapine (Remeron)

Reference Values:
Reference range: 4.0 – 40.0 ng/mL

Expected steady state trough mirtazapine concentrations in patients receiving recommended daily dosages: 4.0 – 40.0 ng/mL

Toxic range not established.

ZW204
91801

Misc Cincinnati Childrens Hospital Medical Center

Reference Values:
Test Performed By: Cincinnati Childrens Hospital Medical Ctr
Molecular Genetics Lab
3333 Burnet Ave
Cincinnati, OH 45229

ZW179 Misc Medical Neurogenetics, LLC
91403

Reference Values:
Test Performed By: Medical Neurogenetics Lab
5424 Glenridge Drive NE
Atlanta, GA 30342

ZW149 Misc Monogram Biosciences, Inc.
91170

Reference Values:
TEST PERFORMED BY: MONOGRAM BIOSCIENCES, INC.
345 OYSTER POINT BOULEVARD
SOUTH SAN FRANCISCO, CA 94080

ZW196 Misc National Jewish Health Mycobacteriology Test
91643

Reference Values:
Test Performed by: National Jewish Health Mycobacteriology Lab
Advanced Diagnostic Laboratories
1400 Jackson Street
Denver, CO 80206-2761

ZW185 Miscellaneous Ambry Genetics
91516

Reference Values:
Test Performed by: Ambry Genetics
100 Columbia No. 200
Aliso Viejo, CA 92656

ZW242 Miscellaneous ARUP Testing
57378

Reference Values:
Test Performed by: ARUP Laboratories
500 Chipeta Way
Salt Lake City, UT 84108

ZW127 Miscellaneous Athena Testing
90566

Reference Values:
Test Performed by: Athena Diagnostics
200 Forest Street, 2nd floor
Marlborough, MA 01752

ZW221 Miscellaneous Baylor Medical Genetics Laboratories
57103

Reference Values:
Test Performed by: Baylor Medical Genetics Laboratories
2450 Holcombe Blvd.
Houston, TX 77021

SCT2 Miscellaneous Biochemical Genetics Testing
20521

Reference Values:
Per request this test was performed outside of our validated test conditions. These test results should not be used for treatment or clinical diagnostic purposes.

ZW172 Miscellaneous Center for Genetic Testing at St. Francis
91302

Reference Values:
Test Performed by: Center for Genetic Testing
St. Francis Hosp-Genetics Lab
6161 S. Yale Ave.
Tulsa, OK 74136

ZW10 Miscellaneous Chemistry Testing, Varies
8921

Reference Values:
Varies

ZW246 Miscellaneous Childrens Hospital of Colorado Testing
57992

Reference Values:
Test Performed by: Childrens Hospital of Colorado
13123 E 16th Ave
Aurora, CO 80045

ZW57 Miscellaneous Esoterix Coagulation
90496

Reference Values:
Varies

Test Performed by: Esoterix Coagulation
8490 Upland Dr
Suite 100
Englewood, CO 80112

ZW266 Miscellaneous Machaon Diagnostics
58067

Reference Values:
Test Performed by: Machaon Diagnostics, Inc.
3023 Summit St.

Oakland, CA 94609

ZW2 99992 Miscellaneous MML Referral Test 2

Clinical Information: NA

Reference Values:
Varies with test

ZW3 99993 Miscellaneous MML Referral Test 3

Reference Values:
Vary with test requested.

ZW85 90524 Miscellaneous National Jewish Health

Reference Values:
Test Performed by: National Jewish Health
Advanced Diagnostic Laboratories
1400 Jackson Street
Denver, CO 80206-2761

ZW194 91602 Miscellaneous Prevention Genetics Lab

Reference Values:
Test Performed By: Prevention Genetics Lab
Diagnostics Lab
3700 Downwind Drive
Marshfield, WI 54449

ZW91 90530 Miscellaneous RFFIT Testing

Reference Values:
Test Performed by: RFFIT/K-State Rabies Laboratory
Manhattan/K-State Innovation Center
2005 Research Park Circle
Manhattan, KS 66502

MISCF 35267 Miscellaneous Studies Using Chromosome-Specific Probes, FISH

Clinical Information: Conventional cytogenetic studies can identify the presence of chromosome abnormalities and most mosaic conditions. In approximately 2% of these chromosomally abnormal cases, the genetic makeup of the chromosome abnormality can be identified, but not completely characterized, by conventional techniques alone. For malignant disorders, the proportion of specimens with unresolvable

chromosome abnormalities is much higher. Chromosomal microarray analysis (CMA) can detect copy number gain or loss of a chromosomal region but cannot identify the mechanism. Fluorescence in situ hybridization using gene-specific probes and various probe strategies can help characterize chromosome abnormalities. This includes abnormalities that cannot be accurately characterized by chromosome analysis or CMA (such as unusual structural alterations) and unbalanced chromosome abnormalities (such as deletions, duplications, and translocations). Scoring large numbers of interphase nuclei can more accurately establish the frequency of chromosome abnormalities.

Useful For: Resolution of unusual or complex structural alterations, questionable mosaicism, and unbalanced chromosome abnormalities that cannot be resolved by chromosome or chromosomal microarray analysis Identifying gain, loss, or rearrangement of chromosome regions using gene or locus-specific probes

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Remstein ED, Dogan A, Einerson RR, et al: The incidence and anatomic site specificity of chromosomal translocations in primary extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in North America. Am J Surg Pathol. 2006 Dec;30(12):1546-1553 2. Fonseca R, Blood E, Rue M, et al: Clinical and biologic implications of recurrent genomic aberrations in myeloma. Blood. 2003 Jun 1;101(11):4569-4575 3. Van Dyke DL, Shanafelt TD, Call TG, et al: A comprehensive evaluation of the prognostic significance of 13q deletions in patients with B-chronic lymphocytic leukaemia. Br J Haematol. 2010 Feb;148(4):544-550 4. Wiktor A, Van Dyke DL: FISH analysis helps identify low-level mosaicism in Ullrich-Turner syndrome patients. Genet Med. 2004 May-Jun;6(3):132-135 5. Swerdlow SH, Campo E, Harris NL, eds, et al: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC; 2017 6. American College of Medical Genetics and Genomics (ACMG): Technical Standards and Guidelines for Clinical Genetics Laboratories. ACMG; 2008. Updated January 2018. Accessed April 28, 2023. Available at www.acmg.net/PDFLibrary/Standards-Guidelines-Cytogenetics.pdf

ZW210 Miscellaneous Univ of IA Molecular Otolaryngology
91857

Reference Values:
Test Performed By: Univ of IA Molecular Otolaryngology
Research Laboratory
5270 Carver Biomedical Research Building
Iowa City, IA 52242

ZW186 Miscellaneous University of Chicago Genetics Sernices
91515

Reference Values:
Test Performed by: University of Chicago Genetics Services
5841 S. Maryland Ave.
Room 035, M/C 0077
Chicago, IL 60637

ZW187 Miscellaneous University of Iowa Diagnostic Labs
91514

Reference Values:
Test Performed by: UI Diagnostic Laboratories
Department of Pathology
200 Hawkins Drive, Rm 5231 RCP
Iowa City, IA 52242

ZW61 90500 Miscellaneous University of Minnesota Outreach Laboratory

Reference Values:
Test Performed by: Univ of MN Outreach Laboratories
420 Delaware St. S.E.
Minneapolis, MN 55455

ZW191 91599 Miscellaneous University of Texas Health Center at Tyler Microbiology

Reference Values:
Test Performed By: University of Texas Health Center
Department of Microbiology
11937 US Hwy 271
Tyler, TX 75708

ZW280 58092 Miscellaneous University of Washington Medical Center (Molecular Diagnosis Clinical Microbiology Lab)

Reference Values:
Test Performed by: Molecular Diagnosis Clinical Microbiology Lab,
University of Washington Medical Center
1959 NE Pacific Street
Seattle, WA 98195

ZW282 58088 Miscellaneous University of Washington Medical Center (UW Virology Dept of Lab Medicine)

Reference Values:
Test Performed by: UW Virology Dept of Lab Medicine,
1616 Eastlake Ave E
Ste 320 BOX 358115
Seattle, WA 98102

ZW278 58078 Miscellaneous University of Washington Medical Center-Clinical Immunology Lab

Reference Values:
Test Performed by: University of Washington Medical Center-Clinical Immunology Lab

1959 NE Pacific St. Room NW220
Seattle, WA 98195-0001

ZW293
75252

Miscellaneous UPMC Molecular and Genomic Pathology

Reference Values:

Test Performed by: UPMC Molecular and Genomic Pathology
3477 Euler Way
Pittsburgh, PA 15213

IHC
35466

Mismatch Repair (MMR) Protein Immunohistochemistry Only, Tumor

Clinical Information: Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant inherited cancer syndrome that predisposes individuals to the development of colorectal, endometrial, gastric, upper urinary tract, and other cancers. Individuals with HNPCC/Lynch syndrome have a germline mutation in 1 of several genes involved in DNA mismatch repair. The majority of mutations associated with HNPCC/Lynch syndrome occur in MSH2 and MLH1; however, mutations in MSH6 and PMS2 have also been identified. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of HNPCC/Lynch syndrome. Typically, the first step is to evaluate tumors for the characteristics common to individuals with HNPCC/Lynch syndrome, which include microsatellite instability (presence of numerous alterations in a type of repetitive DNA called microsatellites) and loss of protein expression of 1 or more of the genes associated with HNPCC/Lynch syndrome. Microsatellite instability (MSI) and immunohistochemistry (IHC) are commonly interpreted together to evaluate risk for HNPCC/Lynch syndrome. High levels of MSI within a tumor are suggestive of defective DNA mismatch repair, however, this finding does not provide information about which gene is involved. IHC is a complementary testing strategy used to evaluate the expression of the MLH1, MSH2, MSH6, and PMS2 proteins in HNPCC/Lynch syndrome-related cancers. Loss of expression of 1 or more of these proteins within the tumor is helpful in identifying which corresponding genes to target for mutation analysis. Although MSI and IHC are best interpreted together, they are also available separately to accommodate clinical situations in which there are barriers to performing these tests concurrently (eg, financial concerns, specimen requirements). IHC alone can determine retention or loss of MLH1, MSH2, MSH6, and PMS2 protein expression. If all 4 proteins are present, the likelihood of HNPCC/Lynch syndrome is reduced, but not eliminated, because approximately 5% of tumors that display MSI also have normal protein expression for these 4 genes. Loss of 1 or more proteins by IHC is suggestive of defective DNA mismatch repair within the tumor and the likelihood of HNPCC/Lynch syndrome is increased. Germline testing (ie, mutation analysis) for the corresponding genes can then be performed to identify the causative germline mutation and allow for predictive testing of at-risk individuals. Of note, loss of protein expression by IHC has also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC/Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1 and PMS2 are observed, the BRMLH / MLH1 Hypermethylation and BRAF Mutation Analysis, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor test may also help to distinguish between a sporadic and germline etiology. It should be noted that this is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome and identifies patients who might benefit from subsequent genetic testing. For more information see Lynch Syndrome Testing Algorithm

Useful For: Evaluating tumor tissue to identify patients at risk for having hereditary nonpolyposis colon cancer/Lynch syndrome

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Baudhuin LM, Burgart LJ, Lentovich O, Thibodeau SN. Use of microsatellite instability and immunohistochemistry testing for the identification of individuals at risk for Lynch Syndrome. Fam Cancer. 2005;4(3):255-265. doi: 10.1007/s10689-004-1447-6 2. Shia J, Klimstra DS, Nafa K, et al. Value of immunohistochemical detection of DNA mismatch repair proteins in predicting germline mutation in hereditary colorectal neoplasms. Am J Surg Pathol. 2005;29(1):96-104 3. Idos G, Valle L. Lynch syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews (Internet). University of Washington, Seattle; 2004. Updated February 2, 2021. Accessed December 5, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1211/

MITF
70509

MiTF Immunostain, Technical Component Only

Clinical Information: Microphthalmia-associated transcription factor is produced by melanocytes and osteoclasts and can be useful in the classification of melanoma.

Useful For: Identification of melanomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Nybakken GE, Sargen M, Abraham R, Zhang PJ, Ming M, Xu. MITF accurately highlights epidermal melanocytes in atypical intraepidermal melanocytic proliferations. Am J Dermatopathol. 2013;35(1):25-29 2. Fox MD, Billings SD, Gleason BC, et al. Expression of MiTF may be helpful in differentiating cellular neurothekeoma from plexiform fibrohistiocytic tumor (histiocytoid predominant) in a partial biopsy specimen. Am J Dermatopathol. 2012;34(2):157-160 3. Wang Y, Radfar S, Liu S, Riker AI, Khong HT. Mitf-Mdel, a novel melanocyte/melanoma-specific isoform of microphthalmia-associated transcription factor-M, as a candidate biomarker for melanoma. BMC Med. 2010;8:14 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

AMA
8176

Mitochondrial Antibodies (M2), Serum

Clinical Information: Primary biliary cholangitis (PBC) is a chronic and progressive autoimmune liver disease characterized by the destruction of the small intrahepatic bile ducts and a variable clinical course, which may include fatigue and pruritus. Untreated patients with PBC have a high risk of liver cirrhosis and related complications, liver failure and death.(1,2) The serological hallmark of PBC is the presence of antimitochondrial antibody (AMA) characterized by cytoplasmic reticular/AMA (anti-cell 21 [AC-21] based on the International Consensus on Antinuclear Antibody Patterns [ICAP] nomenclature) staining pattern on HEp-2 substrate by indirect immunofluorescence assay (IFA).(3) In addition,

autoantibodies associated with the HEp-2 IFA nuclear patterns have been reported in a subset of patients with PBC who are seronegative for AMA or may be positive for AMA but have uncertain clinical or phenotypic attributes.(1,2,4,5) The HEp-2 IFA nuclear patterns in PBC include multiple nuclear dots (MND or AC-6) and punctate nuclear envelope (AC-12), which are associated with anti-Sp100 and anti-gp210 antibodies, respectively. (3) The diagnosis of PBC can be established if 2 out of the 3 following criteria are met: sustained elevated levels of alkaline phosphatase (ALP), evidence AMA or specific antinuclear antibody (ANA) (anti-Sp100 and anti-gp210 antibodies), and diagnostic liver histology.(2) Based on these criteria, a biopsy can be avoided in case of high ALP levels and detection of these PBC-specific autoantibodies.(1,2) Therefore, reliable and accurate serologic determination of PBC-specific autoantibodies play a critical role in disease evaluation. Positivity of AMA ranges from 90% to 95% in patients with PBC, while the PBC-specific ANA (anti-Sp100 and anti-gp210 antibodies) may occur in approximately 30% of all patients with PBC, and up to 50% of patients who are AMA-negative.(6) The M2-type AMA (AMA-M2) is the dominant target of the 9 subunits of the mitochondrial antigenic complex.(1,2) AMA-M2 target components of the 2-oxo-acid dehydrogenase complex: pyruvate dehydrogenase complex (PDC), 2-oxoglutarate dehydrogenase complex (OGDC) and branched-chain 2-oxoacid dehydrogenase complex (BCOADC). Specifically, autoantibodies mainly recognize the E2 subunits of these complexes: PDC-E2 (80%-90% of cases), BCOADC-E2 (50%-80% of cases) and OGDC-E2 (20%-60% of cases), and to a lesser extent, the E1 and E3 subunits.(2). Although the sensitivities of the anti-Sp100 and anti-gp210 antibodies are low, their specificities for PBC are excellent; therefore, both tests have been reported to be useful in confirming a diagnosis of PBC or predicting development of disease in nonestablished PBC cases with positive AMA.(4,5) In addition to the diagnostic relevance of anti-gp210 IgG antibody, a few studies have suggested a role for their use in the risk stratification and prognosis in PBC; however, the significance of these remain contentious. In one study, the presence of anti-gp210 antibodies was reported to pose a significant risk for hepatic failure type progression, more severe interface hepatitis, and lobular inflammation, compared to those with centromere antibodies who had relatively higher ductular reaction.(7) In addition to MND and punctate nuclear envelope, the anticentromere (AC-3) and the speckled (AC-4 and AC-5) patterns can be found in variable prevalence in patients with PBC with overlapping connective tissue diseases (systemic sclerosis [SSc] and Sjogren syndrome).(8) In the context of other liver diseases, the cytoplasmic fibrillar linear (AC-15) HEp-2 IFA pattern associated with autoimmune hepatitis (AIH) may also be seen when PBC overlaps in patients with AIH or other liver diseases, such as hepatitis B virus infection, hepatitis C virus infection, and hepatic carcinoma.(9) In general, a mixed pattern composed of at least two HEp-2 IFA patterns is mostly found in patients with PBC rather than in other liver diseases.(9) Traditionally, the IFA method was used for the detection of AMA; however, antigen-specific solid-phase immunoassays (SPA), such as enzyme-linked immunosorbent assay (ELISA), line blot immunoassay (LIA), and dot immunoassay (DIA) have been developed and are increasingly being used in the laboratory evaluation of PBC.(4,5,7-10) The AMA SPA use a variety of M2 antigens, including fusion protein combining the three E2 subunits, a mixture of recombinant E2 subunits, or the three E2 recombinant subunits isolated, among others.(4,5,7,10) The anti-Sp100 and anti-gp210 antibodies can also be determined using analyte-specific ELISA, LIA and DIA. In addition to the SPA for detecting antibodies to AMA, Sp100, and gp210, the use HEp-2 substrate by IFA provides a simple and strategic approach for confirming the presence of AMA cytoplasmic staining if positive by enzyme immunoassay (EIA) with the possibility of identifying patients who may be AMA-negative but positive to nuclear antibodies. In PBC patients, the nuclear envelope pattern is associated with anti-gp210 antibody while the multiple nuclear dot pattern is specific for anti-Sp100 antibodies. However, expression of the MND and the nuclear envelope patterns may not be easily identified in the presence of other antibodies. Testing for these antibodies is indicated in patients who are AMA positive by EIA as well as patients at-risk for PBC but are AMA negative. In addition to providing additional support for PBC diagnosis in AMA-positive and AMA-negative patients, the use of HEp-2 substrate offers the possibility to identify patients at-risk for PBC who may present with coexisting systemic autoimmune rheumatic diseases (systemic lupus erythematosus, systemic sclerosis, and Sjogren syndrome) or autoimmune liver disease (autoimmune hepatitis) through additional pattern recognition. The use of SPA for ANA testing do not provide these additional diagnostic insights.

Useful For: Establishing the diagnosis of primary biliary cholangitis This test is not useful for indicating the stage or prognosis of the disease or for monitoring the course of the disease.

Interpretation: A positive result for antimitochondrial antibodies of M2 specificity in the setting of chronic cholestasis after exclusion of other causes of liver disease is highly suggestive of primary biliary cholangitis.

Reference Values:
Negative: <0.1 Units
Borderline: 0.1-0.3 Units
Weakly positive: 0.4-0.9 Units
Positive: > or =1.0 Units
Reference values apply to all ages.

Clinical References: 1. Younossi ZM, Bernstein D, Shiffman ML, et al. Diagnosis and management of primary biliary cholangitis. Am J Gastroenterol. 2019;114(1):48-63 2. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance update from the American Association for the Study of Liver Diseases. Hepatology. 2019;69(1):394-419 3. International Consensus on ANA Patterns. AC-20 Cytoplasmic fine speckled. ICAP; 2015. Accessed November 16, 2023. Available at www.anapatterns.org/view_pattern.php?pattern=20 4. Zhang Q, Liu Z, Wu S, et al. Meta-analysis of antinuclear antibodies in the diagnosis of antimitochondrial antibody-negative primary biliary cholangitis. Gastroenterol Res Pract. 2019;2019:8959103 5. Dahlqvist G, Gaouar F, Carrat F, et al. Large-scale characterization study of patients with antimitochondrial antibodies but nonestablished primary biliary cholangitis. Hepatology. 2017;65(1):152-163 6.Trivella J, John BV, Levy C. Primary biliary cholangitis: Epidemiology, prognosis, and treatment. Hepatol Commun. 2023;7(6):e0179 7. Nakamura M, Kondo H, Mori T, et al. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. Hepatology. 2007;45(1):118-127 8. Favoino E, Grapsi E, Barbuti G, et al. Systemic sclerosis and primary biliary cholangitis share an antibody population with identical specificity. Clin Exp Immunol. 2023;212(1):32-38 9. Wei Q, Jiang Y, Xie J, et al. Investigation and analysis of HEp 2 indirect immunofluorescence titers and patterns in various liver diseases [published correction appears in Clin Rheumatol. 2021 Apr;40(4):1667]. Clin Rheumatol. 2020;39(8):2425-2432 10. Munoz-Sanchez G, Perez-Isidro A, Ortiz de Landazuri I, et al. Working algorithms and detection methods of autoantibodies in autoimmune liver disease: A nationwide study. Diagnostics (Basel). 2022;12(3):697

DMITO
618558

Mitochondrial DNA Deletion Heteroplasmy, ddPCR, Varies

Clinical Information: Large deletions in the mitochondrial genome (mtDNA deletions) cause up to 10% of primary mitochondrial disease.(1) mtDNA deletions typically present with 1 of 3 syndromes, but a large amount of clinical overlap exists. The 3 syndromes include Kearns-Sayre syndrome, Pearson syndrome, and progressive external ophthalmoplegia (PEO). Occasionally large mtDNA deletions may cause Leigh syndrome. The phenotypes for these conditions vary. Kearns-Sayre syndrome typically has an age of onset of less than 20 years and is characterized by pigmentary retinopathy or PEO, cardiac conduction defects, ataxia, and an increased spinal fluid (CSF) protein level. A common, recurrent deletion spanning m.8470_13446 causes Kearns-Sayre syndrome; however, there are additional deletions that contribute to the syndrome. These deletions are detected in muscle. Pearson syndrome's clinical features include sideroblastic anemia, exocrine pancreas dysfunction with symptoms in the first year of life. mtDNA deletions that cause Pearson syndrome are abundant in blood. Chronic PEO can be the mildest of the mtDNA deletion phenotypes. This presentation is characterized by progressive ptosis, ophthalmoplegia, oropharyngeal, and proximal muscle weakness. mtDNA deletions that cause PEO are primarily detectable in muscle. Occasionally, mtDNA deletions cause Leigh syndrome, which is characterized by psychomotor regression, abnormal brain MRI, and elevated blood and CSF lactate levels. However, other mtDNA variants may also cause Leigh syndrome. If caused by a large deletion, it is

usually detectable in muscle or blood. Large deletions can be present in only a fraction of mitochondria; a phenomenon known as heteroplasmy. Typically, the severity of disease presentation is a function of the degree of heteroplasmy. Determining the heteroplasmy of large mtDNA deletions is challenging by common clinical methods, such as next-generation sequencing. However, this droplet digital polymerase chain reaction method can obtain an accurate range of heteroplasmy levels in a variety of tissues.

Useful For: Assessing the heteroplasmy level of previously detected large mitochondrial DNA (mtDNA) deletions. Screening family members for previously detected large mtDNA deletions. This test is not recommended for first tier diagnostic testing for mitochondrial disorders. This test does not assess mtDNA depletion.

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Lamont PJ, Surtees R, Woodward CE, Leonard JV, Wood NW, Harding AE. Clinical and laboratory findings in referrals for mitochondrial DNA analysis. Arch Dis Child. 1998;79(1):22-27. doi:10.1136/adc.79.1.22 2. Goldstein A, Falk MJ. Mitochondrial DNA deletion syndromes. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated May 11, 2023. Accessed June 30, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1203/ 3. Legati A, Zanetti N, Nasca A, et al. Current and new next-generation sequencing approaches to study mitochondrial DNA. J Mol Diagn. 2021;23(6), 732-741 4. McCormick EM, Lott MT, Dulik MC, et al. Specifications of the ACMG/AMP standards and guidelines for mitochondrial DNA variant interpretation. Hum Mutat. 2020;41(12):2028-2057

MITOP 62510 Mitochondrial Full Genome Analysis, Next-Generation Sequencing (NGS), Varies

Clinical Information: The mitochondrion occupies a unique position in eukaryotic biology. First, it is the site of energy metabolism, without which aerobic metabolism and life as we know it would not be possible. Second, it is the sole subcellular organelle that is composed of proteins derived from 2 genomes, mitochondrial and nuclear. A group of hereditary disorders due to variants in either the mitochondrial genome or nuclear mitochondrial genes have been well characterized. The diagnosis of mitochondrial disease can be particularly challenging as the presentation can occur at any age, involve virtually any organ system, and have widely varying severity. This test utilizes massively parallel sequencing, also termed next-generation sequencing (NGS), to determine the exact sequence of the entire 16,569 base-pair mitochondrial genome. The utility of this test is to assist in the diagnosis of the subset of mitochondrial diseases that result from variants in the mitochondrial genome. This includes certain types of myopathies and neuro-ophthalmologic diseases, such as MELAS (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes), MERRF (myoclonic epilepsy with ragged red fibers), mitochondrial myopathy, neurogenic muscle weakness, ataxia, retinitis pigmentosa, Leigh syndrome, Leber hereditary optic neuropathy, and chronic progressive external ophthalmoplegia . In addition to the detection of single base changes with these disorders, large deletions, such as those associated with Kearns-Sayre or Pearson syndromes, are also detected. Variants in mitochondrial proteins that are encoded by genes in the nucleus, such as the enzymes of fatty acid oxidation, are not detected using this test. In contrast to variants in nuclear genes, which are present in either 0, 1, or 2 copies, mitochondrial variants can be present in any fraction of the total organelles, a phenomenon known as heteroplasmy. Typically, the severity of disease presentation is a function of the degree of heteroplasmy. Individuals with a higher fraction of altered mitochondria present with more severe

disease than those with lower percentages of altered alleles. The sensitivity for the detection of altered alleles in a background of wild-type (or normal) mitochondrial sequences by NGS is approximately 10%.

Useful For: Diagnosis of the subset of mitochondrial diseases that results from variants in the mitochondrial genome A second-tier test for patients in whom previous targeted gene variant analyses for specific mitochondrial disease-related genes were negative Identifying variants within genes of the mitochondrial genome that are known to be associated with mitochondrial disease, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics guidelines for mitochondrial DNA variant interpretation.(1) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. The degree of heteroplasmy of each single nucleotide or delin (deletion/insertion) variant, defined as the ratio (percentage) of variant sequence reads to the total number of reads, will also be reported. Variants detected at or above 95% will be reported as homoplasmic. Heteroplasmy for large deletions will be reported and is determined by droplet digital polymerase chain reaction. Variants classified as benign or likely benign are not reported.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. McCormick EM, Lott MT, Dulik MC, et al. Specifications of the ACMG/AMP standards and guidelines for mitochondrial DNA variant interpretation. Hum Mutat. 2020;41(12):2028-2057 2. Munnich A, Rotig A, Cormier-Daire V, Rustin P. Clinical presentation of respiratory chain deficiency. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill; 2019. Accessed December 2, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225086827 3. Wallace DC, Lott MT, Brown MD, Kerstann K. Mitochondria and neuro-ophthalmologic diseases. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill; 2019. Accessed December 2, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225088522 4. Wong LJ. Molecular genetics of mitochondrial disorders. Dev Disabil Res Rev. 2010;16(2):154-162. doi:10.1002/ddrr.104

MMPP
616610

Mitochondrial Metabolites, Plasma

Clinical Information: Mitochondrial metabolites occur as physiologic intermediates in a variety of metabolic pathways. Mitochondrial diseases, organic acidurias, and ketone disorders are groups of disorders in which one or more of these pathways are blocked, resulting in a deficiency of normal products and an abnormal accumulation of intermediate metabolites in the body. In some conditions, these excess metabolites are observed in abnormal plasma concentrations. Mitochondrial disorders vary widely in both clinical presentation and age of onset. Patients commonly present with neurologic and myopathic features. In addition, patients may experience involvement of multiple organ systems with features such as myopathy, ophthalmoplegia, ptosis, cardiomyopathy, sensorineural hearing loss, optic atrophy, pigmentary retinopathy, diabetes mellitus, encephalomyopathy, seizures, and stroke-like episodes. Organic acidurias typically present with either an acute life-threatening illness in early infancy or unexplained developmental delay with intercurrent episodes of metabolic decompensations in later childhood. Organic acidurias should be considered when patients present with severe and persistent metabolic acidosis of unexplained origin, elevated anion gap, and severe neurologic manifestations, such as seizures. Other findings, especially during acute episodes of metabolic decompensations, may include elevated ketones in urine or plasma, hyperammonemia, hypoglycemia, and lactic acidemia. Ketone

disorders include disorders of impaired ketone body metabolism and disorders of ketogenesis. Ketones are converted as an energy source when either carbohydrate reserves are depleted or excessive fatty acids are present. Clinical symptoms of ketone body metabolism disorders include episodes of ketoacidosis, vomiting, dehydration, and lethargy with increased risk of symptoms during periods of illness or fasting. Patients with disorders of ketogenesis experience hypoketotic hypoglycemic episodes that may result in long-term sequelae including seizure disorders, intellectual disability, and white matter changes in the brain. Treatment for ketone disorders involves avoidance of fasting and management of acute symptoms. A diagnostic workup for mitochondrial disorders, organic acidurias, and ketone body disorders includes analysis of urine organic acids (OAU / Organic Acids Screen, Random, Urine), plasma amino acids (AAQP / Amino Acids, Quantitative, Plasma) and plasma acylcarnitines (ACRN / Acylcarnitines, Quantitative, Plasma) as recommended first-tier tests for assessment. While the mitochondrial metabolites panel complements this work up and provides additional context, this test should not be used in isolation for diagnostic purposes.

Useful For: Monitoring patients with mitochondrial disorders, organic acidurias, and ketone body disorders

Interpretation: An interpretive report based on pattern recognition is provided. The individual quantitative results support the interpretation of the mitochondrial metabolite profile but are not diagnostic by themselves. The elevation of 3-hydroxyisovaleric acid can be explained by several differential diagnoses that cannot always be distinguished by the mitochondrial metabolite profile. Differential diagnoses will be noted in the interpretative comment. For patients without a prior known diagnosis, abnormal results are typically not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on a mitochondrial metabolite profile, independent biochemical or molecular genetic analyses are required.

Reference Values:

LACTIC ACID
< or = 4000.0 nmol/mL

2-HYDROXYBUTYRIC ACID
< or = 124.0 nmol/mL

3-HYDROXYBUTYRIC ACID
< or = 700.0 nmol/mL

PYRUVIC ACID
< or = 350.0 nmol/mL

cis-ACONITIC ACID
< or = 9.0 nmol/mL

CITRIC ACID
< or = 250.0 nmol/mL

3-HYDROXYPROPIONIC ACID
< or = 12.4 nmol/mL

3-HYDROXY-2-METHYLBUTYRIC ACID
< or = 2.5 nmol/mL

3-HYDROXYISOVALERIC ACID
< or = 15.4 nmol/mL

SUCCINIC ACID
< or = 10.0 nmol/mL

FUMARIC ACID
< or = 5.0 nmol/mL

3-METHYLGLUTACONIC ACID
< or = 1.6 nmol/mL

MALIC ACID
< or = 20.0 nmol/mL

2-KETOBUTYRIC ACID
< or = 16.0 nmol/mL

2-KETOISOVALERIC ACID
< or = 35.0 nmol/mL

ACETOACETIC ACID
< or = 350.0 nmol/mL

3-METHYL-2-KETOVALERIC ACID
< or = 70.0 nmol/mL

2-KETOISOCAPROIC ACID
< or = 70.0 nmol/mL

2-METHYLCITRIC ACID
< or = 1.0 nmol/mL

2-KETOGLUTARIC ACID
< or = 40.0 nmol/mL

Clinical References: 1. Munnich A, Rotig A, Cormier-Daire V, Rustin P. Clinical presentation of respiratory chain deficiency. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed July 5, 2024. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225086827 2. Robinson BH. Lactic acidemia: Disorders of pyruvate carboxylase and pyruvate dehydrogenase. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed July 5, 2024. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225087140 3. Shoffner JM. Oxidative phosphorylation diseases. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019 Accessed July 5, 2024. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225088339 4. Mitchell GA, Fukao T. Inborn errors of ketone body metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease McGraw-Hill Education; 2019. Accessed July 5, 2024. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225087757

FETCE 91844 Mitochondrial Respiratory Chain Enzyme Analysis (ETC) - Skin Fibroblasts

Reference Values:
A final report will be attached in Mayo Access.

Clinical References:

MITAN
621811

Mitotane, Plasma

Clinical Information: This test is intended for the use of therapeutic monitoring of the drug mitotane in patients being treated for adrenal carcinoma. Guidelines suggest monitoring mitotane serum/plasma levels every 2 to 3 weeks for the first 3 months. After reaching a plateau, the interval can be extended (eg, every 6 weeks). Mitotane is a key drug for the treatment of adrenal cortical carcinoma. Due to its narrow therapeutic window (14 to 20 mcg/mL), monitoring its concentration is crucially important.

Useful For: Assessing compliance or making dosage adjustments for mitotane

Interpretation: In the literature when mitotane is used to treat adrenocortical carcinoma, the maximum benefit is seen when plasma mitotane concentrations are between 14-20 mcg/mL.

Reference Values:
Therapeutic: 14-20 mcg/mL

Clinical References: 1. Feliu C, Cazaubon Y, Guillemin H, et al. Therapeutic drug monitoring of mitotane: Analytical assay and patient follow-up. Biomed Chromatogr. 2017;31(11):10.1002/bmc.3993. doi:10.1002/bmc.3993 2. Ando M, Hirabatake M, Yasui H, Fukushima S, Sugioka N, Hashida T. A simplified method for therapeutic drug monitoring of mitotane by gas chromatography-electron ionization-mass spectrometry. Biomed Chromatogr. 2020;34(3):e4776. doi:10.1002/bmc.4776

FMITU
75773

Mitragynine (Qualitative), Urine

Clinical Information: Mitragynine is an alkaloid found in the plant Kratom which originates from Asia. The leaves of plant are consumed for their stimulant and analgesic effects and these effects are attributed to mitragynine. Plant extracts are sold for their medicinal use and may be subject to abuse. Some Kratom materials have also been reported to contain O-desmethyltramadol presumably from exogenous sources.

Reference Values:
Reporting limit determined each analysis.

None Detected ng/mL

FCDX2
75842

Mitragynine Confirmation (Qualitative), Umbilical Cord Tissue

Reference Values:
Reporting limit determined each analysis.
Units: ng/g

Only orderable as a reflex test.

BMLHH
35894

MLH1 Hypermethylation Analysis (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MLHPB
35500

MLH1 Hypermethylation Analysis, Blood

Clinical Information: The lifetime risk of colorectal cancer in the general population is 4% to 6%.(1) Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer) is an autosomal dominant hereditary cancer syndrome accounting for 2% to 4% of all colorectal cancer cases.(2,3) Lynch syndrome is associated with germline variants in the mismatch repair (MMR) genes, MLH1, MSH2, MSH6, and PMS2, or deletions of the EPCAM gene. It is predominantly characterized by significantly increased risks for colorectal and endometrial cancer.(2,3) The lifetime risk for cancer is highly variable and dependent on the gene involved. Other malignancies within the tumor spectrum include gastric, ovarian, and small bowel cancers and hepatobiliary and upper urinary tract carcinomas.(2,3) Several laboratory-based strategies may be utilized to screen for Lynch syndrome, including testing tumor tissue for the presence of microsatellite instability (MSI-H) and assessment of protein expression of MMR proteins (MLH1, MSH2, MSH6, PMS2) by immunohistochemistry (IHC). Defective MMR in sporadic colon cancer is most often due to molecular variation in MLH1, of which promoter hypermethylation (epigenetic silencing) constitutes the most common cause of MLH1 inactivation. A somatic-occurring variant in the BRAF gene (V600E) is present in approximately 70% of tumors with hypermethylation of the MLH1 promoter. Importantly, the V600E variant is rarely identified in cases with disease-causing germline MLH1 variants. While most MLH1 promoter hypermethylation occurs sporadically, some individuals with tumor hypermethylation may have germline inactivation of the MLH1 gene via constitutional promoter hypermethylation. This condition is known as constitutional MLH1 promoter hypermethylation, which is consistent with a diagnosis of Lynch syndrome.(4-7) In contrast to sequence variants in MLH1, current evidence suggests that the risk of transmitting constitutional MLH1 promoter hypermethylation is less than50%. As such, these individuals may not have a strong family history of Lynch-related cancers and often test negative on traditional germline sequencing panels. Thus, testing for constitutional MLH1 promoter hypermethylation may be considered if there is still suspicion for an inherited etiology following negative germline testing for patients with MLH1 promoter methylated tumors. For more information see Lynch Syndrome Testing Algorithm

Useful For: As an adjunct to positive hypermethylation in tumor to distinguish between somatic and germline hypermethylation As an adjunct to negative MLH1 germline testing in cases where colon or endometrial tumor demonstrates microsatellite instability-H (MSI-H) and loss of MLH1 protein expression

Interpretation: The report will include specimen information, assay information, and interpretation of test results. Absence of hypermethylation is reported as not providing evidence for germline (constitutional) MLH1 promoter hypermethylation. Presence of hypermethylation is reported as consistent with germline (constitutional) inactivation of MLH1 by promoter hypermethylation.

Reference Values:
Interpretive report will be provided.

Clinical References: 1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review. 1975-2018. National Cancer Institute. Updated April 2021. Accessed March 24, 2025. Available at: https://seer.cancer.gov/csr/1975_2018 2. Gupta S, Provenzale D, Llor X, et al. NCCN Guidelines Insights: Genetic/familial high-risk assessment: colorectal, version 2.2019. J Natl Compr Canc Netw. 2019;17(9):1032-1041 3. Idos G, Valle L. Lynch syndrome. In: Adam MP, Everman DB, Mirzaa GM, et

al, eds. GeneReviews (Internet). University of Washington, Seattle; 2004. Updated February 4, 2021. Accessed March 24, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1211/ 4. Hitchins MP, Ward RL. Constitutional (germline) MLH1 epimutation as an aetiological mechanism for hereditary non-polyposis colorectal cancer. J Med Genet. 2009;46(12):793-802 5. Hitchins M, Williams R, Cheong K, et al. MLH1 germline epimutations as a factor in hereditary nonpolyposis colorectal cancer. Gastroenterology. 2005;129(5):1392-1399 6. Niessen RC, Hofstra RM, Westers H, et al. Germline hypermethylation of MLH1 and EPCAM deletions are a frequent cause of Lynch syndrome. Genes Chromosomes Cancer. 2009;48(8):737-744 7. Valle L, Carbonell P, Fernandez V, et al. MLH1 germline epimutations in selected patients with early-onset non-polyposis colorectal cancer. Clin Genet. 2007;71(3):232-237

ML1HM
35494

MLH1 Hypermethylation Analysis, Tumor

Clinical Information: Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is an inherited cancer syndrome caused by a germline mutation in one of several genes involved in DNA mismatch repair (MMR), including MLH1, MSH2, MSH6, and PMS2. There are several laboratory-based strategies that help establish the diagnosis of HNPCC/Lynch syndrome, including testing tumor tissue for the presence of microsatellite instability (MSI-H) and loss of protein expression for any one of the MMR proteins by immunohistochemistry (IHC). However, it is important to note that the MSI-H tumor phenotype is not restricted to inherited cancer cases; approximately 20% of sporadic colon cancers are MSI-H. Thus, MSI-H does not distinguish between a somatic (sporadic) and a germline (inherited) mutation, nor does it identify which gene is involved. Although IHC analysis is helpful in identifying the responsible gene, it also does not distinguish between somatic and germline defects. Defective MMR in sporadic colon cancer is most often due to an abnormality in MLH1, and the most common cause of gene inactivation is promoter hypermethylation (epigenetic silencing). A specific mutation in BRAF (V600E) has been shown to be present in approximately 70% of tumors with hypermethylation of the MLH1 promoter. Importantly, the V600E mutation is rarely identified in cases with germline MLH1 mutations. Thus, direct assessment of MLH1 promoter methylation status and testing for the BRAF V600E mutation can be used to help distinguish between a germline mutation and epigenetic/somatic inactivation of MLH1. Tumors that have the BRAF V600E mutation and demonstrate MLH1 promoter hypermethylation are almost certainly sporadic, whereas tumors that show neither are most often caused by an inherited mutation. Although testing for the BRAF V600E mutation and MLH1 promoter hypermethylation are best interpreted together, they are also available separately to accommodate various clinical situations and tumor types. These tests can provide helpful diagnostic information when evaluating an individual suspected of having HNPCC/Lynch syndrome, especially when testing is performed in conjunction with TMSI / Microsatellite Instability, Tumor and IHC / Mismatch Repair (MMR) Protein Immunohistochemistry Only, Tumor studies. It should be noted that these tests are not genetic tests but rather stratify the risk of having an inherited cancer predisposition and identify patients who may benefit from subsequent genetic testing.

Useful For: An adjunct to TMSI / Microsatellite Instability, Tumor and IHC / Mismatch Repair (MMR) Protein Immunohistochemistry Only, Tumor when colon or endometrial tumor demonstrates microsatellite instability (MSI-H) and loss of MLH1 protein expression, to help distinguish a somatic versus germline event prior to performing expensive germline testing An adjunct to negative MLH1 germline testing in cases where colon or endometrial tumor demonstrates MSI-H and loss of MLH1 protein expression

Interpretation: An interpretive report will be provided. The likelihood of a germline (inherited) mutation is very low in those cases where the tumor demonstrates MLH1 promoter hypermethylation and the normal tissue is unmethylated. The likelihood of a germline mutation is high in those cases where the tumor and normal tissue lack MLH1 promoter hypermethylation. In cases where the tumor and normal tissue demonstrate MLH1 promoter hypermethylation, this result will be interpreted as equivocal, and a blood sample will be requested to confirm potential germline hypermethylation.

Reference Values:
An interpretative report will be provided.

Clinical References: 1. Cunningham JM, Kim CY, Christensen ER, et al: The frequency of hereditary defective mismatch repair in a prospective series of unselected colorectal carcinomas. Am J Hum Genet. 2001 Oct;69(4):780-790 2. Wang L, Cunningham JM, Winters JL, et al: BRAF mutations in colon cancer are not likely attributable to defective DNA mismatch repair. Cancer Res. 2003 Sep;63(17):5209-5212 3. Domingo E, Laiho P, Ollikainen M, et al: BRAF screening as a low-cost effective strategy for simplifying HNPCC genetic testing. J Med Genet. 2004 Sep;41(9):664-668 4. Bettstetter M, Dechant S, Ruemmele P, et al: Distinction of hereditary nonpolyposis colorectal cancer and sporadic microsatellite-unstable colorectal cancer through quantification of MLH1 methylation by real-time PCR. Clin Cancer Res. 2007 Jun;13(11):3221-3228 5. Idos G, Valle L: Lynch syndrome. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews Internet). University of Washington, Seattle; 2004. Updated February 2, 2021. Accessed June 27, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1211/

BRMLH
35491

MLH1 Hypermethylation and BRAF Mutation Analysis, Tumor

Clinical Information: Lynch syndrome is an inherited cancer syndrome caused by a germline pathogenic variant in one of several genes involved in DNA mismatch repair (MMR), including MLH1, MSH2, MSH6, and PMS2. There are several laboratory-based strategies that help establish the diagnosis of Lynch syndrome, including testing tumor tissue for the presence of microsatellite instability (MSI-H) and loss of protein expression for any one of the MMR proteins by immunohistochemistry (IHC). It is important to note, however, that the MSI-H tumor phenotype is not restricted to inherited cancer cases; approximately 20% of sporadic colon cancers are MSI-H. Thus, MSI-H does not distinguish between a somatic (sporadic) and a germline (inherited) etiology, nor does it identify which gene is involved. Although IHC analysis is helpful in identifying the responsible gene, it also does not distinguish between somatic and germline defects. Defective MMR in sporadic colon cancer is most often due to an abnormality in MLH1, and the most common cause of gene inactivation is promoter hypermethylation (epigenetic silencing). A specific alteration in the BRAF gene (V600E) has been shown to be present in approximately 70% of tumors with hypermethylation of the MLH1 promoter. Importantly, the V600E alteration is rarely identified in cases with germline MLH1 pathogenic variants. Thus, direct assessment of MLH1 promoter methylation status and testing for the BRAF V600E alteration can be used to help distinguish between germline etiologyand epigenetic/somatic inactivation of MLH1. Tumors that have the BRAF V600E alteration and demonstrate MLH1 promoter hypermethylation are almost certainly sporadic, whereas tumors that show neither are most often caused by an inherited (germline) pathogenic variant. Although testing for the BRAF V600E alteration and MLH1 promoter hypermethylation are best interpreted together, they are also available separately to accommodate various clinical situations and tumor types. These tests can provide helpful diagnostic information when evaluating an individual suspected of having Lynch syndrome, especially when testing is performed in conjunction with MSI / Microsatellite Instability (MSI), Tumor and IHC / Mismatch Repair (MMR) Protein Immunohistochemistry Only, Tumor. It should be noted that these tests are not genetic tests, but rather stratify the risk of having an inherited cancer predisposition and identify patients who might benefit from subsequent genetic testing. See Lynch Syndrome Testing Algorithm

Useful For: An adjunct to MSI / Microsatellite Instability (MSI), Tumor and IHC / Mismatch Repair (MMR) Protein Immunohistochemistry Only, Tumor testing, when colon tumor demonstrates microsatellite instability (MSI-H) and loss of MLH1 protein expression, to help distinguish a somatic versus germline event prior to performing expensive germline testing An adjunct to negative MLH1 germline testing in cases where colon tumor from the same patient demonstrates MSI-H and loss of MLH1 protein expression

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Cunningham JM, Kim CY, Christensen ER, et al: The frequency of hereditary defective mismatch repair in a prospective series of unselected colorectal carcinomas. Am J Hum Genet. 2001;69:780-790 2. Wang L, Cunningham JM, Winters JL, et al: BRAF mutations in colon cancer are not likely attributable to defective DNA mismatch repair. Cancer Res. 2003;63:5209-5212 3. Domingo E, Laiho P, Ollikainen M, et al: BRAF screening as a low-cost effective strategy for simplifying HNPCC genetic testing. J Med Genet. 2004;41:664-668 4. Bettstetter M, Dechant S, Ruemmele P, et al: Distinction of hereditary nonpolyposis colorectal cancer and sporadic microsatellite-unstable colorectal cancer through quantification of MLH1 methylation by real-time PCR. Clin Cancer Res. 2007;13:3221-3228 5. Gupta S, Provenzale D, Llor X, et al: NCCN Guidelines Insights: Genetic/familial high-risk assessment: colorectal, version 2.2019. J Natl Compr Canc Netw. 2019;17(9):1032-1041

MLH1
70510

MLH1 Immunostain, Technical Component Only

Clinical Information: Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline variants in the mismatch repair genes: MLH1, MSH2, MSH6, and PMS2. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 variants (approximately 50%-80%) is generally higher than the risks associated with variants in the other Lynch syndrome-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include sebaceous neoplasms, gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, variants within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous or compound heterozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. Testing tumors from individuals at risk for Lynch syndrome for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair phenotype within the tumor but does not suggest in which gene the abnormality rests. Tumors from individuals affected by Lynch syndrome usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined). The MSI-H phenotype can also be seen in individuals whose tumors have somatic MLH1 promoter hypermethylation. Tumors from individuals that show the MSS/MSI-L phenotype (MSI at <30% of microsatellites examined), are not likely to have Lynch syndrome or somatic hypermethylation of MLH1. Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of Lynch syndrome-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation

analysis of the associated gene can be performed to identify the causative germline variant and allow for predictive testing of at-risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic mutations and germline variants. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that this Lynch syndrome screen is not a genetic test but rather stratifies the risk of having an inherited cancer predisposition syndrome and identifies patients who might benefit from subsequent genetic testing.

Useful For: Evaluation of tumor tissue to identify patients at high risk for having hereditary nonpolyposis colorectal cancer, also known as Lynch syndrome Evaluation of tumor tissue to identify patients at risk for having hereditary endometrial carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Burgart LJ. Testing for defective DNA mismatch repair in colorectal carcinoma: a practical guide. Arch Pathol Lab Med 2005;129(11):1385-1389 2. Klarskov L, Ladelund S, Holck S, et al. Interobserver variability in the evaluation of mismatch repair protein immunostaining. Hum Pathol. 2010;41(10):1387-1396 3. Lanza G, Gafa R, Maestri I, Santini A, Matteuzzi M, Cavazzini L. Immunohistochemical pattern of MLH1/MSH2 expression is related to clinical and pathological features in colorectal adenocarcinomas with microsatellite instability. Mod Pathol. 2002;15(7):741-749 4. Modica I, Soslow RA, Black D, Tornos C, Kauff N, Shia J. Utility of immunohistochemistry in predicting microsatellite instability in endometrial carcinoma. Am J Surg Pathol. 2007;31(5):744-751 5. Mojtahed A, Schrijver I, Ford JM, Longacre TA, Pai RK. A two-antibody mismatch repair protein immunohistochemistry screening approach for colorectal carcinomas, skin sebaceous tumors, and gynecologic tract carcinomas. Mod Pathol. 2011;24(7):1004-1014 6. Rigau V, Sebbagh N, Olschwang S, et al. Microsatellite instability in colorectal carcinoma. The comparison of immunohistochemistry and molecular biology suggests a role for hMLH6 [correction of hMLH6] immunostaining. Arch Pathol Lab Med. 2003;127(6):694-700 7. Shia J. Immunohistochemistry versus microsatellite instability testing for screening colorectal cancer patients at risk for hereditary nonpolyposis colorectal cancer syndrome. Part I. The utility of immunohistochemistry. J Mol Diagn. 2008;10(4):293-300 8. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

MOC31
70505

MOC-31 Immunostain, Technical Component Only

Clinical Information: MOC31 reacts with an antigen present on most normal and malignant epithelia. Antibodies to the MOC31 antigen stain tumors of epithelial origin, adenocarcinomas, papillary serous carcinoma, breast, lung, prostate, and cholangiocarcinoma, among others. MOC31 may be used as part of a panel of stains to rule-out mesothelioma and support the diagnosis of carcinoma.

Useful For: Marker of epithelial cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the

stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

MOLD1
81878

Mold Panel, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mold Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MINT
61696

Molecular Interpretation

Clinical Information: Erythrocytosis (ie, increased red blood cell [RBC] mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, kidney cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma or paraganglioma formation. It is caused by variations in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new variants to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL have normal p50 results. The true prevalence of hereditary erythrocytosis-causing variants is unknown. The hemoglobin genes, HBA1/HBA2 and HBB are not assayed in this profile. Table. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum EPO p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased Normal PHD2/EGLN1 Dominant Normal level Normal BPGM Recessive Normal level Decreased Beta Globin Dominant Normal level to increased Decreased Alpha Globin Dominant Normal level to increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Normal to increased Normal The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteasomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the PHD2 (EGLN1) gene. Variations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants, in PHD2/EGLN1 and HIF2A/EPAS1, has also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating variants in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known variants have been localized to exon 8 and are heterozygous truncating variants. EPOR variants are associated with decreased EPO levels and normal p50 values (see Table).

Useful For: Interpretation of the hereditary erythrocytosis profile

Interpretation: An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any variations in the gene. If positive, the variant

will be correlated with clinical significance if known.

Reference Values:
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations, Whole Blood.

Clinical References: 1. Patnaik MM, Tefferi A. The complete evaluation of erythrocytosis: congenital and acquired. Leukemia. 2009;23(5):834-844 2. McMullin MF. The classification and diagnosis of erythrocytosis. Int J Lab Hematol. 2008;30:447-459 3. Percy MJ, Lee FS. Familial erythrocytosis: molecular links to red blood cell control. Haematologica. 2008;93(7):963-967 4. Huang LJ, Shen YM, Bulut GB. Advances in understanding the pathogenesis of primary familial and congenital polycythaemia. Br J Haematol. 2010;148(6):844-852 5. Maran J, Prchal J. Polycythemia and oxygen sensing. Pathologie Biologie. 2004;52:280-284 6. Lee F. Genetic causes of erythrocytosis and the oxygen-sensing pathway. Blood Rev. 2008;22:321-332 7. Merchant SH, Oliveira JL, Hoyer JD, Viswanatha DS. Erythrocytosis. In: His ED, ed. Hematopathology. 2nd ed. Elsevier Saunders; 2012:22-723 8. Zhuang Z, Yang C, Lorenzo F, et al. Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. N Engl J Med. 2012;367(10):922-930 9. Ladroue C, Carcenac R, Leporrier M, et al. PHD2 mutation and congenital erythrocytosis with paraganglioma. N Engl J Med. 2008;359(25):2685-2692 10. Lorenzo FR, Yang C, Ng Tang Fui M, et al. A novel EPAS1/HIF2A germline mutation in congenital polycythemia with paraganglioma. J Mol Med. 2013;91(4):507-512 11. Tarade D, Robinson CM, Lee JE, Ohh M. HIF-2alpha-pVHL complex reveals broad genotype-phenotype correlations in HIF-2aalpha-driven disease. Nat Commun. 2018;9(1):3359 12. Oliveira JL, Coon LM, Frederick LA, et al. Genotype-phenotype correlation of hereditary erythrocytosis mutations, a single center experience. Am J Hematol. 2018. doi:10.1002/ajh.2515) 13. Oliveira JL. Algorithmic evaluation of hereditary erythrocytosis: Pathways and caveats. Int J Lab Hematol. 2019;41 Suppl 1:89-94

MOLPS
89270

Molybdenum, Serum

Clinical Information: Molybdenum is an essential trace element found in the daily diet. It is a cofactor for some enzymes important in nitrogen metabolism (aldehyde dehydrogenase, xanthine oxidase, nicotinamide adenine dinucleotide dehydrogenase). Due to the wide distribution of molybdenum in the environment and particularly in plant materials, molybdenum deficiency is rare in adults with normal, diverse diets. Typical molybdenum intake in most geographic locations is between 45 and 90 mcg/day. Urine is the primary source of excretion, though excesses are sometimes excreted by the biliary route. Molybdenum deficiency associated with parenteral nutrition is indicated by symptoms such as stunted growth, reduced appetite, tachycardia, tachypnea, blindness, and coma. These symptoms can be corrected by introducing molybdenum supplementation. Molybdenum cofactor disease is a severe genetic disorder that is due to defective variants in the MOCS1, MOCS2, and GEPH genes. Molybdenum toxicity is rare and usually related to molybdenum mining exposure; however, it has been observed in cases of intake above 400 mcg/day. Molybdenum interferes with copper uptake; molybdenum toxicity is predominantly due to copper deficiency (hypochromic anemia and neutropenia) and inhibition of xanthine oxidase (uric acid accumulation). Serum molybdenum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS (low contact stress), PCA (porous-coated anatomic), Osteonics, Richards Company, Tricon, and Whiteside are typically made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Monitoring of parenteral nutrition Monitoring metallic prosthetic implant wear As an indicator of molybdenum cofactor deficiency

Interpretation: Prosthesis wear is known to result in increased circulating concentrations of metal ions.(1) Serum concentrations above 10 ng/mL in a patient with molybdenum-based implant suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. Serum molybdenum levels below 0.3 ng/mL indicate potential deficiency. Increased serum molybdenum may be seen in acute viral hepatitis, chronic active hepatitis, alcoholic liver disease, and other forms of liver inflammation.

Reference Values:
0.3-2.0 ng/mL

Clinical References: 1. Witzleb WC, Ziegler J, Krummenauer F, Neumeister V, Guenther KP. Exposure to chromium, cobalt and molybdenum from metal-on-metal total hip replacement and hip resurfacing arthroplasty. Acta Orthop. 2006;77(5):697-705 2. Centers for Disease Control and Prevention: The Third National Report on Exposure to Environmental Chemicals (NHANES). NCEH Publication 05-0570. National Center for Environmental Health; July 2005. Available at www.jhsph.edu/research/centers-and-institutes/center-for-excellence-in-environmental-health-tracking/Third_Report.pdf 3. Yoshida M, Ota S, Fukunaga K, Nishivama T. Serum molybdenum concentration in healthy Japanese adults determined by inductively coupled plasma-mass spectrometry. J Trace Elem Med Biol. 2006;20(1):19-23 4. Reiss J, Johnson JL. Mutations in the molybdenum cofactor biosynthetic genes MOCS1, MOCS2, and GEPH. Hum Mutat. 2003;21(6):569-576 5. Sodi R. Vitamins and trace elements. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:417-417

QMPTS
620169

Monoclonal Protein Isotype, Quantitative, Serum

Clinical Information:

Useful For: Aiding in the diagnosis and monitoring of monoclonal gammopathies if used in conjunction with free light chain studies This test alone is not considered an adequate screen for monoclonal gammopathies.

Interpretation: Immunoaffinity purification followed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is performed to identify the immunoglobulin heavy and light chains. The assay examines the mass-to-charge distributions of Ig light chains derived from immunoglobulin G, immunoglobulin A, immunoglobulin M, kappa, and lambda immunopurified from patient serum. Over-expressed Ig (ie, M-proteins or paraproteins) are detected as distinct peaks in the mass-to-charge distributions. Quantitation is accomplished by calculating the percent of monoclonal protein in the charge-to-mass distribution and multiplying this by Ig concentration as measured immunonephelometry.

Reference Values:
Only orderable as part of a profile. For more information see QMPSS / Monoclonal Protein Study, Quantitative, Serum.

M-protein Isotype Flag:
Negative
Interpretation:
No monoclonal protein detected.

Clinical References: 1. Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 2005;106(3):812-817 2. Katzmann JA, Dispenzieri A, Kyle RA, et al. Elimination of the need for

urine studies in the screening algorithm for monoclonal gammopathies by using serum immunofixation and free light chain assays. Mayo Clin Proc. 2006;81(12):1575-1578 3. Mills JR, Kohlhagen MC, Dasari S, et al. Comprehensive assessment of M-proteins using nanobody enrichment coupled to MALDI-TOF mass spectrometry. Clin Chem. 2016;62(10):1334-1344 4. Milani P, Murray DL, Barnidge DR, et al. The utility of MASS-FIX to detect and monitor monoclonal proteins in the clinic. Am J Hematol. 2017;92(8):772-779. doi:10.1002/ajh.24772

MPQU
616907

Monoclonal Protein Quantitation, 24 Hour, Urine

Clinical Information: Urine proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin -Alpha-1 -Alpha-2 -Beta-globulin -Gamma-globulin One or more quantifiable monoclonal proteins may be present and reported as M spike The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light chain deposition disease. The following algorithms are available: -Amyloidosis: Laboratory Approach to the Diagnosis -Multiple Myeloma: Laboratory Screening

Useful For: Monitoring patients with monoclonal gammopathies using 24-hour urine collections

Interpretation: The presence of a monoclonal immunoglobulin light chain in the urine is seen in multiple myeloma, macroglobulinemia, primary systemic amyloidosis and light-chain deposition disease, monoclonal gammopathy of undetermined significance, and idiopathic Bence Jones proteinuria. The presence of a monoclonal light chain can produce kidney insufficiency, may be deposited as amyloid fibrils, may damage the proximal tubes producing Fanconi syndrome, or light chains may deposit in the glomerulus and cause light-chain deposition disease. Heavy chain fragments as well as light chains may be seen in the urine of patients with multiple myeloma or amyloidosis.

Reference Values:
PROTEIN, TOTAL
<229 mg/24 hours

Reference values have not been established for patients who are younger than 18 years of age.

ELECTROPHORESIS, PROTEIN
The following fractions, if present, will be reported as mg/24 hours:
Albumin
Alpha-1-globulin
Alpha-2-globulin
Beta-globulin
Gamma-globulin

MASS-FIX M-PROTEIN ISOTYPE
M-protein Isotype MS:
No monoclonal protein detected

Flag M-protein Isotype MS:
Negative

Clinical References: 1. Abraham RS, Barnidge DR: Protein analysis in the clinical immunology laboratory. In: Detrick BD, Hamilton RG, Schmitz JL eds. Manual of Molecular and Clinical Laboratory Immunology. 8th ed. 2016:chap 4 2. Sykes E, Posey Y: Immunochemical characterization of immunoglobulins in serum, urine, and cerebrospinal fluid. In: Detrick B, Hamilton RG, Schmitz JL,

eds. Molecular and Clinical Laboratory Immunology. 8th ed. Wiley; 2016:chap 9

RMPQU
616909

Monoclonal Protein Quantitation, Random, Urine

Clinical Information: Urine proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin -Alpha-1-globulin -Alpha-2-globulin -Beta-globulin -Gamma-globulin One or more quantifiable monoclonal proteins may be present and reported as M spike. The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light-chain deposition disease. The following algorithms are available: -Amyloidosis: Laboratory Approach to Diagnosis -Multiple Myeloma: Laboratory Screening

Useful For: Identifying monoclonal gammopathies using random urine specimens

Interpretation: The presence of a monoclonal immunoglobulin light chain in the urine is seen in multiple myeloma, macroglobulinemia, primary systemic amyloidosis and light-chain deposition disease, monoclonal gammopathy of undetermined significance, and idiopathic Bence Jones proteinuria. The presence of a monoclonal light chain can produce renal insufficiency, may be deposited as amyloid fibrils, may damage the proximal tubes producing Fanconi syndrome, or light chains may deposit in the glomerulus and cause light-chain deposition disease. Heavy-chain fragments as well as light chains may be seen in the urine of patients with multiple myeloma or amyloidosis.

Reference Values:

CREATININE:
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years of age.

PROTEIN/CREATININE RATIO:
> or =18 years: <0.18 mg/mg creatinine
Reference values have not been established for patients younger than 18 years of age.

ELECTROPHORESIS, PROTEIN
The following fractions, if present, will be reported as mg/dL:
-Albumin
-Alpha-1-globulin
-Alpha-2-globulin
-Beta-globulin
-Gamma-globulin
No reference values apply to random urines.

MASS-FIX M-PROTEIN ISOTYPE
M-protein Isotype MS:
No monoclonal protein detected

Flag M-protein Isotype MS:
Negative

Clinical References: 1. Abraham RS, Barnidge DR: Protein analysis in the clinical immunology laboratory. In: Detrick B, Hamilton RG, Schmitz JL, eds. Molecular and Clinical Laboratory Immunology. 8th ed Wiley; 2016:chap 4 2. Sykes E, Posey Y: Immunochemical characterization of immunoglobulins in serum, urine, and cerebrospinal fluid. In: Detrick B, Hamilton RG, Schmitz JL, eds. Molecular and Clinical Laboratory Immunology. 8th ed. Wiley; 2016:chap 9

SMPU
616913

Monoclonal Protein Screen, 24 Hour, Urine

Clinical Information: Urine proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin -Alpha-1 -Alpha-2 -Beta-globulin -Gamma-globulin One or more quantifiable monoclonal proteins may be present and reported as M spike. The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light chain deposition disease. The following algorithms are available: -Amyloidosis: Laboratory Approach to Diagnosis -Multiple Myeloma: Laboratory Screening

Useful For: Monitoring patients with monoclonal gammopathies

Interpretation: The presence of a monoclonal immunoglobulin light chain in the urine is seen in multiple myeloma, macroglobulinemia, primary systemic amyloidosis and light-chain deposition disease, monoclonal gammopathy of undetermined significance, and idiopathic Bence-Jones proteinuria. The presence of a monoclonal light chain can produce renal insufficiency, may be deposited as amyloid fibrils, may damage the proximal tubes producing Fanconi syndrome, or light chains may deposit in the glomerulus and cause light-chain deposition disease. Heavy-chain fragments as well as light chains may be seen in the urine of patients with multiple myeloma or amyloidosis.

Reference Values:
PROTEIN, TOTAL
<229 mg/24 hours

Reference values have not been established for patients younger than 18 years of age.

ELECTROPHORESIS, PROTEIN
The following fractions, if present, will be reported as mg/24 hours:
Albumin
Alpha-1-globulin
Alpha-2-globulin
Beta-globulin
Gamma-globulin

MASS-FIX M-PROTEIN ISOTYPE
M-protein Isotype MS:
No monoclonal protein detected

Flag M-protein Isotype MS:
Negative

Clinical References: 1. Abraham RS, Barnidge DR: Protein analysis in the clinical immunology laboratory. In: Detrick BD, Hamilton RG, Schmitz JL eds. Manual of Molecular and Clinical Laboratory Immunology. 8th ed. 2016:chap 4 2. Sykes E, Posey Y: Immunochemical characterization of immunoglobulins in serum, urine, and cerebrospinal fluid. In: Detrick B, Hamilton RG, Schmitz JL, eds. Molecular and Clinical Laboratory Immunology. 8th ed. Wiley; 2016:chap 9

RSMPU
616915

Monoclonal Protein Screen, Random, Urine

Clinical Information: Urine proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin -Alpha-1-globulin -Alpha-2-globulin -Beta-globulin -Gamma-globulin One or more quantifiable monoclonal proteins may be present and reported as M spike The urine total protein

concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light-chain deposition disease. The following algorithms are available: -Amyloidosis: Laboratory Approach to Diagnosis -Multiple Myeloma: Laboratory Screening

Useful For: Identifying monoclonal gammopathies using random urine specimens

Interpretation: The presence of a monoclonal immunoglobulin light chain in the urine is seen in multiple myeloma, macroglobulinemia, primary systemic amyloidosis and light-chain deposition disease, monoclonal gammopathy of undetermined significance, and idiopathic Bence-Jones proteinuria. The presence of a monoclonal light chain can produce renal insufficiency, may be deposited as amyloid fibrils, may damage the proximal tubes producing Fanconi syndrome, or light chains may deposit in the glomerulus and cause light-chain deposition disease. Heavy chain fragments as well as light chains may be seen in the urine of patients with multiple myeloma or amyloidosis.

Reference Values:
CREATININE:
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients younger than 18 years of age.

PROTEIN/CREATININE RATIO:
> or =18 years: <0.18 mg/mg creatinine
Reference values have not been established for patients younger than 18 years of age.

ELECTROPHORESIS, PROTEIN
The following fractions, if present, will be reported as mg/dL:
-Albumin
-Alpha-1-globulin
-Alpha-2-globulin
-Beta-globulin
-Gamma-globulin
No reference values apply to random urines.

MASS-FIX M-PROTEIN ISOTYPE
M-protein Isotype MS:
No monoclonal protein detected

Flag M-protein Isotype MS:
Negative

Clinical References: 1. Abraham RS, Barnidge DR: Protein analysis in the clinical immunology laboratory. In: Detrick B, Hamilton RG, Schmitz JL, eds. Molecular and Clinical Laboratory Immunology. 8th ed. Wiley; 2016:chap 4 2. Sykes E, Posey Y: Immunochemical characterization of immunoglobulins in serum, urine, and cerebrospinal fluid. In: Detrick B, Hamilton RG, Schmitz JL, eds. Molecular and Clinical Laboratory Immunology. 8th ed. Wiley; 2016:chap 9

MPU
616911

Monoclonal Protein Studies, 24 Hour, Urine

Clinical Information: Urine proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin -Alpha-1 -Alpha-2 -Beta-globulin -Gamma-globulin One or more quantifiable monoclonal proteins may be present and reported as M spike. The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of

monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light chain deposition disease. The following algorithms are available: -Amyloidosis: Laboratory Approach to Diagnosis -Multiple Myeloma: Laboratory Screening

Useful For: Monitoring patients with monoclonal gammopathies

Interpretation: The presence of a monoclonal immunoglobulin light chain in the urine is seen in multiple myeloma, macroglobulinemia, primary systemic amyloidosis and light-chain deposition disease, monoclonal gammopathy of undetermined significance, and idiopathic Bence Jones proteinuria. The presence of a monoclonal light chain can produce renal insufficiency, may be deposited as amyloid fibrils, may damage the proximal tubes producing Fanconi syndrome, or light chains may deposit in the glomerulus and cause light-chain deposition disease. Heavy chain fragments as well as light chains may be seen in the urine of patients with multiple myeloma or amyloidosis.

Reference Values:

PROTEIN, TOTAL:
<229 mg/24 hours
Reference values have not been established for patients <18 years of age.

ELECTROPHORESIS, PROTEIN:
The following fractions, if present, will be reported as mg/24 hours:
Albumin
Alpha-1 globulin
Alpha-2 globulin
Betaglobulin
Gamma globulin

MASS-FIX M-PROTEIN ISOTYPE:
M-protein Isotype MS:
No monoclonal protein detected

Flag M-protein Isotype MS:
Negative

Clinical References: 1. Kyle RA, Katzmann JA, Lust JA, Dispenzieri A: Clinical indications and applications of electrophoresis and immunofixation. In: Rose NR, Hamilton RG, Detrick B, eds. Manual of Clinical Laboratory Immunology. 6th ed. ASM Press; 2002:71-91 2. Abraham RS, Barnidge DR: Protein analysis in the clinical immunology laboratory. In: Detrick BD, Hamilton RG, Schmitz JL eds. Manual of Molecular and Clinical Laboratory Immunology. 8th ed. 2016:chap 4

RMPU
616912

Monoclonal Protein Studies, Random, Urine

Clinical Information: Urine proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin -Alpha-1 -Alpha-2 -Beta-globulin -Gamma globulin One or more quantifiable monoclonal proteins may be present and reported as M spike. The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light-chain deposition disease. The following algorithms are available: -Amyloidosis: Laboratory Approach to Diagnosis -Multiple Myeloma: Laboratory Screening

Useful For: Identifying monoclonal gammopathies using random urine specimens

Interpretation: The presence of a monoclonal immunoglobulin light chain in the urine is seen in multiple myeloma, macroglobulinemia, primary systemic amyloidosis and light-chain deposition disease, monoclonal gammopathy of undetermined significance, and idiopathic Bence-Jones proteinuria. The presence of a monoclonal light chain can produce renal insufficiency, may be deposited as amyloid fibrils, may damage the proximal tubes producing Fanconi syndrome, or light chains may deposit in the glomerulus and cause light-chain deposition disease. Heavy-chain fragments as well as light chains may be seen in the urine of patients with multiple myeloma or amyloidosis.

Reference Values:

CREATININE:
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients younger than 18 years of age.

PROTEIN/CREATINE RATIO:
> or =18 years: <0.18 mg/mg creatinine
Reference values have not been established for patients younger than 18 years of age.

ELECTROPHORESIS, PROTEIN:
The following fractions, if present, will be reported as mg/dL:
Albumin
Alpha-1 globulin
Alpha-2 globulin
Beta globulin
Gamma globulin
No reference values apply to random urines.

MASS-FIX M-PROTEIN ISOTYPE:
M-protein Isotype MS:
No monoclonal protein detected

Flag M-protein Isotype MS:
Negative

Clinical References: 1. Abraham RS, Barnidge DR: Protein analysis in the clinical immunology laboratory. In: Detrick B, Hamilton RG, Schmitz JL, eds. Molecular and Clinical Laboratory Immunology. 8th ed. Wiley; 2016:chap 4 2. Sykes E, Posey Y: Immunochemical characterization of immunoglobulins in serum, urine, and cerebrospinal fluid. In: Detrick B, Hamilton RG, Schmitz JL, eds. Molecular and Clinical Laboratory Immunology. 8th ed. Wiley; 2016:chap 9

MPEP
618167

Monoclonal Protein Study, Expanded Panel, Serum

Clinical Information: Monoclonal proteins are markers of plasma cell proliferative disorders. It is recommended that serum and urine protein electrophoresis (PEL) and immunofixation electrophoresis (IFE) be performed as part of the diagnostic algorithm (eg, MPSS / Monoclonal Protein Study, Serum and MPSU / Monoclonal Protein Study, 24 Hour, Urine). A monoclonal band (M-spike) on serum and/or urine PEL identifies a monoclonal process and quantitates the abnormality. IFE characterizes the type of monoclonal protein (gamma, alpha, mu, delta, or epsilon heavy chain; kappa [K] or lambda [L] light chain). IFE is also more sensitive than PEL for detecting small abnormalities that may be present in diseases such as light chain multiple myeloma, oligosecretory myeloma, and plasmacytomas. With the addition of the serum free light-chain (FLC) assay, the expanded monoclonal protein study provides even more diagnostic sensitivity for the monoclonal light-chain diseases such as primary amyloid and light-chain deposition disease; disorders that often do not have serum monoclonal proteins in high enough concentration to be detected and quantitated by PEL. The FLC assay is specific for free kappa and lambda

light chains and does not recognize light chains bound to intact immunoglobulin. Importantly, the addition of the serum FLC assay to serum PEL and IFE makes the serum diagnostic studies sufficiently sensitive so that urine specimens are no longer required as part of initial diagnostic studies. Monoclonal gammopathies may be present in a wide spectrum of diseases that include malignancies of plasma cells or B lymphocytes (multiple myeloma [MM], macroglobulinemia, plasmacytoma, B-cell lymphoma), disorders of monoclonal protein structure (primary amyloid, light-chain deposition disease, cryoglobulinemia), and apparently benign, premalignant conditions (monoclonal gammopathy of undetermined significance [MGUS], smoldering MM). While the identification of the monoclonal gammopathy is a laboratory diagnosis, the specific clinical diagnosis is dependent on a number of other laboratory and clinical assessments. If a monoclonal protein pattern is detected by IFE or FLC, a diagnosis of a monoclonal gammopathy is established. Once a monoclonal gammopathy has been diagnosed, the size of the clonal abnormality can be monitored by PEL or FLC and, in some instances, by quantitative immunoglobulins. In addition, if the patient is asymptomatic and has a diagnosis of MGUS, the expanded monoclonal protein study panel provides the information (size of M-spike, monoclonal protein isotype, FLC K/L ratio) needed for a MGUS progression risk assessment (see Interpretation).

Useful For: Diagnosis of monoclonal gammopathies Eliminating the need for urine monoclonal studies as a part of initial diagnostic studies (ie, rule-out monoclonal gammopathy) Assessing risk of progression from monoclonal gammopathy of undetermined significance to multiple myeloma

Interpretation: Monoclonal Gammopathies: -A characteristic monoclonal band (M-spike) is often found on protein electrophoresis (PEL) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic PEL pattern is suggestive of a possible monoclonal protein. Immunofixation electrophoresis (IFE) is performed to identify the immunoglobulin heavy chain and/or light chain. -A monoclonal IgG or IgA of greater than 3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgG or IgA of less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. -A monoclonal IgM of greater than 3 g/dL is consistent with macroglobulinemia. -An abnormal serum free light chain (FLC) kappa/lambda (K/L) ratio in the presence of a normal IFE suggests a monoclonal light-chain process and should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of a serum M-spike greater than 1.5 g/dL on PEL should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, should be followed by VISCS / Viscosity, Serum. -After the initial identification of a monoclonal band, quantitation of the M-spike on follow-up PEL can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than PEL. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. -Patients with monoclonal light chain diseases who have no serum or urine M-spike may be monitored with the serum FLC value. -Patients suspected of having a monoclonal gammopathy may have normal serum PEL patterns. Approximately 11% of patients with MM have a completely normal serum PEL, with the monoclonal protein only identified by IFE. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on PEL but identified by IFE and/or FLC. Accordingly, a normal serum PEL does not rule out the disease and PEL alone should not be used to screen for the disorder if the clinical suspicion is high. MGUS Prognosis: -Low-risk MGUS patients are defined as having an M-spike of less than 1.5 g/dL, IgG monoclonal protein, and a normal FLC K/L ratio (0.25-1.65), and these patients have a lifetime risk of progression to MM of less than 5%. -High-risk MGUS patients (M-spike >1.5, IgA or IgM, abnormal FLC ratio) have a lifetime risk of progression to MM of 60%. Other Abnormal PEL Findings: -A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. -A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. -A

decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.2 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephritic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent. -An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).

Reference Values:

PROTEIN, TOTAL
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are younger than 12 months of age.

PROTEIN ELECTROPHORESIS
Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL
M-spike: 0.0 g/dL
An interpretive comment is provided with the report.
Reference values have not been established for patients that are younger than 16 years of age

IMMUNOFIXATION
Immunofixation: No monoclonal protein detected
Flag, Immunofixation: Negative

KAPPA-FREE LIGHT CHAIN
0.33-1.94 mg/dL

LAMBDA-FREE LIGHT CHAIN
0.57-2.63 mg/dL

KAPPA/LAMBDA-FREE LIGHT-CHAIN RATIO
0.26-1.65

Clinical References: 1. Keren DF, Humphrey RL: Clinical indications and applications of serum and urine protein electrophoresis. In: Detrick BD, Hamilton RG, Schmitz JL, eds. Manual of Molecular and Clinical Laboratory Immunology. 8th ed. 2016:chap 8 2. Rajkumar SV, Kyle RA, Therneau TM, et al: Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 2005;106:812-817 3. Katzmann JA, Dispenzieri A, Kyle RA, et al: Elimination of the need for urine studies in the screening algorithm for monoclonal gammopathies by using serum immunofixation and free light chain assays. Mayo Clin Proc. 2006;81(12):1575-1578 4. Katzmann JA, Keren DF. Strategy for detecting and following monoclonal gammopathies. In: Detrick BD, Hamilton RG, Schmitz JL, eds. Manual of Molecular and Clinical Laboratory Immunology. 8th ed. ASM Press; 2016:112-124

QMPSS
620919

Monoclonal Protein Study, Quantitative, Serum

Clinical Information: Monoclonal gammopathy is a general term which includes a spectrum of diagnoses including malignancies of plasma cells or B cells (eg, multiple myeloma [MM], Waldenstrom macroglobulinemia, plasmacytoma, and B-cell lymphomas and leukemias), symptomatic disorders directly related to the M-protein (eg, immunoglobulin light chain [AL] amyloidosis, light chain deposition disease, cryoglobulinemia, monoclonal gammopathy of clinical significance [MGCS], monoclonal

gammopathy of renal significance [MGRS], monoclonal gammopathy of thrombotic significance [MGTS] and POEMS syndrome [polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes]) and asymptomatic premalignant conditions (eg, monoclonal gammopathy of undetermined significance [MGUS] and smoldering MM). While the identification of the monoclonal gammopathy is a laboratory diagnosis, the specific clinical diagnosis is dependent on several other laboratory and clinical assessments. Monoclonal proteins (M-proteins) are the marker of monoclonal gammopathies. An M-protein is defined by the presence of a monoclonal immunoglobulin which is expressed above the polyclonal background. The International Myeloma Working Group (IMWG) guidelines state that to adequately document the presence of a monoclonal protein, a serum protein electrophoresis (SPEP), serum free light chain (FLC) analysis, and serum immunofixation electrophoresis (IFE) or serum mass spectrometry, should all be used. If AL amyloidosis is suspected, a 24-hour urine monoclonal protein study should be performed when all serum testing is negative. Mass-Fix has been demonstrated to be more analytically and clinically sensitive than IFE in detecting M-proteins. Mass-Fix results have also been shown to better predict patient's progression free survival time than IFE in treated MM patients. In addition, Mass-Fix can detect M-proteins with glycosylated light chains, which were demonstrated to be a risk factor for AL amyloidosis, cold agglutin disease, and MGUS progression. When matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) results are combined with quantitative immunoglobulin measurements, the assay can replace traditional SPEP for M-protein quantitation for common M-protein isotypes IgG, IgA, and IgM. M-proteins, which consist of only light chains are best quantitated using serum free light chains measurements. If a M-protein pattern is detected by Mass-Fix or serum FLC measurements, a diagnosis of a monoclonal gammopathy is established. The patient should be assessed clinically for symptomatic conditions such as multiple myeloma and the other diagnoses listed above. Once symptomatic disease is ruled out, a diagnosis of MGUS can be established. The IMWG guidelines suggests follow-up M-protein testing at 6 months for the first two years following a MGUS diagnosis. If the M-protein concentration remains stable over this period (ie, less than 0.5 g/dL increase) and the patient remains asymptomatic, testing can reduce to once per year. The Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) study involving 75,422 participants has online resources to predict the chance that a bone marrow biopsy will have greater than 10 percent plasma cells given the isotype, M-protein concentrations, free light chain ratio and total IgG, IgA, and IgM. This could be an important resource for physicians trying to decide if their patient should have a follow up bone marrow evaluation (https://istopmm.com/riskmodel/).

Useful For: Aiding in the diagnosis and monitoring of monoclonal gammopathies, when used in conjunction with free light chain studies This test alone is not considered an adequate screen for monoclonal gammopathies.

Interpretation: Monoclonal Gammopathies: -A monoclonal IgG or IgA of greater than 3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgM of greater than 3 g/dL is consistent with macroglobulinemia. -A monoclonal IgG, IgM, or IgA of less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), light chain (AL) amyloidosis, well as other monoclonal gammopathies of clinical significance. -If the initial identification of a serum M-spike is greater than 1.5 g/dL, then order a follow-up MPU / Monoclonal Protein Studies, 24 Hour, Urine to evaluate renal impairment due to the M-protein -If the initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, then SVISC / Viscosity, Serum should be ordered to rule out hyperviscosity syndrome. -Patients with monoclonal light chain diseases who have no serum or urine M-spike may be monitored with the quantitative serum free light chain (FLC) assay. -Patients with IgD or IgE can be followed using quantitative IgD or IgE measurements. -Patients with monoclonal Ig heavy chains (gamma, alpha and mu) can be detected by the Mass-Fix assay. -A small subset of MM patients (<1%) have malignant plasma cells that do not secrete an M-protein. Thus, these non-secretory MM patients need additional clinical testing to establish the diagnosis. -Patients with normal serum protein electrophoresis and IFE can have positive results on Mass-Fix testing due to the increased sensitivity of the assay. Detection of Therapeutic Monoclonal Antibodies:) -Patients who are receiving therapeutic monoclonal antibodies (t-mAb) therapies can have

a "pseudo" monoclonal protein (M-protein) depending on the level of the t-mAb in the blood. These t-mAb have predictable light chain mass to charge values. The lab has a limited (but expanding) number of t-mAb for which a comment is provided. If an M-protein is detected with a mass, isotype, and concentration similar to a t-mAb in the database, a comment is added to the report : "A monoclonal [isotype] is present with a light chain mass suggestive of [t-mAb name]. If the patient is not on [t-mAb name] the monoclonal [isotype] is indicative of a monoclonal gammopathy. Given that some M-proteins mass, isotype, and concentration will match a t-mAb, it is possible that the named t-mAb is not present and is in fact a low-level M-protein associated with a monoclonal gammopathy. If the patient has no history of taking the named t-mAb, then the reported M-protein is likely associated with a monoclonal gammopathy." -In studies performed at Mayo Clinic, it is possible to see daratumumab for 9 months after the cessation of treatment. -Mass-fix testing will not quantitate albumin, alpha-1-trypisin, alpha-2-macroglobulins or the beta fractions. MGUS Prognosis: -Low-risk MGUS patients are defined as having an M-spike of less than 1.5 g/dL, IgG monoclonal protein, and a normal FLC K/L (kappa/lambda) ratio (0.25-1.65), and these patients have a lifetime risk of progression to MM of less than 5%. -High-risk MGUS patients (M-spike >1.5, IgA or IgM, abnormal FLC ratio) have a lifetime risk of progression to MM of 60%. Other Abnormal Findings: -IgG, IgA, and free light chain M-proteins with reported light chain glycosylation have demonstrated to be a risk factor for AL amyloidosis. -IgM M-proteins with light chain glycosylation have been demonstrated to be associated with cold agglutinin disease. -Persistent elevated immunoglobulin levels are consistent with autoimmune disease, IgG4 related disease and liver failure.

Reference Values:

Monoclonal-protein Isotype Flag:
Negative
Interpretation:
No monoclonal protein detected.

IgG:
0-<5 months: 100-334 mg/dL
5-<9 months: 164-588 mg/dL
9-<15 months: 246-904 mg/dL
15-<24 months: 313-1,170 mg/dL
2-<4 years: 295-1,156 mg/dL
4-<7 years: 386-1,470 mg/dL
7-<10 years: 462-1,682 mg/dL
10-<13 years: 503-1,719 mg/dL
13-<16 years: 509-1,580 mg/dL
16-<18 years: 487-1,327 mg/dL
> or =18 years: 767-1,590 mg/dL

IgA:
0-<5 months: 7-37 mg/dL
5-<9 months: 16-50 mg/dL
9-<15 months: 27-66 mg/dL
15-<24 months: 36-79 mg/dL
2-<4 years: 27-246 mg/dL
4-<7 years: 29-256 mg/dL
7-<10 years: 34-274 mg/dL
10-<13 years: 42-295 mg/dL
13-<16 years: 52-319 mg/dL
16-<18 years: 60-337 mg/dL
> or =18 years: 61-356 mg/dL

IgM:

0-<5 months: 26-122 mg/dL
5-<9 months: 32-132 mg/dL
9-<15 months: 40-143 mg/dL
15-<24 months: 46-152 mg/dL
2-<4 years: 37-184 mg/dL
4-<7 years: 37-224 mg/dL
7-<10 years: 38-251 mg/dL
10-<13 years: 41-255 mg/dL
13-<16 years: 45-244 mg/dL
16-<18 years: 49-201 mg/dL
> or =18 years: 37-286 mg/dL

Clinical References: 1. Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 2005;106(3):812-817 2. Katzmann JA, Dispenzieri A, Kyle RA, et al. Elimination of the need for urine studies in the screening algorithm for monoclonal gammopathies by using serum immunofixation and free light chain assays. Mayo Clin Proc. 2006;81(12):1575-1578 3. Mills JR, Kohlhagen MC, Dasari S, et al. Comprehensive assessment of M-proteins using nanobody enrichment coupled to MALDI-TOF mass spectrometry. Clin Chem. 2016;62(10):1334-1344 4. Milani P, Murray DL, Barnidge DR, et al. The utility of MASS-FIX to detect and monitor monoclonal proteins in the clinic. Am J Hematol. 2017;92(8):772-779. doi:10.1002/ajh.24772

MPSS
800302

Monoclonal Protein Study, Serum

Clinical Information: Monoclonal proteins are markers of plasma cell proliferative disorders. It has been recommended that serum and urine protein electrophoresis (PEL) and immunofixation electrophoresis (IFE) be performed as the diagnostic algorithm. A monoclonal band (M-spike) on serum and/or urine PEL identifies a monoclonal process and quantitates the abnormality. IFE characterizes the type of monoclonal protein (gamma, alpha, mu, delta, or epsilon heavy chain; kappa or lambda light chain). IFE is also more sensitive than PEL for detecting small abnormalities that may be present in diseases such as light chain multiple myeloma, oligosecretory myeloma, and plasmacytomas. Monoclonal gammopathies may be present in a wide spectrum of diseases that include malignancies of plasma cells or B lymphocytes (multiple myeloma [MM], macroglobulinemia, plasmacytoma, B-cell lymphoma), disorders of monoclonal protein structure (primary amyloid, light chain deposition disease, cryoglobulinemia), and apparently benign, premalignant conditions (monoclonal gammopathy of undetermined significance [MGUS], smoldering MM). While the identification of the monoclonal gammopathy is a laboratory diagnosis, the specific clinical diagnosis is dependent on a number of other laboratory and clinical assessments. The following algorithms are available: -Amyloidosis: Laboratory Approach to Diagnosis -Multiple Myeloma: Laboratory Screening

Useful For: Diagnosis of monoclonal gammopathies, when used in conjunction with urine monoclonal studies Monitoring patients with monoclonal gammopathies Protein electrophoresis alone is not considered an adequate screen for monoclonal gammopathies.

Interpretation: Monoclonal Gammopathies: -A characteristic monoclonal band (M-spike) is often found on protein electrophoresis (PEL) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic PEL pattern is suggestive of a possible monoclonal protein and should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine, which includes immunofixation (IF), to identify the immunoglobulin heavy chain and/or light chain. -A monoclonal IgG or IgA of greater than 3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgG or IgA of less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early

or treated myeloma, as well as a number of other monoclonal gammopathies. -A monoclonal IgM of greater than 3 g/dL is consistent with macroglobulinemia. -The initial identification of a serum M-spike greater than 1.5 g/dL on PEL should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL respectively, should be followed by SVISC / Viscosity, Serum. -After the initial identification of an M-spike, quantitation of the M-spike on follow-up PEL can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than PEL. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. -Patients suspected of having a monoclonal gammopathy may have normal serum PEL patterns. Approximately 11% of patients with MM have a completely normal serum PEL, with the monoclonal protein only identified by IF. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on PEL but identified by IF. Accordingly, a normal serum PEL does not rule out the disease and PEL should not be used to screen for the disorder. Other Abnormal PEL Findings: -A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. -A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. -A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.2 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephritic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent.

Reference Values:

PROTEIN, TOTAL
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are younger than 12 months of age.

PROTEIN ELECTROPHORESIS
Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL
M-Spike: 0.0 g/dL
An interpretive comment is provided with the report.

IMMUNOFIXATION
No monoclonal protein detected

IMMUNOFIXATION FLAG
Negative

Clinical References: 1. Keren DF, Humphrey RL: Clinical indications and applications of serum and urine protein electrophoresis. In: Detrick B, Schmitz JL, Hamilton RG, eds. Manual of Molecular and Clinical Laboratory Immunology. 8th ed. ASM Press; 2016:74-88 2. Katzmann JA, Keren DF: Strategy for detecting and following monoclonal gammopathies. In: Detrick B, Schmitz JL, Hamilton RG, eds. Manual of Molecular and Clinical Laboratory Immunology. 8th ed. ASM Press; 2016:112-124 3. Kyle RA, Katzmann JA, Lust, JA, Dispenzieri A: Clinical indications and applications of electrophoresis and immunofixation. In: Rose NR, Hamilton RG, Detrick B, eds. Manual of Clinical Laboratory Immunology. 6th ed. ASM Press; 2002:66-70

MONOF
610018

Monocyte Repartition by CD14/CD16, Blood

Clinical Information: Chronic myelomonocytic leukemia (CMML) is a myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) overlap syndrome characterized by peripheral blood monocytosis (absolute monocyte count > or =1.0 x 10(9)/L, > or =10% of the total white blood cell count) persisting for 3 months or greater. It could be very challenging to distinguish CMML from a reactive monocytosis or from a MPN (such as primary myelofibrosis or polycythemia vera) with monocytosis. Monocytes can be classified into 3 subsets: classical MO1 (CD14+/CD16-), intermediate MO2 (CD14+/CD16+), and non-classical MO3 (CD14-/CD16+) monocytes, with MO1 constituting the major monocyte population (85%) in healthy individuals. Recent reports using multiparametric flow cytometry have demonstrated a characteristic increase in classical monocytes (> or =94%) in CMML patients, thus distinguishing them from other causes of reactive and clonal monocytosis with greater than 90% sensitivity and specificity.(1) This panel is designed to analyze the repartition of monocytes in these patients and to give a semiquantitative value for the MO1 compartment. This value will aid in the differential diagnosis and monitoring of CMML.

Useful For: Aiding in the diagnosis and monitoring of chronic myelomonocytic leukemia

Interpretation: An interpretive report describing the classical monocytes (MO1) fraction as either increased or normal will be provided. See Cautions.

Reference Values:
% Monocytes of WBC: 1.0-6.6%
MO1 (classical monocytes): <94.0%

Clinical References: 1. Selimoglu-Buet D, Wagner-Ballon O, Saada V, et al. Characteristic repartition of monocyte subsets as a diagnostic signature of chronic myelomonocytic leukemia. Blood. 2015;125(23):3618-3626. doi:10.1182/blood-2015-01-620781 2. Pophali PA, Marinelli LM, Ketterling RP, et al. High level MYC amplification in B-cell lymphomas: is it a marker of aggressive disease? Blood Cancer J. 2020;10(1):5. doi:10.1038/s41408-019-0271-z 3. Patnaik MM, Timm MM, Vallapureddy R, et al. Flow cytometry based monocyte subset analysis accurately distinguishes chronic myelomonocytic leukemia from myeloproliferative neoplasms with associated monocytosis. Blood Cancer J. 2017;7(7):e584. doi:10.1038/bcj.2017.66

FMORS
75144

Morphine Confirmation, Serum

Reference Values:
Report Limit: 1 ng/mL
Reference Range: 21-65 ng/mL

SPSM
9184

Morphology Evaluation (Special Smear), Blood

Clinical Information: Under normal conditions, the morphology and proportion of each blood cell type is fairly consistent in corresponding age groups. The morphology and proportion of each blood cell type may change in various hematologic diseases. Differential leukocyte count and special smear evaluation is helpful in revealing the changes in morphology or proportion of each cell type in the peripheral blood.

Useful For: Detecting disease states or syndromes of the white blood cells, red blood cells, or platelet cell lines of a patient's peripheral blood

Interpretation: The laboratory will provide an interpretive report of percentage of white cells and, if appropriate, evaluation of white cells, red cells, and platelets.

Reference Values:

1-3 years
Neutrophils/bands: 22-51%
Lymphocytes: 37-73%
Monocytes: 2-11%
Eosinophils: 1-4%
Basophils: 0-2%
Metamyelocytes: 0%
Myelocytes: 0%

4-7 years
Neutrophils/bands: 30-65%
Lymphocytes: 29-65%
Monocytes: 2-11%
Eosinophils: 1-4%
Basophils: 0-2%
Metamyelocytes: 0%
Myelocytes: 0%

8-13 years
Neutrophils/bands: 35-70%
Lymphocytes: 23-53%
Monocytes: 2-11%
Eosinophils: 1-4%
Basophils: 0-2%
Metamyelocytes: 0%
Myelocytes: 0%

Adults
Neutrophils/bands: 50-75%
Lymphocytes: 18-42%
Monocytes: 2-11%
Eosinophils: 1-3%
Basophils: 0-2%
Metamyelocytes: <1%
Myelocytes: <0.5%

An interpretive report will be provided.

Clinical References: 1. Kjeldsberg CR, eds. Practical Diagnosis of Hematologic Disorders. 5th ed. American Society of Clinical Pathologists; 2010 2. Pozdnyakova O, Connell NT, Battinelli EM, Connors JM, Fell G, Kim AS. Clinical significance of CBC and WBC morphology in the diagnosis and clinical course of COVID-19 infection. Am J Clin Pathol.. 2021 Feb 11;155(3):364-375. doi: 10.1093/ajcp/aqaa231

MSPP
82845

Mosquito Species, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an

allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mosquito species Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MOTH
82738

Moth, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations.

In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to moth Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FMNPP
75811

Motor Neuropathy Panel

Reference Values:

Myelin Associated Glycoprotein (MAG) Antibody, IgM: 0-999
Less than 1000 TU
An elevated IgM antibody concentration greater than 999 TU against myelin-associated glycoprotein (MAG) suggests active demyelination in peripheral neuropathy. A normal concentration (less than 999 TU) generally rules out an anti-MAG antibody-associated peripheral neuropathy.
TU=Titer Units

Sulfate-3-Glucuronyl Paragloboside (SGPG) Antibody, IgM: 0.00-0.99

Less than 1.00 IV

The majority of sulfate-3-glucuronyl paragloboside (SGPG) IgM-positive sera will show reactivity against MAG. Patients who are SGPG IgM positive and MAG IgM negative may have multi-focal motor neuropathy with conduction block.

Asialo-GM1 Antibodies, IgG/IgM: 0-50 IV
29 IV or less: Negative
30-50 IV: Equivocal
51-100 IV: Positive
101 IV or greater: Strong Positive

GM1 Antibodies, IgG/IgM: 0-50 IV
29 IV or less: Negative
30-50 IV: Equivocal
51-100 IV: Positive
101 IV or greater: Strong Positive

GD1a Antibodies, IgG/IgM: 0-50 IV
29 IV or less: Negative
30-50 IV: Equivocal
51-100 IV: Positive
101 IV or greater: Strong Positive

GD1b Antibodies, IgG/IgM: 0-50 IV
29 IV or less: Negative
30-50 IV: Equivocal
51-100 IV: Positive
101 IV or greater: Strong Positive

GQ1b Antibodies, IgG/IgM: 0-50 IV
29 IV or less: Negative
30-50 IV: Equivocal
51-100 IV: Positive
101 IV or greater: Strong Positive

Ganglioside (Asialo-GM1, GM1, GM2, GD1a, GD1b, and GQ1b) Antibodies, IgG/IgM:

Ganglioside antibodies are associated with diverse peripheral neuropathies. Elevated antibody levels to ganglioside-monosialic acid (GM1), and the neutral glycolipid, asialo GM1 are associated with motor or sensorimotor neuropathies, particularly multifocal motor neuropathy. Anti-GM1 may occur as IgM (polyclonal or monoclonal) or IgG antibodies. These antibodies may also be found in patients with diverse connective tissue diseases as well as normal individuals. GD1a antibodies are associated with different variants of Guillain-Barre syndrome (GBS) particularly acute motor axonal neuropathy while GD1b antibodies are predominantly found in sensory ataxic neuropathy syndrome. Anti-GQ1b antibodies are seen in more than 80 percent of patients with Miller-Fisher syndrome and may be elevated in GBS patients with ophthalmoplegia. The role of isolated anti-GM2 antibodies is unknown. These tests by themselves are not diagnostic and should be used in conjunction with other clinical parameters to confirm disease.

Immunoglobulin G:
0-2 years: 242-1108 mg/dL
3-4 years: 485-1160 mg/dL
5-9 years: 514-1672 mg/dL
10-14 years: 581-1652 mg/dL
15-18 years: 479-1433 mg/dL

19 years and older: 768-1632 mg/dL

Immunoglobulin A:
0-2 years: 2-126 mg/dL
3-4 years: 14-212 mg/dL
5-9 years: 52-226 mg/dL
10-14 years: 42-345 mg/dL
15-18 years: 60-349 mg/dL
19 years and older: 68-408 mg/dL

Immunoglobulin M:
0-2 years: 21-215 mg/dL
3-4 years: 26-155 mg/dL
5-9 years: 26-188 mg/dL
10-14 years: 47-252 mg/dL
15-18 years: 26-232 mg/dL
19 years and older: 35-263 mg/dL

Total Protein, Serum:
Refer to report. Reference intervals may vary based on instrumentation.

Albumin:
3.75-5.01 g/dL

Alpha 1 Globulin:
0.19-0.46 g/dL

Alpha 2 Globulin:
0.48-1.05 g/dL

Beta Globulin:
0.48-1.10 g/dL

Gamma:
0.62-1.51 g/dL

Monoclonal Protein:
<=0.00 g/dL

CED
82668

Mountain Cedar, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mountain cedar Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MOUS
82707

Mouse Epithelium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mouse epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To

investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MOSP
82792

Mouse Serum Protein, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mouse serum protein Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of

allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MOUP
82795

Mouse Urine Protein, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mouse urine protein Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MDS2
606192

Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum

Clinical Information: Autoimmune movement disorders encapsulate a large and diverse group of neurologic disorders occurring either in isolation or accompanying more diffuse autoimmune encephalitic illnesses. The full range of movement phenomena has been described, and, as they often occur in adults, many of the presentations can mimic neurodegenerative disorders, such as autoimmune chorea mimicking Huntington disease. Disorders may be ataxic, hypokinetic (parkinsonism), or hyperkinetic (myoclonus, chorea other dyskinetic disorders). Associated disorders may fall under the rubric of brainstem encephalitis. The autoantibody targets are diverse and include neuronal surface proteins, such as leucine-rich, glioma-inactivated 1 (LGI1), as well as antibodies reactive with intracellular antigens (such as Purkinje cell cytoplasmic antibody type 1 [PCA-1]) that are markers of a central nervous system process mediated by CD8+ cytotoxic T cells. In some instances (such as PCA-1 autoimmunity), antibodies detected in serum and cerebrospinal fluid can be indicative of a paraneoplastic cause and may direct the cancer search. In other instances (such as 65-kDa isoform of glutamic acid decarboxylase [GAD65] autoimmunity), a paraneoplastic cause is very unlikely, and early treatment with immunotherapy may promote improvement or recovery.

Useful For: Evaluating patients with suspected paraneoplastic or other autoimmune movement disorders including patients with ataxia, brainstem encephalitis, chorea, dyskinesias, myoclonus, and parkinsonism using serum specimens

Interpretation: A positive antibody result is consistent with a diagnosis of an autoimmune movement disorder. A search for cancer may be indicated, depending on the antibody profile. A trial of immune

therapy may bring about improvement in neurological symptoms.

Reference Values:

Test ID	Reporting Name	Methodology*	Reference Value
MDSI	Movement Disorder Interp, S	Medical interpretation	Interpretive report
AMPCS	AMPA-R Ab CBA, S	CBA	Negative
AMPHS	Amphiphysin Ab, S	IFA	Negative
AGN1S	Anti-Glial Nuclear Ab, Type 1	IFA	Negative
ANN1S	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2S	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3S	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
APBIS	AP3B2 IFA, S	IFA	Negative
CS2CS	CASPR2-IgG CBA, S	CBA	Negative
CRMWS	CRMP-5-IgG Western Blot, S	WB	Negative
DPPCS	DPPX Ab CBA, S	CBA	Negative
GABCS	GABA-B-R Ab CBA, S	CBA	Negative
GD65S	GAD65 Ab Assay, S	RIA	< or =0.02 nmol/L Reference values apply to all ages.
GFAIS	GFAP IFA, S	IFA	Negative
GRFIS	GRAF1 IFA, S	IFA	Negative
IG5CS	IgLON5 CBA, S	CBA	Negative
ITPIS	ITPR1 IFA, S	IFA	Negative
K11CS	KLHL11 Ab CBA, S	CBA	Negative
LG1CS	LGI1-IgG CBA, S	CBA	Negative
GL1IS	mGluR1 Ab IFA, S	IFA	Negative
NCDIS	Neurochondrin IFA, S	IFA	Negative
NIFIS	NIF IFA, S	IFA	Negative
NMDCS	NMDA-R Ab CBA, S	CBA	Negative
CCPQ	P/Q-Type Calcium Channel Ab	RIA	< or =0.02 nmol/L
PCABP	Purkinje Cell Cytoplasmic Ab Type 1	IFA	Negative
PCAB2	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative

PCATR	Purkinje Cell Cytoplasmic Ab Type Tr	IFA	Negative
PDEIS	PDE10A Ab IFA, S	IFA	Negative
SP5IS	Septin-5 IFA, S	IFA	Negative
SP7IS	Septin-7 IFA, S	IFA	Negative
T46IS	TRIM46 Ab IFA, S	IFA	Negative
Reflex Information: Test ID	Reporting Name	Methodology*	Reference Value
AGNBS	AGNA-1 Immunoblot, S	IB	Negative
AGNTS	AGNA-1 Titer, S	IFA	
AINCS	Alpha Internexin CBA, S	CBA	Negative
AMPIS	AMPA-R Ab IF Titer Assay, S	IFA	
AMIBS	Amphiphysin Immunoblot, S	IB	Negative
AN1BS	ANNA-1 Immunoblot, S	IB	Negative
AN1TS	ANNA-1 Titer, S	IFA	
AN2BS	ANNA-2 Immunoblot, S	IB	Negative
AN2TS	ANNA-2 Titer, S	IFA	
AN3TS	ANNA-3 Titer, S	IFA	
APBCS	AP3B2 CBA, S	CBA	Negative
APBTS	AP3B2 IFA Titer, S	IFA	
APHTS	Amphiphysin Ab Titer, S	IFA	
CRMTS	CRMP-5-IgG Titer, S	IFA	
DPPTS	DPPX Ab IFA Titer, S	IFA	
GABIS	GABA-B-R Ab IF Titer Assay, S	IFA	
GFACS	GFAP CBA, S	CBA	Negative
GFATS	GFAP IFA Titer, S	IFA	
GRFCS	GRAF1 CBA, S	CBA	Negative
GRFTS	GRAF1 IFA Titer, S	IFA	
IG5TS	IgLON5 IFA Titer, S	IFA	
ITPCS	ITPR1 CBA, S	CBA	Negative
ITPTS	ITPR1 IFA Titer, S	IFA	
K11TS	KLHL11 Ab IFA Titer, S	IFA	
GL1CS	mGluR1 Ab CBA, S	CBA	Negative
GL1TS	mGluR1 Ab IFA Titer, S	IFA	
NCDCS	Neurochondrin CBA, S	CBA	Negative

NCDTS	Neurochondrin IFA Titer, S	IFA	
NFHCS	NIF Heavy Chain CBA, S	CBA	Negative
NIFTS	NIF IFA Titer, S	IFA	
NFLCS	NIF Light Chain CBA, S	CBA	Negative
NMDIS	NMDA-R Ab IF Titer Assay, S	IFA	
PC1BS	PCA-1 Immunoblot, S	IB	Negative
PC1TS	PCA-1 Titer, S	IFA	
PC2TS	PCA-2 Titer, S	IFA	
PCTBS	PCA-Tr Immunoblot, S	IB	Negative
PCTTS	PCA-Tr Titer, S	IFA	
PDETS	PDE10A Ab IFA Titer, S	IFA	
SP5CS	Septin-5 CBA, S	CBA	Negative
SP5TS	Septin-5 IFA Titer, S	IFA	
SP7CS	Septin-7 CBA, S	CBA	Negative
SP7TS	Septin-7 IFA Titer, S	IFA	
T46CS	TRIM46 Ab CBA, S	CBA	Negative
T46TS	TRIM46 Ab IFA Titer, S	IFA	

Clinical References: 1. Honorat JA, McKeon A. Autoimmune movement disorders: a clinical and laboratory approach. Curr Neurol Neurosci Rep. 2017;17(1):4. doi:10.1007/s11910-017-0709-2 2. Dubey D, Wilson MR, Clarkson B, et al. Expanded clinical Phenotype, oncological associations, and immunopathologic insights of paraneoplastic Kelch-like protein-11 encephalitis. JAMA Neurol. 2020;77(11):1420-1429. doi:10.1001/jamaneurol.2020.2231

MDC2
606193

Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

Clinical Information: Autoimmune movement disorders encapsulate a large and diverse group of neurologic disorders occurring either in isolation or accompanying more diffuse autoimmune encephalitic illnesses. The full range of movement phenomena has been described, and, as they often occur in adults, many of the presentations can mimic neurodegenerative disorders, such as autoimmune chorea mimicking Huntington disease. Disorders may be ataxic, hypokinetic (parkinsonism), or hyperkinetic (myoclonus, chorea other dyskinetic disorders). Associated disorders may fall under the rubric of brainstem encephalitis. The autoantibody targets are diverse and include neuronal surface proteins, such as leucine-rich, glioma-inactivated 1 (LGI1), as well as antibodies reactive with intracellular antigens (such as Purkinje cell cytoplasmic antibody-1 [PCA-1]) that are markers of a central nervous system process mediated by CD8+ cytotoxic T cells. In some instances (such as PCA-1 autoimmunity), antibodies detected in serum and cerebrospinal fluid can be indicative of a paraneoplastic cause and may direct the cancer search. In other instances (such as 65-kDa isoform of

glutamic acid decarboxylase [GAD65] autoimmunity), a paraneoplastic cause is very unlikely, and early treatment with immunotherapy may promote improvement or recovery.

Useful For: Evaluating patients with suspected paraneoplastic or other autoimmune movement disorders including patients with ataxia, brainstem encephalitis, chorea, dyskinesias, myoclonus, and parkinsonism using spinal fluid specimens

Interpretation: A positive antibody result is consistent with a diagnosis of an autoimmune movement disorder. A search for cancer may be indicated, depending on the antibody profile. A trial of immune therapy may bring about improvement in neurological symptoms.

Reference Values:

Test ID	Reporting name	Methodology*	Reference value
MDCI	Movement Disorder Interp, CSF	Medical interpretation	Interpretive report
AMPCC	AMPA-R Ab CBA, CSF	CBA	Negative
AMPHC	Amphiphysin Ab, CSF	IFA	Negative
AGN1C	Anti-Glial Nuclear Ab, Type 1	IFA	Negative
ANN1C	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2C	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3C	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
APBIC	AP3B2 IFA, CSF	IFA	Negative
CS2CC	CASPR2-IgG CBA, CSF	CBA	Negative
CRMWC	CRMP-5-IgG Western Blot, CSF	WB	Negative
DPPCC	DPPX Ab CBA, CSF	CBA	Negative
GABCC	GABA-B-R Ab CBA, CSF	CBA	Negative
GD65C	GAD65 Ab Assay, CSF	RIA	< or =0.02 nmol/L Reference values apply to all ages.
GRFIC	GRAF1 IFA, CSF	IFA	Negative
GFAIC	GFAP IFA, CSF	IFA	Negative
IG5CC	IgLON5 CBA, CSF	CBA	Negative
ITPIC	ITPR1 IFA, CSF	IFA	Negative
K11CC	KLHL11 Ab CBA, CSF	CBA	Negative
LG1CC	LGI1-IgG CBA, CSF	CBA	Negative
GL1IC	mGluR1 Ab IFA, CSF	IFA	Negative
NCDIC	Neurochondrin IFA, CSF	IFA	Negative

NIFIC	NIF IFA, CSF	IFA	Negative
NMDCC	NMDA-R Ab CBA, CSF	CBA	Negative
PCTRC	Purkinje Cell Cytoplasmic Ab Type Tr	IFA	Negative
PCA1C	Purkinje Cell Cytoplasmic Ab Type 1	IFA	Negative
PCA2C	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
PDEIC	PDE10A Ab IFA, CSF	IFA	Negative
SP5IC	Septin-5 IFA, CSF	IFA	Negative
SP7IC	Septin-7 IFA, CSF	IFA	Negative
T46IC	TRIM46 IFA, CSF	IFA	Negative
Reflex Information: Test ID	Reporting name	Methodology*	Reference value
AGNBC	AGNA-1 Immunoblot, CSF	IB	Negative
AGNTC	AGNA-1 Titer, CSF	IFA	
AINCC	Alpha Internexin CBA, CSF	CBA	Negative
AMPIC	AMPA-R Ab IF Titer Assay, CSF	IFA	
AMIBC	Amphiphysin Immunoblot, CSF	IB	Negative
AN1BC	ANNA-1 Immunoblot, CSF	IB	Negative
AN1TC	ANNA-1 Titer, CSF	IFA	
AN2BC	ANNA-2 Immunoblot, CSF	IB	Negative
AN2TC	ANNA-2 Titer, CSF	IFA	
AN3TC	ANNA-3 Titer, CSF	IFA	
APBCC	AP3B2 CBA, CSF	CBA	Negative
APBTC	AP3B2 IFA Titer, CSF	IFA	
APHTC	Amphiphysin Ab Titer, CSF	IFA	
CRMTC	CRMP-5-IgG Titer, CSF	IFA	
DPPTC	DPPX Ab IFA Titer, CSF	IFA	
GABIC	GABA-B-R Ab IF Titer Assay, CSF	IFA	
GFACC	GFAP CBA, CSF	CBA	Negative
GFATC	GFAP IFA Titer, CSF	IFA	
GRFCC	GRAF1 CBA, CSF	CBA	Negative

GRFTC	GRAF1 IFA Titer, CSF	IFA	
IG5TC	IgLON5 IFA Titer, CSF	IFA	
ITPCC	ITPR1 CBA, CSF	CBA	Negative
ITPTC	ITPR1 IFA Titer, CSF	IFA	
K11TC	KLHL11 Ab IFA Titer, CSF	IFA	
GL1TC	mGluR1 Ab IFA Titer, CSF	IFA	
GL1CC	mGluR1 Ab CBA, CSF	CBA	Negative
NCDCC	Neurochondrin CBA, CSF	CBA	Negative
NCDTC	Neurochondrin IFA Titer, CSF	IFA	
NFHCC	NIF Heavy Chain CBA, CSF	CBA	Negative
NIFTC	NIF IFA Titer, CSF	IFA	
NFLCC	NIF Light Chain CBA, CSF	CBA	Negative
NMDIC	NMDA-R Ab IF Titer Assay, CSF	IFA	
PC1BC	PCA-1 Immunoblot, CSF	IB	Negative
PC1TC	PCA-1 Titer, CSF	IFA	
PC2TC	PCA-2 Titer, CSF	IFA	
PCTTC	PCA-Tr Titer, CSF	IFA	
PCTBC	PCA-Tr Immunoblot, CSF	IB	Negative
PDETC	PDE10A Ab IFA Titer, CSF	IFA	
SP5CC	Septin-5 CBA, CSF	CBA	Negative
SP5TC	Septin-5 IFA Titer, CSF	IFA	
SP7CC	Septin-7 CBA, CSF	CBA	Negative
SP7TC	Septin-7 IFA Titer, CSF	IFA	
T46CC	TRIM46 CBA, CSF	CBA	Negative
T46TC	TRIM46 IFA Titer, CSF	IFA	

Clinical References: 1. Honorat JA, McKeon A. Autoimmune movement disorders: a clinical and laboratory approach. Curr Neurol Neurosci Rep. 2017;17(1):4 doi:10.1007/s11910-017-0709-2 2. Dubey D, Wilson MR, Clarkson B, et.al. Expanded clinical phenotype, oncological associations, and immunopathologic insights of paraneoplastic Kelch-like protein-11 encephalitis. JAMA Neurol. 2020;77(11):1420-1429. doi:10.1001/jamaneurol.2020.2231

MPLFM
618661

MPL Exon 10 Mutation Detection, Bone Marrow

Clinical Information: Mutations in the JAK2, CALR and MPL genes are considered driver events in the BCR::ABL1 negative myeloproliferative neoplasms (MPN) including polycythemia vera (PV), primary myelofibrosis (PMF) and essential thrombocythemia (ET). The JAK2 V617F mutation occurs in 95% to 98% of patients with PV, 50% to 60% of patients with PMF and 50% to 60% of patients with ET respectively at diagnosis. Other JAK2 mutations in exons 12 to 15 occur in the remaining patients with PV. Mutations in the CALR gene occur in 20% to 30% of patients with PMF and 20% to 30% of patients with ET at diagnosis. A 52 base pairs deletion (53%) and a 5 bp deletion (32%) are the most common mutations in the CALR gene while other types of mutations may occur in the remaining cases. MPL exon 10 mutations occur in 5% to 10% of patients with PMF and 5% to 10% of patients with ET. Mutations in JAK2, CALR and MPL are mutually exclusive. The JAK2 V617F mutation is detected by quantitative polymerase chain reaction (PCR). The CALR mutations are detected by PCR targeting exon 9. The MPL mutations in exon 10 are detected by Sanger sequencing. All mutations in JAK2, CALR and MPL can also be detected by next generation of sequencing (NGS). In addition to the mutations in JAK2, CALR and MPL, mutations in many other genes including ASXL1, TET2, DNMT3A, SRSF2, SF3B1, U2AF1, ZRSR2, EZH2, IDH1, IDH2, CBL, KRAS, NRAS, STAG2, and TP53 can occur in MPN. These additional mutations are more frequent in PMF and advanced disease, as compared to PV and ET. It is known that mutations in the ASXL1, SRSF2, U2AF1, EZH2, IDH1 and IDH2 are correlated with a poor prognostic risk. While a single gene test on JAK2, CALR and MPL can be clinically useful, all above mentioned gene mutations can be detected by NGS.

Useful For: Diagnosis or differential diagnosis of myeloproliferative disorders by MPL gene analysis using bone marrow specimens

Interpretation: The results will be reported as 1 of 2 states: -Negative for myeloproliferative leukemia virus oncogene (MPL) exon 10 mutation -Positive for MPL exon 10 mutation If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390 2. Rumi E, Pietra D, Ferretti V, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. Blood. 2014;123(10):1544-1551 3. Greenfield G, McMullin MF, Mills K. Molecular pathogenesis of the myeloproliferative neoplasms. J Hematol Oncol. 2021;14(1):103 4. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumors: myeloid and histiocytic/dendritic neoplasms. Leukemia 2022; 36:1703-1719.

MPLR
36682

MPL Exon 10 Mutation Detection, Reflex, Varies

Clinical Information: The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR::ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as

c.G1849T; p. Val617Phe (V617F). The JAK2 V617F variant is present in 95% to 98% of patients with polycythemia vera, 50% to 60% of patients with primary myelofibrosis (PMF), and 50% to 60% of patients with essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR::ABL1-negative MPN include CALR exon 9 variant (20%-30% of PMF and ET) and MPL exon 10 variant (5%-10% of PMF and 3%-5% of ET). Variants in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR variant is associated with decreased risk of thrombosis in both ET and PMF and confers a favorable clinical outcome in patients with PMF. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

Useful For: Aiding in the distinction between a reactive cytosis and a chronic myeloproliferative disorder Evaluates for mutations in MPL in an algorithmic process for the MPNR / Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies

Interpretation: An interpretation will be provided under the MPNR / Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies

Reference Values:
Only orderable as a reflex. For more information see MPNR / Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies.

An interpretive report will be provided.

MPLVS
602599

MPL Exon 10 Mutation Detection, Varies

Clinical Information: DNA sequence variants in exon 10 of the myeloproliferative leukemia virus oncogene (MPL) have been detected in approximately 5% of patients with primary myelofibrosis (PMF) and essential thrombocythemia (ET), which are hematopoietic neoplasms classified within the broad category of myeloproliferative neoplasms. MPL codes for a transmembrane tyrosine kinase, and the most common MPL variants are single base pair substitutions at codon 515. These alterations have been shown to promote constitutive, cytokine-independent activation of the JAK/STAT signaling pathway and contribute to the oncogenic phenotype. At least 8 different MPL exon 10 variants have been identified in PMF and ET to date, and variants outside of exon 10 have not yet been reported. The vast majority of MPL variants have been found in specimens testing negative for the most common variant identified in myeloproliferative neoplasms, JAK2 V716F, although a small number of cases with both types of variants have been reported. MPL variants have not been identified in patients with polycythemia vera, chronic myelogenous leukemia, or other myeloid neoplasms. Identification of MPL variants can aid in the diagnosis of a myeloproliferative neoplasm and is highly suggestive of either PMF or ET.

Useful For: Aiding in the distinction between a reactive cytosis and a myeloproliferative neoplasm

Interpretation: The results will be reported as 1 of 2 states: -Negative for MPL exon 10 variant -Positive for MPL exon 10 variant If the result is positive, a description of the variant at the nucleotide level and the altered protein sequence is reported. Positive variant status is highly suggestive of a myeloproliferative neoplasm but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative variant status does not exclude the presence of a myeloproliferative or other neoplasm.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Defour JP, Chachoua I, Pecquet C, Constantinescu SN. Oncogenic activation of MPL/thrombopoietin receptor by 17 mutations at W515: implications for myeloproliferative neoplasms. Leukemia. 2016;30(5):1214-1216. doi:10.1038/leu.2015.271 2. Pikman Y, Lee BH, Mercher T, et al. MPLW515L is a novel somatic activating mutation in myelofibrosis with myeloid metaplasia. PLoS Med. 2006;3(7):e270 3. Pardanani AD, Levine RL, Lasho T, et al. MPL515 mutations in myeloproliferative and other myeloid disorders: a study of 1182 patients. Blood. 2006;108(10):3472-3476 4. Kilpivaara O, Levine RL. JAK2 and MPL mutations in myeloproliferative neoplasms: discovery and science. Leukemia. 2008;22(10):1813-1817. doi:10.1038/leu.2008.229

MPNML 44179 MPL Exon 10 Sequencing, Reflex, Varies

Clinical Information: The JAK2 V617F variant is present in 95% to 98% of patients with polycythemia vera, 50% to 60% of patients with primary myelofibrosis (PMF), and 50% to 60% of patients with essential thrombocythemia (ET). Detection of the JAK2 V617F is helps establish the diagnosis of a myeloproliferative neoplasm (MPN). However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR::ABL1-negative MPN include CALR exon 9 alterations (20%-30% of PMF and ET) and MPL exon 10 alterations (5%-10% of PMF and 3%-5% of ET). Variants in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR variant is associated with decreased risk of thrombosis in both ET and PMF and confers a favorable clinical outcome in patients with PMF. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

Useful For: Aiding in the distinction between a reactive cytosis and a myeloproliferative neoplasm when JAK2 V617F testing result is negative Evaluates for variants in MPL in an algorithmic process for MPNCM / Myeloproliferative Neoplasm, CALR with Reflex to MPL, Varies

Interpretation: The results will be reported as 1 of the 3 following states: -Positive for CALR variant -Positive for MPL variant -Negative for CALR and MPL variants Positive variant status is highly suggestive of a myeloid neoplasm and clinicopathologic correlation is necessary in all cases. Negative variant status does not exclude the presence of a myeloproliferative neoplasm or other neoplasms.

Reference Values:
Only orderable as a reflex. For more information see MPNCM / Myeloproliferative Neoplasm, CALR with Reflex to MPL, Varies.

An interpretive report will be provided.

Clinical References: 1. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutation of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390 2. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutation in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med. 2013;369(25):2391-2405 3. Rotunno G, Mannarelli C, Guglielmelli P, et al. Impact of calreticulin mutations on clinical and hematological phenotype and outcome in essential thrombocythemia. Blood. 2014;123(10):1552-1555 4. Tefferi A, Lasho TL, Finke CM, et al. CALR vs JAK2 vs MPL-mutated or triple-negative myelofibrosis: clinical, cytogenetic and molecular comparisons. Leukemia. 2014;28(7):1472-1477 5. Pikman Y, Lee BH, Mercher T, et al. MPLW515L is a novel somatic activating mutation in myelofibrosis with myeloid metaplasia. PLoS Med. 2006;3(7):e270 6. Pardanani AD, Levine RL, Lasho T, et al. MPL515 mutations in myeloproliferative and other myeloid disorders: a study of 1182 patients. Blood. 2006;108(10):3472-3476

MPLJM 606807 MPL Exon 10 Variant Detection, Reflex, Bone Marrow

Clinical Information: The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide variant in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). JAK2 V617F is present in 95% to 98% of polycythemia vera and 50% to 60% of primary myelofibrosis (PMF) and essential thrombocythemia (ET) cases. It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome. Detection of JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 variant (20%-30% of PMF and ET) and MPL exon 10 variant (5%-10% of PMF and 3%-5% of ET). Variants in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR variant is associated with decreased risk of thrombosis in both ET and PMF and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

Useful For: Aiding in the distinction between a reactive cytosis and a chronic myeloproliferative disorder Evaluating for variants in MPL in an algorithmic process

Interpretation: The interpretive report includes an overview of the findings.

Reference Values:
Only orderable as a reflex. For more information see MPNJM / Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Bone Marrow.

An interpretive report will be provided.

Clinical References: 1. Tefferi A, Lasho TL, Finke CM, et al: CALR vs JAK2 vs MPL-mutated or triple-negative myelofibrosis: clinical, cytogenetic and molecular comparisons. Leukemia. 2014;28(7):1472-1477. doi:10.1038/leu.2014.3 2. Rumi E, Pietra D, Ferretti V, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. Blood. 2014;123(10):1544-1551 3. Greenfield G, McMullin MF, Mils K. Molecular pathogenesis of the myeloproliferative neoplasms. J Hematol Oncol. 2021;14(1):103 4. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumors: myeloid and histiocytic/dendritic neoplasms. Leukemia 2022; 36:1703-1719

FMPVP
75817

Mpox Virus DNA, Qualitative Real-Time PCR

Reference Values:
Orthopoxvirus DNA, QL PCR: Not Detected
Mpox Virus DNA, QL PCR: Not Detected

MSH2
70512

MSH2 Immunostain, Technical Component Only

Clinical Information: Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline variants in the mismatch repair genes: MLH1, MSH2, MSH6, and PMS2. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 variants (approximately 50%-80%) is generally higher than the risks

associated with variants in the other Lynch syndrome-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include sebaceous neoplasms, gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, variants within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair alterations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous or compound heterozygous mismatch repair alterations, characterized by the presence of biallelic deleterious alterations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. Testing tumors from individuals at risk for Lynch syndrome for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair phenotype within the tumor but does not suggest in which gene the abnormality rests. Tumors from individuals affected by Lynch syndrome usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined). The MSI-H phenotype can also be seen in individuals whose tumors have somatic MLH1 promoter hypermethylation. Tumors from individuals that show the MSS/MSI-L phenotype (MSI at <30% of microsatellites examined), are not likely to have Lynch syndrome or somatic hypermethylation of MLH1. Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of Lynch syndrome-related cancers. If defective DNA mismatch repair is identified within the tumor, variant analysis of the associated gene can be performed to identify the causative germline variant and allow for predictive testing of at-risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline variants. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that this Lynch syndrome screen is not a genetic test but rather stratifies the risk of having an inherited cancer predisposition syndrome and identifies patients who might benefit from subsequent genetic testing.

Useful For: Identifying patients at high risk for having hereditary nonpolyposis colorectal cancer, also known as Lynch syndrome, in an immunopanel including MSH2 and other mismatch repair markers Evaluation of tumor tissue to identify patients at risk for having hereditary endometrial carcinoma in an immunopanel including MSH2 and other mismatch repair markers

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Burgart LJ. Testing for defective DNA mismatch repair in colorectal carcinoma: a practical guide. Arch Pathol Lab Med 2005;129(11):1385-1389 2. Klarskov L, Ladelund

S, Holck S, et al. Interobserver variability in the evaluation of mismatch repair protein immunostaining. Hum Pathol. 2010;41(10):1387-1396 3. Lanza G, Gafa R, Maestri I, et al. Immunohistochemical pattern of MLH1/MSH2 expression is related to clinical and pathological features in colorectal adenocarcinomas with microsatellite instability. Mod Pathol. 2002;15(7):741-749 4. Modica I, Soslow RA, Black D, et al. Utility of immunohistochemistry in predicting microsatellite instability in endometrial carcinoma. Am J Surg Pathol. 2007;31(5):744-751 5. Mojtahed A, Schrijver I, Ford JM, Longacre TA, Pai RK. A two-antibody mismatch repair protein immunohistochemistry screening approach for colorectal carcinomas, skin sebaceous tumors, and gynecologic tract carcinomas. Mod Pathol. 2011;24(7):1004-1014. doi:10.1038/modpathol.2011.55 6. Rigau V, Sebbagh N, Olschwang S, et al. Microsatellite instability in colorectal carcinoma. The comparison of immunohistochemistry and molecular biology suggests a role for hMLH6 [correction of hMLH6] immunostaining. Arch Pathol Lab Med. 2003;127(6):694-700 7. Shia J. Immunohistochemistry versus microsatellite instability testing for screening colorectal cancer patients at risk for hereditary nonpolyposis colorectal cancer syndrome. J Mol Diagn .2008;10(4):293-300 8. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

MSH6
70513

MSH6 Immunostain, Technical Component Only

Clinical Information: Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes: MLH1, MSH2, MSH6, and PMS2. Hereditary nonpolyposis colorectal cancer is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other HNPCC-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include sebaceous neoplasms, gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the HNPCC spectrum. Several clinical variants of HNPCC have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous or compound heterozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of HNPCC. Testing tumors from individuals at risk for HNPCC for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair phenotype within the tumor but does not suggest in which gene the abnormality rests. Tumors from individuals affected by HNPCC usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined). The MSI-H phenotype can also be seen in individuals whose tumors have somatic MLH1 promoter hypermethylation. Tumors from individuals that show the MSS/MSI-L phenotype (MSI at <30% of microsatellites examined), are not likely to have HNPCC or somatic hypermethylation of MLH1. Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of HNPCC-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation analysis of the associated gene can be performed to identify the causative germline mutation and allow for predictive testing of at-risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC

have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that this HNPCC screen is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome and identifies patients who might benefit from subsequent genetic testing.

Useful For: Identifying patients at high risk for having hereditary nonpolyposis colorectal cancer, also known as Lynch syndrome, in an immunopanel including MSH6 and other mismatch repair markers Evaluation of tumor tissue to identify patients at risk for having hereditary endometrial carcinoma in an immunopanel including MSH6 and other mismatch repair markers

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

CSMRT 607626 mSMART Plasma Cell Proliferative Disorder, Pre-Analysis Cell Sorting, Bone Marrow

Clinical Information: Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options. MSMRT / Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy Report, Bone Marrow classifies patients into either standard or high-risk categories based on the results of 2 assays: plasma cell proliferation and FISH for specific multiple myeloma-associated abnormalities.

Useful For: Risk stratification of patients with multiple myeloma, which can assist in determining treatment and management decisions Sorting plasma cells for fluorescence in situ hybridization analysis Risk stratification of patients with newly diagnosed multiple myeloma

Interpretation: Correlation with clinical, histopathologic and additional laboratory findings is required for final interpretation of these results. The final interpretation of results for clinical management of the patient is the responsibility of the managing physician.

Reference Values:
Only orderable as a reflex. For more information see MSMRT / Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy Report, Bone Marrow or MSMRD / Myeloma Stratification and Risk-Adapted Therapy with Reflex to Minimal Residual Disease, Bone Marrow

An interpretive report will be provided.

Clinical References:

MPCDS 606090 mSMART, Plasma Cell Proliferative Disorder, FISH, Bone Marrow

Clinical Information: Multiple myeloma is a hematologic neoplasm that generally originates in the bone marrow and develops from malignant plasma cells. There are 4 main categories of plasma cell proliferative disorders: monoclonal gammopathy of undetermined significance (MGUS), monoclonal immunoglobulin deposition diseases (amyloidosis), plasmacytoma, and multiple myeloma. MGUS, which occurs in 3% to 4% of individuals over age 50 years, represents the identification of an asymptomatic monoclonal protein, yet approximately 1% per year will progress to multiple myeloma. Amyloidosis represents a rare group of deposition disorders including primary amyloidosis vs. light-chain and heavy-chain disease. Plasmacytomas represent isolated collections of bone or extramedullary plasma cells with a risk for development of multiple myeloma. Generalized bone pain, anemia, limb numbness or weakness, symptoms of hypercalcemia, and recurrent infections are all symptoms that may indicate multiple myeloma. As myeloma progresses, the malignant plasma cells interfere with normal blood product formation in the bone marrow, resulting in anemia and leukopenia. Myeloma also causes an overstimulation of osteoclasts, causing excessive breakdown of bone tissue without the normal corresponding bone formation. These bone lesions are seen in approximately 66% of myeloma patients. In advanced disease, bone loss may reach a degree where the patient suffers fractures easily. Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Patients with more aggressive multiple myeloma experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options.

Useful For: Aiding in the diagnosis of new cases of multiple myeloma or other plasma cell proliferative disorders as a part of a profile Identifying prognostic markers based on the anomalies found

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values:
Only orderable as part of a profile. For more information see MSMRT / Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy Report, Bone Marrow.

An interpretive report will be provided.

Clinical References: 1. Swerdlow SH, Campo E, Harris NL, et al, eds: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours, Vol 2 2. Kumar SK, Rajkumar SV: The multiple myelomas-current concepts in cytogenetic classification and therapy. Nat Rev Clin Oncol. 2018 Jul;15(7):409-421. doi: 10.1038/s41571-018-0018-y 3. Rajkumar SV, Landgren O, Mateos MV: Smoldering multiple myeloma. Blood. 2015 May 14;125(20):3069-3075. doi: 10.1182/blood-2014-09-568899 4. Muchtar E, Dispenzieri A, Kumar SK, et al: Interphase fluorescence in situ hybridization in untreated AL amyloidosis has an independent prognostic impact by abnormality type and treatment category. Leukemia. 2017 Jul;31(7);1562-1569. doi: 10.1038/leu.2016.369 5. Lakshman A, Paul S, Rajkumar SV, et al: Prognostic significance of interphase FISH in monoclonal gammopathy of undetermined significance. Leukemia. 2018 Aug;32(8);1811-1815. doi: 10.1038/s41375-018-0030-3 6. Bochtler T, Hegenbart U, Kunz C, et al: Prognostic impact of cytogenetic aberrations in AL amyloidosis patients after high-dose melphalan: a long-term follow-up study. Blood. 2016 Jul 28;128(4):594-602. doi: 10.1182/blood-2015-10-676361 7. Treatment guidelines:

multiple myeloma. mSMART 3.0. Accessed May 09, 2023. Available at www.msmart.org/mm-treatment-guidelines

MUCN2 605116 Mucin 2, Immunostain, Technical Component Only

Clinical Information: Mucin 2 (MUC2) is a 520 kDa glycoprotein belonging to the family of secretory mucins. MUC2 is expressed in the cytoplasm of goblet cells. An immunopanel consisting of MUC1, MUC2, MUC5AC, and MUC6 is useful in subtyping intraductal papillary mucinous neoplasms.

MUCN4 601740 Mucin 4, Immunostain, Technical Component Only

Clinical Information: Mucin 4 (MUC4) is a large membrane-anchored glycoprotein that belongs to the mucin family. Mucins play important roles in the protection of epithelial cells and have been implicated in epithelial renewal and differentiation. MUC4 is expressed in the cytoplasm and membrane of respiratory, gastrointestinal, cervical, and prostatic epithelial cells. Overexpression of MUC4 has been observed in many carcinomas. It has been shown to be useful for the distinction between sarcomatoid carcinoma (often expressed) versus sarcomatoid mesothelioma (usually negative).

Useful For: Aids in the differentiation of sarcomatoid carcinoma from sarcomatoid mesothelioma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Tamura Y, Higashi M, Kitamoto S, et al. MUC4 and MUC1 expression in adenocarcinoma of the stomach correlates with vessel invasion and lymph node metastasis: an immunohistochemical study of early gastric cancer. PLoS One. 2012;7(11):e49251 2. Kwon K, Ro J, Singhal N, et al. MUC4 expression in non-small cell lung carcinomas: relationship to tumor histology and patient survival. Arch Pathol Lab Med. 2007;131(4):593-598 3. Majhi PD, Lakshmanan I, Ponnusamy M, et al. Pathobiological implications of MUC4 in non-small-cell lung cancer. J Thorac Oncol. 2013;8(4):398-407 4. Cowan M, Thompson L, Leon M, et al. Low-Grade Fibromyxoid Sarcoma of the Head and Neck: A Clinicopathologic Series and Review of the Literature. Head Neck Pathol. 2016;10(2):161-166 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

MUCN5 605118 Mucin 5AC, Immunostain, Technical Component Only

Clinical Information: Mucins are high-molecular weight glycoproteins produced by epithelial cells and can be divided into 2 families. Mucin 5AC (MUC5AC) is a glycoprotein belonging to the family of secretory mucins and is expressed in the regenerative zone of gastric epithelium. An immunopanel consisting of MUC1, MUC2, MUC5AC, and MUC6 is useful in subtyping intraductal papillary mucinous neoplasms.

Useful For: Aiding in subtyping intraductal papillary mucinous neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of

the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Lau SK, Weiss LM, Chu PG. Differential expression of MUC1, MUC2, and MUC5AC in carcinomas of various sites: an immunohistochemical study. Am J Clin Pathol. 2004;122(1):61-69. doi:10.1309/9R66-73QE-C06D-86Y42. Pezhouh MK, Park JY. Gastric pyloric gland adenoma. Arch Pathol Lab Med. 2015;139(6):823-826. doi:10.5858/arpa.2013-0613-RS 3. Kwak HA, Liu X, Allende DS, Pai RK, Hart J, Xiao SY. Interobserver variability in intraductal papillary mucinous neoplasm subtypes and application of their mucin immunoprofiles. Mod Pathol. 2016;29(9):977-984. doi:10.1038/modpathol.2016.934. Kim DH, Shin N, Kim GH, et al. Mucin expression in gastric cancer: reappraisal of its clinicopathologic and prognostic significance. Arch Pathol Lab Med. 2013;137(8):1047-1053. doi:10.5858/arpa.2012-0193-OA 5. Castellano-Megias VM, Andres CI, Lopez-Alonso G, Colina-Ruizdelgado F. Pathological features and diagnosis of intraductal papillary mucinous neoplasm of the pancreas. World J Gastrointest Oncol. 2014;6(9):311-324. doi:10.4251/wjgo.v6.i9.311 6. Horinouchi M, Nagata K, Nakamura A, et al. Expression of different glycoforms of membrane mucin (MUC1) and secretory mucin (MUC2, MUC5AC and MUC6) in pancreatic neoplasms. Acta Histochem Cytochem. 2003;36(5):443-453. doi:10.1267/ahc.36.443 7. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

MUCN6
605120

Mucin 6, Immunostain, Technical Component Only

Clinical Information: Mucin 6 (MUC6) is a large glycoprotein that plays a major role in the protection of the gastrointestinal tract and belongs to the family of secretory mucins. MUC6 is expressed in the cytoplasm/membrane of gastric pyloric epithelial cells. An immunopanel consisting of MUC1, MUC2, MUC5AC, and MUC6 is useful in subtyping intraductal papillary mucinous neoplasms.

Useful For: Aiding in subtyping intraductal papillary mucinous neoplasms as part of an immunopanel

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Lau SK, Weiss LM, Chu PG. Differential expression of MUC1, MUC2, and MUC5AC in carcinomas of various sites: an immunohistochemical study. Am J Clin Pathol. 2004;122(1):61-69. doi:10.1309/9R66-73QE-C06D-86Y4 2. Pezhouh MK, Park JY. Gastric pyloric gland adenoma. Arch Pathol Lab Med. 2015;139(6):823-826. doi:10.5858/arpa.2013-0613-RS 3. Kwak HA, Liu X, Allende DS, Pai RK, Hart J, Xiao SY. Interobserver variability in intraductal papillary mucinous neoplasm subtypes and application of their mucin immunoprofiles. Mod Pathol. 2016;29(9):977-984. doi:10.1038/modpathol.2016.93 4. Kim DH, Shin N, Kim GH, et al. Mucin expression in gastric cancer: reappraisal of its clinicopathologic and prognostic significance. Arch Pathol Lab Med. 2013;137(8):1047-1053. doi:10.5858/arpa.2012-0193-OA 5. Castellano-MegIas VM, AndrEs CI, LOpez-Alonso G, Colina-Ruizdelgado F. Pathological features and diagnosis of intraductal papillary mucinous neoplasm of the pancreas. World J Gastrointest Oncol. 2014;6(9):311-324. doi:10.4251/wjgo.v6.i9.311 6. Horinouchi M, Nagata K, Nakamura A, et al. Expression of different glycoforms of membrane mucin (MUC1) and secretory mucin (MUC2, MUC5AC and MUC6) in pancreatic neoplasms. Acta Histochem Cytochem. 2003;36(5):443-453. doi:10.1267/ahc.36.443 7. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298.

doi:10.1007/978-1-4939-8935-5_25

MPSQU 606299 Mucopolysaccharides Quantitative, Random, Urine

Clinical Information: The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin-6-sulfate, which are collectively called glycosaminoglycans (GAG). Undegraded or partially degraded GAG are stored in lysosomes and excreted in the urine. Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in mucopolysaccharidosis (MPS) disorders. There are 11 known enzyme deficiencies that result in the accumulation of GAG. In addition, abnormal GAG storage is observed in multiple sulfatase deficiency and in I-cell disease. Finally, abnormal excretion of GAG in urine is observed occasionally in other disorders including active bone diseases, connective tissue disease, hypothyroidism, urinary dysfunction, and oligosaccharidoses. Mucopolysaccharidoses are autosomal recessive disorders except for MPS II, which follows an X-linked inheritance pattern. Affected individuals typically experience a period of normal growth and development followed by progressive disease involvement encompassing multiple systems. The severity and features vary and may include facial coarsening, organomegaly, skeletal changes, cardiac abnormalities, and developmental delays. Moreover, disease presentation varies from as early as late infancy to adulthood. A diagnostic workup for individuals with suspected MPS should begin with this test, which includes the quantitative liquid chromatography tandem mass spectrometry (LC-MS/MS) analysis of the specific sulfates or GAG. Interpretation is based upon pattern recognition of the specific sulfates detected by MS/MS and the quantitative analysis of their amounts of excretion. However, an abnormal mucopolysaccharide analysis is not sufficient to conclusively establish a specific diagnosis. It is strongly recommended to seek confirmation by an independent method, typically in vitro enzyme assay (available in either blood or cultured fibroblasts from a skin biopsy) or molecular analysis. After a specific diagnosis has been established, this test can be appropriate for monitoring the effectiveness of treatment, such as a bone marrow transplant or enzyme replacement therapy (ERT). This test allows for monitoring of the excretion of specific sulfates, as these may change in patients with an MPS disorder undergoing treatment. Table: Enzyme Defects and Excretion Products of Mucopolysaccharidoses Disorder Alias Enzyme deficiency Sulfates excreted MPS I Hurler/Scheie Alpha-L-iduronidase DS/HS MPS II Hunter Iduronate 2-sulfatase DS/HS MPS III A Sanfilippo A Heparan N-sulfatase HS MPS III B Sanfilippo B N-acetyl-alpha-D-glucosaminidase HS MPS III C Sanfilippo C Acetyl-CoA:alpha-glucosaminide N-acetyltransferase HS MPS III D Sanfilippo D N-acetylglucosamine-6-sulfatase HS MPS IV A Morquio A Galactosamine-6-sulfatase KS/C6S MPS IV B Morquio B Beta-galactosidase KS MPS VI Maroteaux-Lamy Arylsulfatase B DS MPS VII Sly Beta-glucuronidase DS, HS, C6S MPS IX Hyaluronidase deficiency Hyaluronidase None KEY: C6S, chondroitin 6-sulfate; DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate MPS I is caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized into 3 main types: MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), which are not typically distinguishable via biochemical methods. Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroglossia, and respiratory tract infections. Developmental delay is noticed as early as 12 months of age, with death occurring usually before 10 years of age when left untreated. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-adolescence. Survival into adulthood is common. Cause of death usually results from cardiac complications or upper airway obstruction. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do

experience joint involvement, visual impairment, and obstructive airway disease. MPS II (Hunter syndrome) is caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. The inheritance pattern is X-linked and as such MPS II is observed almost exclusively in male patients with an estimated incidence of 1 in 170,000 male births. Female patients who are symptomatic carriers are very rare but have been reported. Treatment options include hematopoietic stem cell transplantation and ERT. MPS III (Sanfilippo syndrome) is caused by a reduced or absent activity of 1 of 4 enzymes (see Table above), resulting in a defect of heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes, and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. MPS III is characterized by severe central nervous system (CNS) degeneration but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPS. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the third decade of life (20s). The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. Treatment options are limited to symptomatic management. MPS IVA (Morquio A syndrome) is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with ERT is available. MPS IVB (Morquio B syndrome) is caused by a reduced or absent beta-galactosidase activity, which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI (Maroteaux-Lamy syndrome) is caused by a deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Estimates of the incidence of MPS VI range from 1 in 200,000 to 1 in 300,000 live births. Treatment options include hematopoietic stem cell transplantation and ERT. MPS VII (Sly syndrome) is caused by a deficiency of the enzyme beta-glucuronidase. The phenotype varies significantly from mild to severe presentations and may include macrocephaly, short stature, dysostosis multiplex, hepatomegaly, coarse facies, and impairment of cognitive function. Likewise, the age of onset is variable ranging from prenatal to adulthood. MPS VII is extremely rare, affecting approximately 1 in 1,500,000 individuals. Treatment options include hematopoietic stem cell transplantation and ERT. MPS IX is a very rare disorder caused by a deficiency of the enzyme hyaluronidase. Patients present with short stature, flat nasal bridge, and joint findings. Urine GAG are normal in MPS IX.

Useful For: Supporting the biochemical diagnosis of one of the mucopolysaccharidoses: types I, II, III, IV, VI, or VII

Interpretation: Elevations of dermatan sulfate, heparan sulfate, keratan sulfate, and/or chondroitin-6-sulfate may be indicative of one of the mucopolysaccharidoses types I, II, III, IV, VI, or VII. Elevations of any or all sulfate species may be indicative of multiple sulfatase deficiency or mucolipidosis II/III. Rarely, an elevation of keratan sulfate may be indicative of alpha-fucosidosis.

Reference Values:
DERMATAN SULFATE
< or =1.00 mg/mmol creatinine

HEPARAN SULFATE
< or =4 years: < or =0.50 mg/mmol creatinine
> or =5 years: < or =0.25 mg/mmol creatinine

CHONDROITIN-6 SULFATE
< or =24 months: < or =10.00 mg/mmol creatinine
25 months-10 years: < or =2.50 mg/mmol creatinine
> or =11 years: < or =1.50 mg/mmol creatinine

KERATAN SULFATE
< or =12 months: < or =2.00 mg/mmol creatinine
13-24 months: < or =1.50 mg/mmol creatinine
25 months-4 years: < or =1.00 mg/mmol creatinine
5-18 years: < or =0.50 mg/mmol creatinine
> or =19 years: < or =0.30 mg/mmol creatinine

Clinical References: 1. Newborn Screening ACT Sheet [alpha-L-iduronidase deficiency with or without glycosaminoglycan (GAG) accumulation] Mucopolysaccharidosis Type I (MPS I). American College of Medical Genetics and Genomics; 2023. Updated November 2023. Accessed June 10, 2024. Available at www.acmg.net/PDFLibrary/MPSI-ACT-Sheet.pdf 2. de Ru MH, van der Tol L, van Vlies N, et al. Plasma and urinary levels of dermatan sulfate and heparan sulfate derived disaccharides after long-term enzyme replacement (ERT) in MPS I: correlation with the timing of ERT and with total urinary excretion of glycosaminoglycans. J Inherit Metab Dis. 2013;36(2):247-255 3. Neufeld EF, Muenzer J: The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed November 29, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 4. Puckett Y, Mallorga-Hernandez A, Montano AM. Epidemiology of mucopolysaccharidoses (MPS) in the United States: challenges and opportunities. Orphanet J Rare Dis. 2021;16(1):241 5. Freeze HH. Genetic disorders of glycan degradation. In: Varki A, Cummings RD, Esko JD, et al, eds. Essentials of Glycobiology. 2nd ed. Cold Spring Harbor Laboratory Press; 2009. Accessed November 29, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1934/

MPSER
604905

Mucopolysaccharides Quantitative, Serum

Clinical Information: The mucopolysaccharidoses are a group of disorders caused by a deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin-6- sulfate, collectively called glycosaminoglycans (GAG). Undegraded or partially degraded GAG are stored in lysosomes and excreted in the urine. Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in mucopolysaccharidosis (MPS) disorders. Depending on the extent of the enzyme deficiency and type of accumulating storage material, MPS patients may present with a variety of clinical findings that can include coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature, and skeletal abnormalities. MPS I is an autosomal recessive disorder caused by reduced or absent activity of the enzyme alpha-L-iduronidase due to variants in the IDUA gene. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized as MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), which are not typically distinguishable via biochemical methods. Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting

of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroglossia, and respiratory tract infections. Developmental delay is noticed as early as 12 months of age, and death usually occurs before 10 years of age when left untreated. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-adolescence. Survival into adulthood is common. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy (ERT). MPS II (Hunter syndrome) is an X-linked lysosomal storage disorder caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents later in life with a milder clinical presentation. In general, symptoms may include coarse facial features, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. Due to the X-linked inheritance pattern, MPS II is observed almost exclusively in male patients with an estimated incidence of 1 in 170,000 male births. Female patients who are symptomatic carriers are very rare but have been reported. Treatment options include hematopoietic stem cell transplantation and ERT. MPS III (Sanfilippo syndrome) is caused by a reduced or absent activity of any 1 of 4 enzymes involved in heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. MPS III is characterized by severe central nervous system (CNS) degeneration but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPS. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the third decade of life (20s). The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. Treatment is limited to symptomatic management. MPS IVA (Morquio A syndrome) is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with ERT is available. MPS IVB (Morquio B syndrome) is caused by a reduced or absent beta-galactosidase activity, which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI (Maroteaux-Lamy syndrome) is an autosomal recessive lysosomal storage disorder caused by the deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Rapidly progressing forms have an early onset of symptoms, significantly elevated GAG especially dermatan sulfate, and can lead to death before the second or third decade of life. A more slowly progressing form has a later onset, milder skeletal manifestations, smaller elevations of GAG, and typically a longer lifespan. Estimates of the incidence of MPS VI range from 1 in 250,000 to 1 in 300,000. Treatment options include hematopoietic stem cell transplantation and ERT. MPS VII (Sly syndrome) is caused by a deficiency of the enzyme beta-glucuronidase and is extremely rare. The phenotype varies significantly from mild to severe presentations and may include macrocephaly, short stature, dysostosis multiplex,

hepatomegaly, coarse facies, and impairment of cognitive function. Likewise, the age of onset is variable ranging from prenatal to adulthood. Treatment options include hematopoietic stem cell transplantation and ERT. Elevations of dermatan sulfate and/or heparan sulfate are seen MPS types I, II, III, VI, and VII. Elevations of keratan sulfate are seen in MPS types IVA and IVB.

Useful For: Quantification of dermatan sulfate, heparan sulfate, and keratan sulfate in serum to support the biochemical diagnosis of mucopolysaccharidoses types I, II, III, IV, VI, or VII

Interpretation: Elevations of dermatan sulfate, heparan sulfate, and/or keratan sulfate may be indicative of one of the mucopolysaccharidoses types I, II, III, IV, VI, or VII. Elevations of all three sulfate species may be indicative of multiple sulfatase deficiency. Rarely, an elevation of keratan sulfate may be indicative of alpha-fucosidosis.

Reference Values:
DERMATAN SULFATE
< or =300.00 ng/mL

HEPARAN SULFATE
< or =55.00 ng/mL

TOTAL KERATAN SULFATE
< or =5 years: < or =1800.00 ng/mL
6-18 years: < or =1500.00 ng/mL
> or =19 years: < or =1200.00 ng/mL

Clinical References: 1. de Ruijter J, de Ru MH, Wagemans T, et al. Heparan sulfate and dermatan sulfate derived disaccharides are sensitive markers for newborn screening for mucopolysaccharidoses types I, II and III. Mol Genet Metab. 2012;107(4):705-710 2. de Ru MH, van der Tol L, van Vlies N, et al. Plasma and urinary levels of dermatan sulfate and heparan sulfate derived disaccharides after long-term enzyme replacement (ERT) in MPS I: correlation with the timing of ERT and with total urinary excretion of glycosaminoglycans. J Inherit Metab Dis. 2013;36(2):247-255 3. Osago H, Shibata T, Hara N, et al. Quantitative analysis of glycosaminoglycans, chondroitin/dermatan sulfate, hyaluronic acid, heparan sulfate, and keratan sulfate by liquid chromatography-electrospray ionization-tandem mass spectrometry. Anal Biochem. 2014;467:62-74 4. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed November 29, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 5. Puckett Y, Mallorga-Hernandez A, Montano AM. Epidemiology of mucopolysaccharidoses (MPS) in the United States: challenges and opportunities. Orphanet J Rare Dis. 2021;16(1):241

MP8BS
616836

Mucopolysaccharidoses, Eight-Enzyme Panel, Blood Spot

Clinical Information: The mucopolysaccharidoses (MPS) are a group of disorders caused by a deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate also known as glycosaminoglycans (GAG). Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs. There are 11 known disorders that involve the accumulation of GAG which affects multiple organ systems. These disorders have a broad clinical spectrum and can present with coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature, and skeletal abnormalities. This assay detects 8 of the 11 known MPS, including MPSII, MPSIIIA, MPSIIIB, MPSIIIC, MPSIVA, MPSIVB, MPSVI, and MPSVII. Multiple sulfatase deficiency (MSD) is a rare autosomal recessive lysosomal disorder caused by mutations in the sulfatase-modifying factor 1 (SUMF1) gene. SUMF1

encodes for a formylglycine-generating enzyme that performs a critical posttranslational modification necessary for activation of all human sulfatases, including arylsulfatase A and B. The clinical features of MSD resemble symptoms of every single sulfatase deficiency, including metachromatic leukodystrophy, the mucopolysaccharidoses, X-linked ichthyosis, and chondrodysplasia punctata type I. Age of onset and clinical severity are variable and correspond with the level of residual enzyme activity. Individuals with MSD typically demonstrate reduced activity of several sulfatase enzymes including those on this panel (iduronate-2-sulfatase, heparan sulfate sulfatase, galactosamine-6-sulfate sulfatase, and arylsulfatase B). Mucolipidosis II (MLII), also known as I-cell disease, is a rare autosomal recessive disorder with features of both mucopolysaccharidoses and sphingolipidoses. I-cell disease is a progressive disorder characterized by congenital or early infantile manifestations including coarse facial features, short stature, skeletal anomalies, cardio- and hepatomegaly, and developmental delays. While not intended for I-cell disease, a pattern of reduced activity of several enzymes and increased activity of others may indicate MLII.

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidoses types II, IIIA, IIIB, IIIC, IVA, IVB, VI, and VII, and of multiple sulfatase deficiency This test is not useful for carrier detection.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular genetic analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

Iduronate-2-sulfatase: >4.30 nmol/mL/hour
Heparan-N-sulfatase: >0.06 nmol/mL/hour
N-acetyl-alpha-D-glucosaminidase: >0.70 nmol/mL/hour
Heparan-alpha-glucosaminide N-acetyltransferase: >0.50 nmol/mL/hour
N-acetylgalactosamine-6-sulfatase: >0.70 nmol/mL/hour
Beta-galactosidase: >1.30 nmol/mL/hour
Arylsulfatase B: >0.90 nmol/mL/hour
Beta-glucuronidase: >2.60 nmol/mL/hour

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. Eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 18, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ, Ballabio A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. Eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 18, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546905

MP9W
616837

Mucopolysaccharidoses, Nine-Enzyme Panel, Leukocytes

Clinical Information: The mucopolysaccharidoses (MPS) are a group of disorders caused by a deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate, also known as glycosaminoglycans (GAG). Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs. There are 11 known disorders that involve the accumulation of GAG which affects multiple organ systems. These disorders

have a broad clinical spectrum and can present with coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature, and skeletal abnormalities. This assay detects 9 of the 11 known MPS, including MPSII, MPSIIIA, MPSIIIB, MPSIIIC, MPSIIID, MPSIVA, MPSIVB, MPSVI, and MPSVII. Multiple sulfatase deficiency (MSD) is a rare autosomal recessive lysosomal disorder caused by mutations in the sulfatase-modifying factor 1 (SUMF1) gene. SUMF1 encodes for a formylglycine-generating enzyme that performs a critical posttranslational modification necessary for activation of all human sulfatases, including arylsulfatase A and B. The clinical features of MSD resemble symptoms of every single sulfatase deficiency, including metachromatic leukodystrophy, the mucopolysaccharidoses, X-linked ichthyosis, and chondrodysplasia punctata type I. Individuals with MSD typically demonstrate reduced activity of several sulfatase enzymes including those on this panel (iduronate-2-sulfatase, heparan sulfate sulfatase, galactosamine-6-sulfate sulfatase, N-acetylglucosamine-6-sulfatase, and arylsulfatase B). Mucolipidosis II (MLII), also known as I-cell disease, is a rare autosomal recessive disorder with features of both mucopolysaccharidoses and sphingolipidoses. I-cell disease is a progressive disorder characterized by congenital or early infantile manifestations including coarse facial features, short stature, skeletal anomalies, cardio- and hepatomegaly, and developmental delays. While not intended for I-cell disease, a pattern of reduced activity of several enzymes may indicate MLII.

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidoses types II, IIIA, IIIB, IIIC, IIID, IVA, IVB, VI, and VII, and of multiple sulfatase deficiency This test is not useful for carrier detection.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
Iduronate-2-sulfatase: >2.20 nmol/hour/mg protein

Heparan-N-sulfatase: >0.13 nmol/hour/mg protein

N-acetyl-alpha-D-glucosaminidase: >0.09 nmol/hour/mg protein

Heparan-alpha-glucosaminide N-acetyltransferase: >0.24 nmol/hou/mg protein

N-acetylglucosamine-6-sulfatase: >0.03 nmol/hour/mg protein

N-acetylgalactosamine-6-sulfatase: >1.60 nmol/hour/mg protein

Beta-galactosidase: >0.28 nmol/hour/mg protein

Arylsulfatase B: >0.34 nmol/hour/mg protein

Beta-glucuronidase: >3.50 nmol/hour/mg protein

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 17, 2023. Available at

https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ, Ballabio A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 17, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546905

MPS3W
618293

Mucopolysaccharidosis III, Four-Enzyme Panel, Leukocytes

Clinical Information: Mucopolysaccharidosis III (MPS III; Sanfilippo syndrome) is caused by reduced or absent activity of 1 of 4 enzymes involved in heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. MPS III is characterized by severe central nervous system (CNS) degeneration but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPS. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years of age in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age accompanied by a rapid deterioration of social and adaptive skills with death generally occurring by their 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. This assay detects all MPSIII types (MPS IIIA, IIIB, IIIC, and IIID). A diagnostic workup for MPS typically also includes GAG determination in urine (MPSQU / Mucopolysaccharides Quantitative, Random, Urine) or blood (MPSBS / Mucopolysaccharidosis, Blood Spot, or MPSER / Mucopolysaccharides Quantitative, Serum) and molecular genetic analysis of the relevant gene(s). For MPS III, a molecular panel is available that includes SGSH, NAGLU, GNS, HGSNAT (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-7YM613).

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidoses types IIIA, IIIB, IIIC, IIID This test is not useful for carrier detection.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
HEPARAN-N-SULFATASE:
>0.13 nmol/hour/mg protein

N-ACETYL-ALPHA-D-GLUCOSAMINIDASE:
>0.09 nmol/hour/mg protein

HEPARAN-ALPHA-GLUCOSAMINIDE N-ACETYLTRANSFERASE:
>0.24 nmol/hour/mg protein

N-ACETYLGLUCOSAMINE-6-SULFATASE:
>0.03 nmol/hour/mg protein

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 18, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ, Ballabio A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 18, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546905

MPS3B
618292

Mucopolysaccharidosis III, Three-Enzyme Panel, Blood Spot

Clinical Information: Mucopolysaccharidosis III (MPS III; Sanfilippo syndrome) is caused by reduced or absent activity of 1 of 4 enzymes involved in heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. MPS III is characterized by severe central nervous system (CNS) degeneration but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPS. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years of age in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age accompanied by a rapid deterioration of social and adaptive skills with death generally occurring by their 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. This assay detects 3 of the 4 MPSIII types (MPS IIIA, IIIB, and IIIC). A diagnostic workup for MPS typically also includes GAG determination in urine (MPSQU / Mucopolysaccharides Quantitative, Random, Urine) or blood (MPSBS / Mucopolysaccharidosis, Blood Spot or MPSER / Mucopolysaccharides Quantitative, Serum) and molecular genetic analysis of the relevant gene(s). For MPS III, a molecular panel is available that includes SGSH, NAGLU, GNS, HGSNAT (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-7YM613).

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidoses types IIIA, IIIB, IIIC
This test is not useful for carrier detection.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular genetic analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
HEPARAN-N-SULFATASE:
>0.06 nmol/mL/hour

N-ACETYL-ALPHA-D-GLUCOSAMINIDASE:
>0.70 nmol/mL/hour

HEPARAN-ALPHA-GLUCOSAMINIDE N-ACETYLTRANSFERASE:
>0.50 nmol/mL/hour

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 17, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ, Ballabio A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 17, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546905

MPS4B
618294

Mucopolysaccharidosis IV Enzyme Panel, Blood Spot

Clinical Information: Mucopolysaccharidosis IVA, (MPS IVA; Morquio A syndrome) is caused by reduced or absent N-acetylgalactosamine-6-sulfate sulfatase (GALNS) enzyme activity. The glycosaminoglycans, keratan and chondroitin sulfate, accumulate in multiple tissues but mainly bone, cartilage, heart valves, and cornea. Clinical features and severity of symptoms of MPS IVA are widely variable affecting multiple body systems, in particular the skeletal system. Other clinical features may include short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Mucopolysaccharidosis type IVB (MPS IVB or Morquio syndrome B) is caused by reduced or absent beta-galactosidase activity leading to the accumulation of glycosaminoglycans, particularly keratan sulfate. MPS IVB typically manifests as a systemic skeletal disorder with variable severity ranging from early severe disease to a later onset attenuated form. Virtually all patients have dysostosis multiplex and short stature along with other symptoms that may include coarse facies, hepatosplenomegaly, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. GM1 gangliosidosis is also caused by reduced or absent beta-galactosidase activity, however the clinical features include neurological involvement in addition to the skeletal and other systemic findings associated with MPS IVB. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. Galactosialidosis is associated with a combined deficiency of beta-galactosidase and neuraminidase secondary to a defect in the cathepsin A protein. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. Typical clinical presentation is coarse facial features, cherry-red spots, and skeletal dysplasia. The early infantile form is associated with fetal hydrops, skeletal dysplasia, and early death, while the late infantile form is characterized by short stature, dysostosis multiplex, coarse facial features, corneal clouding, hepatosplenomegaly, and heart valve problems. A diagnostic workup for MPS typically also includes glycosaminoglycan (GAG) determination in urine (MPSQU / Mucopolysaccharides Quantitative, Random, Urine) or blood (MPSBS / Mucopolysaccharidosis, Blood Spot, or MPSER / Mucopolysaccharidosis Quantitative, Serum) and molecular genetic analysis of the relevant gene. For MPS IVA, molecular analysis of the GALNS gene (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: EMCP-JUFPRX) and for MPS IVB and GM1 gangliosidosis, molecular analysis of the GLB1 gene (CGPH; specify Gene List ID: EMCP-D5F3YS) allows for detection of disease-causing variants in affected patients and subsequent carrier detection in relatives. A diagnostic workup for galactosialidosis traditionally includes determination of beta-galactosidase enzyme activity in leukocytes or fibroblasts and neuraminidase activity in fibroblasts followed by molecular analysis of CTSA (CGPH; specify Gene List ID: IEMCP-D1J7U5). Analysis of urine mucopolysaccharides, oligosaccharides, ceramide trihexoside, and sulfatides (LSDS / Lysosomal Storage Disorders Screen, Random, Urine) can help differentiate between galactosialidosis, MPS IVA, and MPS IVB/GM1 to guide physicians in choosing the best confirmatory molecular testing option. See Lysosomal Disorders Diagnostic Algorithm, Part 1 .

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidosis type IVA and IVB This test is not useful for carrier detection.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses

are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular genetic analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

N-acetylgalactosamine-6-sulfatase: >0.70 nmol/mL/hour
Beta-galactosidase: >1.30 nmol/mL/hour

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 14, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ, Ballabio A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 14, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546905

MPS4W 618295 Mucopolysaccharidosis IV Enzyme Panel, Leukocytes

Clinical Information: Mucopolysaccharidosis IVA, (MPS IVA; Morquio A syndrome) is caused by reduced or absent N-acetylgalactosamine-6-sulfate sulfatase (GALNS) enzyme activity. The glycosaminoglycans, keratan and chondroitin sulfate, accumulate in multiple tissues but mainly bone, cartilage, heart valves, and cornea. Clinical features and severity of symptoms of MPS IVA are widely variable affecting multiple body systems, in particular the skeletal system. Other clinical features may include short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Mucopolysaccharidosis type IVB (MPS IVB or Morquio syndrome B) is caused by reduced or absent beta-galactosidase activity leading to the accumulation of glycosaminoglycans, particularly keratan sulfate. MPS IVB typically manifests as a systemic skeletal disorder with variable severity ranging from early severe disease to a later onset attenuated form. Virtually all patients have dysostosis multiplex and short stature along with other symptoms that may include coarse facies, hepatosplenomegaly, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. GM1 gangliosidosis is also caused by reduced or absent beta-galactosidase activity, however the clinical features include neurological involvement in addition to the skeletal and other systemic findings associated with MPS IVB. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. Galactosialidosis is associated with a combined deficiency of beta-galactosidase and neuraminidase secondary to a defect in the cathepsin A protein. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. Typical clinical presentation is coarse facial features, cherry-red spots, and skeletal dysplasia. The early infantile form is associated with fetal hydrops, skeletal dysplasia, and early death, while the late infantile form is characterized by short stature, dysostosis multiplex, coarse facial features, corneal clouding, hepatosplenomegaly, and heart valve problems. A diagnostic workup for MPS also includes glycosaminoglycan (GAG) determination in urine (MPSQU / Mucopolysaccharides Quantitative, Random, Urine) or blood (MPSBS / Mucopolysaccharidosis, Blood Spot or MPSER / Mucopolysaccharidosis Quantitative, Serum) and molecular genetic analysis of the relevant gene. For MPS IVA, molecular analysis of the GALNS gene (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-JUFPRX) and for MPS IVB and GM1 gangliosidosis, molecular analysis of the GLB1 gene (CGPH; specify Gene List ID: IEMCP-D5F3YS) allows for detection of disease-causing variants in affected patients and subsequent carrier detection in relatives. A diagnostic workup for galactosialidosis traditionally includes determination of beta-

galactosidase enzyme activity in leukocytes or fibroblasts and neuraminidase activity in fibroblasts followed by molecular analysis of CTSA (CGPH; specify Gene List ID: IEMCP-D1J7U5). Analysis of urine mucopolysaccharides, oligosaccharides, ceramide trihexoside, and sulfatides (LSDS / Lysosomal Storage Disorders Screen, Random, Urine) can help differentiate between galactosialidosis, MPS IVA, and MPS IVB/GM1 to guide physicians in choosing the best confirmatory molecular testing option. See Lysosomal Disorders Diagnostic Algorithm, Part 1.

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidosis type IVA and IVB in whole blood specimens This test is not useful for carrier detection.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
N-acetylgalactosamine-6-sulfatase: >1.60 nmol/hour/mg protein
Beta-galactosidase: >0.28 nmol/hour/mg protein

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 14, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ, Ballabio A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 14, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546905

MPSWB
113435

Mucopolysaccharidosis, Blood

Clinical Information: The mucopolysaccharidoses (MPS) are a group of disorders caused by a deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAG, also called mucopolysaccharides). Undegraded or partially degraded GAG are stored in lysosomes and excreted in the urine. Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. Depending on the extent of the enzyme deficiency and type of accumulating storage material, MPS patients may present with a variety of clinical findings, including coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature, and skeletal abnormalities. MPS I is an autosomal recessive disorder caused by reduced or absent activity of the enzyme alpha-L-iduronidase due to variants in the IDUA gene. This enzyme deficiency results in a wide range of clinical phenotypes, which cannot be distinguished via biochemical methods and are further categorized as MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome). Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroglossia, and respiratory tract infections. Developmental delay is noticed as early as 12 months, and without treatment, death usually occurs before 10 years of age. MPS IH/S has an intermediate clinical presentation

characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS II, Hunter syndrome, is an X-linked lysosomal storage disorder caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents later in life with a milder clinical presentation. In general, symptoms may include coarse facial features, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. Due to the X-linked inheritance pattern, MPS II is observed almost exclusively in male patients with an estimated incidence of 1 in 170,000 male births. Symptomatic female carriers have been reported but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS-III, Sanfilippo syndrome, is caused by a reduced or absent activity of 1 of 4 enzymes involved in heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. MPS-III is characterized by severe central nervous system (CNS) degeneration but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPS. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years of age in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills with death generally occurring by their 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. MPS IVA, Morquio A syndrome, is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase activity. Clinical features and severity of symptoms of MPS IVA are widely variable but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is available. MPS IVB, Morquio B syndrome, is caused by a reduced or absent beta-galactosidase activity, which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable, ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI, Maroteaux-Lamy syndrome, is an autosomal recessive lysosomal storage disorder caused by the deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Rapidly progressing forms have an early onset of symptoms, significantly elevated GAG (especially dermatan sulfate), and can lead to death before the second or third decade. A more slowly progressing form has a later onset, milder skeletal manifestations, smaller elevations of GAG, and typically a longer lifespan. Estimates of the incidence of MPS VI range from 1 in 250,000 to 1 in 300,000. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Elevations of dermatan or heparan sulfate are seen in MPS types I, II, III, and VI. Elevations of keratan sulfate are seen in MPS IV.

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidoses type I, II, III, IV, or VI
Quantification of heparan sulfate, dermatan sulfate, and keratan sulfate in whole blood specimens

Interpretation: Elevations of dermatan sulfate and/or heparan sulfate may be indicative of one of the mucopolysaccharidoses types I, II, III, or VI. Elevations of keratan sulfate may be indicative of mucopolysaccharidoses type IV.

Reference Values:

DERMATAN SULFATE (DS)
Newborn-< or =2 weeks: < or =200 nmol/L
>2 weeks: < or =130 nmol/L

HEPARAN SULFATE (HS)
Newborn-< or =2 weeks: < or =96 nmol/L
>2 weeks: < or =95 nmol/L

TOTAL KERATAN SULFATE (KS)
< or =5 years: < or =1900 nmol/L
6-10 years: < or =1750 nmol/L
11-15 years: < or =1500 nmol/L
>15 years: < or =750 nmol/L

Clinical References: 1. Newborn Screening ACT Sheet [alpha-L-iduronidase deficiency with or without glycosaminoglycan (GAG) accumulation] Mucopolysaccharidosis Type I (MPS I). American College of Medical Genetics and Genomics; 2023. Updated November 2023. Accessed June 10, 2024. Available at www.acmg.net/PDFLibrary/MPSI-ACT-Sheet.pdf 2. de Ruijter J, de Ru MH, Wagemans T, et al. Heparan sulfate and dermatan sulfate derived disaccharides are sensitive markers for newborn screening for mucopolysaccharidoses types I, II and III. Mol Genet Metab. 2012;107(4):705-710 3. de Ru MH, van der Tol L, van Vlies N, et al. Plasma and urinary levels of dermatan sulfate and heparan sulfate derived disaccharides after long-term enzyme replacement (ERT) in MPS I: correlation with the timing of ERT and with total urinary excretion of glycosaminoglycans. J Inherit Metab Dis. 2013;36(2):247-255 4. Osago H, Shibata T, Hara N, et al. Quantitative analysis of glycosaminoglycans, chondroitin/dermatan sulfate, hyaluronic acid, heparan sulfate, and keratan sulfate by liquid chromatography-electrospray ionization-tandem mass spectrometry. Anal Biochem. 2014 15;467:62-74 5. Peck DS, Lacey JM, White AL et al. Incorporation of second-tier biomarker testing improves the specificity of newborn screening for mucopolysaccharidosis type I. Int J Neonatal Screen. 2020;6(1):10. doi:10.3390/ijns6010010 6. Clarke LA, Dickson P, Ellinwood NM, Klein TL. Newborn screening for mucopolysaccharidosis I: Moving forward learning from experience. Int J Neonatal Screen. 2020;6(4):91. doi:10.3390/ijns6040091

MPSBS
65095

Mucopolysaccharidosis, Blood Spot

Clinical Information: The mucopolysaccharidoses (MPS) are a group of disorders caused by a deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAG, also called mucopolysaccharides). Undegraded or partially degraded GAG are stored in lysosomes and excreted in the urine. Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. Depending on the extent of the enzyme deficiency and type of accumulating storage material, MPS patients may present with a variety of clinical findings, including coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature, and skeletal abnormalities. MPS I is an autosomal recessive disorder caused by reduced or absent activity of the enzyme alpha-L-iduronidase due to variants in the IDUA gene. This enzyme deficiency results in a wide range of clinical phenotypes, which cannot be distinguished via biochemical methods and are further categorized as MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome). Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroglossia,

and respiratory tract infections. Developmental delay is noticed as early as 12 months, and without treatment, death usually occurs before 10 years of age. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS II, Hunter syndrome, is an X-linked lysosomal storage disorder caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents later in life with a milder clinical presentation. In general, symptoms may include coarse facial features, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. Due to the X-linked inheritance pattern, MPS II is observed almost exclusively in male patients with an estimated incidence of 1 in 170,000 male births. Symptomatic female carriers have been reported but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS-III, Sanfilippo syndrome, is caused by a reduced or absent activity of 1 of 4 enzymes involved in heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPS. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years of age in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills with death generally occurring by their 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. MPS IVA, Morquio A syndrome, is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase activity. Clinical features and severity of symptoms of MPS IVA are widely variable but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is available. MPS IVB, Morquio B syndrome, is caused by a reduced or absent beta-galactosidase activity, which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable, ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI, Maroteaux-Lamy syndrome, is an autosomal recessive lysosomal storage disorder caused by the deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Rapidly progressing forms have an early onset of symptoms, significantly elevated GAG (especially dermatan sulfate), and can lead to death before the second or third decade. A more slowly progressing form has a later onset, milder skeletal manifestations, smaller elevations of GAG, and typically a longer lifespan. Estimates of the incidence of MPS VI range from 1 in 250,000 to 1 in 300,000. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Elevations of dermatan and/or heparan sulfate are seen in MPS types I, II, III, and VI. Elevations of keratan sulfate are seen in MPS IV.

Useful For: Supporting the biochemical diagnosis of mucopolysaccharidoses types I, II, III, IV, or VI
Quantification of heparan sulfate, dermatan sulfate, and keratan sulfate in dried blood spot specimens

Interpretation: Elevations of dermatan sulfate and/or heparan sulfate may be indicative of one of the mucopolysaccharidoses: type I, II, III, or VI. Elevations of keratan sulfate may be indicative of mucopolysaccharidoses type IV.

Reference Values:
DERMATAN SULFATE (DS)
Newborn-< or =2 weeks: < or =200 nmol/L
>2 weeks: < or =130 nmol/L

HEPARAN SULFATE (HS)
Newborn-< or =2 weeks: < or =96 nmol/L
>2 weeks: < or =95 nmol/L

TOTAL KERATAN SULFATE (KS)
< or =5 years: < or =1,900 nmol/L
6-10 years: < or =1,750 nmol/L
11-15 years: < or =1,500 nmol/L
>15 years: < or =750 nmol/L

Clinical References: 1. Newborn Screening ACT Sheet [alpha-L-iduronidase deficiency with or without glycosaminoglycan (GAG) accumulation] Mucopolysaccharidosis Type I (MPS I). American College of Medical Genetics and Genomics; 2023. Updated November 2023. Accessed June 10, 2024. Available at www.acmg.net/PDFLibrary/MPSI-ACT-Sheet.pdf 2. de Ruijter J, de Ru MH, Wagemans T, et al. Heparan sulfate and dermatan sulfate derived disaccharides are sensitive markers for newborn screening for mucopolysaccharidoses types I, II and III. Mol Genet Metab. 2012;107(4):705-710 3. de Ru MH, van der Tol L, van Vlies N, et al. Plasma and urinary levels of dermatan sulfate and heparan sulfate derived disaccharides after long-term enzyme replacement (ERT) in MPS I: correlation with the timing of ERT and with total urinary excretion of glycosaminoglycans. J Inherit Metab Dis. 2013;36(2):247-255 4. Osago H, Shibata T, Hara N, et al. Quantitative analysis of glycosaminoglycans, chondroitin/dermatan sulfate, hyaluronic acid, heparan sulfate, and keratan sulfate by liquid chromatography-electrospray ionization-tandem mass spectrometry. Anal Biochem. 2014;467:62-74 5. Peck DS, Lacey JM, White AL, et al. Incorporation of second-tier biomarker testing improves the specificity of newborn screening for mucopolysaccharidosis type I. Int J Neonatal Screen. 2020;6(1):10. doi:10.3390/ijns6010010 6. Clarke LA, Dickson P, Ellinwood NM, Klein TL. Newborn screening for mucopolysaccharidosis I: Moving forward learning from experience. Int J Neonatal Screen. 2020;6(4):91. doi:10.3390/ijns6040091

MUC
82675

Mucor, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mucor Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MUG
82683

Mugwort, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mugwort Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the

specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MULB
82864

Mulberry, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mulberry Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen

specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

RETZZ
614587

Multiple Endocrine Neoplasia Type 2 Syndrome, RET, Full Gene Analysis, Varies

Clinical Information: Variants in the RET proto-oncogene are associated with two distinct and, in rare cases, overlapping clinical syndromes: multiple endocrine neoplasia type 2 (MEN2) and Hirschsprung disease (HSCR).(1) MEN2: MEN2 is an autosomal dominant cancer syndrome, which has classically been divided into 3 subtypes: MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC). The characteristic features of MEN2A include medullary thyroid carcinoma (MTC), pheochromocytoma, and primary hyperparathyroidism.(1-3) MEN2B is characterized by early-onset MTC, pheochromocytoma, mucosal neuromas, and distinctive facies with enlarged lips. Other features of MEN2B include enlarged nerves of the gastrointestinal tract (ganglioneuromatosis), marfanoid habitus, hypotonia, and corneal nerve thickening.(1-3) FMTC has traditionally been diagnosed in families of MTC in the absence of pheochromocytoma or parathyroid involvement. All MEN2 subtypes are inherited in an autosomal dominant inheritance pattern. The National Comprehensive Cancer Network and the American Thyroid Association provide recommendations regarding the medical management of individuals with MEN2 syndrome.(1,4) HSCR: HSCR, also known as aganglionic megacolon, is a congenital disorder of impaired intestinal motility.(1,5,6) Variable lengths of the colon may be affected, resulting in either total aganglionosis, long-segment HSCR, or short-segment HSCR. HSCR affects approximately 1 in 5000 live births and is resolved via surgical intervention.(1,5,6) HSCR can result from chromosome abnormalities, single gene disorders (both syndromic and non-syndromic), a combination of variants in multiple genes, and unknown causes.(1,5,6) However, disease-causing RET variants are considered the most common cause of HSCR cases, particularly in families

with multiple cases of HSCR and long-segment disease.(1,5,6) It has been reported that up to 50% of familial cases of HSCR and up to 33% of sporadic HSCR cases are due to RET germline variants.(1,5,6) While gain-of-function variants in RET are typically associated with MEN2, loss-of-function variants have been reported in patients with HSCR including full or partial RET gene deletions.(1) In addition to clearly disease-causing RET variants that cause HSCR, additional benign variants in RET (which may not be causative in themselves) confer increased susceptibility to HSCR.(1)

Useful For: Evaluating patients with a personal or family history suggestive of a multiple endocrine neoplasia type 2 (MEN2) or Hirschsprung disease (HSCR) Establishing a diagnosis of MEN2 or HSCR allowing for targeted cancer surveillance based on associated risks Identifying variants within genes known to be associated with MEN2 or HSCR allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

MRDMR 616031 Multiple Myeloma Minimal Residual Disease by Flow Cytometry, Bone Marrow

Clinical Information: Multiple myeloma is an incurable malignant neoplasm of plasma cells. One of the best prognostic factors in multiple myeloma is the level of minimal residual disease post chemotherapy or autologous stem cell transplantation. The greater depth of the response (less malignant cells present), the longer time to progression and overall survival.(1)

Useful For: Detecting low level (minimal residual disease) myeloma cells after therapy to confirm remission has been achieved

Interpretation: The interpretation of the test is done by evaluating automated and manually gated populations to isolate abnormal plasma cells. If there is an abnormal plasma cell population (cluster of 20 cells or more), then the result is minimal residual disease (MRD)-positive, with the percentage of abnormal plasma cells out of total analyzed events. If no abnormal population is found, then the result will be interpreted as MRD-negative. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the previous patient history will be provided by a hematopathologist for every case.

Reference Values:
Only orderable as a reflex. For more information see MSMRD / Myeloma Stratification and Risk-Adapted Therapy with Reflex to Minimal Residual Disease, Bone Marrow

An interpretive report will be provided.

Clinical References: 1. Martinez-Lopez J, Lahuerta JJ, Pepin F, et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. Blood. 2014 May;123(20):3073-3079 2. Rawstron AC, Child JA, de Tute RM, et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the medical research

council myeloma IX Study. J Clin Oncol. 2013;31(20):2540-2547 3. Roschewski M, Stetler-Stevenson M, Yuan C, et al. Minimal residual disease: What are the minimum requirements? J Clin Oncol. 2014 Feb 10;32(5):475-476 4. Stetler-Stevenson M, Paiva B, Stoolman L, et al. Consensus guidelines for myeloma minimal residual disease sample staining and data acquisition. Cytometry B Clin Cytom. 2016;90(1):26-30 doi: 10.1002/cyto.b.21249 5. Callander NS, Baljevic M, Adekola K, et al. NCCN Guidelines Insights: Multiple Myeloma, Version 3.2022. J Natl Compr Canc Netw. 2022;20(1):8-19. doi:10.6004/jnccn.2022.0002

MRDMM 65218 Multiple Myeloma Minimal Residual Disease, Flow Cytometry, Bone Marrow

Clinical Information: Multiple myeloma is an incurable malignant neoplasm of plasma cells. One of the best prognostic factors in multiple myeloma is the level of minimal residual disease post chemotherapy or autologous stem cell transplantation. The greater depth of the response (less malignant cells present), the longer time to progression and overall survival.(1)

Useful For: Detecting low level (minimal residual disease) myeloma cells after therapy.

Interpretation: The interpretation of the test is done by evaluating automated and manually gated populations to isolate abnormal plasma cells. If there is an abnormal plasma cell population (cluster of 20 cells or more), then the result is minimal residual disease (MRD)-positive, with the percentage of abnormal plasma cells out of total analyzed events. If no abnormal population is found, then the result will be interpreted as MRD-negative. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the previous patient history will be provided by a hematopathologist for every case.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Martinez-Lopez J, Lahuerta JJ, Pepin F, et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. Blood. 2014;123(20):3073-3079 2. Rawstron AC, Child JA, de Tute RM, et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the medical research council myeloma IX Study. J Clin Oncol. 2013;31(20):2540-2547 3. Roschewski M, Stetler-Stevenson M, Yuan C, et al. Minimal residual disease: What are the minimum requirements? J Clin Oncol. 2014;32(5):475-476 4. Stetler-Stevenson M, Paiva B, Stoolman L, et al. Consensus guidelines for myeloma minimal residual disease sample staining and data acquisition. Cytometry B Clin Cytom. 2016;90(1):26-30. doi:10.1002/cyto.b.21249 5. Callander NS, Baljevic M, Adekola K, et al. NCCN Guidelines Insights: Multiple Myeloma, Version 3.2022. J Natl Compr Canc Netw. 2022;20(1):8-19. doi: 10.6004/jnccn.2022.0002

MSP3 607837 Multiple Sclerosis (MS) Cascade, Serum and Spinal Fluid

Clinical Information: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease characterized by visual, motor, and sensory disturbances. The diagnosis of MS is dependent on clinical, radiological, and laboratory findings. The detection of increased intrathecal immunoglobulin synthesis is the basis for current diagnostic laboratory tests for MS. These tests include the kappa free light chain detection in cerebrospinal fluid (CSF) and CSF oligoclonal bands detection.

Useful For: Diagnosing multiple sclerosis, especially helpful in patients with equivocal clinical or

radiological findings

Interpretation: When result is less than 0.0600 mg/dL, the kappa free light-chain concentration measured in cerebrospinal fluid (CSF) is lower than the threshold associated with demyelinating disease. This is a negative result. Testing for oligoclonal banding is not performed. Clinical correlation is recommended. When result is between 0.0600 and 0.0999 mg/dL, this is a borderline result. These findings are not specific for multiple sclerosis (MS) because CSF-specific immunoglobulin synthesis may also be detected in patients with other neurologic diseases (infectious, inflammatory, cerebrovascular, autoimmune, and paraneoplastic). Clinical correlation is recommended. Automatic reflexing to oligoclonal bands will occur. When result is 0.1000 mg/dL or more, the kappa free light chain concentration measured in CSF is at or greater than the threshold associated with demyelinating disease. This is a positive result. These findings, however, are not specific for MS because CSF-specific immunoglobulin synthesis may also be detected in patients with other neurologic diseases (infectious, inflammatory, cerebrovascular, autoimmune, and paraneoplastic). Clinical correlation is recommended. Automatic reflexing to oligoclonal bands will occur. A Mayo Clinic study published in 2018 with 325 patients suggested that a kappa free light-chain concentration in CSF greater than or equal to 0.06 mg/dL has 92% clinical sensitivity for the diagnosis of MS.(1) A second, larger Mayo Clinic study with 1355 patients published in 2021 showed that a kappa CSF concentration greater than or equal to 0.06 mg/dL had approximately 89% sensitivity. When kappa value was greater than or equal to 0.1 mg/dL, it had similar sensitivity (87%) to the finding of two unique CSF oligoclonal bands (89%).(2) Given the difference in thresholds based on these studies and highest sensitivity at the threshold of 0.06 mg/dL, any CSF kappa free light-chain result greater than or equal to 0.06 mg/dL will reflex to oligoclonal banding when the multiple sclerosis cascade test is ordered. When the oligoclonal band assay detects 2 or more unique IgG bands in the CSF, the result is positive. Cerebrospinal fluid is used in the diagnosis of MS by identifying increased intrathecal IgG synthesis qualitatively (oligoclonal bands). The presence of 2 or more unique CSF oligoclonal bands was reintroduced as one of the diagnostic criteria for MS in the 2017 revised McDonald criteria.(3) These findings, however, are not specific for MS as CSF-specific IgG synthesis may also be found in patients with other neurologic diseases including infectious, inflammatory, cerebrovascular, and paraneoplastic disorders. Clinical correlation is recommended.

Reference Values:

KAPPA FREE LIGHT CHAIN
Medical decision point: 0.1000 mg/dL
Positive: > or =0.1000 mg/dL
Borderline: 0.0600 mg/dL-0.0999 mg/dL
Negative <0.0600 mg/dL

OLIGOCLONAL BANDS:
<2 bands

Clinical References: 1. Gurtner KM, Shosha E, Bryant SC, et al. CSF free light chain identification of demyelinating disease: comparison with oligoclonal banding and other CSF indexes. Clin Chem Lab Med. 2018;56(7):1071-1080 2. Saadeh RS, Bryant SC, McKeon A, et al. CSF kappa free light chains: cutoff validation for diagnosing multiple sclerosis. Mayo Clin Proc. 2022;97(4):738-751. doi:10.1016/j.mayocp.2021.09.014 3. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-173 4. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis: A review. JAMA. 2021;325(8):765-779. doi:10.1001/jama.2020.26858 5. Hegen H, Walde J, Milosavljevic D, et al. Free light chains in the cerebrospinal fluid. Comparison of different methods to determine intrathecal synthesis. Clin Chem Lab Med. 2019;57(10):1574-1586. doi:10.1515/cclm-2018-1300 6. Hegen H, Zinganell A, Auer M, Deisenhammer F. The clinical significance of single or double bands in cerebrospinal fluid isoelectric focusing. A retrospective study and systematic review. PLoS One. 2019;14(4):e0215410. doi:10.1371/journal.pone.0215410 7. Deisenhammer F, Zetterberg H, Fitzner B, Zettl UK. The Cerebrospinal fluid in multiple sclerosis. Front Immunol. 2019;10:726.

doi:10.3389/fimmu.2019.00726 8. Susse M, Hannich M, Petersmann A, et al. Kappa free light chains in cerebrospinal fluid to identify patients with oligoclonal bands. Eur J Neurol. 2018;25(9):1134-1139. doi:10.1111/ene.13667 9. Hegen H, Arrambide G, Gnanapavan S, et al. Cerebrospinal fluid kappa free light chains for the diagnosis of multiple sclerosis: A consensus statement. Mult Scler. 2023;29(2):182-195. doi:10.1177/13524585221134217 10. Hegen H, Walde J, Berek K, et al. Cerebrospinal fluid kappa free light chains for the diagnosis of multiple sclerosis: A systematic review and meta-analysis. Mult Scler. 2023;29(2):169-181. doi:10.1177/13524585221134213

MSDBS
618296

Multiple Sulfatase Deficiency, Blood Spot

Clinical Information: Multiple sulfatase deficiency (MSD) is a rare autosomal recessive lysosomal disorder caused by mutations in the sulfatase-modifying factor 1 (SUMF1) gene. SUMF1 encodes for a formylglycine-generating enzyme that performs a critical posttranslational modification necessary for activation of all human sulfatases, including arylsulfatase A and B. The clinical features of MSD encompass symptoms of every single sulfatase deficiency, including metachromatic leukodystrophy (MLD), the mucopolysaccharidoses, X-linked ichthyosis, and chondrodysplasia punctata type I. Age of onset and clinical severity are variable and correspond with the level of residual enzyme activity. A severe neonatal form of MSD closely overlaps the clinical presentation of the mucopolysaccharidoses, but it is often fatal within 1 year. Late-infantile MSD (onset 0-2 years) accounts for most cases and is characterized by a clinical presentation similar to MLD. A diagnostic workup for MSD demonstrates reduced enzyme activity of several sulfatase enzymes including those on this panel (iduronate-2-sulfatase, heparan sulfate sulfatase, galactosamine-6-sulfate sulfatase, and arylsulfatase B). Individuals with MSD typically have an increased urinary excretion of sulfatides as well as increased urinary glycosaminoglycans, therefore a combined analysis of urine ceramide trihexoside, mucopolysaccharides, oligosaccharides, and sulfatides (LSDS/ Lysosomal Storage Disorders Screen, Random, Urine) may support a diagnosis. Molecular genetic analysis of the SUMF1 gene (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-PCUBX1) allows for detection of disease-causing variants in affected patients and subsequent carrier detection in relatives.

Useful For: Supporting the biochemical diagnosis of multiple sulfatase deficiency This test is not useful for carrier detection.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular genetic analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
Iduronate-2-sulfatase: >4.30 nmol/mL/hour
Heparan-N-sulfatase: >0.06 nmol/mL/hour
N-acetylgalactosamine-6-sulfatase: >0.70 nmol/mL/hour

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 14, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ,

Ballabio A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 14, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225546905

MSDW
618297

Multiple Sulfatase Deficiency, Leukocytes

Clinical Information: Multiple sulfatase deficiency (MSD) is a rare autosomal recessive lysosomal disorder caused by mutations in the sulfatase-modifying factor 1 (SUMF1) gene. SUMF1 encodes for a formylglycine-generating enzyme that performs a critical posttranslational modification necessary for activation of all human sulfatases, including arylsulfatase A and B. The clinical features of MSD encompass symptoms of every single sulfatase deficiency, including metachromatic leukodystrophy (MLD), the mucopolysaccharidoses, X-linked ichthyosis, and chondrodysplasia punctata type I. Age of onset and clinical severity are variable and correspond with the level of residual enzyme activity. A severe neonatal form of MSD closely overlaps the clinical presentation of the mucopolysaccharidoses, but it is often fatal within 1 year. Late-infantile MSD (onset 0-2 years) accounts for most cases and is characterized by a clinical presentation similar to MLD. A diagnostic workup for MSD demonstrates reduced enzyme activity of several sulfatase enzymes including those on this panel (iduronate-2-sulfatase, heparan sulfate sulfatase, galactosamine-6-sulfate sulfatase, and arylsulfatase B). Individuals with MSD typically have an increased urinary excretion of sulfatides as well as increased urinary glycosaminoglycans, therefore a combined analysis of urine ceramide trihexoside, mucopolysaccharides, oligosaccharides, and sulfatides (LSDS/ Lysosomal Storage Disorders Screen, Random, Urine) may support a diagnosis. Molecular genetic analysis of the SUMF1 gene (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify Gene List ID: IEMCP-PCUBX1) allows for detection of disease-causing variants in affected patients and subsequent carrier detection in relatives.

Useful For: Supporting the biochemical diagnosis of multiple sulfatase deficiency in whole blood specimens This test is not useful for carrier detection.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular analysis), a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
Iduronate-2-sulfatase: >2.20 nmol/hour/mg protein
Heparan-N-sulfatase: >0.13 nmol/hour/mg protein
N-acetylglucosamine-6-sulfatase: >0.03 nmol/hour/mg protein
N-acetylgalactosamine-6-sulfatase: >1.60 nmol/hour/mg protein

An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 14, 2023. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161 2. Hopwood JJ, Ballabio A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 14, 2023.

MUM1B
603217

MUM-1/IRF4 Immunostain, Bone Marrow, Technical Component Only

Clinical Information: MUM-1 (multiple myeloma oncogene-1), expressed by the IRF4 gene, is seen in a subset of B cells in the light zone of the germinal center (representing late stages of B cell differentiation), plasma cells, activated T cells, and a variety of hematolymphoid neoplasms derived from these cells. Among non-hematolymphoid neoplasms, MUM-1 expression has been reported in melanomas. A separate protocol optimized for B5 fixed/decalcified bone marrow specimens has been validated.

Useful For: Aiding in the identification of hematolymphoid neoplasms and melanomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Rada G, Nagla S, Ali G: MUM1 and Ki67 Expression Best Predictors of Treatment Response in Diffuse Large B Cell Lymphoma Not Otherwise Specified. Amer J Clin Pathol. 2015 Oct;144(2,1):A147 2. Cozzolino I, Varone V, Picardi M, et al: CD10, BCL6, and MUM1 expression in diffuse large B-cell lymphoma on FNA samples. Cancer Cytopathol. 2016 Feb;124(2):135-143. doi:10.1002/cncy.21626 3. Heo MH, Park HY, Ko YH, Kim WS, Kim SJ: IRF4/MUM1 expression is associated with poor survival outcomes in patients with peripheral T-cell lymphoma. J Cancer. 2017 Mar;8(6):1018-1024. doi: 10.7150/jca.17358

MUM1
70514

MUM-1/IRF4 Immunostain, Technical Component Only

Clinical Information: MUM-1 (multiple myeloma oncogene-1), expressed by the IRF4 gene, is seen in a subset of B cells in the light zone of the germinal center (representing late stages of B cell differentiation), plasma cells, activated T cells, and a variety of hematolymphoid neoplasms derived from these cells. Among non-hematolymphoid neoplasms, MUM-1 expression has been reported in melanomas. A separate protocol optimized for B5 fixed/decalcified bone marrow specimens has been validated.

Useful For: Aids in the identification of hematolymphoid neoplasms and melanomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Rada G, Nagla S, Ali G. MUM1 and Ki67 expression best predictors of treatment response in diffuse large B cell lymphoma not otherwise specified. Am J Clin Pathol. 2015;144(2,1):A147 2. Cozzolino I, Varone V, Picardi M, et al. CD10, BCL6, and MUM1 expression in

diffuse large B-cell lymphoma on FNA samples. Cancer Cytopathol. 2016;124(2):135-143. doi:10.1002/cncy.21626 3. Heo MH, Park HY, Ko YH, Kim WS, Kim SJ. IRF4/MUM1 expression is associated with poor survival outcomes in patients with peripheral T-cell lymphoma. J Cancer. 2017;8(6):1018-1024. doi:10.7150/jca.17358 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CMUMP
81435

Mumps Virus Antibodies, IgG and IgM, Spinal Fluid

Clinical Information: There is only one serotype of mumps virus that infects humans. Mumps has been recognized since antiquity by virtue of the parotitis, which is often a striking clinical feature of the disease. Generally, a trivial childhood illness, the varied presentation of mumps reflects the widespread invasion of visceral organs and central nervous system that commonly follows infection with mumps virus.

Useful For: Aiding in the diagnosis of central nervous system infection by mumps virus

Interpretation: Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection.

Reference Values:
IgG: <1:5
IgM: <1:10
Reference values apply to all ages.

Clinical References: Litman N, Baum SG. Mumps virus. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2087-2092

MPPG
34947

Mumps Virus Antibody, IgG, Serum

Clinical Information: The mumps virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, measles, respiratory syncytial virus, and metapneumovirus. Mumps is highly infectious among unvaccinated individuals and is typically transmitted through inhalation of infected respiratory droplets or secretions. Following an approximately 2-week incubation period, symptom onset is typically acute with a prodrome of low-grade fever, headache, and malaise.(1,2) Painful enlargement of the salivary glands, the hallmark of mumps, occurs in approximately 60% to 70% of infections and in 95% of patients with symptoms. Testicular pain (orchitis) occurs in approximately 15% to 30% of postpubertal men and abdominal pain (oophoritis) is found in 5% of postpubertal women.(1) Other complications include mumps-associated pancreatitis (<5% of cases) and central nervous system disease (meningitis <10% and encephalitis <1%). Widespread routine immunization of infants with attenuated mumps virus has dramatically decreased the number of reported mumps cases in the United States. However, outbreaks continue to occur, indicating persistence of the virus in the general population. Laboratory diagnosis of mumps is typically accomplished by detection of IgM- and IgG-class antibodies to the mumps virus. However, due to the widespread mumps vaccination program, in clinically suspected cases of acute mumps infection, serologic testing should be supplemented with virus isolation in culture or detection of viral nucleic acid by polymerase chain reaction testing in throat, saliva, or urine specimens.

Useful For: Determination of postimmunization immune response of individuals to the mumps vaccine Documentation of previous infection with mumps virus in an individual with no previous record of immunization to mumps virus

Interpretation: Positive: The presence of detectable IgG-class antibodies indicates prior exposure to the mumps virus through infection or immunization. Individuals testing positive are considered immune to the mumps virus. Equivocal: Submit an additional specimen for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: The absence of detectable IgG-class antibodies suggests no prior exposure to the mumps virus or the lack of a specific immune response to immunization.

Reference Values:
Vaccinated: Positive (> or =1.1 AI)
Unvaccinated: Negative (< or =0.8 AI)
Reference values apply to all ages.

Clinical References: 1. Hviid A, Rubin S, Muhlemann K: Mumps. Lancet. 2008;371(9616):932-944 2. Hodinka RL, Moshal KL: Childhood infections. In: Storch GA ed. Essentials of Diagnostic Virology. Churchill Livingstone; 2000:168-178 3. Litman N, Baum SG: Mumps virus. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2087-2092

MMPGM 61854 Mumps Virus Antibody, IgM and IgG, Serum

Clinical Information: The mumps virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, measles, respiratory syncytial virus, and metapneumovirus. Mumps is highly infectious among unvaccinated individuals and is typically transmitted through inhalation of infected respiratory droplets or secretions. Following an approximate 2-week incubation period, symptom onset is typically acute with a prodrome of low-grade fever, headache, and malaise.(1,2) Painful enlargement of the salivary glands, the hallmark of mumps, occurs in approximately 60% to 70% of infections and in 95% of patients with symptoms. Testicular pain (orchitis) occurs in approximately 15% to 30% of postpubertal men and abdominal pain (oophoritis) is found in 5% of postpubertal women.(1) Other complications include mumps-associated pancreatitis (<5% of cases) and central nervous system disease (meningitis <10% and encephalitis <1%). Widespread routine immunization of infants with attenuated mumps virus has dramatically decreased the number of reported mumps cases in the United States. However, outbreaks continue to occur, indicating persistence of the virus in the general population. Laboratory diagnosis of mumps is typically accomplished by detection of IgM- and IgG-class antibodies to the mumps virus. However, due to the widespread mumps vaccination program, in clinically suspected cases of acute mumps infection, serologic testing should be supplemented with virus isolation in culture or detection of viral nucleic acid by polymerase chain reaction testing in throat, saliva, or urine specimens.

Useful For: Diagnosis of mumps virus infection Determination of postimmunization immune response of individuals to the mumps vaccine Documentation of previous infection with mumps virus in an individual with no previous record of immunization to mumps virus

Interpretation: A positive IgG result coupled with a positive IgM result suggests recent infection with mumps virus. This result should not be used alone to diagnose mumps infection and should be interpreted in the context of clinical presentation. A positive IgG result coupled with a negative IgM result indicates previous vaccination to or infection with mumps virus. These individuals are considered to have protective immunity to reinfection. A negative IgG result coupled with a negative IgM result indicates the absence of prior exposure to mumps virus and nonimmunity. However, a negative result

does not rule-out mumps infection or response to vaccination. The specimen may have been collected before the appearance of detectable antibodies. Negative results in suspected early mumps infection or within a week following vaccination should be followed by testing a new serum specimen in 2 to 3 weeks. Equivocal results should be followed up with testing of a new serum specimen within 10 to 14 days.

Reference Values:

IgM:
Negative: Index value 0.00-0.79
Reference value applies to all ages.

IgG:
Vaccinated: Positive (> or =1.1 AI)
Unvaccinated: Negative (< or =0.8 AI)
Reference values apply to all ages.

Clinical References: 1. Hviid A, Rubin S, Muhlemann K. Mumps. Lancet. 2008;371(9616):932-944 2. Hodinka RL, Moshal KL. Childhood infections. In: Storch GA, ed. Essentials of Diagnostic Virology. Churchill Livingstone; 2000:168-178 3. Litman N, Baum SG. Mumps virus. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2087-2092

MMPM
80977

Mumps Virus Antibody, IgM, Serum

Clinical Information: The mumps virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, measles, respiratory syncytial virus, and metapneumovirus. Mumps is highly infectious among unvaccinated individuals and is typically transmitted through inhalation of infected respiratory droplets or secretions. Following an approximately 2-week incubation period, symptom onset is typically acute with a prodrome of low-grade fever, headache, and malaise.(1,2) Painful enlargement of the salivary glands, the hallmark of mumps, occurs in approximately 60% to 70% of infections and in 95% of patients with symptoms. Testicular pain (orchitis) occurs in approximately 15% to 30% of postpubertal men and abdominal pain (oophoritis) is found in 5% of postpubertal women.(1) Other complications include mumps-associated pancreatitis (<5% of cases) and central nervous system disease (meningitis <10% and encephalitis <1%). Widespread routine immunization of infants with attenuated mumps virus has dramatically decreased the number of reported mumps cases in the United States. However, outbreaks continue to occur, indicating persistence of the virus in the general population. Laboratory diagnosis of mumps is typically accomplished by detection of IgM- and IgG-class antibodies to the mumps virus. However, due to the widespread mumps vaccination program, in clinically suspected cases of acute mumps infection, serologic testing should be supplemented with virus isolation in culture or detection of viral nucleic acid by polymerase chain reaction testing in throat, saliva, or urine specimens.

Useful For: Laboratory diagnosis of mumps virus infection

Interpretation: Positive: Presence of IgM-class antibodies to mumps virus may support a clinical diagnosis of recent or acute phase infection with this virus. Negative: Absence of IgM-class antibodies to mumps virus suggests lack of acute phase infection with mumps virus. However, serology may be negative in early disease, and results should be interpreted in the context of clinical findings.

Reference Values:

Negative: Index value 0.00-0.79
Reference value applies to all ages.

Clinical References: 1. Hviid A, Rubin S, Muhlemann K. Mumps. Lancet. 2008;371(9616):932-944 2. Hodinka RL, Moshal KL. Childhood infections. In: Storch GA, ed. Essentials of Diagnostic Virology. Churchill Livingstone; 2000:168-178 3. Harmsen T, Jongerius MC, van der Zwan CW, Plantinga AD, Kraaijeveld CA, Berbers GA. Comparison of a neutralization enzyme immunoassay and an enzyme-linked immunosorbent assay for evaluation of immune status of children vaccinated for mumps. J Clin Microbiol. 1992;30(8):2139-2144 4. Litman N, Baum SG. Mumps virus. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2087-2092

MUMPR
617823

Mumps Virus, Molecular Detection, PCR, Buccal

Clinical Information: The mumps virus is a single-stranded, negative-sense RNA paramyxovirus belonging to the Rubulavirus family. Symptoms of infection include painful swollen salivary glands (parotitis), fever, headache, muscle aches, weakness, and fatigue. Complications may include pancreatitis, orchitis, encephalitis, meningitis, or hearing loss. Oftentimes, mumps is diagnosed based on the characteristic swollen salivary glands. The mumps virus is spread person-to-person through contact with infected respiratory droplets or saliva. It can also be transmitted by direct contact with contaminated fomites. Laboratory diagnosis of mumps cases can be through serologic detection of mumps-specific IgM antibodies, molecular detection of mumps virus RNA, or viral culture. The use of real-time polymerase chain reaction assays can provide more rapid laboratory confirmation of mumps shortly after symptom onset compared to serologic testing and provides a shorter turnaround time than viral culture. Buccal swabs are the preferred specimen type for the detection of mumps virus, but urine may also be collected for viral detection.

Useful For: Rapid qualitative detection of mumps virus using buccal swab specimens

Interpretation: A positive result indicates the presence of mumps virus RNA in the specimen.

Reference Values:
Negative

Clinical References: 1. Grennan D: Mumps. JAMA. 2019;322(10):1022 2. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases: Mumps For Healthcare Providers. CDC; Updated March 08, 2021. Accessed September 13, 2022. Available at www.cdc.gov/mumps/hcp.html 3. Su SB, Chang HL, Chen AK: Current status of mumps virus infection: Epidemiology, pathogenesis, and vaccine. Int J Environ Res Public Health. 2020;17(5):1686

MUMPU
617824

Mumps Virus, Molecular Detection, PCR, Random, Urine

Clinical Information: The mumps virus is a single-stranded, negative-sense RNA paramyxovirus belonging to the Rubulavirus family. Symptoms of infection include painful swollen salivary glands (parotitis), fever, headache, muscle aches, weakness, and fatigue. Complications may include pancreatitis, orchitis, encephalitis, meningitis, or hearing loss. Oftentimes, mumps is diagnosed based on the characteristic swollen salivary glands. The mumps virus is spread person-to-person through contact with infected respiratory droplets or saliva. It can also be transmitted by direct contact with contaminated fomites. Laboratory diagnosis of mumps cases can be through serologic detection of mumps-specific IgM antibodies, molecular detection of mumps virus RNA, or viral culture. The use of real-time polymerase chain reaction assays can provide more rapid laboratory confirmation of mumps shortly after symptom onset compared to serologic testing and provides a shorter turnaround time than viral culture. Buccal swabs are the preferred specimen type for the detection of mumps virus, but urine may also be collected for viral detection.

Useful For: Rapid qualitative detection of mumps virus using random urine specimens

Interpretation: A positive result indicates the presence of mumps virus RNA in the specimen.

Reference Values:
Negative

Clinical References: 1. Grennan D: Mumps. JAMA. 2019;322(10):1022 2. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases: Mumps For Healthcare Providers. CDC; Updated March 08, 2021. Accessed September 13, 2022. Available at www.cdc.gov/mumps/hcp.html 3. Su SB, Chang HL, Chen AKT: Current status of mumps virus infection: Epidemiology, pathogenesis, and vaccine. Int J Environ Res Public Health. 2020;17(5):1686

FMTAG
57260

Murine Typhus Antibodies, IgG

Clinical Information:

Useful For: Detect antibodies following infection with murine typhus.

Reference Values:
Reference Interval:

Negative	<1:64
Present or Past	1:64
Recent/Active	>1:64

MBX
70594

Muscle Pathology Consultation

Clinical Information: Muscle diseases are a heterogeneous group of diseases that cause muscle weakness, muscle pain, and elevated creatine kinase. They can be acquired and potentially treatable or inherited. A muscle biopsy allows the diagnosis of a specific muscle disease and is helpful for guiding treatment and genetic testing, as well as investigating relevance of genetic variants of unknown significance. The Mayo Clinic Muscle Pathology Laboratory is staffed by neuromuscular neurologists with expertise in the whole spectrum of muscle pathology and complementary clinical competence, and research interest in muscle diseases. This unique set of skills ensures the highest quality of diagnostic muscle pathology in the shortest possible time to the patients, regardless of their geographic location. A series of 14 stains is routinely performed on each frozen muscle specimen. Client-submitted and in-house stained slides are reviewed in conjunction with the provided clinical history, electromyography, and other laboratory findings. A variety of ancillary studies are available (eg, immunohistochemistry, immunofluorescence) to aid in establishing the diagnosis. These ancillary studies are most efficiently utilized and interpreted in the context of the morphologic features. Each muscle pathology report includes a description of findings and diagnosis, as well as a comment to facilitate integration of pathological findings with other laboratory and clinical data and to guide subsequent testing (eg, serological or genetic tests). The goal is to provide the highest quality diagnostic service, while balancing optimal patient care with a cost-conscious approach to solve difficult diagnostic problems.

Useful For: Obtaining a rapid, expert opinion on muscle biopsy specimens for diagnosis of acquired or inherited muscle diseases Guiding treatment and genetic testing, as well as investigating relevance of genetic variants of unknown significance

Interpretation: Results are reported in a formal neuromuscular pathology report that includes

diagnosis and an interpretive comment, if necessary. The formal pathology report is faxed or sent by mail according to the preference of the referring institution.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Engel AG: The muscle biopsy. In: Engel AG, Franzini-Armstrong C, eds. Myology. 3rd ed. McGraw-Hill; 2004:681-690 2. Liewluck T, Sorenson EJ, Walkiewicz MA, Rumilla KM, Milone M. Autosomal dominant distal myopathy due to a novel ACTA1 mutation. Neuromuscul Disord. 2017;27(8):742-746 3. Engel AG, Redhage KR, Tester DJ, Ackerman MJ, Selcen D. Congenital myopathy associated with the triadin knockout syndrome. Neurology. 2017;88(12):1153-1156 4. Niu Z, Pontifex CS, Berini S, et al: Myopathy with SQSTM1 and TIA1 variants. Clinical and pathological features. Front Neurol. 2018;9:147 5. Nicolau S, Liewluck T, Shen XM, Selcen D, Engel AG, Milone M. A homozygous mutation in GMPPB leads to centronuclear myopathy with combined pre- and postsynaptic defects of neuromuscular transmission. Neuromuscul Disord. 2019;29(8):614-617 6. Nicolau S, Liewluck T, Tracy JA, Laughlin RS, Milone M. Congenital myopathies in the adult neuromuscular clinic: Diagnostic challenges and pitfalls. Neurol Genet. 2019;5(4):e341 7. Liewluck T, Niu Z, Moore SA, Alsharabati M, Milone M. ACTA1-myopathy with prominent finger flexor weakness and rimmed vacuoles. Neuromuscul Disord. 2019;29(5):388-391 8. Nicolau S, Liewluck T, Elliott JL, Engel AG, Milone M. A novel heterozygous mutation in the C-terminal region of HSPB8 leads to limb-girdle rimmed vacuolar myopathy. Neuromuscul Disord. 2020;30(3):236-240

FCDU9 (75784) Muscle Relaxants, Umbilical Cord Tissue

Reference Values:
Reporting limit determined each analysis.

Units: ng/g

Only orderable as part of a profile-see FCDSU.

MUSK (64277) Muscle-Specific Kinase (MuSK) Autoantibody, Serum

Clinical Information: Fatigable weakness due to impaired synaptic transmission at the neuromuscular junction is characteristic of myasthenia gravis (MG). The diagnosis is made by clinical and electromyographic criteria. Positive autoimmune serology must be interpreted in the clinical and electrophysiological context and response to anticholinesterase medication. Most cases are autoimmune and are caused by IgG autoantibodies binding to critical postsynaptic membrane molecules (nicotinic acetylcholine receptor or its interacting proteins).(1) Autoantibody detection frequency is lowest in patients with weakness confined to extraocular muscles (71% muscle acetylcholine receptor: AChR binding).(2) Mayo Clinic Laboratories first-line serological evaluation detects muscle AChR antibody in 92% of nonimmunosuppressed patients with generalized weakness due to MG. Muscle-specific kinase (MuSK) antibody is detectable in more than one-third of those seronegative for muscle AChR antibody (less than 4% of all patients).(3) Physiologically, MuSK is involved in integrating and stabilizing AChR clusters in the motor endplate. MuSK is activated when the nerve-derived proteoglycan agrin binds to its receptor, lipoprotein-related protein 4 (LRP4). Antibodies to LRP4 itself have been described in rare patients.(1) Six percent of nonimmunosuppressed patients with generalized MG lack demonstrable AChR or MuSK antibodies (double seronegative). Other rare autoantibodies no doubt remain to be discovered in such cases. However, as in autoimmune AChR MG and MuSK MG, testing for common organ-specific and nonorgan-specific autoantibodies is a valuable ancillary investigation in evaluating seronegative acquired generalized MG. General serological testing, coupled with family or personal

history, will disclose autoimmune phenomena in 77% of those cases.(3) These disorders may include thyroid disease, type 1 diabetes, vitiligo, premature greying, rheumatoid arthritis, or lupus. Testing may also reveal antinuclear antibodies, glutamic acid decarboxylase (GAD65) antibodies, thyroperoxidase/thyroglobulin antibodies, or gastric parietal cell antibodies.(3) Objective improvement in strength following a therapeutic trial of plasmapheresis or intravenous immune globulin would justify consideration of long-term immunosuppression. Female patients are generally affected by autoimmune MuSK MG more often than male patients. Onset can occur at any age (pediatric to older adults). Patients may derive limited benefit from anticholinesterase medication. The thymus is normal, and patients are generally not benefited by thymectomy. Antibody-lowering therapies are effective. Bulbar, facial, and respiratory weakness are prominent, and crises are common.(1,4)

Useful For: Diagnosis of autoimmune muscle-specific kinase (MuSK) myasthenia gravis Second-order test to aid in the diagnosis of autoimmune myasthenia gravis when first-line serologic tests are negative Establishing a quantitative baseline value for MuSK antibodies that allows comparison with future levels if weakness is worsening

Interpretation: A positive result, in the appropriate clinical context, confirms the diagnosis of autoimmune muscle-specific kinase myasthenia gravis. Seropositivity justifies consideration of immunotherapy.

Reference Values:
< or =0.02 nmol/L

Clinical References: 1. Li Y, Arora Y, Levin K. Myasthenia gravis: newer therapies offer sustained improvement. Cleve Clin J Med. 2013;80(11):711-721 2. Lennon VA: Serological profile of myasthenia gravis and distinction from the Lambert-Eaton myasthenic syndrome. Neurology 1997;48 (Suppl 5):S23-S27 3. Chan KH, Lachance DH, Harper CM, Lennon VA. Frequency of seronegativity in adult-acquired generalized myasthenia gravis. Muscle Nerve. 2007;36(5):651-658 4. Skjei KL, Lennon VA, Kuntz NL. Muscle specific kinase autoimmune myasthenia gravis in children: A case series. Neuromuscul Disord. 2013;23(11):874-882

FMUSG
57659

Mushroom IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

MUSH
82626

Mushroom, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In

individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to mushroom Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FMTFG
57679

Mustard Food IgG

Interpretation:

Reference Values:

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should

only be ordered by physicians who recognize the limitations of the test.

MSTD
82801

Mustard, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to mustard Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MUXF3
609437

MUXF3 (Cross-reactive Carbohydrate Determinant), IgE, Serum

Clinical Information: Antibodies to glycoprotein carbohydrate determinants are prone to interact with a broad variety of plant and invertebrate allergens. These glycoprotein carbohydrates have therefore been termed cross-reactive carbohydrate determinants (CCD). The MUXF3 carbohydrate epitope obtained from digested pineapple bromelain glycoprotein can be used as a representative epitope marker for assessing the presence of IgE antibodies that interact with CCD. As true allergic sensitization to the pineapple bromelain glycoprotein itself is rare, assessing for the presence IgE antibodies reactive with the bromelain MUXF3 CCD glycoprotein carbohydrate epitope serves as a well-established marker for the determination of the presence of anti-CCD IgE antibodies. CCD epitopes are widely distributed in plants and invertebrate animals, and antibodies against CCD, such as MUXF2, may be associated with a number of positive IgE antibody tests (cross-reactivity) to many different and unrelated plant allergens, but also to a number of potential invertebrate allergens such as bee/wasp venom, cockroaches, mites, and shellfish. Plant protein allergens that contain CCD epitopes include peanuts, grass, pollen, and latex. The presence of anti-CCD IgE antibodies can hinder assessment of the presence of IgE antibodies to these other plant and invertebrate allergens, as it is not possible to distinguish whether observed reactivity is due to the presence of antibodies specific to other proteins, or is the result of the presence of interfering anti-CCD antibodies. When very broad allergen sensitivity profiles are observed in the course allergy testing, it may be due to the presence of cross-reactive anti-CCD IgE antibodies, although the presence of IgE antibodies to profilin proteins should also be considered. The degree to which antibodies to CCD may be associated with clinical allergic reaction has not been completely resolved. In general, the presence of cross-reactive antibodies to CCD, such as MUXF3, is not thought to be clinically relevant and does not give rise to symptoms consistent with allergic reaction. However, antibodies to CCD may be linked to clinically relevant allergic reactions in extremely rare cases, including in individuals with celery and tomato allergy.

Useful For: Evaluation for the presence of antibodies to cross-reactive carbohydrate determinates (CCD) Investigation of clinically unexpected positive IgE antibody testing in a wide variety of plant and invertebrate allergens

Interpretation: Antibody to bromelain MUXF3 has widely been used for assessing for potential cross-reactive carbohydrate determinate (CCD) cross-reactivity since its CCD chain is also found in many other plant proteins, including peanuts. While sensitization to CCD is generally not associated with an allergic reaction, the presence of IgE antibodies to CCD may give rise to confounding positive IgE antibody sensitization profiles for a wide variety of plant and invertebrate allergens.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Altmann F: Coping with cross-reactive carbohydrate determinants in allergy diagnosis. Allergo J Int. 2016;25(4):98-105. doi:10.1007/s40629-016-0115-3 2. Hemmer W, Altmann F, Holzweber F, Gruber C, Wantke F, Wohrl S: ImmunoCAP cellulose displays cross-reactive carbohydrate determinant (CCD) epitopes and can cause false-positive test results in patients with high anti-CCD IgE antibody levels. J Allergy Clin Immunol. 2018 Jan;141(1):372-381.e3. doi: 10.1016/j.jaci.2017.04.028 3. Sinson E, Ocampo C, Liao C, et al: Cross-reactive carbohydrate determinant interference in cellulose-based IgE allergy tests utilizing recombinant allergen components. PLoS One. 2020 Apr 23;15(4):e0231344. doi: 10.1371/journal.pone.0231344 4. van Ree R. Clinical importance of cross-reactivity in food allergy. Curr Opin Allergy Clin Immunol. 2004;4:235-40 5. Fotish K, Altmann F, Haustein D, Vieths S: Involvement of carbohydrate epitopes in the IgE response of celery-allergic patients. Int Arch Allergy Immunol. 1999 Sep;120:30-42. doi: 10.1159/000024217

FBMO
75510

MVista Blastomyces Quantitative Antigen, Fluid

Reference Values:

FMVCO
57122

MVista Coccidioides Quantitative Antigen EIA

Reference Values:
Reference interval: None Detected
Results reported as ng/mL in 0.07 - 8.2 ng/mL range
Results above 8.2 ng/mL are reported as 'Positive, Above the Limit of Quantification'

FHST
91957

MVista Histoplasma Ag Quantitative EIA

Reference Values:

FHSAG
90017

MVista Histoplasma Ag Quantitative, Spinal Fluid

Reference Values:

MGMR
608980

Myasthenia Gravis Evaluation with Muscle-Specific Kinase (MuSK) Reflex, Serum

Clinical Information: Fatigable weakness due to impaired postsynaptic transmission at the neuromuscular junction is characteristic of myasthenia gravis (MG). A clinical diagnosis should be supported by electrodiagnostic testing, ie, clinical-electrodiagnosis (EDX). Positive autoimmune serology increases certainty of MG diagnosis but needs to be interpreted in the proper clinical-EDX context with response to anticholinesterase medications supporting the diagnosis. Most cases are autoimmune and are caused by IgG autoantibodies binding to critical postsynaptic membrane molecules (nicotinic muscle acetylcholine receptor [AChR] or its interacting proteins, such as muscle-specific kinase [MuSK]). Serologically, the detection of AChR binding antibody provides the best diagnostic sensitivity. However, the presence of both AChR binding and modulating activity improves diagnostic accuracy. Autoantibody detection frequency is lowest in patients with weakness confined to extraocular muscles (72% are positive for AChR binding antibodies) and highest in patients with generalized weakness due to MG (92% are positive for AChR binding antibodies). In adults with MG and AChR antibodies, approximately 20% will have thymoma and, very rarely (<1%), extrathymic cancers. Computerized tomography imaging of the

chest is considered the standard of care to evaluate for thymoma. MuSK antibody is detectable in more than one-third of patients with MG who are seronegative for muscle AChR antibodies. MuSK is involved in integrating and stabilizing AChR clusters at the motor endplate. MuSK is activated when the nerve-derived proteoglycan agrin binds to its receptor, lipoprotein-related protein 4 (LRP4). Patients with MuSK MG are more commonly female. Onset can occur at any age (pediatric to older adult). Patients derive less benefit from anticholinesterase medications, and no neoplasm has been associated with MuSK MG. Although beneficial, thymectomy has not been demonstrated to be helpful in MuSK MG. Patients with both AChR and MuSK autoantibodies benefit from immunotherapy, however, patients with MuSK autoantibodies tend to have more steroid dependence. In patients with seronegative MG, reconsideration of the diagnosis is important. If clinical-EDX criteria are still met, repeating serological testing within one year can increase serological positivity for AChR antibodies by 15%. The diagnostic sensitivity of these tests depends on the disease severity and duration of symptoms. AChR binding antibodies may be undetectable for 6 to 12 months after MG symptom onset. Only about 5% of adult patients with generalized MG who are not immunosuppressed remain seronegative for muscle AChR beyond 12 months. Objective improvement by electrodiagnostic and strength testing following a therapeutic trial of plasmapheresis or intravenous immune globulin can justify consideration of long-term immunosuppression in patients who are seronegative meeting clinical-EDX criteria. Note: Single antibody tests may be requested in the follow-up of patients with positive results previously documented in this laboratory.

Useful For: Diagnosing autoimmune myasthenia gravis (MG) in adults and children Distinguishing autoimmune from congenital MG in adults and children or other acquired forms of neuromuscular junction transmission disorders Establishing a quantitative baseline value that allows comparison with future levels if weakness is worsening

Interpretation: Positive results in this antibody evaluation are indicative of autoimmune myasthenia gravis (MG). These results should be interpreted in the appropriate clinical and electrophysiological context. In the presence of either acetylcholine receptor antibodies, a paraneoplastic basis should be considered with thymoma being the most frequently associated tumor with myasthenia gravis. Currently, muscle-specific kinase antibody positive MG is not associated with a paraneoplastic etiology. Negative results do not exclude the diagnosis of an autoimmune neuromuscular junction disorder. If clinical suspicion remains and symptoms persistent or worsen, consider re-testing.

Reference Values:

Test ID	Reporting Name	Methodology	Reference Value
MGMRI	MG with MuSK Interpretation, S	Interpretation	NA
ARBI	ACh Receptor (Muscle) Binding Ab	Radioimmunoassay (RIA)	< or =0.02 nmol/L
Reflex Information: Test ID	Reporting Name	Methodology	Reference Value
ACMFS	AChR Modulating Flow Cytometry, S	Flow Cytometry	Negative
MUSK	MuSK Autoantibody, S	RIA	< or =0.02 nmol/L

Clinical References: 1. Li Y, Arora Y, Levin K. Myasthenia gravis: Newer therapies offer sustained improvement. Cleve Clin J Med. 2013;80(11):711-721. doi:10.3949/ccjm.80a.13044 2. Vernino S, Lennon VA. Autoantibody profiles and neurological correlations of thymoma. Clin Cancer

Res. 2004;10(21):7270-7275. doi:10.1158/1078-0432.CCR-04-0735 3. Skjei KL, Lennon VA, Kuntz NL. Muscle specific kinase autoimmune myasthenia gravis in children: A case series. Neuromuscul Disord. 2013;23(11):874-882. doi:10.1016/j.nmd.2013.07.010 4. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Nat Med. 2001;7(3):365-368. doi:10.1038/85520 5. Chan KH, Lachance DH, Harper CM, Lennon VA. Frequency of seronegativity in adult-acquired generalized myasthenia gravis. Muscle Nerve. 2007;36(5):651-658. doi:10.1002/mus.20854 6. Shelly S, Paul P, Bi H, et al. Improving accuracy of myasthenia gravis autoantibody testing by reflex algorithm. Neurology. 2020 1;95(22):e3002-e3011. doi:10.1212/WNL.0000000000010910

MGLE
608979

Myasthenia Gravis/Lambert-Eaton Myasthenic Syndrome Evaluation, Serum

Clinical Information: Myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) are acquired autoimmune disorders of neuromuscular transmission. MG is caused by pathogenic autoantibodies binding and potentially removing (modulation) the muscle's nicotinic acetylcholine receptor (AChR) from the surface of the neuromuscular junction. Serologically, the detection of AChR binding antibody provides the best diagnostic sensitivity. However, the presence of both AChR binding and modulating activity improves diagnostic accuracy. A subset of patients who are AChR seronegative will have muscle-specific kinase (MuSK) antibodies. LEMS is caused by autoantibodies binding to motor nerve terminal's voltage-gated P/Q-type calcium channel. Synaptic transmission fails when autoantibodies cause a critical loss of junctional cation channel proteins that activate the muscle action potential. Both MG and LEMS can affect children as well as adults, although LEMS is very rare in children. In adults MG is 10 times more frequent than LEMS, but it is sometimes difficult to distinguish the two disorders clinically. Electrophysiological testing is extremely helpful in distinguishing these 2 disorders. MG patients have decrements of compound muscle action potential (CMAP) amplitudes on repetitive stimulation whereas LEMS has immediate and dramatic post exercise facilitation (elevation) of CMAP amplitudes. Neoplasms associated with LEMS or MG are an endogenous source of the antigens driving production of the autoantibodies that characterize each disorder. In adults with MG, there is at least a 20% occurrence of thymoma and, very rarely (<1%), extrathymic cancers. LEMS is frequently associated (80%) with small-cell lung carcinoma (SCLC). Thus far, MuSK antibody associated MG has not been associated with any neoplasm. The diagnostic sensitivity of these tests depends on the disease severity and duration of symptoms. AChR binding antibodies may be undetectable for 6 to 12 months after MG symptom onset and similarly P/Q-type calcium channel antibody may be undetectable for 6 to 12 months after LEMS onset. Only about 5% of adult patients with generalized MG who are not immunosuppressed remain seronegative for muscle AChR beyond 12 months. Although immunotherapy is universally beneficial for MG, in LEMS resection of the identified SCLC and initiation of 3,4-diaminopyridine, which facilitates acetylcholine release by increasing presynaptic calcium concentration, is most beneficial. Note: Single antibody tests may be requested in the follow-up of patients with positive results previously documented in this laboratory.

Useful For: Confirming the autoimmune basis of a defect in neuromuscular transmission (eg, myasthenia gravis [MG], Lambert-Eaton myasthenic syndrome [LEMS]) Distinguishing LEMS from autoimmune forms of MG Providing a quantitative autoantibody baseline for future comparisons in monitoring a patient's clinical course and response to immunomodulatory treatment

Interpretation: Positive results in this antibody evaluation are indicative of an autoimmune neuromuscular junction disorder. These results should be interpreted in the appropriate clinical and electrophysiological context. In the presence of either acetylcholine receptor antibodies or P/Q antibodies, a paraneoplastic basis should be considered with thymoma being the most commonly associated tumor with myasthenia gravis and small cell lung cancer being the most commonly associated cancer with

Lambert-Eaton myasthenic syndrome. Currently, muscle-specific kinase antibody positive myasthenia gravis is not associated with a paraneoplastic etiology. Negative results do not exclude the diagnosis of an autoimmune neuromuscular junction disorder. If clinical suspicion remains and symptoms persistent or worsen consider retesting.

Reference Values:

Test ID	Reporting name	Methodology	Reference value
MGLEI	MG Lambert-Eaton Interpretation, S	Interpretation	NA
ARBI	ACh Receptor (Muscle) Binding Ab	Radioimmunoassay (RIA)	< or =0.02 nmol/L
CCPQ	P/Q-Type Calcium Channel Ab	RIA	< or =0.02 nmol/L
Reflex Information: Test ID	Reporting name	Methodology	Reference value
ACMFS	AChR Modulating Flow Cytometry, S	Flow cytometry	Negative
MUSK	MuSK Autoantibody, S	RIA	< or =0.02 nmol/L

Clinical References: 1. Lennon VA. Serological profile of myasthenia gravis and distinction from the Lambert-Eaton myasthenic syndrome. Neurology. 1997;48(Suppl 5):S23-S27. doi:10.1212/WNL.48.Suppl_5.23S 2. Harper CM, Lennon VA: Lambert-Eaton syndrome. In: Kaminski HJ, ed. Current Clinical Neurology: Myasthenia Gravis and Related Disorders. 2nd ed. Humana Press; 2008;209-226 3. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Nat Med. 2001;7(3):365-368. doi:10.1038/85520 4. Shelly S, Paul P, Bi H, et al. Improving accuracy of myasthenia gravis autoantibody testing by reflex algorithm. Neurology. 2020;95(22):e3002-e3011. doi:10.1212/WNL.0000000000010910

SGTF
35860

MYB (6q23) Rearrangement FISH, Tissue

Clinical Information: Salivary adenoid cystic carcinomas (ACC), although uncommon, are frequent among salivary gland malignancies. ACC is typically an aggressive tumor with a poor prognosis. Histologically, ACC show significant morphologic overlap with other salivary gland tumors, but have a much different clinical course. Because ACC requires a management distinct from histologically similar lesions, it is important to make an accurate diagnosis. Translocations between MYB (6q23.3) and NFIB (9p24) have been identified in a large proportion of primary salivary gland ACC. These alterations have not been identified in other salivary gland tumors. Therefore, separation of MYB, in the proper clinical and histologic context, is diagnostic for ACC and can be confirmed by FISH with MYB break-apart probes.

Useful For: Assessing for MYB gene rearrangements in patients with primary salivary gland carcinoma to aid in confirming or excluding the diagnosis of primary salivary gland adenoid cystic carcinomas

Interpretation: A positive result is detected when the percent of cells with an abnormality exceeds

the normal cutoff for the probe set. A positive result suggests rearrangement of the MYB locus. The presence of a MYB rearrangement in conjunction with the proper clinical and histologic features is diagnostic of adenoid cystic carcinomas (ACC). A confirmed diagnosis of ACC results in specific clinical management that may be distinct from the management of other salivary gland neoplasms. A negative result suggests no rearrangement of the MYB gene region at 6q23.3. The absence of a MYB rearrangement does not exclude the diagnosis of ACC, as a subset of ACCs do not show an MYB rearrangement.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Mitani Y, Rao PH, Futreal PA, et al: Novel chromosomal rearrangements and break points at the t(6;9) in salivary adenoid cystic carcinoma: association with MYB-NFIB chimeric fusion, MYB expression, and clinical outcome. Clin Cancer Res 2011;17(22):7003-7014 2. West RB, Kong C, Clarke N, et al: MYB expression and translocation in adenoid cystic carcinomas and other salivary gland tumors with clinicopathologic correlation. Am J Surg Pathol 2011;35(1):92-99 3. Bell D, Roberts D, Karpowicz M, et al: Clinical significance of Myb protein and downstream target genes in salivary adenoid cystic carcinoma. Cancer Biol Ther 2011;12:569-573

MYC
70515

MYC Immunostain, Technical Component Only

Clinical Information: MYC is a proto-oncogene commonly overexpressed in many malignant neoplasms, including some B-cell lymphomas. MYC translocations are a hallmark abnormality of Burkitt lymphoma. The presence of the MYC translocation may be a helpful indicator of poor prognosis or an aggressive clinical course in diffuse large B-cell lymphoma.

Useful For: Assessment of MYC expression

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: V1. Mentzel T, Schildhaus HU, Palmedo G, Buttner R, Kutzner H. Postradiation cutaneous angiosarcoma after treatment of breast carcinoma is characterized by MYC amplification in contrast to atypical vascular lesions after radiotherapy and control cases: clinicopathological, immunohistochemical and molecular analysis of 66 cases. Mod Pathol. 2012;25(1):75-85 2. Faria M, Khayat A, Burbano R, Rabenhorst SH. c-MYC amplification and expression in astrocytic tumors. Acta Neuropathol. 2008;116:87-95 3. Ruzinova M, Caron T, Rodig S. Altered subcellular localization of c-Myc protein identifies aggressive B-cell lymphomas harboring a c-MYC translocation. Am J Surg Pathol. 2010;34(6):882-891 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CTB
8205

Mycobacteria and Nocardia Culture, Varies

Clinical Information: Mycobacteria species are responsible for significant morbidity and mortality in both immunocompromised and immunocompetent hosts. Mycobacterium tuberculosis is the causative agent of tuberculosis, and it kills nearly 2 million people in the world each year. Nontuberculous mycobacteria such as Mycobacterium avium complex and Mycobacterium abscessus cause a variety of

infections (eg, respiratory, skin, and soft tissue) and are important to detect and correctly identify in order to aid in clinical decision making. There are approximately 200 recognized species of mycobacteria and identification of these organisms to the species level is often required to help guide appropriate therapy. Although there are direct detection methods available for M tuberculosis, growth of the organism on culture media is still necessary to allow for antimicrobial susceptibility testing. At this time, direct molecular detection methods are lacking for the nontuberculous mycobacteria and growth in culture is critical for identification and antimicrobial susceptibility testing. Nocardia species and other aerobic actinomycetes (eg, Tsukamurella species, Gordonia species, Rhodococcus species) are also important causes of disease and isolation on culture media is important to facilitate identification and antimicrobial susceptibility testing. Nocardia and the other aerobic actinomycetes grow well on mycobacterial medium, and therefore, ordering a mycobacterial culture is recommended when infection with this group of organisms is suspected.

Useful For: Detection and identification of Mycobacterium species, Nocardia species, and other aerobic actinomycetes

Interpretation: A final negative report is issued after 42 days of incubation. Positive cultures are reported as soon as detected.

Reference Values:
Negative

Clinical References: 1. Martin I, Pfyffer GE, Parrish N: Mycobacterium: General characteristics, laboratory detection and staining procedures. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. Vol 1. ASM Press;2011:472-5022. 2.Banaei N, Musser KA, Salfinger M, Somoskovi A, Zelazny AM. Novel assays/applications for patients suspected of mycobacterial diseases. Clin Lab Med. 2020;40(4):535-552. doi:10.1016/j.cll.2020.08.010 3. Lafont E, Conan PL, Rodriguez-Nava V, Lebeaux D. Invasive nocardiosis: Disease presentation, diagnosis and treatment - old questions, new answers? Infect Drug Resist. 2020;13:4601-4613. doi:10.2147/IDR.S249761

CTBBL
82443

Mycobacterial Culture, Blood

Clinical Information: Mycobacteremia occurs most often in immunocompromised hosts. The majority of disseminated mycobacterial infections are due to Mycobacterium avium complex but bacteremia can also be caused by other mycobacterial species including, but not limited to, Mycobacterium tuberculosis complex, Mycobacterium kansasii, Mycobacterium fortuitum, Mycobacterium chelonae, Mycobacterium scrofulaceum, Mycobacterium szulgai, and Mycobacterium xenopi.(1) Mycobacterial blood cultures may be indicated for patients presenting with signs and symptoms of sepsis, especially fever of unknown origin.

Useful For: Diagnosing mycobacteremia

Interpretation: A positive result may support the diagnosis of mycobacteremia.

Reference Values:
Negative
If positive, mycobacteria are identified.
A final negative report will be issued after 42 days of incubation.

Clinical References: 1. Martin I, Pfyffer GE, Parrish N. Mycobacterium: General characteristics,

laboratory detection, and staining procedures. In: Carroll KC, Pfaller MA, Landry ML, et al, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019:558-575 2. Crump JA, Morrissey AB, Ramadhani HO, et al. Controlled comparison of BacT/Alert MB system, manual myco/f lytic procedure, and isolator 10 system for diagnosis of mycobacterium tuberculosis bacteremia. J Clin Microbiol. 2011;49(8):3054-7. doi:10.1128/JCM.01035-11 3. Reimer LG. Laboratory detection of mycobacteremia. Clin Lab Med. 1994;14(1):99-105

TBSP 607364 Mycobacterium tuberculosis Complex Species Identification, PCR, Varies

Clinical Information: This assay provides a species-level identification of microbiologic culture isolates previously identified to be a member of the Mycobacterium tuberculosis complex. Species level identification can be important for patient care or for epidemiologic investigations. For example, the species-level identification of Mycobacterium bovis bacillus Calmette-Guerin (BCG) can assist with identification of disseminated infections following use of the vaccine as an adjuvant during chemotherapy.

Useful For: Determining the species of a Mycobacterium tuberculosis complex culture isolate

Interpretation: This assay can differentiate the most common species within the Mycobacterium tuberculosis complex, which are, M tuberculosis, Mycobacterium bovis, Mycobacterium bovis bacillus Calmette-Guerin (BCG; the vaccine strain), Mycobacterium canettii, Mycobacterium caprae, Mycobacterium microti, and Mycobacterium pinnepedii. This assay cannot distinguish Mycobacterium africanum from Mycobacterium mungi so if that result is obtained, the organism will be reported as M africanum/M mungi.

Reference Values:
Not applicable

Clinical References: Fitzgerald DW, Sterling TR, Haas DW. Mycobacterium tuberculosis. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2985-3021

MTBXS 619564 Mycobacterium tuberculosis Complex, Molecular Detection and Rifampin Resistance, PCR, Sputum

Clinical Information: Mycobacterium tuberculosis is a highly transmissible bacterial pathogen and is the causative agent of tuberculosis, a disease causing significant worldwide morbidity and mortality. Each year, M tuberculosis accounts for 1.6 million deaths and is responsible for 10.6 million newly diagnosed cases of tuberculosis worldwide. M tuberculosis is spread from person to person via respiratory transmission and has the potential to become resistant to many of the antibiotics currently used if not treated appropriately. Therefore, rapid and accurate detection of M tuberculosis in patient specimens is of paramount clinical and public health importance. Conventional culture methods can generally detect M tuberculosis in 2 to 3 weeks, although up to 6 weeks of incubation may be required in some instances. This qualitative molecular assay utilizes polymerase chain reaction-based nucleic acid amplification for the direct detection of M tuberculosis DNA within respiratory specimens without relying on culture growth, leading to more rapid diagnosis and appropriate patient care. This assay also detects the presence of mutations in the rpoB gene that have been documented to confer more than 95% of cases of rifampin resistance.

Useful For: Rapid detection of Mycobacterium tuberculosis DNA from respiratory specimens for the diagnosis of pulmonary tuberculosis Presumptive detection of rifampin resistance based on the presence of resistance-associated mutations

Interpretation: A positive result indicates the presence of Mycobacterium tuberculosis complex DNA. A negative result indicates the absence of detectable M tuberculosis complex DNA. Presumptive rifampin resistance mediated through mutations within the resistance determining region of the rpoB gene will be reported when detected. One to 2 negative polymerase chain reaction results in conjunction with 1 to 2 negative acid-fast smears may provide evidence supporting the removal of a patient from airborne isolation. Consult your local Infection Prevention and Control for guidance.

Reference Values:
Negative

Clinical References: 1. World Health Organization. Global Tuberculosis Report 2022. WHO; 2022 Available at www.who.int/publications/i/item/9789240061729 2. Centers for Disease Control and Prevention (CDC). Availability of an assay for detecting Mycobacterium tuberculosis, including rifampin-resistant strains, and considerations for its use - United States, 2013. MMWR Morb Mortal Wkly Rep. 2013 Oct 18;62(41):821-827 3. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med. 2010;363(11):1005-1015 4. US Food and Drug Administration. New data shows test can help physicians remove patients with suspected TB from isolation earlier. Press Release. 2015. Available at www.tbonline.info/posts/2015/2/12/fda-new-data-shows-test-can-help-physicians-remove/

MTBT 62203 Mycobacterium tuberculosis Complex, Molecular Detection, PCR, Paraffin, Tissue

Clinical Information: Each year, Mycobacterium tuberculosis accounts for more than a million deaths and is responsible for millions of newly diagnosed cases of tuberculosis worldwide. M tuberculosis is spread from person-to-person via respiratory transmission and has the potential to become resistant to many or all antibiotics currently used if antimycobacterial treatment is not promptly initiated. Therefore, rapid and accurate detection of M tuberculosis in patient specimens is of clinical and public health importance. Conventional culture methods can generally detect M tuberculosis in 2 to 3 weeks, although up to 8 weeks of incubation may be required in some instances. Developed at Mayo Clinic, this rapid polymerase chain reaction (PCR) assay detects M tuberculosis complex DNA directly from specimens without waiting for growth in culture and, therefore, the results are available rapidly after receipt in the laboratory. A mycobacterial culture must always be performed in addition to the PCR assay. The PCR assay is rapid, but culture has increased sensitivity over the PCR assay. The PCR assay targets a unique sequence within the katG gene, which is present in members of the M tuberculosis complex. In addition, the assay can detect genotypic resistance to isoniazid mediated by mutations in the katG target, when present.

Useful For: Preferred method for rapid detection of Mycobacterium tuberculosis complex DNA in formalin-fixed, paraffin-embedded tissue specimens Detecting M tuberculosis complex This test is not intended for the detection of latent tuberculosis and must not be used as a substitute for tests intended for detection of latent tuberculosis such as the tuberculin skin test or an interferon gamma release assay.

MTBRP 88807 Mycobacterium tuberculosis Complex, Molecular Detection, PCR, Varies

Clinical Information: Each year, Mycobacterium tuberculosis accounts for more than a million deaths and is responsible for millions of newly diagnosed cases of tuberculosis worldwide. M tuberculosis is spread from person-to-person via respiratory transmission and has the potential to become resistant to many or all antibiotics currently used if antimycobacterial treatment is not promptly initiated. Therefore, rapid and accurate detection of M tuberculosis in patient specimens is of clinical and public health importance. Conventional culture methods can generally detect M tuberculosis in 2 to 3 weeks, although up to 8 weeks of incubation may be required in some instances. Developed at Mayo Clinic, this rapid polymerase chain reaction (PCR) assay detects M tuberculosis complex DNA directly from specimens without waiting for growth in culture and, therefore, the results are available rapidly after receipt in the laboratory. A mycobacterial culture must always be performed in addition to the PCR assay. The PCR assay is rapid, but the culture has increased sensitivity over the PCR assay. The PCR assay targets a unique sequence within the katG gene, which is present in members of the M tuberculosis complex. In addition, the assay can detect genotypic resistance to isoniazid mediated by mutations in the katG target, when present.

Useful For: Rapid detection of Mycobacterium tuberculosis complex DNA (preferred method) Detection of M tuberculosis, when used in conjunction with mycobacterial culture This test does not assess M tuberculosis rifampin resistance. This test should not be used to determine bacteriologic cure or to monitor response to therapy. This test is not intended for the detection of latent tuberculosis and must not be used as a substitute for tests intended for detection of latent tuberculosis such as the tuberculin skin test or an interferon gamma release assay.

Interpretation: A positive result indicates the presence of Mycobacterium tuberculosis complex DNA. Members of the M tuberculosis complex detected by this assay include M tuberculosis, Mycobacterium bovis, Mycobacterium bovis bacillus Calmette-Guerin, Mycobacterium africanum, Mycobacterium canettii, and Mycobacterium microti. Other species within the M tuberculosis complex (eg, Mycobacterium caprae, Mycobacterium pinnipedii, and Mycobacterium mungi) should, in theory, be detected using the primer and probe sequences in this assay, but they have not been tested. This assay method does not distinguish between the species of the M tuberculosis complex. If an isolate of M tuberculosis complex is already available, species identification can be performed; order TBSP / Mycobacterium tuberculosis Complex Species Identification, PCR, Varies. A negative result indicates the absence of detectable M tuberculosis complex DNA. Isoniazid (INH) resistance mediated through a katG variant will be reported when observed but lack of a katG variant does not imply that the isolate is susceptible to INH. There are other genetic loci in addition to katG that can contribute to resistance for this drug.

Reference Values:
Not applicable

Clinical References: 1. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis. 2017;64(2):e1-e33. doi:10.1093/cid/ciw694 2. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016;63(7):e147-e195. doi:10.1093/cid/ciw376 3. Ortiz-Brizuela E, Menzies D, Behr MA. Testing and treating Mycobacterium tuberculosis infection. Med Clin North Am. 2022;106(6):929-947. doi:10.1016/j.mcna.2022.08.001

MTBPZ 56099 Mycobacterium tuberculosis Complex, Pyrazinamide Resistance by pncA DNA Sequencing, Varies

Clinical Information: The protein product of the Mycobacterium tuberculosis complex pncA gene is an enzyme that is responsible for activation of the prodrug pyrazinamide (PZA). DNA sequencing of the Mycobacterium tuberculosis complex pncA gene can be used to detect mutations that correlate with in vitro PZA resistance.(1,2) The sequencing result can be available in as little as 1 day after the Mycobacterium tuberculosis complex isolate grows in culture, thereby providing a more rapid susceptibility result than the average 10 to 14 days required by phenotypic broth methods.

Useful For: Detection of genotypic resistance to pyrazinamide by Mycobacterium tuberculosis complex isolates

Interpretation: Polymorphisms in the pncA gene that have been previously correlated in our laboratory with pyrazinamide (PZA) resistance will be reported as "Mutation was detected in pncA suggesting resistance to pyrazinamide." Wildtype pncA or a silent pncA gene polymorphism (ie, no change in the amino acid translation) will be reported as "No mutation was detected in pncA." New polymorphisms in the pncA gene that have not previously been seen in our laboratory will require additional testing using a reference broth method to determine their correlation with PZA resistance.

Reference Values:
Pyrazinamide resistance not detected

Clinical References: 1. Somoskovi A, Dormandy J, Parson LM, et al: Sequencing of the pncA Gene in members of the Mycobacterium tuberculosis complex has important diagnostic applications: identification of a species-specific pncA mutation in "Mycobacterium canettii" and the reliable and rapid predictor of pyrazinamide resistance. J Clin Microbiol. 2007;45(2):595-599 2. Dormandy J, Somoskovi A, Kreiswirth BN, Driscoll JR, Ashkin D, Salfinger M: Discrepant results between pyrazinamide susceptibility testing by the reference BACTEC 460TB method and pncA DNA sequencing in patients infected with multi-drug resistant W-Beijing Mycobacterium tuberculosis strains. Chest. 2007;131(2):497-501 3. Somoskovi A, Parson LM, Salfinger M: The molecular basis of resistance to isoniazid, rifampin, and pyrazinamide in Mycobacterium tuberculosis. Respir Res. 2001;2(3):164-168 4. Bouzouita I, Cabibbe AM, Trovato A, Draoui H, Ghariani A, Midouni B, Essalah L, Mehiri E, Cirillo DM, Slim-Saidi L. Is sequencing better than phenotypic tests for the detection of pyrazinamide resistance? Int J Tuberc Lung Dis. 2018 Jun 1;22(6):661-666. doi:10.5588/ijtld.17.0715

MPA
81563

Mycophenolic Acid, Serum

Clinical Information: Mycophenolate mofetil (CellCept) is an immunosuppressive agent useful in organ transplantation. It is approved for use in renal, hepatic, and cardiac transplants. When mycophenolate mofetil enters the blood, it is immediately metabolized to the active drug, mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase and interferes with the de novo pathway of guanosine nucleotide synthesis selectively in lymphocytes. MPA inhibits proliferative responses of T and B lymphocytes to both mitogenic and allo-specific stimulation. MPA acts in the same fashion as azathioprine, and MPA is suggested as replacement therapy for azathioprine. The drug is deactivated by the hepatic enzyme, uridine diphosphate glucuronosyltransferase to form MPA glucuronide (MPA-G). The principle clinical problem encountered in MPA therapy is excessive immunosuppression, which predisposes the patient to systemic infection. Measurement of the blood level of MPA and MPA-G can be useful to guide therapy. Monitoring is recommended before and after making any changes to immunosuppressive therapy or when initiating or discontinuing concomitant medications. Additional monitoring is indicated if the MPA level is not in the therapeutic range or if a major change in health status occurs.

Useful For: Monitoring therapy to ensure adequate blood levels and avoid over-immunosuppression

Interpretation: Trough steady-state serum levels of mycophenolic acid (MPA) (>2 weeks at the same dose) in the range of 1.0 to 3.5 mcg/mL indicate adequate therapy. MPA glucuronide (MPA-G) levels in the range of 35 to 100 mcg/mL indicate that the patient has normal uridine diphosphate glucuronosyltransferase (UGT) metabolic capacity. MPA-G levels are typically in the range of 100 to 250 mcg/mL during the 2 weeks following transplantation. MPA-G typically decreases after this initial post-transplant phase. Trough steady-state serum MPA levels over 4.0 mcg/mL indicate that the patient is over-immunosuppressed and susceptible to systemic infections. Decreased dosages may be indicated in these cases. Low MPA levels and high MPA-G levels suggest that the patient has an active UGT metabolic capability; higher doses may be required to maintain therapeutic levels of MPA. Some patients have a high UGT metabolic capacity. These patients may require 1 or more grams 3 times a day to maintain trough serum MPA levels in the range of 1.0 mcg/mL to 3.5 mcg/mL. They are likely to have MPA-G levels over 100 mcg/mL. MPA-G is inactive; MPA-G levels only describe the patient's metabolic status. Patients who have low UGT conjugating capability may become over-immunosuppressed, indicated by a trough steady-state serum MPA level over 4.0 mcg/mL and an MPA-G level below 40 mcg/mL. Dose reduction or interval prolongation is indicated in this case.

Reference Values:
MYCOPHENOLIC ACID (MPA)
1.0-3.5 mcg/mL

MPA GLUCURONIDE
35-100 mcg/mL

Clinical References: 1. Moyer TP, Shaw LM. Therapeutic drug monitoring. In: Burtis CA, Ashwood ER, Bruns DE, eds. Tietz Textbook of Clinical Chemistry. 4th ed. WB Saunders Company; 2005:1237-1285 2. Milone M, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Rossa WKC, Young I, Carey-Ann DB, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 42 3. Shaw LM, Sollinger HW, Halloran P, et al. Mycophenolate mofetil: a report of the consensus panel. Ther Drug Monit. 1995;17:690-699

RPMPM 610248 Mycoplasma (Mycoplasmoides) pneumoniae Macrolide (Azithromycin) Resistance Prediction, Molecular Detection, PCR, Varies

Clinical Information:

Useful For: Predicting macrolide susceptibility in Mycoplasma (Mycoplasmoides) pneumoniae

Interpretation: A macrolide resistance predicted or not predicted result indicates the presence of Mycoplasma (Mycoplasmoides) pneumoniae 23S ribosomal RNA (rRNA) gene and indicates whether one of the 2 most common 23S rRNA gene single nucleotide variations (A2064G and A2063G) associated with high-level macrolide resistance is predicted. An "unable to assess" result for M pneumoniae macrolide resistance indicates the absence of detectable M pneumoniae 23S rRNA DNA but does not negate the presence of the organism and may occur due to inhibition of the polymerase chain reaction, sequence variability underlying primers or probes, or the presence of M pneumoniae 23S rRNA DNA in quantities less than the limit of detection of the assay.

Reference Values:
Not Predicted

Clinical References: 1. Waites KB, Taylor-Robinson D: Mycoplasma and Ureaplasma. In.

Versalovic J, Carroll K, Funke G, et al, eds. Manual of Clinical Microbiology. ASM Press; 2011: 970-985 2. Jensen JS, Heilmann C, Valerius NH. Mycoplasma pneumoniae infection in a child with AIDS. Clin Infect Dis. 1994;19(1):207 3. Waites KB, Xiao L, Liu Y, Balish MF, Atkinson TP. Mycoplasma pneumoniae from the Respiratory Tract and Beyond. Clin Microbiol Rev. 2017;30(3):747-809 4. Rothstein TE, Cunningham SA, Rieke RA, Mainella JM, Mutchler MM, Patel R. Macrolide Resistance in Mycoplasma pneumoniae, Midwestern United States, 2014 to 2021. Antimicrob Agents Chemother. 2022;66(4):e0243221 5. Schmitt BH, Sloan LM, Patel R. Real-time PCR detection of Mycoplasma pneumoniae in respiratory specimens. Diagn Microbiol Infect Dis. 2013;77(3):202-205

MPRP
62394

Mycoplasma (Mycoplasmoides) pneumoniae with Macrolide Resistance Reflex, Molecular Detection, PCR, Varies

Clinical Information: Mycoplasma (Mycoplasmoides) pneumoniae is a small bacterium transmitted via organism-containing droplets. It is a cause of upper respiratory infection, pharyngitis, and tracheobronchitis, particularly in children, and has been associated with approximately 20% of cases of community acquired pneumonia.(1) Central nervous system and cardiac manifestations are some of the extrapulmonary complications of infections due to M pneumoniae. The disease is usually self-limited although severe disease may occur, including in patients who are immunocompromised.(2) Identification of M pneumoniae by culture-based methods is time consuming and insensitive. Serologic assays have drawbacks; the development of IgM antibodies takes approximately 1 week, and the IgM response in adults may be variable or may be decreased in immunosuppressed individuals.(3,4) Confirmation of the disease may be dependent on the observation of a 4-fold rise in IgG antibody titers between acute and convalescent specimens, only after several weeks following the initial onset of illness, only providing clinical application for retrospective testing and not individual patient care.(4) Real-time polymerase chain reaction (PCR) testing offers a rapid and sensitive option for detection of M pneumoniae DNA from clinical specimens.(5) Macrolide resistance in M pneumoniae is increasingly reported. In a study performed at Mayo Clinic, 10% of M pneumoniae detections were associated with macrolide resistance.(6) Real-time PCR testing can be used to assess for common mutations associated with macrolide resistance in M pneumoniae.

Useful For: Diagnosing infections due to Mycoplasma (Mycoplasmoides) pneumoniae Assessing macrolide susceptibility

Interpretation: A positive result indicates the presence of Mycoplasma (Mycoplasmoides) pneumoniae. If detected, common mutations associated with macrolide resistance in M pneumoniae may be assessed. A negative result does not rule out the presence of M pneumoniae and may be due to the presence of inhibitors within the specimen matrix or the presence of target DNA below the limit of detection of the assay.

Reference Values:
Negative

Clinical References: 1. Waites KB, Taylor-Robinson D: Mycoplasma and Ureaplasma. In. Versalovic J, Carroll K, Funke G, et al, eds. Manual of Clinical Microbiology. ASM Press; 2011:970-985 2. Jensen JS, Heilmann C, Valerius NH. Mycoplasma pneumoniae infection in a child with AIDS. Clin Infect Dis. 1994;19(1):207 3. Daxboeck F, Krause R, Wenisch C. Laboratory diagnosis of Mycoplasma pneumoniae infection. Clin Microbiol Infect. 2003;9(4):263-273 4. Waites KB, Talkington DF. Mycoplasma pneumoniae and its role as a human pathogen. Clin Microbiol Rev. 2004;17(4):697-728 5. Schmitt BH, Sloan LM, Patel R. Real-time PCR detection of Mycoplasma pneumoniae in respiratory specimens. Diagn Microbiol Infect Dis. 2013;77(3):202-205 6. Rothstein TE, Cunningham SA, Rieke RA, Mainella JM, Mutchler MM, Patel R. Macrolide resistance in Mycoplasma

pneumoniae, Midwestern United States, 2014 to 2021. Antimicrob Agents Chemother. 2022;66(4):e0243221

MMGEN 620733 Mycoplasma genitalium, Transcription-Mediated Amplification, Post-Prostatic Massage Fluid/Urine or Peritoneal Fluids

Clinical Information: Mycoplasma genitalium, an under-recognized sexually transmitted infection (STI), causes acute and chronic non-gonococcal urethritis, cervicitis, and pelvic inflammatory disease. Due to its growing prevalence, M genitalium was cited as an emerging public health threat by the Centers for Disease Control and Prevention (CDC) in 2015. In high-risk populations, prevalence has been reported as high as 9% to 24% in male patients and 11% to 16% in female patients. M genitalium is commonly misdiagnosed as other STIs (eg, Chlamydia trachomatis or gonorrhea), which can lead to improper treatment of the underlying cause and an increase in duration of infection. In 2021, the CDC updated their STI guidelines to recommend that men with recurrent non-gonococcal urethritis and women with recurrent cervicitis or pelvic inflammatory disease should be tested for M genitalium.

Useful For: Detecting Mycoplasma genitalium in cases of suspected infection in peritoneal fluid or prostatic secretion (VBIII) fluid/urine This test is not intended for use in medico-legal applications.

Interpretation: A positive result indicates the presence of nucleic acid from Mycoplasma genitalium and strongly supports the diagnosis of a M genitalium infection. A negative result indicates that nucleic acid from M genitalium was not detected in the specimen. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in a specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being truly positive. In settings with a low prevalence of sexually transmitted infections, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with urogenital infection, positive results should be carefully assessed, and if appropriate, the patient retested by other methods.

Reference Values:
Negative

Clinical References: Waites KB, Crabb DM, Ratliff AE, Geisler WM, Atkinson TP, Xiao L. Latest advances in laboratory detection of Mycoplasma genitalium. J Clin Microbiol. 2023;61(3):e0079021. doi:10.1128/jcm.00790-21

AMGEN 616513 Mycoplasma genitalium, Transcription-Mediated Amplification, Urine or Urogenital Swab

Clinical Information: Mycoplasma genitalium, an under-recognized sexually transmitted infection (STI), causes acute and chronic non-gonococcal urethritis, cervicitis, and pelvic inflammatory disease. Due to its growing prevalence, M genitalium was cited as an emerging public health threat by the Centers for Disease Control and Prevention (CDC) in 2015. In high-risk populations, prevalence has been reported as high as 9% to 24% in male patients and 11% to 16% in female patients. M genitalium is commonly misdiagnosed as other STIs (eg, Chlamydia trachomatis or gonorrhea), which can lead to improper treatment of the underlying cause and an increase in duration of infection. In 2021, the CDC updated their STI guidelines to recommend that men with recurrent non-gonococcal urethritis and women with recurrent cervicitis or pelvic inflammatory disease should be tested for M genitalium.

Useful For: Detecting Mycoplasma genitalium in cases of suspected infection This test is not intended

for use in medico-legal applications.

Interpretation: A positive result indicates the presence of nucleic acid from Mycoplasma genitalium and strongly supports the diagnosis of a M genitalium infection. A negative result indicates that nucleic acid from M genitalium was not detected in the specimen. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in a specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being truly positive. In settings with a low prevalence of sexually transmitted infections, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with urogenital infection, positive results should be carefully assessed, and if appropriate, the patient retested by other methods.

Reference Values:
Negative

Clinical References: Waites KB, Crabb DM, Ratliff AE, Geisler WM, Atkinson TP, Xiao L. Latest advances in laboratory detection of mycoplasma genitalium. J Clin Microbiol. 2023;61(3):e0079021. doi:10.1128/jcm.00790-21

MYCO
48394

Mycoplasma pneumoniae Antibodies, IgG and IgM, Serum

Clinical Information: Mycoplasma pneumoniae is a small bacterium transmitted via organism-containing droplets. It is a cause of upper respiratory infection, pharyngitis, and tracheobronchitis, particularly in children, and has been associated with approximately 20% of cases of community-acquired pneumonia. Central nervous system and cardiac manifestations are probably the most frequent extrapulmonary complications of infections due to M pneumoniae. The disease is usually self-limited, although severe disease has been reported in immunocompromised patients. Identification of M pneumoniae by culture-based methods is time consuming and insensitive. Serology-based assays for M pneumoniae have several drawbacks. The development of IgM antibodies takes approximately 1 week, and the IgM response may be variable in adults or decreased in immunosuppressed individuals. Confirmation of the disease is dependent on the observation of a 4-fold rise in IgG antibody titers between acute and convalescent specimens, several weeks following the initial onset of illness, providing clinical utility only for retrospective testing. Real-time polymerase chain reaction offers a rapid and sensitive option for detection of M pneumoniae DNA from clinical specimens allows for diagnosis of acute or current infection.

Useful For: Screening for recent or past exposure to Mycoplasma pneumoniae This test should not be used as a screening procedure for the general population.

Interpretation:

Reference Values:
IgG: Negative
IgM: Negative
IgM by indirect immunofluorescence: Negative

Clinical References: 1. Smith T: Mycoplasma pneumoniae infections: diagnosis based on immunofluorescence titer of IgG and IgM antibodies. Mayo Clin Proc. 1986;61(10):830-831 2. Holzman RS, Simberkoff MS, Leaf HL: Mycoplasma pneumoniae and atypical pneumonia. In Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2332-2339

MYCOG
48317

Mycoplasma pneumoniae Antibodies, IgG, Serum

Clinical Information: Mycoplasma pneumoniae is a small bacterium transmitted via organism-containing droplets. It is a cause of upper respiratory infection, pharyngitis, and tracheobronchitis, particularly in children, and has been associated with approximately 20% of cases of community acquired pneumonia. Central nervous system and cardiac manifestations are probably the most frequent extrapulmonary complications of infections due to M pneumoniae. The disease is usually self-limited, although severe disease has been reported in immunocompromised patients. Identification of M pneumoniae by culture-based methods is time consuming and insensitive. Serology-based assays for M pneumoniae have several drawbacks. The development of IgM antibodies takes approximately 1 week, and the IgM response may be variable in adults or decreased in immunosuppressed individuals. Confirmation of the disease is dependent on the observation of a 4-fold rise in IgG antibody titers between acute and convalescent specimens, several weeks following the initial onset of illness, providing clinical utility only for retrospective testing. Real-time polymerase chain reaction analysis offers a rapid and sensitive option for detection of M pneumoniae DNA from clinical specimens allows for diagnosis of acute or current infection.

Useful For: Screening for IgG antibodies in the indication of recent or past exposure to Mycoplasma pneumoniae

Interpretation: IgG ELISA result IgM ELISA result Interpretation Positive Negative Results suggest past exposure. Positive Reactive Prior exposure to Mycoplasma pneumoniae detected. Confirmatory testing for IgM to M pneumonia will be performed by an immunofluorescence assay. Equivocal Negative Negative No antibodies to M pneumoniae detected. Acute infection cannot be ruled out as antibody levels may be below the limit of detection. If clinically indicated, a second serum should be submitted in 14 to 21 days. Negative Reactive No prior exposure to Mycoplasma pneumoniae. Confirmatory testing for IgM to M pneumonia will be performed by an immunofluorescence assay. Equivocal Equivocal Negative Recommend follow-up testing in 10 to 14 days if clinically indicated. Reactive Confirmatory testing for IgM to M pneumonia will be performed by an immunofluorescence assay. Equivocal ELISA = Enzyme-linked immunosorbent assay

Reference Values:
Only orderable as part of a profile. For more information see MYCO / Mycoplasma pneumoniae Antibodies, IgG and IgM, Serum.

Negative

Clinical References: 1. Smith T. Mycoplasma pneumoniae infections: diagnosis based on immunofluorescence titer of IgG and IgM antibodies. Mayo Clin Proc. 1986;61(10):830-831 2. Holzman RS, Simberkoff MS, Leaf HL. Mycoplasma pneumoniae and atypical pneumonia. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2332-2339

MYCOM
48318

Mycoplasma pneumoniae Antibodies, IgM, Serum

Clinical Information: Mycoplasma pneumoniae is a small bacterium transmitted via organism-containing droplets. It is a cause of upper respiratory infection, pharyngitis, and tracheobronchitis, particularly in children, and has been associated with approximately 20% of cases of community-acquired pneumonia. Central nervous system and cardiac manifestations are probably the most frequent extrapulmonary complications of infections due to M pneumoniae. The disease is usually self-limited, although severe disease has been reported in immunocompromised patients. Identification of M pneumoniae by culture-based methods is time consuming and insensitive. Serology-based assays for M

pneumoniae have several drawbacks. The development of IgM antibodies takes approximately 1 week, and the IgM response may be variable in adults or decreased in immunosuppressed individuals. Confirmation of the disease is dependent on the observation of a 4-fold rise in IgG antibody titers between acute and convalescent specimens, several weeks following the initial onset of illness, providing clinical utility only for retrospective testing. Real-time polymerase chain reaction offers a rapid and sensitive option for detection of M pneumoniae DNA from clinical specimens for diagnosis of acute or current infection.

Useful For: Screening for IgM antibodies in the indication of recent or past exposure to Mycoplasma pneumoniae

Interpretation:

Reference Values:
Only orderable as part of a profile. For more information see MYCO / Mycoplasma pneumoniae Antibodies, IgG and IgM, Serum.

Negative

Clinical References: 1. Smith T. Mycoplasma pneumoniae infections: diagnosis based on immunofluorescence titer of IgG and IgM antibodies. Mayo Clin Proc 1986;61(10):830-831 2. Holzman RS, Simberkoff MS, Leaf HL. Mycoplasma pneumoniae and atypical pneumonia. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2332-2339

MYCON
48319

Mycoplasma pneumoniae Antibody Interpretation

Clinical Information: Mycoplasma pneumoniae is a small bacterium transmitted via organism-containing droplets. It is a cause of upper respiratory infection, pharyngitis, and tracheobronchitis, particularly in children, and has been associated with approximately 20% of cases of community-acquired pneumonia. Central nervous system and cardiac manifestations are probably the most frequent extrapulmonary complications of infections due to M pneumoniae. The disease is usually self-limited, although severe disease has been reported in immunocompromised patients. Identification of M pneumoniae by culture-based methods is time consuming and insensitive. Serology-based assays for M pneumoniae have several drawbacks. The development of IgM antibodies takes approximately 1 week, and the IgM response may be variable in adults or decreased in immunosuppressed individuals. Confirmation of the disease is dependent on the observation of a 4-fold rise in IgG antibody titers between acute and convalescent specimens, several weeks following the initial onset of illness, providing clinical utility only for retrospective testing. Real-time polymerase chain reaction analysis offers a rapid and sensitive option for detection of M pneumoniae DNA from clinical specimens allows for diagnosis of acute or current infection.

Useful For: Interpretation for Mycoplasma pneumoniae screening results

Interpretation: IgG ELISA result IgM ELISA result Interpretation Positive Negative Results suggest past exposure. Positive Reactive Prior exposure to Mycoplasma pneumoniae detected. Confirmatory testing for IgM to M pneumonia will be performed by an immunofluorescence assay. Equivocal Negative Negative No antibodies to M pneumoniae detected. Acute infection cannot be ruled out as antibody levels may be below the limit of detection. If clinically indicated, a second serum should be submitted in 14 to 21 days. Negative Reactive No prior exposure to Mycoplasma pneumoniae. Confirmatory testing for IgM to M pneumonia will be performed by an immunofluorescence assay. Equivocal Equivocal Negative Recommend follow-up testing in 10 to 14 days if clinically indicated.

Equivocal Reactive Confirmatory testing for IgM to M pneumonia will be performed by an immunofluorescence assay. Equivocal ELISA = Enzyme-linked immunosorbent assay

Reference Values:
Only orderable as part of a profile. For more information see MYCO / Mycoplasma pneumoniae Antibodies, IgG and IgM, Serum.

Negative

Clinical References: 1. Smith T: Mycoplasma pneumoniae infections: diagnosis based on immunofluorescence titer of IgG and IgM antibodies. Mayo Clin Proc 1986;61(10):830-831 2. Holzman RS, Simberkoff MS, Leaf HL: Mycoplasma pneumoniae and atypical pneumonia. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2332-2339

CXCFX
601508

MYD88 Reflex to CXCR4 Mutation Detection, Varies

Clinical Information: Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) is a B-cell lymphoma characterized by an aberrant accumulation of malignant lymphoplasmacytic cells in the bone marrow, lymph nodes, and spleen. It is a B-cell neoplasm that can exhibit excess production of serum IgM symptoms related to hyperviscosity, tissue filtration, and autoimmune-related pathology. CXCR4 mutations are identified in approximately 30% to 40% of patients with LPL/WM and are almost always in association with MYD88 L265P, which is highly prevalent in this neoplasm. The status of CXCR4 muations in the context of MYD88 L265P is clinically relevant as important determinants of clinical presentation, overall survival, and therapeutic response to ibrutinib. A MYD88-L265P/CXCR4-WHIM (C-terminus nonsense/frameshift mutations) molecular signature is associated with intermediate to high bone marrow disease burden and serum IgM levels, less adenopathy, and intermediate response to ibrutinib in previously treated patients. A MYD88-L265P/CXCR4-WT (wildtype) molecular signature is associated with intermediate bone marrow disease burden and serum IgM levels, more adenopathy, and highest response to ibrutinib in previously treated patients. The MYD88-WT/CXCR4-WT molecular signature is associated with inferior overall survival, lower response to ibrutinib therapy in previously treated patients, and lower bone marrow disease burden in comparison to those harboring a MYD88-L265 variant.

Useful For: The prognosis and clinical management of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia

Interpretation: Mutation present or not detected; an interpretive report will be issued under LPLFX / Lymphoplasmacytic Lymphoma/Waldenstrom Macroglobulinemia, MYD88 L265P with Reflex to CXCR4, Varies.

Reference Values:
Only orderable as a reflex. For more information see LPLFX / Lymphoplasmacytic Lymphoma/Waldenstrom Macroglobulinemia, MYD88 L265P with Reflex to CXCR4, Varies.

An interpretive report will be provided

Clinical References: 1. Hunter Z, Xu L, Yang G, et al: The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood. 2014 Mar 13;123(11):1637-1646. doi: 10.1182/blood-2013-09-525808 2. Landgren O, Tageja N: MYD88 and beyond: novel opportunities for diagnosis, prognosis and treatment in Waldenstrom's Macroglobulinemia.

Leukemia. 2014 Sep;28(9):1799-1803. doi: 10.1038/leu.2014.88 3. Poulain S, Roumier C, Venet-Caillault A, et al: Genomic Landscape of CXCR4 Mutations in Waldenstrom Macroglobulinemia. Clin Cancer Res. 2016 Mar 15;22(6):1480-1488. doi: 10.1158/1078-0432.CCR-15-0646 4. Roccaro A, Sacco A, Jimenez C, et al: C1013G/CXCR4 acts as a driver mutation of tumor progression and modulator of drug resistance in lymphoplasmacytic lymphoma. Blood. 2014 Jun 26;123(26):4120-4131. doi: 10.1182/blood-2014-03-564583 5. Schmidt J, Federmann B, Schindler N, et al: MYD88 L265P and CXCR4 mutations in lymphoplasmacytic lymphoma identify cases with high disease activity. Br J Haematol. 2015 Jun;169(6):795-803. doi: 10.1111/bjh.13361 6. Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR: Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. Blood. 2014 May 1;123(18):2791-2796. doi: 10.1182/blood-2014-01-550905 7. Treon SP, Tripsas CK, Meid K, et al: Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med. 2015 Apr 9;372(15):1430-1440. doi: 10.1056/NEJMoa1501548 8. Xu L, Hunter ZR, Tsakmaklis N, et al: Clonal architecture of CXCR4 WHIM-like mutations in Waldenstrom Macroglobulinaemia. Br J Haematol. 2016 Mar;172(5):735-744. doi: 10.1111/bjh.13897

MYD88 62927 MYD88, L265P, Somatic Gene Mutation, DNA Allele-Specific PCR, Varies

Clinical Information: The single point alteration in MYD88, L265P, is present in 67% to 100% of patients with lymphoplasmacytic lymphoma, and these patients typically have clinical manifestations of Waldenstrom macroglobulinemia (often designated LPL/WM).

Useful For: Establishing the diagnosis of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia Helping to distinguish lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (low-grade B-cell lymphoma) from other subtypes

Interpretation: Mutation present or not detected; an interpretive report will be issued.

Reference Values:
Variant present or absent based on expected alteration polymerase chain reaction product size. Concurrent amplification of wild type MYD88 fragment determined for sample amplification integrity. MYD88 gene (NCBI accession NM_002468.4)

Clinical References: 1. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. N Engl J Med. 2012;367(9):826-833 2. Varettoni M, Arcaini L, Zibellini S, et al. Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in Waldenstrom's macroglobulinemia and related lymphoid neoplasms. Blood. 2013;121(13):2522-2528 3. Xu L, Hunter ZR, Yang G, et al. MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. Blood. 2013;121(11);2051-2058 4. Poulain S, Roumier C, Decambron A, et al. MYD88 L265P mutation in Waldenstrom macroglobulinemia. Blood. 2013;121(22);4504-4511 5. Gachard N, Parrens M, Soubeyran I, et al. IGHV gene features and MYD88 L265P mutation separate the three marginal zone lymphoma entities and Waldenstrom macroglobulinemia/lymphoplasmacytic lymphomas. Leukemia. 2013;27(1):183-189. doi: 10.1038/leu.2012.257 6. Ondrejka SL, Lin JJ, Warden DW, Durkin L, Cook JR, Hsi ED. MYD88 L265P somatic mutation: its usefulness in the differential diagnosis of bone marrow involvement by B-cell lymphoproliferative disorders. Am J Clin Pathol. 2013;140(3):387-394

MOGFS 65563 Myelin Oligodendrocyte Glycoprotein (MOG-IgG1)

Fluorescence-Activated Cell Sorting (FACS) Assay, Serum

Clinical Information: Neuromyelitis optica (NMO), sometimes called Devic disease or opticospinal multiple sclerosis (MS) is a severe, relapsing, autoimmune, inflammatory and demyelinating central nervous system disease (IDD) that predominantly affects optic nerves and spinal cord.(1) The disorder is now recognized as a spectrum of autoimmunity (termed NMO spectrum disorders: NMOSD).(1-3) Brain lesions are observed in more than 60% of patients with NMOSD and approximately 10% will be MS-like.(4) Children tend to have greater brain involvement than adults, and brain lesions are more symptomatic than is typical for adult patients.(3) The clinical course is characterized by relapses of optic neuritis or transverse myelitis or both. Some patients may present with acute disseminated encephalomyelitis (ADEM). Many patients with NMOSD are misdiagnosed as having MS. More effective treatments combined with earlier and more accurate diagnosis has led to improved outcomes. Approximately 80% of patients with NMO are seropositive for aquaporin-4 (AQP4)-IgG.(5-7) In the remaining 20% of patients, myelin oligodendrocyte glycoprotein (MOG)-IgG is detected in up to a third.(8) The pathogenic target for the remaining patients remains unknown. Detection of MOG-IgG is diagnostic of central nervous system (CNS) inflammatory demyelination, where the clinical phenotype (NMOSD, optic neuritis, transverse myelitis, ADEM) may be similar, but the immunopathology (astrocytopathy vs oligodendrogyopathy) and clinical outcome (worse vs better) are different.(9) Detection of MOG-IgG also predicts relapse.(10) More importantly, MOG-IgG seropositive IDDs are distinct from MS and treated differently.(8, 9) Treatments for IDDs seropositive for MOG-IgG include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Disease-modifying agents, treatments promoted for MS, have been reported to exacerbate MOG-IgG1 seropositive IDDs. Therefore, early diagnosis and initiation of appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. In 2015, Waters and colleagues (11) from Oxford University established a novel cell-based assay for the measurement of IgG1 MOG antibodies based on previous findings that MOG antibodies are almost exclusively of the IgG1 subclass. They showed that their MOG-IgG1 flow cytometry assay eliminated false positive results without losing true positive results with low titers. The detection of MOG-IgG1 allowed non-MS demyelinating diseases (ADEM, AQp4-IgG negative neuromyelitis optica spectrum disorder including ON,TM) to be distinguished from MS.(12) Using a similar assay to this MOG-IgG1 flow cytometry assay, demonstrated high specificity of their MOG-IgG1 assay in which 49 patients with MS, 13 healthy control sera, and 37 AQP4-seropositive serum samples were all negative at a dilution of 1:20. Of 58 patients fulfilling 2006 Wingerchuk criteria for NMO, 21 (36%) tested negative for AQP4-IgG. MOG-IgG1 was detected by cell-based assay in 8 (38%) of these cases.(13) Testing of 1109 consecutive sera sent for AQP4-IgG testing(12) revealed 40 AQP4-IgG and 65 MOG-IgG1-positive cases. None were positive for both. The clinical diagnoses obtained in 33 MOG-IgG1-positive patients included 4 NMO, 1 ADEM, and 11 optic neuritis (n = 11). All 7 patients with probable MS were MOG-IgG1 negative. This study provides Class II evidence that the presence of serum MOG-IgG1 distinguishes non-MS CNS demyelinating disorders from MS (sensitivity 24%, 95% CI 9%-45%; specificity 100%, 95% CI 88%-100%). This assay was developed using the MOG construct provided by Dr Waters,(11) and the validation was based on a blinded comparison with the Oxford assay. Comparison was also made with the Euroimmun fixed cell-based kit assay.(14) A recent longitudinal analysis with 2-year follow-up suggested that persistence of MOG-IgG is associated with relapses thus warranting relapse prevention.(10) Detection of MOG-IgG1 allows distinction from MS and is generally indicative of a relapsing disease, mandating initiation of immunosuppression, even after the first attack in some, thereby reducing attack frequency and disability in the future.

Useful For: Diagnosis of inflammatory demyelinating diseases (IDD) with similar phenotype to neuromyelitis optica (NMO) spectrum disorder (NMOSD), including optic neuritis (single or bilateral) and transverse myelitis Diagnosis of autoimmune myelin oligodendrocyte glycoprotein (MOG)-opathy Diagnosis of NMO Distinguishing NMOSD, acute disseminated encephalomyelitis (ADEM), optic neuritis, and transverse myelitis from multiple sclerosis early in the course of disease Diagnosis of ADEM Prediction of a relapsing disease course

Interpretation: A positive value for myelin oligodendrocyte glycoprotein (MOG)-IgG is consistent with a neuromyelitis optica-like phenotype and, in the setting of acute disseminated encephalomyelitis, optic neuritis and transverse myelitis, indicates an autoimmune oligodendrogliopathy with potential for relapsing course. Identification of MOG-IgG allows distinction from multiple sclerosis (MS) and may justify initiation of appropriate immunosuppressive therapy (not MS disease-modifying agents) at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 6 to 12 months, as persistence of MOG-IgG seropositivity predicts a relapsing course. This autoantibody is not found in healthy subjects.

Reference Values:
Negative

Clinical References: 1. Wingerchuk DM, Lennon VA, Lucchinetti CF, et al. The spectrum of neuromyelitis optica. Lancet Neurol. 2007;6(9):805-815 2. Apiwattanakul M, Popescu BF, Matiello M, et al. Intractable vomiting as the initial presentation of neuromyelitis optica. Ann Neurol. 2010;68(5):757-761 3. McKeon A, Lennon VA, Lotze T, et al. CNS aquaporin-4 autoimmunity in children. Neurology 2008;71(2):93-100 4. Pittock SJ, Weinshenker BG, Lucchinetti CF, et al. Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. Arch Neurol. 2006;63(7):964-968 5. Fryer JP, Lennon VA, Pittock SJ, et al. AQP4 autoantibody assay performance in clinical laboratory service. Neurol Neuroimmunol Neuroinflamm. 2014;1(1):e11 6. Waters PJ, McKeon A, Leite MI, et al. Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. Neurology. 2012;78(9):665-669 7. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet. 2004;364(9451):2106-2112 8. Peschl P, Bradl M, Hoftberger R, et al. Myelin oligodendrocyte glycoprotein: deciphering a target in inflammatory demyelinating diseases. Front Immunol. 2017;8:529 9. Pittock SJ, Lucchinetti CF. Neuromyelitis optica and the evolving spectrum of autoimmune aquaporin-4 channelopathies: a decade later. Ann NY Acad Sci. 2016;1366(1):20-39 10. Hyun JW, Woodhall MR, Kim SH, et al. Longitudinal analysis of myelin oligodendrocyte glycoprotein antibodies in CNS inflammatory diseases. J Neurol Neurosurg Psychiatry. 2017;88(10):811-817 11. Waters P, Woodhall M, O'Connor KC, et al. MOG cell-based assay detects non-MS patients with inflammatory neurologic disease. Neurol Neuroimmunol Neuroinflamm. 2015;2(3):e89 12. Reindl M, Jarius S, Rostasy K, Berger T. Myelin oligodendrocyte glycoprotein antibodies: How clinically useful are they? Curr Opin Neurol. 2017;30(3):295-301 13. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2):177-189 14. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: Frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. J Neuroinflammation. 2016;13(1):279

MAGES
607034

Myelin-Associated Glycoprotein Autoantibodies, IgM, Serum

Clinical Information: Autoantibodies directed against myelin-associated glycoprotein (MAG) are associated with sensory motor demyelinating peripheral neuropathy. A distal acquired demyelinating symmetric (DADS) neuropathy phenotype is the most commonly associated presentation. Patients typically have a slowly progressive symmetric sensory ataxia with/without distal weakness and an IgM monoclonal gammopathy of undetermined significance. Nerve conductions studies typically demonstrate a characteristic progressive sensory predominant mixed axonal and demyelinating neuropathy with reduced distal conduction velocities that are greater distally. In general, patients with a DADS neuropathy show limited treatment responses to intravenous immunoglobulin and more aggressive immunotherapy may be needed. MAG antibody titers do not correlate with disease severity nor treatment responses. The presence of MAG antibodies is not exclusively diagnostic of an acquired neuropathy and results must be interpreted in the correct clinical and electrophysiological context. MAG antibodies are present in approximately 50% to 70% of those with an IgM M-protein and a DADS neuropathy phenotype. However, MAG antibodies may also be identified in those with an IgM M-

protein and a chronic inflammatory demyelinating polyneuropathy (CIDP) presentation as well as in other IgM paraproteinemic disorders that present with neuropathy including in myeloma, lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia) and amyloid light chain (AL)-IgM primary amyloidosis. Higher MAG antibody titers (>10,000 Buhlmann titer unit) are better predictors of an electrophysiological DADS phenotype whereas low titer MAG antibodies may be associated with a more diverse group of neuropathies. Detection of MAG IgM antibody by enzyme-linked immunosorbent assay based on human MAG (100 kDa) antigen is significantly more sensitive and specific than MAG western blot and immunofluorescence assays using primate antigen.

Useful For: Evaluating peripheral neuropathy Evaluating paraproteinemic neuropathy

Interpretation: A positive result is consistent with anti-myelin-associated glycoprotein neuropathy.

Reference Values:
<1500 Buhlmann Titer Unit

Clinical References: 1. Kuijf ML, Eurelings M, Tio-Gillen AP, et al: Detection of anti-MAG antibodies in polyneuropathy associated with IgM monoclonal gammopathy. Neurology. 2009 Sep;73(9):688-695. doi: 10.1212/WNL.0b013e3181b59a80 2. Katz JS, Saperstein DS, Gronseth G, Amato AA, Barohn RJ: Distal acquired demyelinating symmetric neuropathy. Neurology. 2000 Feb;54(3):615-620. doi: 10.1212/wnl.54.3.615 3. Magy L, Kabore R, Mathis S, et al: Heterogeneity of polyneuropathy associated with anti-MAG antibodies. J Immunol Res. 2015;2015:450391. doi: 10.1155/2015/450391

MDSDF
614276

Myelodysplastic Syndrome (MDS), Diagnostic FISH, Varies

Clinical Information: Myelodysplastic syndromes (MDS) primarily occur in the older adult population and have a yearly incidence of 30 in 100,000 in persons older than 70 years of age. These disorders are typically associated with a hypercellular bone marrow and low peripheral blood counts, and with significant morbidity and mortality. The eventual clinical outcome for patients with MDS relates to either bone marrow failure or transformation to acute myeloid leukemia. MDS can be either primary (de novo) or secondary (due to previous treatment with alkylating or etoposide chemotherapy, with or without radiation). Cytogenetic studies can provide confirmatory evidence of clonality in MDS and can be used to provide clinical prognostic or diagnostic information. Clonal cytogenetic abnormalities are more frequently observed in cases of secondary MDS (80% of patients) than in primary MDS (40%-60% of patients). The common chromosomal abnormalities associated with MDS include: inv(3), -5/5q-, -7/7q-, +8, and 20q-. These abnormalities can be observed singly or in concert. In addition, t(1;3) and t(3;21) are more frequently associated with secondary MDS. Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities in MDS; however, some of the subtle rearrangements associated with secondary MDS can be missed.

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with myelodysplastic syndromes or other myeloid malignancies using a laboratory-designated probe set algorithm Evaluating specimens in which standard cytogenetic analysis is unsuccessful

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Bernasconi P, Klersy C, Boni M, et al: World Health Organization classification in combination with cytogenetic markers improves the prognostic stratification of patients with de novo primary myelodysplastic syndromes. Br J Haematol. 2007 May;137(3):193-205 2. Swerdlow SH, Campo E, Harris NL, et al, eds: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours. Vol 2 3. He R, Wiktor AE, Durnick DK, et al: Bone marrow conventional karyotyping and fluorescence in situ hybridization: Defining an effective utilization strategy for evaluation of myelodysplastic syndromes. Am J Clin Pathol. 2016 Jul;146(1):86-94. doi: 10.1093/ajcp/aqw077

MDSMF
614287

Myelodysplastic Syndrome (MDS), Specified FISH, Varies

Clinical Information: Myelodysplastic syndromes (MDS) primarily occur in the older adult population and have a yearly incidence of 30 in 100,000 in persons older than 70 years of age. These disorders are typically associated with a hypercellular bone marrow and low peripheral blood counts, and with significant morbidity and mortality. The eventual clinical outcome for patients with MDS relates to either bone marrow failure or transformation to acute myeloid leukemia. MDS can be either primary (de novo) or secondary (due to previous treatment with alkylating or etoposide chemotherapy, with or without radiation). Cytogenetic studies can provide confirmatory evidence of clonality in MDS and can be used to provide clinical prognostic or diagnostic information. Clonal cytogenetic abnormalities are more frequently observed in cases of secondary MDS (80% of patients) than in primary MDS (40%-60% of patients). The common chromosomal abnormalities associated with MDS include: inv(3), -5/5q-, -7/7q-, +8, and 20q-. These abnormalities can be observed singly or in concert. Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities in MDS; however, some of the subtle rearrangements associated with secondary MDS can be missed. Fluorescence in situ hybridization (FISH) analysis of nonproliferating (interphase) cells can be used to detect the common diagnostic and prognostic chromosome abnormalities observed in patients with MDS. When recurrent translocations or inversions are identified, FISH testing can also be used to track response to therapy.

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with myelodysplastic syndromes or other myeloid malignancies using client specified probes Evaluating specimens in which standard cytogenetic analysis is unsuccessful

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Bernasconi P, Klersy C, Boni M, et al: World Health Organization classification in combination with cytogenetic markers improves the prognostic stratification of patients with de novo primary myelodysplastic syndromes. Br J Haematol. 2007 May;137(3):193-205 2. Swerdlow SH, Campo E, Harris NL, et al, eds: WHO Classification of Tumour of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017 3. He R, Wiktor AE, Durnick DK, et al: Bone marrow conventional karyotyping and fluorescence in situ hybridization: Defining an effective utilization strategy for evaluation of myelodysplastic syndromes. Am J Clin Pathol. 2016 July;146(1):86-94. doi: 10.1093/ajcp/aqw077

MYEFL
63414

Myelodysplastic Syndrome by Flow Cytometry, Bone Marrow

Clinical Information: Myelodysplastic syndromes (MDS) encompass a heterogeneous group of clonal hematopoietic neoplasms characterized by cytopenias due to ineffective hematopoiesis, variable degrees of dysmyelopoietic morphologic features, and increased risks of evolution to acute myeloid leukemia. Per 2008 World Health Organization recommendations, a definitive diagnosis of MDS requires identification of 1 or more of the following findings: clear-cut morphologic features of dysplasia in greater than or equal to 10% of the cells in 1 or more of the 3 hematopoietic lineages; increased (but <20%) blood or marrow blasts with or without Auer rods; and well-characterized clonal cytogenetic abnormalities.(3-4) However, at present, in approximately 50% of MDS patients, no informative or diagnostic clonal cytogenetic abnormalities are identified. Not infrequently, morphologic review of the patient's blood and marrow specimen is inconclusive. And yet it is important to distinguish MDS and other clonal myeloid neoplasms from other nonmalignant and nonneoplastic possibilities in the differential diagnosis such as medication effects or other toxic exposures, copper deficiency, infections, and left-shifted hematopoietic regeneration, among others. In such settings, when used in conjunction with appropriate clinical and morphologic findings, flow cytometry immunophenotyping analysis can provide additional diagnostic information to help distinguish an underlying clonal hematopoietic neoplasm from a reactive or secondary response.(2,5)

Useful For: Detecting increased blasts Characterizing blast phenotypes Identifying abnormal patterns of myeloid maturation as seen in myelodysplastic syndromes and other clonal myeloid neoplasms Providing additional adjunct diagnostic information in cases with equivocal or suspicious morphologic features for myelodysplastic syndrome (MDS), MDS/myeloproliferative neoplasms including chronic myelomonocytic leukemia, and other clonal myeloid neoplasms

Interpretation: The final interpretation integrates 1) the quantity of blasts; 2) blast phenotype with respect to CD13/HLA-DR expression and/or abnormal coexpression of CD2, CD7, and/or CD56; and 3) myeloid maturation patterns based on CD13/CD16 plot. In combination, the total number of abnormalities detected and the distinctiveness of the abnormalities themselves help determine the likelihood of specimen involvement by a clonal myeloid neoplasm.

Reference Values:
An interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and, if available, morphologic features will be provided by a board-certified hematopathologist for every case.

Clinical References: 1. Kussick SJ, Fromm JR, Rossini A, et al. Four-color flow cytometry shows strong concordance with bone marrow morphology and cytogenetics in the evaluation for myelodysplasia. Am J Clin Pathol. 2005;124(2):170-181 2. Jevremovic D, Timm MM, Reichard KK, et al. Loss of blast heterogeneity in myelodysplastic syndrome and other chronic myeloid neoplasms. Am J Clin Pathol. 2014;142(3):292-298 3. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Lyon, 2008, pp 88-107 4. Cioc AM, Nguyen PL. Myelodysplastic syndromes. In Hematopathology. Hsi E, ed. Elsevier Saunders. Philadelphia, 2012, pp 523-546 5. van de Loosdrecht AA, Westers TM. Cutting edge: flow cytometry in myelodysplastic syndromes. J Natl Compr Canc Netw, 2013;11(7):892-902

MSTF 35844 Myeloid Sarcoma, FISH, Tissue

Clinical Information: Myeloid sarcomas are tumors made up of myeloblasts or immature myeloid cells that occur in extramedullary sites or in bone. They can occur concurrently with acute or chronic myeloid leukemia (AML or CML) or may precede the leukemia or other myeloid neoplasms. They may also be the initial manifestation of relapse of a previously treated primary AML in remission. Due to this extramedullary presentation, the bone marrow may have a low number of myeloblasts due to a lack of bone marrow involvement. The most common abnormalities seen in myeloid sarcomas are fusion of

RUNX1T1/RUNX1 (t[8;21][q22;q22]), PML/RARA (t[15;17][q24;q21]), BCR/ABL1 (t[9;22][q34;q11.2]), inversion of MYH11/CBFB (inv[16][q13.1q22]), and rearrangements of MLL (KMT2A; t[11q23;var]). In general, AML patients with an inv(16), t(8;21), t(9;22), or t(15;17) have a favorable prognosis, while AML patients with a rearrangement of t(11q23) have an unfavorable prognosis. Thus, the detection of these abnormalities in an extramedullary presentation of AML can be prognostically important.

Useful For: Supporting the diagnosis of myeloid sarcoma when coordinated with a surgical pathology consultation

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for a given probe set. A positive result supports the diagnosis of a myeloid sarcoma. A negative result does not exclude the diagnosis of a myeloid sarcoma.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Slovak ML, Kopecky KJ, Cassileth PA, et al: Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. Blood. 2000;96:4075-4083 2. Swerdlow SH, Campo E, Harris NL, et al: WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. International Agency for Research on Cancer; 2008:140-141 3. Grimwade D, Hills RK, Moorman AV, et al: Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood. 2010;116:354-365

MSMRD 616030 Myeloma Stratification and Risk-Adapted Therapy with Reflex to Minimal Residual Disease, Bone Marrow

Clinical Information: Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options. The Mayo algorithmic approach for stratification of myeloma and risk-adapted therapy classifies patients into either standard or high-risk categories based on the results of 2 assays: plasma cell proliferation and fluorescence in situ hybridization for specific multiple myeloma-associated abnormalities.

Useful For: Risk stratification of patients with treated multiple myeloma, which can assist in determining treatment and management decisions Risk stratification of patients with newly diagnosed multiple myeloma

Interpretation: The interpretation of results includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
PLASMA CELL CLONALITY:
Normal bone marrow
No monotypic clonal plasma cells detected

DNA INDEX:

Normal polytypic plasma cells
DNA index (G0/G1 cells): Diploid 0.95-1.05

Clinical References: 1. Gonsalves WI, Buadi FK, Ailawadhi S, et al. Utilization of hematopoietic stem cell transplantation for the treatment of multiple myeloma: a Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus statement. Bone Marrow Transplant. 2019;54(3):353-367. doi:10.1038/s41409-018-0264-8 2. Kapoor P, Ansell SM, Fonseca R, et al. Diagnosis and management of waldenstrom macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) guidelines 2016. JAMA Oncol. 2017;3(9):1257-1265. doi:10.1001/jamaoncol.2016.5763 3. Mikhael JR, Dingli D, Roy V, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. Mayo Clin Proc. 2013;88(4):360-376. doi:10.1016/j.mayocp.2013.01.019. 4. Swerdlow S, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours, Vol. 2 5. Kumar SK, Rajkumar SV. The multiple myelomas-current concepts in cytogenetic classification and therapy. Nat Rev Clin Oncol. 2018;15(7):409-421 doi:10.1038/s41571-018-0018-y 6. Rajkumar SV, Landgren O, Mateos MV. Smoldering multiple myeloma. Blood. 2015;125(20):3069-3075 doi:10.1182/blood-2014-09-568899 7. Aljama MA, Sidiqi MH, Lakshman A, et al. Plasma cell proliferative index is an independent predictor of progression in smoldering multiple myeloma. Blood Adv. 2018;2(22):3149-3154 8. Mellors PW, Binder M, Ketterling RP, et al. Metaphase cytogenetics and plasma cell proliferation index for risk stratification in newly diagnosed multiple myeloma. Blood Adv. 2020;4(10):2236-2244 9. Sidana S, Jevremovic D, Ketterling RP, et al. Rapid assessment of hyperdiploidy in plasma cell disorders using a novel multi-parametric flow cytometry method. Am J Hematol. 2019;94(4):424-430 10. Ghosh T, Gonsalves WI, Jevremovic D, et al. The prognostic significance of polyclonal bone marrow plasma cells in patients with relapsing multiple myeloma. Am J Hematol. 2017;92(9):E507-E512

MFCDF
614298

Myeloma, High Risk with Reflex Probes, Diagnostic FISH Evaluation, Fixed Cell Pellet

Clinical Information: Multiple myeloma is a hematologic neoplasm that generally originates in the bone marrow and develops from malignant plasma cells. There are 4 main categories of plasma cell proliferative disorders: monoclonal gammopathy of undetermined significance (MGUS), monoclonal immunoglobulin deposition diseases (amyloidosis), plasmacytoma, and multiple myeloma. MGUS, which occurs in 3% to 4% of individuals over 50 years of age, represents the identification of an asymptomatic monoclonal protein, yet approximately 1% per year will progress to multiple myeloma. Amyloidosis represents a rare group of deposition disorders including primary amyloidosis vs. light chain and heavy chain disease. Plasmacytomas represent isolated collections of bone or extramedullary plasma cells with a risk for development of multiple myeloma. Generalized bone pain, anemia, limb numbness, or weakness, symptoms of hypercalcemia, and recurrent infections are all symptoms that may indicate multiple myeloma. As myeloma progresses, the malignant plasma cells interfere with normal blood product formation in the bone marrow resulting in anemia and leukopenia. Myeloma also causes an overstimulation of osteoclasts, causing excessive breakdown of bone tissue without the normal corresponding bone formation. These bone lesions are seen in approximately 66% of myeloma patients. In advanced disease, bone loss may reach a degree where the patient suffers fractures easily. Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options.

Useful For: Aiding in the diagnosis of new cases of multiple myeloma or other plasma cell proliferative disorders using a fixed cell pellet derived from bone marrow Identifying prognostic markers

based on the abnormalities found This test should not be used to track the progression of disease.

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow S, Campo E, Harris NL, et al, eds: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press; 2017 2. Kumar SK, Rajkumar SV: The multiple myelomas-current concepts in cytogenetic classification and therapy. Nat Rev Clin Oncol. 2018;15(7):409-421. doi: 10.1038/s41571-018-0018-y 3. Rajkumar SV, Landgren O, Mateos MV: Smoldering multiple myeloma. Blood. 2015 May 14;125(20):3069-3075. doi: 10.1182/blood-2014-09-568899 4. Muchtar E, Dispenzieri A, Kumar S, et al: Interphase fluorescence in situ hybridization in untreated AL amyloidosis has an independent prognostic impact by abnormality type and treatment category. Leukemia. 2017 Jul;31(7);1562-1569. doi: 10.1038/leu.2016.369 5. Lakshman A, Paul S, Rajkumar SV, et al: Prognostic significance of interphase FISH in monoclonal gammopathy of undetermined significance. Leukemia. 2018 Aug;32(8);1811-1815. doi: 10.1038/s41375-018-0030-3 6. Bochtler T, Hegenbart U, Kunz C, et al: Prognostic impact of cytogenetic aberrations in AL amyloidosis patients after high-dose melphalan: a long-term follow-up study. Blood. 2016 Jul 28;128(4):594-602. doi: 10.1182/blood-2015-10-7 7. Treatment guidelines: multiple myeloma. mSMART 3.0. Accessed 01/16/2020. Available at www.msmart.org/mm-treatment-guidelines

MAS1
605125

Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum

Clinical Information: Patients with autoimmune myelopathy present with subacute onset and rapid progression of spinal cord symptoms with one or more of the following: weakness, gait difficulties, loss of sensation, neuropathic pain, and bowel and bladder dysfunction. Clinical history and examination, spinal cord magnetic resonance imaging, and cerebrospinal fluid (CSF) testing may provide clues to an autoimmune diagnosis. Autoimmune myelopathy evaluation of both serum and CSF can assist in the diagnosis (paraneoplastic or idiopathic autoimmune) and aid distinction from other causes of myelopathy (multiple sclerosis, sarcoidosis, vascular disease). Early testing may assist in early diagnosis of occult cancer, prompt initiation of immune therapies, or both.

Useful For: Evaluating patients with suspected autoimmune myelopathy, myelitis, and paraneoplastic myelopathy using serum specimens

Interpretation: A positive result is consistent with a diagnosis of autoimmune myelopathy in the appropriate clinical context.

Reference Values:

Test ID	Reporting name	Methodology*	Reference value
MSI1	Autoimmune Myelopathy Interp, S	Medical interpretation	Interpretive report
AMPHS	Amphiphysin Ab, S	IFA	Negative
AGN1S	Anti-Glial Nuclear Ab, Type 1	IFA	Negative

ANN1S	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2S	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3S	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
APBIS	AP3B2 IFA, S	IFA	Negative
CRMWS	CRMP-5-IgG Western Blot, S	WB	Negative
DPPCS	DPPX Ab CBA, S	CBA	Negative
GABCS	GABA-B-R Ab CBA, S	CBA	Negative
GD65S	GAD65 Ab Assay, S	RIA	< or =0.02 nmol/L Reference values apply to all ages.
GFAIS	GFAP IFA, S	IFA	Negative
GL1IS	mGluR1 Ab IFA, S	IFA	Negative
MOGFS	MOG FACS, S	FCM	Negative
NCDIS	Neurochondrin IFA, S	IFA	Negative
NIFIS	NIF IFA, S	IFA	Negative
NMOFS	NMO/AQP4 FACS, S	FCM	Negative
PCABP	Purkinje Cell Cytoplasmic Ab Type 1	IFA	Negative
PCAB2	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
SP7IS	Septin-7 IFA, S	IFA	Negative
T46IS	TRIM46 IFA, S	IFA	Negative
Reflex Information Test ID	Reporting name	Methodology*	Reference value
AGNBS	AGNA-1 Immunoblot, S	IB	Negative
AGNTS	AGNA-1 Titer, S	IFA	
AINCS	Alpha Internexin CBA, S	CBA	Negative
AMIBS	Amphiphysin Immunoblot, S	IB	Negative
AN1BS	ANNA-1 Immunoblot, S	IB	Negative
AN1TS	ANNA-1 Titer, S	IFA	
AN2BS	ANNA-2 Immunoblot, S	IB	Negative
AN2TS	ANNA-2 Titer, S	IFA	
AN3TS	ANNA-3 Titer, S	IFA	
APBCS	AP3B2 CBA, S	CBA	Negative
APBTS	AP3B2 IFA Titer, S	IFA	
APHTS	Amphiphysin Ab Titer,	IFA	

S			
CRMTS	CRMP-5-IgG Titer, S	IFA	
DPPTS	DPPX Ab IFA Titer, S	IFA	
GABIS	GABA-B-R Ab IF Titer Assay, S	IFA	
GFACS	GFAP CBA, S	CBA	Negative
GFATS	GFAP IFA Titer, S	IFA	
GL1CS	mGluR1 Ab CBA, S	CBA	Negative
GL1TS	mGluR1 Ab IFA Titer, S	IFA	
MOGTS	MOG FACS Titer, S	FCM	
NCDCS	Neurochondrin CBA, S	CBA	Negative
NCDTS	Neurochondrin IFA Titer, S	IFA	
NFHCS	NIF Heavy Chain CBA, S	CBA	Negative
NIFTS	NIF IFA Titer, S	IFA	
NFLCS	NIF Light Chain CBA, S	CBA	Negative
NMOTS	NMO/AQP4 FACS Titer, S	FCM	
PC1BS	PCA-1 Immunoblot, S	IB	Negative
PC1TS	PCA-1 Titer, S	IFA	
PC2TS	PCA-2 Titer, S	IFA	
SP7CS	Septin-7 CBA, S	CBA	Negative
SP7TS	Septin-7 IFA Titer, S	IFA	
T46CS	TRIM46 CBA, S	CBA	Negative
T46TS	TRIM46 IFA Titer, S	IFA	

Clinical References: 1. Dubey D, Pittock SJ, Krecke KN, et al. Clinical, radiologic, and prognostic features of myelitis associated with myelin oligodendrocyte glycoprotein autoantibody. JAMA Neurol. 2019;76(3):301-309 2. Zalewski NL, Flanagan EP. Autoimmune and paraneoplastic myelopathies. Semin Neurol. 2018;38(3):278-289 3. Flanagan EP, Hinson SR, Lennon VA, et al. Glial fibrillary acidic protein immunoglobulin G as biomarker of autoimmune astrocytopathy: Analysis of 102 patients. Ann Neurol. 2017;81(2):298-309 4. Keegan BM, Pittock SJ, Lennon VA. Autoimmune myelopathy associated with collapsin response-mediator protein-5 immunoglobulin G. Ann Neurol. 2008;63(4):531-534 5. Weinshenker BG, Wingerchuk DM, Vukusic S, et al. Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. Ann Neurol. 2006;59(3):566-569

MAC1 605126 Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

Clinical Information: Patients with autoimmune myelopathy present with subacute onset and rapid progression of spinal cord symptoms with one or more of the following: weakness, gait difficulties, loss

of sensation, neuropathic pain, and bowel and bladder dysfunction. Clinical history and examination, spinal cord magnetic resonance imaging, and cerebrospinal fluid (CSF) testing may provide clues to an autoimmune diagnosis. Autoimmune myelopathy evaluation of both serum and CSF can assist in the diagnosis (paraneoplastic or idiopathic autoimmune) and aid distinction from other causes of myelopathy (multiple sclerosis, sarcoidosis, vascular disease). Early testing may assist in early diagnosis of occult cancer, prompt initiation of immune therapies, or both.

Useful For: Evaluating patients with suspected autoimmune myelopathy, myelitis, and paraneoplastic myelopathy using spinal fluid specimens

Interpretation: A positive result is consistent with a diagnosis of autoimmune myelopathy in the appropriate clinical context.

Reference Values:

Test ID	Reporting name	Methodology*	Reference value
MCI1	Autoimmune Myelopathy Interp, CSF	Medical interpretation	Interpretive report
AMPHC	Amphiphysin Ab, CSF	IFA	Negative
AGN1C	Anti-Glial Nuclear Ab, Type 1	IFA	Negative
ANN1C	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2C	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3C	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
APBIC	AP3B2 IFA, CSF	IFA	Negative
CRMWC	CRMP-5-IgG Western Blot, CSF	WB	Negative
DPPCC	DPPX Ab CBA, CSF	CBA	Negative
GABCC	GABA-B-R Ab CBA, CSF	CBA	Negative
GD65C	GAD65 Ab Assay, CSF	RIA	< or =0.02 nmol/L Reference values apply to all ages.
GFAIC	GFAP IFA, CSF	IFA	Negative
GL1IC	mGluR1 Ab IFA, CSF	IFA	Negative
NCDIC	Neurochondrin IFA, CSF	IFA	Negative
NIFIC	NIF IFA, CSF	IFA	Negative
NMOFC	NMO/AQP4 FACS, CSF	FCM	Negative
PCA1C	Purkinje Cell Cytoplasmic Ab Type 1	IFA	Negative
PCA2C	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative

SP7IC	Septin-7 IFA, CSF	IFA	Negative
T46IC	TRIM46 IFA, CSF	IFA	Negative
Reflex Information: Test ID	Reporting name	Methodology*	Reference value
AGNBC	AGNA-1 Immunoblot, CSF	IB	Negative
AGNTC	AGNA-1 Titer, CSF	IFA	
AINCC	Alpha Internexin CBA, CSF	CBA	Negative
AMIBC	Amphiphysin Immunoblot, CSF	IB	Negative
AN1BC	ANNA-1 Immunoblot, CSF	IB	Negative
AN1TC	ANNA-1 Titer, CSF	IFA	
AN2BC	ANNA-2 Immunoblot, CSF	IB	Negative
AN2TC	ANNA-2 Titer, CSF	IFA	
AN3TC	ANNA-3 Titer, CSF	IFA	
APBCC	AP3B2 CBA, CSF	CBA	Negative
APBTC	AP3B2 IFA Titer, CSF	IFA	
APHTC	Amphiphysin Ab Titer, CSF	IFA	
CRMTC	CRMP-5-IgG Titer, CSF	IFA	
DPPTC	DPPX Ab IFA Titer, CSF	IFA	
GABIC	GABA-B-R Ab IF Titer Assay, CSF	IFA	
GFACC	GFAP CBA, CSF	CBA	Negative
GFATC	GFAP IFA Titer, CSF	IFA	
GL1CC	mGluR1 Ab CBA, CSF	CBA	Negative
GL1TC	mGluR1 Ab IFA Titer, CSF	IFA	
NCDCC	Neurochondrin CBA, CSF	CBA	Negative
NCDTC	Neurochondrin IFA Titer, CSF	IFA	
NFHCC	NIF Heavy Chain CBA, CSF	CBA	Negative
NIFTC	NIF IFA Titer, CSF	IFA	
NFLCC	NIF Light Chain CBA, CSF	CBA	Negative
NMOTC	NMO/AQP4 FACS Titer, CSF	FCM	

PC1BC	PCA-1 Immunoblot, CSF	IB	Negative
PC1TC	PCA-1 Titer, CSF	IFA	
PC2TC	PCA-2 Titer, CSF	IFA	
SP7CC	Septin-7 CBA, CSF	CBA	Negative
SP7TC	Septin-7 IFA Titer, CSF	IFA	
T46CC	TRIM46 CBA, CSF	CBA	Negative
T46TC	TRIM46 IFA Titer, CSF	IFA	

Clinical References: 1. Dubey D, Pittock SJ, Krecke KN, et al. Clinical, radiologic, and prognostic features of myelitis associated with myelin oligodendrocyte glycoprotein autoantibody. JAMA Neurol. 2019;76(3):301-309. doi:10.1001/jamaneurol.2018.4053 2. Zalewski NL, Flanagan EP. Autoimmune and paraneoplastic myelopathies. Semin Neurol. 2018;38(3):278-289. doi:10.1055/s-0038-1660856 3. Flanagan EP, Hinson SR, Lennon VA, et al. Glial fibrillary acidic protein immunoglobulin G as biomarker of autoimmune astrocytopathy: Analysis of 102 patients. Ann Neurol. 2017;81(2):298-309. doi:10.1002/ana.24881 4. Keegan BM, Pittock SJ, Lennon VA. Autoimmune myelopathy associated with collapsin response-mediator protein-5 immunoglobulin G. Ann Neurol. 2008;63(4):531-534. doi:10.1002/ana.21324 5. Weinshenker BG, Wingerchuk DM, Vukusic S, et al. Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. Ann Neurol. 2006;59(3):566-569. doi:10.1002/ana.20770

MYPO
70511

Myeloperoxidase (MPO) Immunostain, Technical Component Only

Clinical Information: Myeloperoxidase shows strong cytoplasmic immunoreactivity in neutrophilic and eosinophilic granulocytes and their precursors. Virtually all other cell types are negative for myeloperoxidase staining. Antibodies to myeloperoxidase are most useful diagnostically to support myeloid lineage in acute leukemias. These antibodies also facilitate the detection of granulocyte precursors in myeloproliferative disorders and myelodysplastic syndromes.

Useful For: A marker of myeloid lineage

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chuang SS, Li CY. Useful panel of antibodies for the classification of acute leukemia by immunohistochemical methods in bone marrow trephine biopsy specimens. Am J Clin Pathol. 1997;107(4):410-418. doi:10.1093/ajcp/107.4.410 2. Li WV, Kapadia SB, Sonmez-Alpan E, Swerdlow SH. Immunohistochemical characterization of mast cell disease in paraffin sections using tryptase, CD68, myeloperoxidase, lysozyme, and CD20 antibodies. Mod Pathol. 1996;9(10):982-988 3. Liu W, Hasserjian RP, Hu Y, et al. Pure erythroid leukemia: A reassessment of the entity using the 2008 World Health Organization classification. Mod Pathol. 2011;24:375-383. doi:10.1038/modpathol.2010.194 4. O;Malley DP, Young SK, Perkins SL, Baldridge L, Juliar BE, Orazi A. Morphologic and immunohistochemical evaluation of splenic hematopoietic proliferations in neoplastic and benign disorders. Mod Pathol. 2005;18:1550-1561. doi:10.1038/modpathol.3800480 5.

Pileri SA, Ascani S, Milani M, et al. Acute leukaemia immunophenotyping in bone-marrow routine sections. Br J Hematol .1999;105:394-401 6. Gao L, Lu GT, Lu YY, et al: Diabetes aggravates acute pancreatitis possibly via activation of NLRP3 inflammasome in db/db mice. Am J Transl Res. 2018;10(7):2015-2025 7. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

MPO
80389

Myeloperoxidase Antibodies, IgG, Serum

Clinical Information: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides are characterized by a pauci-immune inflammation within the walls of small blood vessels.(1) There are 3 specific diseases which are identified as ANCA-associated vasculitides: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The serological hallmark of these disorders is the presence of ANCA, which are antibodies that bind to cytoplasmic antigens found in the granules of neutrophils.(2) Patients with GPA frequently have antibodies specific for proteinase 3 (PR3), while individuals with MPA or EGPA are more likely to have antibodies that bind to myeloperoxidase (MPO). The presence of PR3-ANCA and MPO-ANCA can be detected using antigen-specific immunoassays or indirect immunofluorescence (IIF). IIF is typically performed using ethanol-fixed neutrophils. Using this substrate, anti-PR3 antibodies produce a granular cytoplasmic staining pattern, which is referred to as cANCA. In comparison, due to an artefact that is a result of the fixation process, anti-MPO antibodies display a perinuclear pattern (pANCA). Patients with suspected ANCA-associated vasculitis should be evaluated for the presence of PR3-ANCA, MPO-ANCA and ANCA by IIF. A consensus guideline published in 2017 recommends that patients with possible GPA or MPA be tested for PR3-ANCA and MPO-ANCA using antigen-specific immunoassays.(3) ANCA by IIF should then be used in cases where there is a high degree of suspicion for GPA or MPA, but the PR3-ANCA and MPO-ANCA testing is negative. To improve specificity of the testing, this guideline also suggests that ANCA be used in situations where a low-positive PR3-ANCA or MPO-ANCA level is detected. The classification criteria for MPA, GPA, and EGPA published by the American College of Rheumatology and the European Alliance of Associations for Rheumatology include PR3-ANCA and MPO-ANCA detected by either antigen-specific immunoassay or IIF.(4-6) These classification criteria incorporate serological ANCA testing along with clinical symptoms, imaging, and biopsy results to determine a score that allows for the classification of the various ANCA-associated vasculitides.

Useful For: Evaluating patients with clinical features anti-neutrophil cytoplasmic antibody associated vasculitis, specifically granulomatosis with polyangiitis, microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis Distinguishing between MPA and other forms of ANCA-associated vasculitis, in conjunction with proteinase 3 antibody and cytoplasmic neutrophil antibody testing Following treatment response or monitoring disease activity in patients with myeloperoxidase (MPO) antibodies

Interpretation: Positive results for myeloperoxidase (MPO)-antineutrophil cytoplasmic antibodies (ANCA) by antigen-specific immunoassay and perinuclear ANCA by indirect immunofluorescence are consistent with the diagnosis of microscopic polyangiitis (MPA) or eosinophilic granulomatosis with polyangiitis, in patients with the appropriate clinical presentation. The reactivity of MPO-ANCA may decline with treatment of patients with MPA.

Reference Values:
<0.4 U (negative)
0.4-0.9 U (equivocal)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References: 1. Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. Nat Rev Dis Primers. 2020;6(1):71 2. Ramponi G, Folci M, De Santis M, et al. The biology, pathogenetic role, clinical implications, and open issues of serum anti-neutrophil cytoplasmic antibodies. Autoimmun Rev. 2021;20(3):102759 3. Bossuyt X, Cohen Tervaert W, Arimura Y, et al. Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol. 2017;13(11):683-692 4. Suppiah R, Robson JC, Grayson PC, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. Ann Rheum Dis. 2022;81(3):321-326. doi:10.1136/annrheumdis-2021-221796 5. Robson JC, Grayson PC, Ponte C, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. Ann Rheum Dis. 2022;81(3):315-320. doi:10.1136/annrheumdis-2021-221795 6. Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. Ann Rheum Dis. 2022;81(3):309-314. doi:10.1136/annrheumdis-2021-221794

MPNCM
65115

Myeloproliferative Neoplasm, CALR with Reflex to MPL, Varies

Clinical Information: The JAK2 V617F variant is present in 95% to 98% of patients with polycythemia vera , 50% to 60% of patients with primary myelofibrosis (PMF), and 50% to 60% of patients with essential thrombocythemia (ET) patients. Detection of the JAK2 V617F variant helps establish the diagnosis of a myeloproliferative neoplasm (MPN). However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR::ABL1-negative MPN include CALR exon 9 variants (20%-30% of PMF and ET) and MPL exon 10 variants (5%-10% of PMF and 3%-5% of ET). Variants in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR variant is associated with decreased risk of thrombosis in both ET and PMF and confers a favorable clinical outcome in patients with PMF. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

Useful For: Aiding in the distinction between a reactive cytosis and a myeloproliferative neoplasm when JAK2V617F testing result is negative

Interpretation: The results will be reported as 1 of the 3 following states: -Positive for CALR variant -Positive for MPL variant -Negative for CALR and MPL variants Positive variants status is highly suggestive of a myeloid neoplasm and clinicopathologic correlation is necessary in all cases. Negative variant status does not exclude the presence of a myeloproliferative neoplasm or other neoplasms.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutation of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390 2. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutation in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med. 2013;369(25):2391-2405 3. Rotunno G, Mannarelli C, Guglielmelli P, et al. Impact of calreticulin mutations on clinical and hematological phenotype and outcome in essential thrombocythemia. Blood. 2014;123(10):1552-1555 4. Tefferi A, Lasho TL, Finke CM, et al. CALR vs JAK2 vs MPL-mutated or triple-negative myelofibrosis: clinical, cytogenetic and molecular comparisons. Leukemia. 2014;28(7):1472-1477 5. Pikman Y, Lee BH, Mercher T, et al. MPLW515L is a novel somatic activating mutation in myelofibrosis with myeloid metaplasia. PLoS Med. 2006;3(7):e270 6. Pardanani AD, Levine RL, Lasho T, et al. MPL515 mutations in myeloproliferative and other myeloid disorders: a study of 1182 patients. Blood. 2006;108(10):3472-3476 7. Defour JP, Chachoua I, Pecquet C, Constantinescu SN. Oncogenic activation of MPL/thrombopoietin receptor by 17 mutations at W515: implications for myeloproliferative neoplasms. Leukemia. 2016;30(5):1214-1216.

doi:10.1038/leu.2015.271

MPNJM 606805 Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Bone Marrow

Clinical Information: The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide variant in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). JAK2 V617F is present in 95% to 98% of polycythemia vera (PV) and 50% to 60% of primary myelofibrosis (PMF) and essential thrombocythemia (ET) cases. It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome. Detection of JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 variant (20%-30% of PMF and ET) and MPL exon 10 variant (5%-10% of PMF and 3%-5% of ET). Variants in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR variant is associated with decreased risk of thrombosis in both ET and PMF and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

Useful For: Aiding in the distinction between a reactive cytosis and a chronic myeloproliferative disorder in bone marrow specimens Evaluating for variants in JAK2, CALR, and MPL genes in an algorithmic process

Interpretation: The results will be reported as 1 of the 4 following states: -Positive for JAK2 V617F variant -Positive for CALR variant -Positive for MPL variant -Negative for JAK2 V617F, CALR, and MPL variants Positive variant status is highly suggestive of a myeloid neoplasm but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative variant status does not exclude the presence of a myeloproliferative neoplasm or other neoplasms. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutation of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390. doi:10.1056/NEJMoa1311347 2. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutation in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med. 2013;369(25):2391-2405 3. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95(12):1599-1613 4. Luque Paz D, Kralovics R, Skoda RC. Genetic basis and molecular profiling in myeloproliferative neoplasms. Blood. 2023;141(16):1909-1921 5. Tefferi A, Vannucchi AM, Barbui T. Essential thrombocythemia: 2024 update on diagnosis, risk stratification, and management. Am J Hematol. 2024;99(4):697-718

MPNR 63031 Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies

Clinical Information: The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR::ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide variant in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). The JAK2 V617F variant is present in 95% to 98% of patients with polycythemia vera, 50% to 60% of patients with primary myelofibrosis (PMF), and 50% to 60% of patients with essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome. Detection of JAK2 V617F helps establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR::ABL1-negative MPN include CALR exon 9 variant (20%-30% of PMF and ET) and MPL exon 10 variant (5%-10% of PMF and 3%-5% of ET). Variants in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR variant is associated with decreased risk of thrombosis in both ET and PMF and confers a favorable clinical outcome in patients with PMF. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

Useful For: Aiding in the distinction between a reactive cytosis and a chronic myeloproliferative disorder Evaluating for variants in JAK2, CALR, and MPL genes in an algorithmic process

Interpretation: The results will be reported as 1 of the 4 following states: -Positive for JAK2 V617F variant -Positive for CALR variant -Positive for MPL variant -Negative for JAK2 V617F, CALR, and MPL variants Positive variant status is highly suggestive of a myeloid neoplasm but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative variant status does not exclude the presence of a myeloproliferative neoplasm or other neoplasms. Results below the laboratory cutoff for positivity are of unclear clinical significance currently.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. 2005;365(9464):1054-1061 2. James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive signaling causes polycythaemia vera. Nature. 2005;434(7037):1144-1148 3. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med. 2005;352(17):1779-1790 4. Steensma DP, Dewald GW, Lasho TL, et al. The JAK2 V617F activating tyrosine kinase mutation is an infrequent event in both "atypical" myeloproliferative disorders and the myelodysplastic syndrome. Blood. 2005;106(4):1207-1209 5. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutation of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390 6. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutation in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med. 2013;369(25):2391-2405 7. Pikman Y, Lee BH, Mercher T, et al. MPLW515L is a novel somatic activating mutation in myelofibrosis with myeloid metaplasia. PLoS Med. 2006;3(7):e270 8. Pardanani AD, Levine RL, Lasho T, et al. MPL515 mutations in myeloproliferative and other myeloid disorders: a study of 1182 patients. Blood. 2006;108:3472-3476 9. Kilpivaara O, Levine RL. JAK2 and MPL mutations in myeloproliferative neoplasms: discovery and science. Leukemia. 2008;22(10):1813-1817 10. Defour JP, Chachoua I, Pecquet C, Constantinescu SN. Oncogenic activation of MPL/thrombopoietin receptor by 17 mutations at W515: implications for myeloproliferative neoplasms. Leukemia. 2016;30(5):1214-1216. doi:10.1038/leu.2015.271

GNMY9 MYH9-Related Disorders, MYH9 Gene, Next-Generation
619299

Sequencing, Varies

Clinical Information: Platelets have essential roles in primary hemostasis. Patients with either hereditary or acquired platelet disorders usually have bleeding diathesis, which can potentially be life-threatening, and may also have issues with the development and/or functioning of major organs.(2) Inherited platelet disorders can be syndromic (ie, associated with current or future development of other organ system defects) or nonsyndromic (ie, isolated to thrombocytopenia with no other organ system defects). A reliable laboratory diagnosis of a platelet disorder can significantly impact patients' and, potentially, their family members' clinical management and outcome. Identification of an alteration that is known or suspected to cause disease aids in confirmation of the diagnosis and, potentially, provides prognostic information especially in the syndromic inherited platelet disorders. This test evaluates the MYH9 gene, which is associated with a variety of MYH9-related disorders, including May-Hegglin disorder/anomaly, Sebastian syndrome, Fechtner syndrome, Epstein syndrome, MYH9-related syndromic thrombocytopenia, macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss, and macrothrombocytopenia with leukocyte inclusions. The risk for developing bleeding or other phenotypic features associated with these disorders and syndromes varies. The MYH9 gene has established bleeding, thrombocytopenia, and syndromic risk, and also expert group guidelines.(1,3-5) It is recommended that genetic testing be offered to all patients suspected of having a heritable platelet disorder since some patients may have normal platelet laboratory testing results.(1,6) Genetic testing is integral to the conclusive diagnosis of an MYH9-related disorder.(5,6)

Useful For: Evaluating MYH9-related disorders, including May-Hegglin disorder/anomaly and Sebastian syndrome, in patients with a personal or family history suggestive of an MYH9-related disorder Diagnosing MYH9-related disorders, including May-Hegglin disorder/anomaly and Sebastian syndrome, for patients in whom phenotypic testing is nondiagnostic, but there is a strong clinical suspicion of the MYH9-related disorder Confirming an MYH9-related disorder diagnosis with the identification of a known or suspected disease-causing alteration in the MYH9 gene Determining the disease-causing alterations within the MYH9 gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of an MYH9-related disorder Identifying the causative alteration for genetic counseling purposes Prognosis and risk assessment based on the genotype-phenotype correlations Providing a prognosis in syndromic MYH9-related disorders Carrier testing for close family members of an individual with an MYH9-related disorder diagnosis This test is not intended for prenatal diagnosis

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Gomez K, Anderson J, Baker P, et al: Clinical and laboratory diagnosis of heritable platelet disorders in adults and children: a British Society for Haematology Guideline. Brit J Haematol. 2021 Oct;195(1):46-72 2. Nurden AT, Freson K, Selifsohn U: Inherited platelet disorders. Haemophilia. 2012 July;18 Suppl 4:154-160 3. International Society on Thrombosis and Haemostasis: Bleeding Thrombotic and Platelet Disorder TIER1 genes. ISTH; 2018. Updated July 2022. Accessed October 6, 2022. Available at: www.isth.org/page/GinTh_GeneLists 4. Megy K, Downes K, Simeoni I, et al: Curated disease-causing genes for bleeding, thrombotic, and platelet disorders: Communication from the SSC of the ISTH. J Thromb Haemost. 2019 Aug;17(8):1253-1260 5. Bolton-Maggs PHB, Chalmers EA, Collins PW, et al: A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. Brit J Haematol. 2006 Dec;135(5):603-633 6. Watson SP,

Lowe GC, Lordkipanidze M, Morgan NV, GAPP consortium: Genotyping and phenotyping of platelet function disorders. J Thromb Haemost. 2013 June;11 Suppl 1:351-363 7. Bury L, Megy K, Stephens JC, et al: Next-generation sequencing for the diagnosis of MYH9-RD: Predicting pathogenic variants. Hum Mutat. 2020 Jan;41(1):277-290 8. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

MEF2B
619494

Myocyte Enhancer Factor 2 (MEF2B) Immunostain, Technical Component Only

Clinical Information: Myocyte enhancer factor 2 (MEF2B) is a marker of normal germinal center (GC) B cells and lymphomas derived from GC B cells. MEF2B expression is found in follicular lymphoma, Burkitt lymphoma, and nodular lymphocyte predominant Hodgkin lymphoma, as well as in most cases of mantle cell lymphoma and diffuse large cell B-cell lymphoma.

Useful For: Lymphoma classification

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Krenacs D, Borbenyi Z, Bedekovics J, Mehes G, Bagdi E, Krenacs L: Pattern of MEF2B expression in lymphoid tissues and in malignant lymphomas. Virchows Arch. 2015 Sep;467(3):345-355 2. Moore EM, Swerdlow SH, Gibson SE: Comparison of myocyte enhancer factor 2B versus other germinal center-associated antigens in the differential diagnosis of B-cell non-Hodgkin lymphomas. Am J Surg Pathol. 2018 Mar;42(3):342-350 3. El Jamal SM, Grada Z, El Dinali MH, et al: MEF2B is a member of the BCL6 gene transcriptional complex and induces its expression in diffuse large B-cell lymphoma of the germinal center B-cell-like type. Lab Invest. 2019 Apr;99(4):539-550 4. Salama A, Marcellino BK, Saad AG, et al: Correlation analysis between the expression of MEF2B, and germinal center and nongerminal center markers in diffuse large B-cell lymphoma. Appl Immunohistochem Mol Morphol. 2020 Aug;28(7):e63-e64

MYOD1
70565
619685

MyoD1 Mutation Analysis, Next-Generation Sequencing, Tumor Technical Component Only

Clinical Information: Myogenic differentiation antigen 1 (MyoD1) is a myogenic nuclear regulatory protein that is normally expressed during embryogenesis. Nuclear expression of MyoD1 is restricted to myoblasts of developing skeletal muscle tissue. MyoD1 is present in the majority of rhabdomyosarcomas.

MYOGE
70516

Myogenin Immunostain, Technical Component Only

Clinical Information: Myogenin is a member of a family of myogenic regulatory genes that include MyoD, myf5, and MRF4. These genes encode a set of transcription factors that are essential for muscle development. Expression of myogenin is restricted to cells showing skeletal muscle differentiation. Myogenin is found in the majority of rhabdomyosarcomas and Wilms tumors and is absent in Ewing sarcoma and mature skeletal muscle.

Useful For: Marker of skeletal muscle differentiation

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Cessna MH, Zhou H, Perkins SL, et al: Are myogenin and MyoD1 expression specific for rhabdomyosarcoma? A study of 150 cases, with emphasis on spindle cell mimics. Am J Surg Pathol. 2001;25(9):1150-1157 2. Folpe AL. MyoD1 and myogenin expression in human neoplasia: a review and update. Adv Anat Pathol. 2002;9(3):198-203 3. Kumar S, Perlman E, Harris CA, Raffeld M, Tsokos M. Myogenin is a specific marker for rhabdomyosarcoma: an immunohistochemical study in paraffin-embedded tissues. Mod Pathol. 2000;13(9):988-993 4. Morgenstern DA, Rees H, Sebire NJ, Shipley J, Anderson J. Rhabdomyosarcoma subtyping by immunohistochemical assessment of myogenin: tissue array study and review of the literature. Pathol Oncol Res. 2008;14(3):233-238 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

MYOGL
70517

Myoglobin Immunostain, Technical Component Only

Clinical Information: Myoglobin is found in skeletal and cardiac muscle, but not in smooth muscle, and functions as an oxygen transporting pigment. Antibodies to myoglobin may be useful in the diagnosis of rhabdomyosarcomas, but the proportion of positive cells may be small and may be distributed unevenly in the section. Staining for myoglobin is not seen in carcinomas or in other sarcomas.

Useful For: Marker of skeletal and cardiac muscle

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Brooks JJ. Immunohistochemistry of soft tissue tumors. Myoglobin as a tumor marker for rhabdomyosarcoma. Cancer. 1982;50:1757-1763 2. Furlong MA, Mentzel T, Fanburg-Smith JC. Pleomorphic rhabdomyosarcoma in adults: a clinicopathologic study of 38 cases with emphasis on morphologic variants and recent skeletal muscle-specific markers. Mod Pathol. 2001;14(6):595-603 3. Kagawa N, Sano T, Inaba H, Mori K, Hizawa K. Immunohistochemistry of myoglobin in rhabdomyosarcomas. Acta Pathol Jpn. 1983;33(3):515-522 4. Elsherbiny ME, Shaaban M, El-Tohamy R, et al. Expression of myoglobin in normal and cancer brain tissues: Correlation with hypoxia markers. Front Oncol. 2021;11:590771. doi:10.3389/fonc.2021.590771 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

MYGLU
621087

Myoglobin, Random, Urine

Clinical Information: Myoglobin is a small 17.8 kDa oxygen-binding heme protein, present in striated muscle to carry and store oxygen in muscle cells. By virtue of its small size, myoglobin is readily filtered by the glomerulus and catabolized by endocytosis and proteolysis in the proximal tubule. Healthy subjects normally have low concentrations (less than 5%) of protein appearing in the urine.

Injury to skeletal or cardiac muscle results in a large release of myoglobin into systemic circulation within a few hours, which can overwhelm tubular resorption causing notable quantities of myoglobin to appear in urine giving it a red-brown appearance. The presence of myoglobin in the urine is a risk factor for developing acute kidney injury. Myoglobin concentration declines rapidly, with a serum half-life of 2 to 3 hours and has been studied for its ability to predict acute kidney injury. High concentrations appear very rapidly in the urine in various conditions, including some metabolic diseases. Conditions that can lead to rhabdomyolysis associated with myoglobinuria include: -Trauma or crush injury -Heatstroke, hypothermia, malignant hyperthermia -Seizures, strenuous exercise, prolonged immobility -Hypoxic injury -Metabolic disturbances in electrolyte concentrations -Genetic disorders that lead to muscle cell breakdown -Infections -Drugs or toxins The presence of myoglobin in the urine can indicate serious muscle injury, which is a risk factor for developing acute kidney injury. Rhabdomyolysis is often confirmed and monitored by measuring serum creatine kinase, electrolytes, kidney function, and urine tests for protein and blood. Myoglobin will give a positive reaction with hemoglobin test strips, though red blood cells will be absent upon microscopic review.

Useful For: Confirming the presence of a myopathy

Interpretation: Increased excretion of urinary myoglobin is suggestive of one of the disorders or conditions listed in Clinical Information. Most clinically significant elevations are elevated 2 to 10 times normal.

Reference Values:
0-24 mcg/L

Reference values have not been established for patients younger than 18 years; however myoglobin is not expected to be detectable in urine.

Clinical References: 1. Chavez LO. Leon M, Einav S, Varon J. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. Crit Care. 2016;20(1):135 2. Rodriguez-Capote K, Balion CM, Hill SA, Cleve R, Yang L, El Sharif A. Utility of urine myoglobin for the prediction of acute renal failure in patients with suspected rhabdomyolysis: a systematic review. Clin Chem. 2009;55(12):2190-2197 3. Dawley C. Myalgias and myopathies: rhabdomyolysis. FP Essent. 2016;440:28-36 4. Nance JR, Mammen AL. Diagnostic evaluation of rhabdomyolysis. Muscle Nerve. 2015;51(6):793-810. doi:10.1002/mus.24606 5. Yao Z, Yuan P, Hong S, Li M, Jiang L. Clinical features of acute rhabdomyolysis in 55 pediatric patients. Front. Pediatr. 2020;8:539. doi:10.3389/fped.2020.00539 6. Lamb EJ, Jones GRD. Kidney function tests. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 34

MYGLS
621090

Myoglobin, Serum

Clinical Information: Myoglobin is a heme protein found in smooth and skeletal muscles. Serum myoglobin reflects a balance between intravascular release of myoglobin from muscle and renal clearance. Previously serum myoglobin had been advocated as a sensitive marker for early acute myocardial injury (eg, acute myocardial infarction: AMI). However, more recent studies indicate that newer markers (eg, troponin) provide superior diagnostic utility in detecting early myocardial injury. Elevation of serum myoglobin may occur as a result of muscle trauma, resuscitation, myopathies, AMI, shock, strenuous body activity, or decreased elimination during renal insufficiency. Extreme elevations occur in rhabdomyolysis. Creatine kinase is released from muscle and used more commonly for this purpose.

Useful For: Assessing muscle damage from any cause

Interpretation: Elevated myoglobin levels are seen in conditions of acute muscle injury.

Reference Values:
Males: 0 to 72 mcg/L
Females: 0 to 58 mcg/L

Clinical References: 1. Lamb EJ, Jones GRD. Kidney functions tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:489 2. Cappenllini MD, Lo SF, Swinkels DW. Hemoglobin, iron, bilirubin. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:747

FMMPP
75594

MyoMarker 3 Plus Profile

Clinical Information: The MyoMarker Panel 3 Plus can be used to assist in the diagnosis of dermatomyositis, polymyositis and the anti-synthetase syndrome. Furthermore, it allows characterization of various subsets of these disorders and offers prognostic information.

Reference Values:
Anti-PL-7 Ab, Anti-PL-12 Ab, Anti-EJ Ab, Anti-OJ Ab, Anti-SRP Ab, Anti-Mi-2-Ab, Anti-U3 RNP (Fibrillarin), Anti-U2 RNP Ab, Anti-Ku Ab:
Reference Range: Negative

Interpretation for:
Anti-Jo-1 Ab, Anti-TIF-1gamma Ab, Anti-MDA-5-Ab (CADM-140), Anti-NXP-2 (P140) Ab, Anti-SAE1 Ab IgG, Anti-PM/Scl-100 Ab, Anti-SS-A 52kD Ab IgG, Anti-U1-RNP Ab:

Reference Range: <20
Negative: <20 units
Weak Positive: 20-39 units
Moderate Positive: 40-80 units
Strong Positive:>80 units

FMYO3
75595

MyoMarker 3 Profile

Clinical Information: The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disorders characterized by muscle weakness, resulting from chronic muscle inflammation of unknown cause. Patients with IIM have a variety of autoantibodies with various clinical utilities that fall into two main groups. One group of autoantibodies are found in patients with myositis and are known as Myositis Specific Autoantibodies (MSA). The MSAs are highly specific for patients with polymyositis (PM) dermatomyositis (DM), anti-synthetase syndrome and necrotizing myositis. The second group of autoantibodies are considered Myositis Associated Autoantibodies (MAA). These appear in myositis overlap syndrome and in other connective tissue diseases, which correlate with certain clinical and/or pathophysiological conditions.

Reference Values:
Anti-PL-7 Ab, Anti-PL-12 Ab, Anti-EJ Ab, Anti-OJ Ab, Anti-SRP Ab, Anti-Mi-2-Ab, Anti-U3 RNP (Fibrillarin), Anti-U2 RNP Ab, Anti-Ku Ab:
Reference Range: Negative

Interpretation for:

Anti-Jo-1 Ab, Anti-TIF-1gamma Ab, Anti-MDA-5-Ab (CADM-140), Anti-NXP-2 (P140) Ab, Anti-PM/Scl-100 Ab, Anti-SS-A 52kD Ab IgG, Anti-U1-RNP Ab:
Reference Range: <20
Negative: <20 units
Weak Positive: 20-39 units
Moderate Positive: 40-80 units
Strong Positive: >80 units

MSAES
622116

Myositis Specific Antibody Evaluation, Serum

Clinical Information:

Useful For: Accurately diagnosing, classifying, and managing idiopathic inflammatory myopathies (IIM) by identifying subtype-specific biomarkers that guide prognosis and treatment Enabling early detection of IIM, particularly in atypical or severe cases, and reducing diagnostic uncertainty for personalized care

Interpretation: The presence of a myositis-specific antibody provides supportive evidence of an idiopathic inflammatory myopathy and/or related disorder. However, these results must be interpretated in the appropriate clinical context. A negative result does not exclude the possibility of an idiopathic inflammatory myopathy.

Reference Values:

Test ID	Reporting Name	Methodology*	Reference Value
MYSI	Myositis Specific Ab Interp, S	Technical interpretation	Interpretive report
EJS	EJ Ab, S	PMAT	Negative
HMGCR	HMG-CoA Reductase Ab, S	CIA	
JO1	Jo 1 Ab, IgG, S	MFI	
MDA5S	MDA5 Ab, S	PMAT	Negative
MI2S	Mi2 Ab, S	PMAT	Negative
NXP2S	NXP2 Ab, S	PMAT	Negative
OJS	OJ Ab, S	PMAT	Negative
PL12S	PL12 Ab, S	PMAT	Negative
PL7S	PL7 Ab, S	PMAT	Negative
SAE1S	SAE1 Ab, S	PMAT	Negative
SRPIS	SRP IFA Screen, S	IFA	Negative
TIFGS	TIF1G Ab, S	PMAT	Negative

Clinical References: 1. Chinoy H, Fertig N, Oddis CV, Ollier WE, Cooper RG. The diagnostic utility of myositis autoantibody testing for predicting the risk of cancer-associated myositis. Ann Rheum

Dis. 2007;66(10):1345-1349 2. Betteridge Z, McHugh N. Myositis-specific autoantibodies: an important tool to support the diagnosis of myositis. J Intern Med. 2016;280(1):8-23

DDITF 35265 Myxoid/Round Cell Liposarcoma, 12q13 (DDIT3 or CHOP) Rearrangement, FISH, Tissue

Clinical Information: Myxoid/round cell liposarcoma is the second most common subtype of liposarcoma, accounting for more than one-third of all liposarcomas and representing about 10% of all adult soft-tissue sarcomas. Myxoid/round cell liposarcoma is described as a malignant tumor composed of uniform round to oval shaped primitive nonlipogenic mesenchymal cells and a variable number of small signet-ring lipoblasts in a prominent myxoid stroma with a characteristic branching vascular pattern. A unique chromosome translocation, t(12;16)(q13;p11), resulting in a fusion of the DDIT3 gene (also known as CHOP or GADD153) on chromosome 12 and the FUS gene (also referred to as TLS) on chromosome 16, is the key genetic aberration in myxoid/round cell liposarcoma. More than 90% of myxoid/round cell liposarcoma are cytogenetically characterized by this translocation. In rare cases, a variant t(12;22)(q13;q12) has been described in which DDIT3 (CHOP) fuses with EWS, a gene highly related to FUS.

Useful For: Aiding in the diagnosis of myxoid/round cell liposarcoma by detecting a neoplastic clone associated with gene rearrangement involving the DDIT3 (CHOP) gene region at 12q13

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the DDIT3 (CHOP) probe set. A positive result is consistent with a subset of myxoid/round cell liposarcoma. A negative result suggests no rearrangement of the DDIT3 (CHOP) gene region is present but does not exclude the diagnosis of myxoid/round cell liposarcoma.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board. Soft Tissue and Bone. 5th ed. IARC; 2020:42-44. World Health Organization Classification of Tumours. Vol 3 2. Meis-Kindblom JM, Sjogren H, Kindblom LG, et al. Cytogenetic and molecular genetic analyses of liposarcoma and its soft tissue simulators: recognition of new variants and differential diagnosis. Virchows Arch. 2001;439(2):141-51 3. Rabbitts TH, Forster A, Larson R, et al. Fusion of the dominant negative transcription regulator CHOP with a novel gene FUS by translocation t(12;16) in malignant liposarcoma. Nat Genet. 1993;4(2):175-180 4. Sandberg AA. Updates on the cytogenetics and molecular genetics of bone and soft tissue tumors: liposarcoma. Cancer Genet Cytogenet. 2004;155(1):1-24 5. Downs-Kelly E, Goldblum JR, Patel RM, et al. The utility of fluorescence in situ hybridization (FISH) in the diagnosis of myxoid soft tissue neoplasms. Am J Surg Pathol. 2008;32:8-13

NAACD 621423 N-Acetylaspartic Acid, Canavan Disease, Random, Urine

Clinical Information:

Useful For: Diagnosis and monitoring of individuals with Canavan disease Follow-up quantitation of abnormal organic acid elevations of N-acetylaspartic acid

Interpretation: When abnormal results are detected, a detailed interpretation is given including an overview of the results and of their significance; a correlation to available clinical information; elements of differential diagnosis; recommendations for additional biochemical testing and in vitro confirmatory

studies (enzyme assay, molecular analysis).

Reference Values:
< or =50.00 mmol/mol creatinine

Clinical References: 1. Bley A, Denecke J, Kohlschutter A, et al. The natural history of Canavan disease: 23 new cases and comparison with patients from literature. Orphanet J Rare Dis. 2021;16(1):227. doi:10.1186/s13023-020-01659-3 2. Nagy A, Bley AE, Eichler F. Canavan disease. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated December 21, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1234/

NAT2Q
610617

N-Acetyltransferase 2 (NAT2) Genotype, Varies

Clinical Information: Arylamine N-acetyltransferase type 2 (NAT2) is a highly polymorphic phase 2 metabolic enzyme that conjugates hydrazine derivatives and aromatic amine drugs with acetyl-groups.(1) NAT2 also is involved in the acetylation and activation of some procarcinogens.(1,2) Individuals acetylate drugs at different rates by NAT2 and are described as having slow, intermediate, or rapid (fast) acetylator phenotypes. Some studies, which have examined diversity of NAT2 haplotypes among individuals of different ethnicities hypothesize that the NAT2 slow acetylator phenotype was positively selected for in the transition from hunter-gatherer or nomadic lifestyle to an agricultural or pastoral lifestyle.(3) The prevalence of slow acetylator phenotypes increases with decreasing distance to the equator. Near the equator, up to 80% of individuals may be slow acetylators, while in some more northern countries, as few as 10% of the population may have the slow acetylator phenotype. A number of drugs are metabolized by NAT2 including procainamide, dapsone, nitrazepam, hydralazine, sulfasalazine, amifampridine, and isoniazid.(4) Isoniazid is used to treat and prevent tuberculosis and is still used as a primary treatment agent. Adverse reactions with isoniazid, which include nausea, drug-induced hepatitis, peripheral neuropathy, and sideroblastic anemia, are associated more often with a slow NAT2 acetylator phenotype. These individuals may require a lower dose to avoid adverse reactions.(4) Of note, acetaminophen is a significant NAT2 inhibitor. The NAT2 gene contains a single intronless exon of 870 base pairs and encodes 290 amino acids. NAT2 is highly polymorphic and contains at least 16 known single nucleotide variants and 1 single base pair deletion. These genetic variants are combined into 36 known haplotypes or alleles. Each individual haplotype is predictive of either a rapid (fast) or slow acetylator phenotype. Individuals with 2 rapid haplotypes are predicted to be rapid (normal) metabolizers, while those with 1 rapid and 1 slow haplotype are intermediate metabolizers, and those with 2 slow haplotypes are poor metabolizers.(5,6) Studies with patients who have different acetylator haplotypes have correlated the ratio of plasma N-acetylisoniazid/isoniazid drug concentrations with haplotypes, with slow and intermediate acetylators having lower ratios than rapid acetylators.(7) NAT2 genotype results are used to predict metabolizer phenotypes, as indicated in the Table. Note that the reference allele for NAT2 is *4. If no variants are detected, the default genotype and phenotype reported are *4/*4 and rapid acetylator phenotype, respectively. Table. NAT2 allele Predicted acetylator phenotype *4 Rapid (normal) *5 Slow *6 Slow *7 Slow *10 Slow, but may be substrate dependent *12D Slow *14 Slow *17 Slow *19 Slow

Useful For: Identifying patients who may be at risk for altered metabolism of drugs that are substrates of arylamine N-acetyltransferase type 2, including isoniazid

Interpretation: An interpretive report will be provided. The wild-type (normal) genotype for NAT2 is *4. This is the most commonly occurring allele in some, but not all, ethnic groups.(8) Individuals are classified as being slow, intermediate, or rapid (fast) acetylators depending on their diplotypes. Slow acetylators have 2 slow haplotypes, rapid acetylators have 2 rapid (fast, normal) haplotypes, and intermediate acetylators have one of each. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as described by the Human NAT2 Alleles (Haplotypes) Database (http://nat.mbg.duth.gr/Human%20NAT2%20alleles_2013.htm). For additional information regarding

pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Drug-drug interactions and drug-metabolite inhibition must be considered when adjusting medication dosage. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age. For applicable medications, therapeutic drug monitoring is useful to verify that the drug concentration is within the therapeutic range.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Salazar-Gonzalez RA, Doll MA, Hein DW. Human arylamine N-acetyltransferase 2 genotype-dependent protein expression in cryopreserved human hepatocytes. Sci Rep. 2020;10(1):7566 2. Meyer UA. Polymorphism of human acetyltransferases. Environ Health Perspect. 1994;102 Suppl 6(Suppl 6):213-216 3. McDonagh EM, Boukouvala S, Aklillu E, Hein DW, Altman RB, Klein TE. PharmGKB summary: very important pharmacogene information for N-acetyltransferase 2. Pharmacogenet and Genomics. 2014;24(8):409-425 4. Hein DW, Millner LM. Arylamine N-acetyltransferase acetylation polymorphisms: paradigm for pharmacogenomic-guided therapy- a focused review. Expert Opin Drug Metab Toxicol. 2021;17(1):9-21 5. Sabbagh A, Darlu P. Inferring haplotypes at the NAT2 locus: the computational approach. BMC Genet. 2005;6:30 6. Leff MA, Fretland AJ, Doll MA, Hein DW. Novel human N-acetyltransferase 2 alleles that differ in mechanism for slow acetylator phenotype. J Biol Chem. 1999;274(49):34519-34522 7. Chen B, Li JH, Xu YM, Wang J, Cao XM. The influence of NAT2 genotypes on the plasma concentration of isoniazid and acetylisoniazid in Chinese pulmonary tuberculosis patients. Clin Chim Acta. 2006;365(1-2):104-108 8. Lin HJ, Han CY, Lin BK, Hardy S. Ethnic distribution of slow acetylator mutations in the polymorphic N-acetyltransferase (NAT2) gene. Pharmacogenetics. 1994;4(3):125-134

NMH24
605135

N-Methylhistamine, 24 Hour, Urine

Clinical Information: N-methylhistamine (NMH) is the major metabolite of histamine, which is produced by mast cells. Increased histamine production is seen in conditions associated with increased mast-cell activity, such as allergic reactions, but also in mast-cell proliferation disorders, particularly mastocytosis. Mastocytosis is a rare disease. Its most common form, urticarial pigmentosa (UP), affects the skin and is characterized by multiple persistent small reddish-brown lesions that result from infiltration of the skin by mast cells. Systemic mastocytosis is caused by the accumulation of mast cells in other tissues and can affect organs such as the liver, spleen, bone marrow, and small intestine. The mast-cell proliferation in systemic mastocytosis can be either benign or malignant. In children, benign systemic mastocytosis tends to resolve over time, while in most adults, the disease is progressive. Systemic mastocytosis may or may not be accompanied by UP.(1,2) Patients with UP or systemic mastocytosis can have symptoms ranging from itching, gastrointestinal distress, bone pain, and headaches; to flushing and anaphylactic shock. Definitive diagnosis of systemic mastocytosis is made by bone marrow biopsy; however, patients with systemic mastocytosis also usually exhibit elevated levels of NMH.(1-5) Other biochemical markers include 11-beta prostaglandin F2 alpha, a metabolite of prostaglandin D2 (23BPT / 2,3-Dinor 11 Beta-Prostaglandin F2 Alpha, 24 Hour, Urine) and tryptase, alpha or beta (TRYPT / Tryptase, Serum). Histamine in blood or urine is also sometimes measured, but it generally has less diagnostic value than NMH measurement in urine, particularly if measurements in blood are not undertaken during a spell.

Useful For: Screening for and monitoring of mastocytosis and disorders of systemic mast-cell activation, such as anaphylaxis and other forms of severe systemic allergic reactions using 24-hour urine collection specimens Monitoring therapeutic progress in conditions that are associated with secondary, localized, low-grade persistent, mast-cell proliferation and activation such as interstitial cystitis

Interpretation: Increased concentrations of urinary N-methylhistamine (NMH) are consistent with urticaria pigmentosa (UP), systemic mastocytosis, or mast-cell activation. Because of its longer half-life, urinary NMH measurements have superior sensitivity and specificity than histamine, the parent compound. However, not all patients with systemic mastocytosis or anaphylaxis will exhibit concentrations outside the reference range and healthy individuals may occasionally exhibit values just above the upper limit of normal. The extent of the observed increase in urinary NMH excretion is correlated with the magnitude of mast-cell proliferation and activation, UP patients, or patients with other localized mast-cell proliferation and activation, show usually only mild elevations, while systemic mastocytosis and anaphylaxis tend to be associated with more significant rises in NMH excretion (2-fold or more). There is, however, significant overlap in values between UP and systemic mastocytosis, and urinary NMH measurements should not be relied upon alone in distinguishing localized from systemic disease. Up to 25% variability in random urine excreted levels may be observed, making 24-hour urine collections preferable for cases with borderline results. Children have higher NMH levels than adults. By the age of 16 years, adult levels have been reached.

Reference Values:

N-METHYLHISTAMINE
0-5 years: 120-510 mcg/g creatinine
6-16 years: 70-330 mcg/g creatinine
>16 years: 30-200 mcg/g creatinine

CREATININE
Males: 930-2955 mg/24 hours
Females: 603-1783 mg/24 hours
Reference values have not been established for patients who are younger than 18 years.

Clinical References: 1. Roberts LJ II, Oates JA. Disorders of vasodilator hormones: the carcinoid syndrome and mastocytosis. In: Wilson JD, Foster DW, eds. Williams Textbook of Endocrinology. 8th ed. WB Saunders Company; 1992:1625-1634 2. Keyzer JJ, de Monchy JG, van Doormaal JJ, van Voorst Vader PC. Improved diagnosis of mastocytosis by measurement of urinary histamine metabolites. N Engl J Med. 1983;309(26):1603-1605 3. Akin C, Metcalfe DD. Mastocytosis. In: Leung DYM, Greaves MW, eds. Allergic Skin Disease: A Multidisciplinary Approach. Marcel Dekker, Inc; 2000:337-352 4. Heide R, Riezebos P, van Toorenbergen AW, Mulder PGH, Tank B, Oranje AP. Abstract 347: Predictive value of urinary N-methylhistamine for bone marrow involvement in mastocytosis. J Invest Dermatol. 2000;115(3):587 5. Van Gysel D, Oranje AP, Vermeiden I, de Lijster de Raadt J, Mulder PG, van Toorenenbergen AW. Value of urinary N-methylhistamine measurements in childhood mastocytosis. J Am Acad Derm. 1996;35(4):556-558 6. Divekar R, Butterfield J. Urinary 11beta-PGF2a and N-methyl histamine correlate with bone marrow biopsy findings in mast cell disorders. Allergy. 2015;70(10):1230-1238. doi:10.1111/all.12668 7. Butterfield J, Weiler CR. The utility of measuring urinary metabolites of mast cell mediators in systemic mastocytosis and mast cell activation syndrome. J Allergy Clin Immunol Pract. 2020;8(8):2533-2541. doi:10.1016/j.jaip.2020.02.021

NMH1D
605159

N-Methylhistamine, 24 Hour, Urine

Clinical Information: N-methylhistamine (NMH) is the major metabolite of histamine, which is produced by mast cells. Increased histamine production is seen in conditions associated with increased mast-cell activity, such as allergic reactions, but also in mast-cell proliferation disorders, particularly mastocytosis. Mastocytosis is a rare disease. Its most common form, urticaria pigmentosa (UP), affects the skin and is characterized by multiple persistent small reddish-brown lesions that result from infiltration of the skin by mast cells. Systemic mastocytosis is caused by the accumulation of mast cells in other tissues and can affect organs such as the liver, spleen, bone marrow, and small intestine. The mast-cell proliferation in systemic mastocytosis can be either benign or malignant. In children, benign systemic mastocytosis tends to resolve over time, while in most, but not all adults, the disease is progressive.

Systemic mastocytosis may or may not be accompanied by UP.(1,3) Patients with UP or systemic mastocytosis can have symptoms ranging from itching, gastrointestinal distress, bone pain, and headaches; to flushing and anaphylactic shock. Definitive diagnosis of mastocytosis is made by bone marrow biopsy; however, patients with systemic mastocytosis usually exhibit elevated levels of NMH.(1-5) Other biochemical markers include 11-beta prostaglandin F(2) alpha, a metabolite of prostaglandin D2 (23BPT / 2,3-Dinor 11 Beta-Prostaglandin F2 Alpha, 24 Hour, Urine), and alpha or beta tryptase (TRYPT / Tryptase, Serum).

Useful For: Screening for and monitoring of mastocytosis and disorders of systemic mast-cell activation, such as anaphylaxis and other forms of severe systemic allergic reactions as a part of a profile Monitoring therapeutic progress in conditions that are associated with secondary, localized, low-grade persistent, mast-cell proliferation and activation such as interstitial cystitis

Interpretation: Increased concentrations of urinary N-methylhistamine (NMH) are consistent with urticaria pigmentosa (UP), systemic mastocytosis, or mast-cell activation. Because of its longer half-life, urinary NMH measurements have superior sensitivity and specificity than histamine, the parent compound. However, not all patients with systemic mastocytosis or anaphylaxis will exhibit concentrations outside the reference range and healthy individuals may occasionally exhibit values just above the upper limit of normal. The extent of the observed increase in urinary NMH excretion is correlated with the magnitude of mast-cell proliferation and activation, UP patients, or patients with other localized mast-cell proliferation and activation, show usually only mild elevations, while systemic mastocytosis and anaphylaxis tend to be associated with more significant rises in NMH excretion (2-fold or more). There is, however, significant overlap in values between UP and systemic mastocytosis, and urinary NMH measurements should not be relied upon alone in distinguishing localized from systemic disease. Up to 25% variability in random urine excreted levels may be observed, making 24-hour urine collections preferable for cases with borderline results. Children have higher NMH levels than adults. By the age of 16 years, adult levels have been reached.

Reference Values:
Only orderable as part of a profile. For more information see NMH24 / N-Methylhistamine, 24 Hour, Urine.

0-5 years: 120-510 mcg/g creatinine
6-16 years: 70-330 mcg/g creatinine
>16 years: 30-200 mcg/g creatinine

Clinical References: 1. Roberts LJ II, Oates JA. Disorders of vasodilator hormones: the carcinoid syndrome and mastocytosis. In: Wilson JD, Foster DW, eds. Williams Textbook of Endocrinology. 8th ed. WB Saunders Company; 1992:1625-1634 2. Akin C, Metcalfe DD. Mastocytosis. In: Leung DYM, Greaves MW eds. Allergic Skin Disease: A Multidisciplinary Approach. Marcel Dekker, Inc; 2000:337-352 3. Keyzer JJ, de Monchy JG, van Doormaal JJ, van Voorst Vader PC. Improved diagnosis of mastocytosis by measurement of urinary histamine metabolites. N Engl J Med. 1983;309(26):1603-1605 4. Heide R, Riezebos P, van Toorenbergen AW, et al. Predictive value of urinary N-methylhistamine for bone marrow involvement in mastocytosis. J Invest Dermatol. 2000;115(3):587 5. Van Gysel D, Oranje AP, Vermeiden I, et al. Value of urinary N-methylhistamine measurements in childhood mastocytosis. J Am Acad Derm. 1996;35(4):556-558 6. Divekar R, Butterfield J. Urinary 11b-PGF2a and N-methyl histamine correlate with bone marrow biopsy findings in mast cell disorders. Allergy. 2015;70(10):1230-1238. doi:10.1111/all.1266 7. Butterfield J, Weiler CR. The utility of measuring urinary metabolites of mast cell mediators in systemic mastocytosis and mast cell activation syndrome. J Allergy Clin Immunol Pract. 2020;8(8):2533-2541. doi:10.1016/j.jaip.2020.02.021

NMHR1
605015

N-Methylhistamine, Random, Urine

Clinical Information: N-methylhistamine (NMH) is the major metabolite of histamine, which is produced by mast cells. Increased histamine production is seen in conditions associated with increased mast-cell activity, such as allergic reactions, but also in mast-cell proliferation disorders, in particular mastocytosis. Mastocytosis is a rare disease. Its most common form, urticaria pigmentosa (UP), affects the skin and is characterized by multiple persistent small reddish-brown lesions that result from infiltration of the skin by mast cells. Systemic mastocytosis is caused by the accumulation of mast cells in other tissues and can affect organs such as the liver, spleen, bone marrow, and small intestine. The mast-cell proliferation in systemic mastocytosis can be either benign or malignant. In children, benign systemic mastocytosis tends to resolve over time, while in most but not all adults, the disease is progressive. Systemic mastocytosis may or may not be accompanied by UP.(1,3) Patients with UP or systemic mastocytosis can have symptoms ranging from itching, gastrointestinal distress, bone pain, and headaches; to flushing and anaphylactic shock. Definitive diagnosis of mastocytosis is made by bone marrow biopsy; however, patients with systemic mastocytosis usually exhibit elevated levels of NMH.(1-5) Other biochemical markers include 11-beta prostaglandin F(2) alpha, a metabolite of prostaglandin D2 (23BPR / 2,3-Dinor 11 Beta-Prostaglandin F2 Alpha, Random, Urine), and alpha or beta tryptase (TRYPT / Tryptase, Serum).

Useful For: Screening for and monitoring of mastocytosis and disorders of systemic mast-cell activation, such as anaphylaxis and other forms of severe systemic allergic reactions as a part of a random urine collection profile Monitoring therapeutic progress in conditions that are associated with secondary, localized, low-grade persistent, mast-cell proliferation and activation such as interstitial cystitis

Interpretation: Increased concentrations of urinary N-methylhistamine (NMH) are consistent with urticaria pigmentosa (UP), systemic mastocytosis, or mast-cell activation. Because of its longer half-life, urinary NMH measurements have superior sensitivity and specificity than histamine, the parent compound. However, not all patients with systemic mastocytosis or anaphylaxis will exhibit concentrations outside the reference range and healthy individuals may occasionally exhibit values just above the upper limit of normal. The extent of the observed increase in urinary NMH excretion is correlated with the magnitude of mast-cell proliferation and activation, UP patients, or patients with other localized mast-cell proliferation and activation, show usually only mild elevations, while systemic mastocytosis and anaphylaxis tend to be associated with more significant rises in NMH excretion (2-fold or more). There is, however, significant overlap in values between UP and systemic mastocytosis, and urinary NMH measurements should not be relied upon alone in distinguishing localized from systemic disease. Up to 25% variability in random-urine excreted levels may be observed, making 24-hour urine collections preferable for cases with borderline results. Children have higher NMH levels than adults. By the age of 16, adult levels have been reached.

Reference Values:
Only orderable as part of a profile. For more information see NMHR / N-Methylhistamine, Random, Urine.

0-5 years: 120-510 mcg/g creatinine
6-16 years: 70-330 mcg/g creatinine
>16 years: 30-200 mcg/g creatinine

Clinical References: 1. Roberts LJ II, Oates JA. Disorders of vasodilator hormones: the carcinoid syndrome and mastocytosis. In: Wilson JD, Foster DW, eds. Williams Textbook of Endocrinology. 8th ed. WB Saunders Company;1992:1625-1634 2. Akin C, Metcalfe DD. Mastocytosis. In: Leung DYM, Greaves MW, eds. Allergic Skin Disease: A Multidisciplinary Approach. Marcel Dekker, Inc.:2000:337-352 3. Keyzer JJ, de Monchy JG, van Doormaal JJ, van Voorst Vader PC. Improved diagnosis of mastocytosis by measurement of urinary histamine metabolites. N Engl J Med. 1983;309(26):1603-1605 4. Heide R, Riezebos P, van Toorenbergen AW, et al. Predictive value of

urinary N-methylhistamine for bone marrow involvement in mastocytosis. J Invest Dermatol. 2000;115(3):587 5. Van Gysel D, Oranje AP, Vermeiden I, et al. Value of urinary N-methylhistamine measurements in childhood mastocytosis. J Am Acad Derm. 1996;35(4):556-558 6. Divekar R, Butterfield J. Urinary 11b-PGF2a and N-methyl histamine correlate with bone marrow biopsy findings in mast cell disorders. Allergy. 2015;70(10):1230-1238. doi:10.1111/all.12668 7. Butterfield J, Weiler CR: The utility of measuring urinary metabolites of mast cell mediators in systemic mastocytosis and mast cell activation syndrome. J Allergy Clin Immunol Pract. 2020;8(8):2533-2541. doi:10.1016/j.jaip.2020.02.021

NMHR
604981

N-Methylhistamine, Random, Urine

Clinical Information: N-methylhistamine (NMH) is the major metabolite of histamine, which is produced by mast cells. Increased histamine production is seen in conditions associated with increased mast-cell activity, such as allergic reactions, but also in mast-cell proliferation disorders, particularly mastocytosis. Mastocytosis is a rare disease. Its most common form, urticarial pigmentosa (UP), affects the skin and is characterized by multiple persistent small reddish-brown lesions that result from infiltration of the skin by mast cells. Systemic mastocytosis is caused by the accumulation of mast cells in other tissues and can affect organs such as the liver, spleen, bone marrow, and small intestine. The mast-cell proliferation in systemic mastocytosis can be either benign or malignant. In children, benign systemic mastocytosis tends to resolve over time, while in most adults, the disease is progressive. Systemic mastocytosis may or may not be accompanied by UP.(1,2) Patients with UP or systemic mastocytosis can have symptoms ranging from itching, gastrointestinal distress, bone pain, and headaches; to flushing and anaphylactic shock. Definitive diagnosis of systemic mastocytosis is made by bone marrow biopsy; however, patients with systemic mastocytosis also usually exhibit elevated levels of NMH.(1-5) Other biochemical markers include 11-beta prostaglandin F2 alpha, a metabolite of prostaglandin D2 (23BPR / 2,3-Dinor 11 Beta-Prostaglandin F2 Alpha, Random, Urine) and tryptase, alpha or beta (TRYPT / Tryptase, Serum). Histamine in blood or urine is also sometimes measured, but it generally has less diagnostic value than NMH measurement in urine, in particular if measurements in blood are not undertaken during a spell.

Useful For: Screening for and monitoring of mastocytosis and disorders of systemic mast-cell activation, such as anaphylaxis and other forms of severe systemic allergic reactions using random urine specimens Monitoring therapeutic progress in conditions that are associated with secondary, localized, low-grade persistent, mast-cell proliferation and activation such as interstitial cystitis

Interpretation: Increased concentrations of urinary N-methylhistamine (NMH) are consistent with urticaria pigmentosa (UP), systemic mastocytosis, or mast-cell activation. Because of its longer half-life, urinary NMH measurements have superior sensitivity and specificity than histamine, the parent compound. However, not all patients with systemic mastocytosis or anaphylaxis will exhibit concentrations outside the reference range and healthy individuals may occasionally exhibit values just above the upper limit of normal. The extent of the observed increase in urinary NMH excretion is correlated with the magnitude of mast-cell proliferation and activation, UP patients, or patients with other localized mast-cell proliferation and activation, show usually only mild elevations, while systemic mastocytosis and anaphylaxis tend to be associated with more significant rises in NMH excretion (2-fold or more). There is, however, significant overlap in values between UP and systemic mastocytosis, and urinary NMH measurements should not be relied upon alone in distinguishing localized from systemic disease. Up to 25% variability in random-urine excreted levels may be observed, making 24-hour urine collections preferable for cases with borderline results. Children have higher NMH levels than adults. By the age of 16, adult levels have been reached.

Reference Values:
0-5 years: 120-510 mcg/g creatinine

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>16 years: 30-200 mcg/g creatinine

Clinical References: 1. Roberts LJ II, Oates JA. Disorders of vasodilator hormones: the carcinoid syndrome and mastocytosis. In: Wilson JD, Foster DW, eds. Williams Textbook of Endocrinology. 8th ed. WB Saunders Company; 1992:1625-1634 2. Keyzer JJ, de Monchy JG, van Doormaal JJ, van Voorst Vader PC. Improved diagnosis of mastocytosis by measurement of urinary histamine metabolites. N Engl J Med. 1983;309(26):1603-1605 3. Akin C, Metcalfe DD. Mastocytosis. In: Leung DYM, Greaves MW, eds. Allergic Skin Disease: A Multidisciplinary Approach. Marcel Dekker, Inc.; 2000:337-352 4. Heide R, Riezebos P, van Toorenbergen AW, Mulder PGH, Tank B, Oranje AP. Abstract 347: Predictive value of urinary N-methylhistamine for bone marrow involvement in mastocytosis. J Invest Dermatol. 2000;115(3):587 5. Van Gysel D, Oranje AP, Vermeiden I, de Lijster de Raadt J, Mulder PG, van Toorenenbergen AW. Value of urinary N-methylhistamine measurements in childhood mastocytosis. J Am Acad Derm. 1996;35(4):556-558 6. Divekar R, Butterfield J. Urinary 11beta-PGF2a and N-methyl histamine correlate with bone marrow biopsy findings in mast cell disorders. Allergy. 2015;70(10):1230-1238. doi:10.1111/all.12668 7. Butterfield J, Weiler CR: The utility of measuring urinary metabolites of mast cell mediators in systemic mastocytosis and mast cell activation syndrome. J Allergy Clin Immunol Prac. 2020;8(8):2533-2541. doi:10.1016/j.jaip.2020.02.021

FINA
91447

NAbFeron (IFNB-1) Neutralizing Antibody Test

Useful For: Detection of antibodies to interferon-B-1

Reference Values:
Final report has been sent to the referring laboratory.

Clinical References: Goodin, DS, et al. (2007) Neurology 68:977-984 (PMID: 17389300) Polman, CH, et al.(2010) Lancet Neurol 9:740-50 (PMID: 20610349) Creeke, Pl, et al. (2013) Ther Adv Neurol Disord 6:3-17 (PMID: 23277789)

FNAD
80761

Nadolol, Serum/Plasma

Reference Values:

FNALO
91784

Naloxone - Total (Conjugated/Unconjugated), Screen, Urine

Reference Values:

NAPSN
70519

Napsin A Immunostain, Technical Component Only

Clinical Information: Napsin A is an aspartic proteinase involved in the proteolytic processing of surfactant precursors in the normal alveolar epithelium. In normal tissues, napsin A is expressed in the cytoplasm of alveolar macrophages, type II pneumocytes, pancreatic ducts and acini, and in renal tubules. Napsin A has clinical utility for the identification of primary lung adenocarcinomas. Napsin A is also positive in a subset of thyroid and renal cell carcinomas (especially papillary type).

Useful For: Identification of primary lung adenocarcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chuman Y, Bergman A, Ueno T, et al. Napsin A, a member of the aspartic protease family, is abundantly expressed in normal lung and kidney tissue and is expressed in lung adenocarcinomas. FEBS Lett. 1999;462(1-2):129-134. doi:10.1016/s0014-5793(99)01493-3 2. Suzuki A, Shijubo N, Yamada G, et al. Napsin A is useful to distinguish primary lung adenocarcinoma from adenocarcinomas of other organs. Pathol Res Pract. 2005;201(8-9):579-586. doi:10.1016/j.prp.2005.05.010 3. Dejmek A, Naucler P, Smedjeback A, et al. Napsin A (TA02) is a useful alternative to thyroid transcription factor-1 (TTF-1) for the identification of pulmonary adenocarcinoma cells in pleural effusions. Diagn Cytopathol. 2007;35(8):493-497. doi:10.1002/dc.20667 4. Zhang C, Schmidt LA, Hatanaka K, Thomas D, Lagstein A, Myers JL. Evaluation of napsin A, TTF-1, p63, p40, and CK5/6 immunohistochemical stains in pulmonary neuroendocrine tumors. Am J Clin Pathol. 2014;142(3):320-324. doi:10.1309/AJCPGA0IUA8BHQEZ 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

NARC
82026

Narcolepsy-Associated Antigen, HLA-DQB1 Typing, Blood

Clinical Information: Narcolepsy is a neurological condition affecting about 0.02% of African American, White, and Japanese individuals. It is characterized by excessive daytime somnolence and abnormal rapid eye movement (REM) sleep. Cataplexy (weakness precipitated by emotions, especially laughter) is present in 64% to 79% of patients with narcolepsy. Studies have identified DQB1*06:02 as a useful marker of narcolepsy. DQB1*06:02 is found in 90% to 95% of African American, White, and Japanese patients with narcolepsy who also have cataplexy (narcolepsy type 1) but only in 45% to 50% of patients with narcolepsy without cataplexy (narcolepsy type 2). It must also be clearly understood that about 25% of normal people have this gene. Because DQB1*06:02 is present in the normal population, no test for an HLA gene constitutes a test for narcolepsy. A more reliable approach would be to consider that, in an appropriate patient who has cataplexy, the absence of the strongly associated DQB1*06:02 provides good evidence that the patient does not have narcolepsy. However, its absence does not rule-out narcolepsy without cataplexy (narcolepsy type 2).

Useful For: Ruling out a diagnosis of narcolepsy

Interpretation: If DQB1*06:02 is not detected, the narcolepsy-associated antigen test result will be reported as negative for DQB1*06:02. If the allele is detected, the result will be reported as positive for DQB1*06:02.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Hurley CK, Kempenich J, Wadsworth K, et al. Common, intermediate and well-documented HLA alleles in world populations: CIWD version 3.0.0. HLA. 2020;95(6):516-531. doi:10.1111/tan.13811 2. Mignot E, Lin X, Arrigoni J, et al. DQB1*0602 and DQA1*0102 (DQ1) are better markers than DR2 for narcolepsy in Caucasian and Black Americans. Sleep. 1994;17(8 Suppl):S60-S67 3. Chabas D, Taheri S, Renier C, Mignot E. The genetics of narcolepsy. Annu Rev Genomics Hum Genet. 2003;4:459-483 4. Andlauer O, Moore H 4th, Hong SC, et al. Predictors of hypocretin (orexin) deficiency in narcolepsy without cataplexy. Sleep. 2012;35(9):1247-1255F 5. Bassetti CLA, Adamantidis A, Burdakov D, et al. Narcolepsy - clinical spectrum, aetiopathophysiology,

diagnosis and treatment. Nat Rev Neurol. 2019;15(9):519-539. doi:10.1038/s41582-019-0226-9 6. Capittini C, De Silvestri A, Terzaghi M, et al. Correlation between HLA-DQB1*06:02 and narcolepsy with and without cataplexy: approving a safe and sensitive genetic test in four major ethnic groups. A systematic meta-analysis. Sleep Med. 2018;52:150-157 7. Miyagawa T, Tokunaga K. Genetics of narcolepsy. Hum Genome Var. 2019;6:4. doi:10.1038/s41439-018-0033-7

QNKS 60616 Natural Killer (NK)/Natural Killer T-Cell Subsets, Quantitative, Blood

Clinical Information: Natural killer (NK) cells are derived from pluripotent hematopoietic stem cell precursors but develop independently of the thymus. They comprise a key lymphocyte subset (approximately 10%-15% of peripheral blood mononuclear cells) and are a constituent of the innate immune system since these cells do not rearrange their germline DNA to obtain specificity. NK cells serve an important role in host defense against viral infections, as well as tumor surveillance. They are also a component of the adaptive immune response through cytokine production. NK cell functions are governed by a balance between activating receptors and inhibitory receptors. NK cells are identified by expression of different cell-surface receptors, and they are not a homogeneous population.(1) In general, the most common combination of surface markers used to identify the majority of NK cells is the absence of CD3 (CD3-), along with expression of CD56 (neural cell adhesion molecule) and CD16 (low-affinity IgG Fc receptor-Fc gamma RIII). However, not all NK cells express the CD56 and CD16 markers uniformly and, therefore, can be divided into subsets based on expression of these 2 molecules.(2) The CD16+ CD56+/- (dim or negative) that are CD3- are referred to as cytotoxic NK cells, while the CD56+ (bright) CD16- NK cells are called regulatory or cytokine secreting NK cells.(3) These are not only phenotypically and functionally distinct subsets but also developmentally separate. The majority of human NK cells (approximately 90%) have dim expression of CD56 and moderate to high levels of CD16, as well as perforin and granzymes (2 proteins mediating cytolytic activity) and are therefore high in cytotoxic capability. The remaining minority (approximately 10%) of NK cells are the CD56(bright) cytokine-producing NK cells. Therefore, cytotoxicity and cytokine production are the major functions of NK cells. Cytotoxicity can be subdivided into natural cytotoxicity directed largely toward virally infected cells or tumor cells, in the absence of prior stimulation or immunization, and antibody-dependent cellular cytotoxicity (ADCC) directed against antibody-coated target cells.(4) Circulating NK cells are enriched for the CD56(dim) phenotype, while within the lymph nodes, NK cells are largely CD56(bright). This differential localization is related to the pattern of homing receptors expressed on NK cells: CD56(dim) NK cells express homing markers for inflamed peripheral sites, while CD56(bright) NK cells express receptors for secondary lymphoid organs. The majority of circulating human NK cells, which have cytotoxic function and phenotype (CD56[dim]), are CD27-, while the CD56(bright) cells are CD27+. Therefore, the absence of CD27 expression identifies cytotoxic effector cells within the mature NK cell subsets.(5) Natural killer T (NKT) cells represent a specialized T-cell population that is distinct from conventional T cells. They express an invariant T-cell receptor (TCR) that recognizes self and bacterial glycosphingolipid antigens presented by the MHC class I-like molecule, CD1d.(11) The development of NKT cells is also unique from regular T cells, as NKT cell precursors are positively selected by CD4+CD8+ cortical thymocytes and the signaling pathways differ from the conventional T cells. Activated NKT cells rapidly produce large amounts of Th1 and Th2 cytokines that transactivate other immune components and, therefore, NKT cells are involved in both innate and adaptive immune responses.(11) NK cell deficiencies can be present as part of a larger immunological syndrome or as an isolated deficiency. Some of the primary (monogenic) immunodeficiencies that affect NK cell function or numbers include autoimmune lymphoproliferative syndrome (ALPS) related to CASP8 (caspase 8 variants); familial hemophagocytic lymphohistiocytosis (FHL) types 2, 3, and 4 due to variants in the PFP1 (encoding perforin), UNC13D (encoding the Munc13-4 protein) and STX-11 (encoding syntaxin -11), respectively; Hermansky-Pudlak syndrome (AP3B1); Papillon-Lefevre syndrome (CTSC: cathepsin C); nuclear factor kappa-beta essential modulator deficiency (NEMO) due to variants in the IKBKG gene; severe combined immunodeficiencies due to mutations in the IL-2RG, JAK3, ADA, PNP, ADK2 genes; bare lymphocyte syndrome (TAP2 gene); X-linked inhibitor of apoptosis protein deficiency (XIAP gene);

X-linked lymphoproliferative disease (XLP): XLP-1 (due to variants in the SAP gene); Griscelli syndrome (RAB27A gene); Chediak-Higashi syndrome (LYST gene); and Wiskott-Aldrich syndrome (WAS gene).(12) Patients with X-linked inhibitor of apoptosis protein (XIAP) deficiency have been variably reported as having either normal numbers of NKT cells (13) or low numbers of NKT cells.(14) The apparent discrepancy in the numbers of NKT cells is likely related to the difference in size of the sample control groups and disease stage of patients between the 2 reports. At the present time, the role of XIAP in development of NKT cells has not been clearly delineated. The isolated NK-cell deficiencies include the absolute NK-cell deficiency (ANKD), the classic NK-cell deficiency (CNKD), and the functional NK-cell deficiency (FNKD). NK-cell function is absent in ANKD and CNKD and deficient in FNKD, while NK cells are present in the latter but absent in the former 2 conditions. NKT cells are absent only in ANKD and present in both CNKD and FNKD.(12) NK-cell dysfunction has also been reported in systemic juvenile rheumatoid arthritis and macrophage activation syndrome.(15) There is also more data emerging on the pathogenic role of NK cells in atopic and autoimmune diseases.(4) Patients with HIV-1 show a gradual loss of NK cells that correlates with disease progression. There is a selective loss of CD56(dim) NK cells, while the numbers of CD56(bright) NK cells remain the same. There appears to be a defect in differentiation from immature CD56- NK cells to mature CD56(dim) NK cells (16), with an expansion of the former (CD56-CD16+) NK cells in HIV viremic patients.(17) Differential mobilization of NK-cell subsets has also been reported related to acute exercise, with CD56(bright) NK cells being less responsive than CD56(dim) NK cells and the ratio of CD56(bright):CD56(dim) favors the former at least up to 1-hour post-exercise.(18) NK cells also play an important role in regulating viral infections, and their deficiency predisposes individuals to susceptibility with herpes virus infections. NKG2D expression has been reported to decrease during human cytomegalovirus infection.(19) NK cells that express inhibitory receptors to self-MHC class I molecules are called "licensed," which means they are functionally more responsive to stimulation, while "unlicensed" NK cells lack receptors for self-MHC class I and are hyporesponsive. Contrary to the hypothesis that "licensed" NK cells are key for viral immunity, the depletion of "unlicensed" NK cells impairs control of viremia, suggesting that these cells are critical for protection against viral infection. NK-cell lymphocytosis is seen in NK-neoplasias, extranodal NK/T-cell lymphoma, aggressive NK-cell leukemia, and blastic NK-cell lymphoma. Chronic NK-cell lymphocytosis is an indolent disorder characterized by proliferation of CD3-CD56+CD16- NK cells. Epstein-Barr virus (EBV) can infect nonneoplastic NK cells(20), and there is an expansion of CD16+CD56(dim) NK cells. Chronic active EBV infection involving NK cells can present with severe inflammatory and necrotic skin reactions typically associated with EBV+ NK-cell lymphoproliferative disease.(21)

Useful For: Quantitation of the major natural killer (NK)-cell subsets relative to total NK cells (NK cell subsets) or total lymphocytes (NK T cells) Assessment in the following clinical contexts: HIV, primary immune deficiencies with NK cell defects, NK-cell lymphocytosis, solid-organ transplantation, immune reconstitution following bone marrow or hematopoietic cell transplantation This test is not useful for diagnosis or classification of NK cell malignancies. This test should not be used for assessing NK cell cytotoxic function.

Interpretation: Interpretive comments will be provided, where applicable, along with reference range values for adult patients and pediatric patients from age 7 to 17 years. Since a separate pediatric reference range could not be established for patients younger than 7 years at this time, interpretation of these samples will be made using the 7- to 17-year old reference range as an approximate guideline.

Reference Values:
The appropriate age-related reference values will be provided on the report. Pediatric reference values are not available for patients younger than 7 years and therefore, interpretation will be based on the 7- to 17-year old ranges with appropriate cautionary statements in the interpretation.

Clinical References: 1. Fan YY, Yang BY, Wu CY. Phenotypically and functionally distinct subsets of natural killer cells in human PBMCs. Cell Biol Int. 2008;32(2):188-197 2. Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. Trends Immunol.

2001;22(11):633-640 3. Poli A, Michel T, Theresine M, Andres E, Hentges F, Zimmer J. CD56bright natural killer (NK) cells: an important NK cell subset. Immunology. 2009126(4):458-465. doi:10.1111/j.1365-2567.2008.03027.x 4. von Bubnoff D, Andres E, Hentges F, Bieber T, Michel T, Zimmer Jl. Natural killer cells in atopic and autoimmune diseases of the skin. J Allergy Clin Immunol. 2010;125(1):60-68. doi:10.1016/j.jaci.2009.11.020 5. Vossen MT, Matmati M, Hertoghs KM, et al. CD27 defines phenotypically and functionally different human NK cell subsets. J Immunol. 2008;180(6):3739-3745. doi:10.4049/jimmunol.180.6.3739 6. Suarez-Alvarez B, Lopez-Vazquez A, Baltar JM, Ortega F, Lopez-Larrea C. Potential role of NKG2D and its ligands in organ transplantation: a new target for immunointervention. Am J Transplant. 2009;9(2):251-257. doi:10.1111/j.1600-6143.2008.02526.x 7. Borrego F, Robertson MJ, Ritz J, Pena J, Solana R. CD69 is a stimulatory receptor for NK cell and its cytotoxic effect is blocked by CD94 inhibitory receptor. Immunology. 1999;97(1):159-165. doi:10.1046/j.1365-2567.1999.00738.x 8. Takahashi K, Aranami T, Endoh M, Miyake S, Yamamura T. The regulatory role of natural killer cells in multiple sclerosis. Brain. 2004;127(Pt 9):1917-1927. doi:10.1093/brain/awh219 9. Alter G, Malenfant JM, Altfeld M: CD107a as a functional marker for the identification of natural killer cell activity. J Immunol Methods. 2004;294(1-2):15-22 10. Mathew PA, Chuang SS, Vaidya SV, Kumaresan PR, Boles KS, Pham HTK. The LLT1 receptor induces IFN-gamma production by human natural killer cells. Mol Immunol. 2004;40(16):1157-1163. doi:10.1016/j.molimm.2003.11.024 11. Godfrey DI, Stankovic S, Baxter AG. Raising the NKT cell family. Nat Immunol. 2010;11(3):197-206. doi:10.1038/ni.1841 12. Orange JS. Human natural killer cell deficiencies. Curr Opin Allergy Clin Immunol. 2006;6(6):399-409 13. Marsh RA, Villaneuva J, Kim MO, et al. Patients with X-linked lymphoproliferative disease due to BIRC4 mutation have normal invariant natural killer T-cell populations. Clin Immunol. 2009;132(1):116-123. doi:10.1016/j.clim.2009.03.517 14. Rigaud S, Fondaneche MC, Lambert N, et al. XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. Nature. 2006;444:110-114. doi:10.1038/nature05257 15. Villanueva J, Lee S, Giannini EH, et al. Natural killer cell dysfunction is a distinguishing feature of systemic onset juvenile rheumatoid arthritis and macrophage activation syndrome. Arthritis Res Ther. 2005;7:R30-R37. doi:10.1186/ar1453 16. Tarazona R, Casado JG, Delarosa O, et al. Selective depletion of CD56(dim) NK cell subsets and maintenance of CD56(bright) NK cells in treatment-naive HIV-1-seropositive individuals. J Clin Immunol. 2002;22(3):176-183. doi:10.1023/a:1015476114409 17. Mavilio D, Lombardo G, Benjamin J, et al. Characterization of CD56-/CD16+ natural killer (NK) cells: a highly dysfunctional NK subset expanded in HIV-infected viremic individuals. Proc Natl Acad Sci USA. 2005;102(8):2886-2891. doi:10.1073/pnas.0409872102 18. Timmons BW, Cieslak T. Human natural killer subsets and acute exercise: a brief review. Exerc Immunol Rev. 2008;14:8-23 19. Muntasell A, Magri G, Pende D, Angulo A, Lopez-Botet M. Inhibition of NKG2D in NK cells by cytokines secreted in response to human cytomegalovirus infection. Blood. 2010;115(25):5170-5179. doi:10.1182/blood-2009-11-256479 20. Trempat P, Tabiasco J, Andre P, et al. Evidence for early infection on nonneoplastic natural killer cells by Epstein-Barr virus. J Virol. 2002;76(21):11139-11142. doi:10.1128/jvi.76.21.11139-11142.2002 21. Pacheco SE, Gottschalk SM, Gresik MV, Dishop MK, Okmaura T, McCormick TG. Chronic active Epstein-Barr virus infection of natural killer cells presenting as severe skin reaction to mosquito bites. J Allergy Clin Immunol. 2005 Aug;116(2):470-472. doi:10.1016/j.jaci.2005.04.044 22. Mace EM, Orange JS. Emerging insights into human health and NK cell biology from the study of NK cell deficiencies. Immunol Rev. 2019;287(1):202-225 23. Delmonte OM, Fleisher TA. Flow cytometry: Surface markers and beyond. J Allergy Clin Immunol. 2019;143(2):528-537 24. Knight V, Heimall JR, Chong H, et al. A toolkit and framework for optimal laboratory evaluation of individuals with suspected primary immunodeficiency. J Allergy Clin Immunol Pract. 2021;9(9):3293-3307.e6

NMS1
603542

Necrotizing Myopathy Evaluation, Serum

Clinical Information:

Useful For: Evaluating patients with suspected necrotizing autoimmune myopathy

Interpretation: Seropositivity for 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) or signal recognition protein (SRP) autoantibodies supports the clinical diagnosis of necrotizing autoimmune myopathy (NAM). A paraneoplastic basis should be considered, according to age, sex, and other risk factors. In cases of NAM, immune therapy is required and often multiple simultaneously utilized immunotherapies are needed to successfully treat patients.

Reference Values:
3-Hydroxy-3-Methylglutaryl Coenzyme-A (HMG-CoA) Reductase:
<20.0 CU

Signal Recognition Particle Antibody Screen:
Negative

Signal Recognition Particle Antibody:
Negative

Signal Recognition Particle Antibody, Titer:
<1:240

Clinical References: 1. Kassardjian CD, Lennon VA, Alfugham NB, et al: Clinical Features and Treatment Outcomes of Necrotizing Autoimmune Myopathy. JAMA Neurol 2015 Sep;72(9):996-1003 2. Emslie-Smith A M, Engel A G: Necrotizing myopathy with pipestem capillaries, microvascular deposition of the complement membrane attack complex (MAC), and minimal cellular infiltration. Neurology 1991;41(6):936-939 3. Ramanathan S, Langguth D, Hardy T, et al: Clinical course and treatment of anti-HMGCR antibody-associated necrotizing autoimmune myopathy. Neurol Neuroimmunol Neuroinflamm 2015 June;2(3):e96 4. Allenbach Y, Keraen J, Bouvier AM, et al: High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. Brain 2016 Aug;139(Pt 8):2131-2135 5. Christopher-Stine L, Casciola-Rosen L, Hong G, et al: A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy. Arthritis Rheum 2010 May;62(9):2757-2766 6. Mammen AL, Chung T, Christopher-Stine L, et al: Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum 2011 Mar;63(3):713-721 7. Hengstman GJ, ter Laak HJ, Vree Egberts WT, et al: Anti-signal recognition particle autoantibodies: marker of a necrotising myopathy. Ann Rheum Dis 2006;65(12):1635-1638 8. Miller T, Al-Lozi MT, Lopate G, Pestronk A: Myopathy with antibodies to the signal recognition particle: clinical and pathological features. J Neurol Neurosurg Psychiatry 2002 Oct;73(4):420-428 9. Watanabe Y, Uruha A, Suzuki S, et al: Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy. J Neurol Neurosurg Psychiatry 2016 Oct;87(10):1038-1044

FNECT 57941 Nectarine (Prunus spp) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

NEGCT 70410 Negative Control, Technical Component Only

Clinical Information: Patterns of protein expression as determined by immunohistochemistry can

be useful for pathologic diagnosis and classification.

Useful For: Qualitative detection of protein expression within cells in paraffin-embedded tissues

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

MGRNA 61646 Neisseria gonorrhoeae, Miscellaneous Sites, Nucleic Acid Amplification, Varies

Clinical Information: Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is a very common sexually transmitted infection (STI), with over 677,000 cases of gonorrhea reported to the Centers for Disease Control and Prevention (CDC) in 2020. Like chlamydia, many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STIs, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups, such as those in communities with high STI prevalence). The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. Culture was previously considered to be the gold standard test for diagnosis of Chlamydia trachomatis and N gonorrhoeae infections. However, these organisms are labile in vitro; therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now considered the reference standard method for diagnosis in most cases. Immunoassays and nonamplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT. Improved screening rates and increased sensitivity of NAAT have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from improved performance characteristics of the assays and patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detecting Neisseria gonorrhoeae in non-US Food and Drug Administration-approved specimen types This test is not intended for use in medico-legal applications.

Interpretation: A positive result indicates the presence of nucleic acid from Neisseria gonorrhoeae and strongly supports the diagnosis of gonorrheal infection. A negative result indicates the absence of N gonorrhoeae nucleic acid. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a

high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually transmitted infections, or in any settings in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal urogenital infection, positive results should be carefully assessed, and the patient retested by other methods (eg, culture for N gonorrhoeae) if appropriate.

Reference Values:
Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic tests for detecting Chlamydia trachomatis and Neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:10.1128/JCM.00211-21

GCRNA
61552

Neisseria gonorrhoeae, Nucleic Acid Amplification, Varies

Clinical Information: Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is a very common sexually transmitted infection (STI), with over 677,000 cases of gonorrhea reported to the Centers for Disease Control and Prevention (CDC) in 2020. Like chlamydia, many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STIs, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence). The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. Culture was previously considered to be the gold standard test for diagnosis of Chlamydia trachomatis and N gonorrhoeae infections. However, these organisms are labile in vitro; therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now considered the reference standard method for diagnosis in most cases. Immunoassays and nonamplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT. Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from improved performance characteristics of the assays and patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detecting Neisseria gonorrhoeae This test is not intended for use in medico-legal applications.

Interpretation: A positive result indicates the presence of nucleic acid from Neisseria gonorrhoeae and supports a diagnosis of gonorrhea. A negative result indicates that nucleic acid from N gonorrhoeae was not detected. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a high prevalence

of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually transmitted infections, or in any settings in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal urogenital infection, positive results should be carefully assessed, and the patient retested by other methods (eg, culture for N gonorrhoeae) if appropriate.

Reference Values:
Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic test for detecting Chlamydia trachomatis and Neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:10.1128/JCM.00211-21

SCGCV
621939

Neisseria gonorrhoeae, Self-Collect, Amplified RNA, Vaginal

Clinical Information: Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is a very common sexually transmitted infection (STI), with over 677,000 cases of gonorrhea reported to the Centers for Disease Control and Prevention (CDC) in 2020. Like chlamydia, many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STIs, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups, such as those in communities with high STI prevalence). The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. Culture was previously considered to be the gold standard test for diagnosis of Chlamydia trachomatis and N gonorrhoeae infections. However, these organisms are labile in vitro; therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now considered the reference standard method for diagnosis in most cases. Immunoassays and nonamplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT. Improved screening rates and increased sensitivity of NAAT have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from improved performance characteristics of the assays and patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detecting Neisseria gonorrhoeae using vaginal swabs collected by the patient in a healthcare setting This test is not intended for use in medico-legal applications.

Interpretation: A positive result indicates the presence of nucleic acid from Neisseria gonorrhoeae and strongly supports the diagnosis of gonorrheal infection. A negative result indicates the absence of N gonorrhoeae nucleic acid. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being

true-positive results. In settings with a low prevalence of sexually transmitted infections, or in any settings in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal urogenital infection, positive results should be carefully assessed, and the patient retested by other methods (eg, culture for N gonorrhoeae) if appropriate.

Reference Values:
Only orderable as part of a profile. For more information see SCCGV / Chlamydia trachomatis and Neisseria gonorrhoeae, Self-Collect, Amplified RNA, Vaginal.

Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic test for detecting Chlamydia trachomatis and Neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:10.1128/JCM.00211-21

SCGCR 621936 Neisseria gonorrhoeae, Self-Collect, Nucleic Acid Amplification, Rectal

Clinical Information: Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is a very common sexually transmitted infection (STI) with over 677,000 cases of gonorrhea reported to the Centers for Disease Control and Prevention (CDC) in 2020. Like chlamydia, many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STIs, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups, such as those in communities with high STI prevalence). The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. Culture was previously considered to be the gold standard test for diagnosis of Chlamydia trachomatis and N gonorrhoeae infections. However, these organisms are labile in vitro; therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now considered the reference standard method for diagnosis in most cases. Immunoassays and nonamplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT. Improved screening rates and increased sensitivity of NAAT have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from improved performance characteristics of the assays and patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detecting Neisseria gonorrhoeae using rectal swabs collected by the patient in a healthcare setting This test is not intended for use in medico-legal applications.

Interpretation: A positive result indicates the presence of nucleic acid from Neisseria gonorrhoeae and strongly supports the diagnosis of gonorrheal infection. A negative result indicates the absence of N gonorrhoeae nucleic acid. A negative result does not exclude the possibility of infection. If clinical

indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually transmitted infections, or in any settings in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal urogenital infection, positive results should be carefully assessed, and the patient retested by other methods (eg, culture for N gonorrhoeae) if appropriate.

Reference Values:

Only orderable as part of a profile. For more information see SCCGR / Chlamydia trachomatis and Neisseria gonorrhoeae, Self-Collect, Amplified RNA, Rectal

Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic test for detecting Chlamydia trachomatis and Neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:10.1128/JCM.00211-21

SCGCT 621933 Neisseria gonorrhoeae, Self-Collect, Nucleic Acid Amplification, Throat

Clinical Information: Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is a very common sexually transmitted infection (STI) with over 677,000 cases of gonorrhea reported to the Centers for Disease Control and Prevention (CDC) in 2020. Like chlamydia, many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria as well as vaginal, urethral, or Throat discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STIs, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups, such as those in communities with high STI prevalence). The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. Culture was previously considered to be the gold standard test for diagnosis of Chlamydia trachomatis and N gonorrhoeae infections. However, these organisms are labile in vitro; therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now considered the reference standard method for diagnosis in most cases. Immunoassays and nonamplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT. Improved screening rates and increased sensitivity of NAAT have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from improved performance characteristics of the assays and patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detecting Neisseria gonorrhoeae using throat swabs collected by the patient in a healthcare setting This test is not intended for use in medico-legal applications.

Interpretation: A positive result indicates the presence of nucleic acid from Neisseria gonorrhoeae and strongly supports the diagnosis of gonorrheal infection. A negative result indicates the absence of N gonorrhoeae nucleic acid. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually transmitted infections, or in any settings in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal urogenital infection, positive results should be carefully assessed, and the patient retested by other methods (eg, culture for N gonorrhoeae) if appropriate.

Reference Values:

Only orderable as part of a profile. For more information see: SCCGT/ Chlamydia trachomatis and Neisseria gonorrhoeae, Self-Collect, Amplified RNA, Throat

Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1 2. Adamson PC, Klausner JD. Diagnostic test for detecting Chlamydia trachomatis and Neisseria gonorrhoeae in rectal and pharyngeal specimens. J Clin Microbiol. 2022;60(4):e0021121. doi:10.1128/JCM.00211-21

FNMEN
91669

Neisseria Meningitidis IgG Vaccine Response

Reference Values:

Reference Ranges (pre-vaccination):

Serogroup A	<4.0 ug/mL
Serogroup C	<5.0 ug/mL
Serogroup Y	<4.0 ug/mL
Serogroup W-135	<3.0 ug/mL

This assay measures serum IgG antibodies recognizing polysaccharide antigens from the four Neisseria meningitidis serogroups included in the licensed meningococcal vaccine. The meningococcal vaccine response is best evaluated by testing pre-vaccination and post-vaccination samples in parallel. A two-fold or greater increase for at least two sero-groups is expected when comparing post-vaccination to pre-vaccination results. N. meningitidis IgG levels peak approximately one month post-vaccination, but decline markedly by two years.

NBILI
82133

Neonatal Bilirubin, Serum

Clinical Information: Bilirubin is one of the most frequently used tests to assess liver function. Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin, while the remaining 15% is produced from red blood cell precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce bilirubin

mono- and diglucuronide, which are then excreted in the bile. A number of inherited and acquired diseases affect 1 or more of the steps involved in the production, uptake, storage, metabolism, and excretion of bilirubin. Bilirubinemia is frequently a direct result of these disturbances. The most commonly occurring form of unconjugated hyperbilirubinemia is that seen in newborns and referred to as physiological jaundice. The increased production of bilirubin, that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis, results in hyperbilirubinemia in the absence of any liver abnormality. The rare genetic disorders, Crigler-Najjar syndromes type I and type II, are caused by a low or absent activity of bilirubin uridine 5'-diphospho-glucuronosyltransferase. In type I, the enzyme activity is totally absent, the excretion rate of bilirubin is greatly reduced, and the serum concentration of unconjugated bilirubin is greatly increased. Patients with this disease may die in infancy owing to the development of kernicterus. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin are retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubins are increased in hepatitis, space-occupying lesions of the liver, and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

Useful For: Assessing liver function Evaluating a wide range of diseases affecting the production, uptake, storage, metabolism, or excretion of bilirubin Monitoring the efficacy of neonatal phototherapy

Interpretation: The level of bilirubinemia that results in kernicterus in a given infant is unknown. In preterm infants, the risk of a handicap increases by 30% for each 2.9 mg/dL increase of maximal total bilirubin concentration. While central nervous system damage is rare when total serum bilirubin (TSB) is less than 20 mg/dL, premature infants may be affected at lower levels. The decision to institute therapy is based on a number of factors including TSB, age, clinical history, physical examination, and coexisting conditions. Phototherapy typically is discontinued when TSB level reaches 14 to 15 mg/dL. Physiologic jaundice should resolve in 5 to 10 days in full-term infants and by 14 days in preterm infants. When any portion of the biliary tree becomes blocked, bilirubin levels will increase.

Reference Values:

DIRECT
> or =12 months: 0.0-0.3 mg/dL
Reference values have not been established for patients who are younger than 12 months of age.

TOTAL
0-6 days: Refer to www.bilitool.org for information on age-specific (postnatal hour of life) serum bilirubin values.
7-14 days: 0.0-14.9 mg/dL
15 days to 17 years: 0.0-1.0 mg/dL
> or =18 years: 0.0-1.2 mg/dL

Clinical References: 1. Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 2. Scharschmidt BF, Blanckaert N, Farina FA, et al. Measurement of serum bilirubin and its mono- and diconjugates: Applications to patients with hepatobiliary disease. Gut 1982;23(8):643-649 3. Practice parameter: management of hyperbilirubinemia in the healthy term newborn. American Academy of Pediatrics. Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia [published correction appears in Pediatrics. Pediatrics. 1994;94(4 Pt 1):558-565.

FNEOS
75451

Neopterin

Clinical Information: Neopterin, a pyrazolopyridine compound, is produced by macrophages after

induction by interferon ? and serves as a marker of cellular immune system activation. Measurable levels of neopterin have been detected in both the serum and urine of patients suffering from various types of malignancies and viral infections. Changes in neopterin concentrations in serum or urine can predict complications such as graft rejection in organ transplant recipients. Elevated neopterin levels are found in autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus (SLE). Neopterin levels can be used as prognostic predictors for certain types of malignancies. Measurement of neopterin levels has particular value for monitoring patients infected with HIV. Neopterin is eliminated primarily in the urine, so evaluation of urinary neopterin levels may be useful in assessing activation of the cellular immunity system even in the absence of typical clinical symptoms, since a correlation has been observed with the course of diseases involving cellular immunity activation and urinary neopterin levels.

Useful For: Increased levels of neopterin are found during impaired renal function and viral infection in transplant patients. Elevated levels are also indicators for conditions related to impaired cellular immunity.

Reference Values:
Adults: <2.5 ng/mL

Clinical References: Fahey JL, Taylor JM, Detels R, et al. The prognostic value of cellular and serologic markers in infection with human immunodeficiency virus type I. N Engl J Med. 1990 Jan; 322(3):166-172. PubMed 1967191 Fuchs D, Hausen A, Reibnegger G, Werner ER, Dierich MP, Wachter H. Neopterin as a marker for activated cell-mediated immunity: Application in HIV infection. Immunol Today. 1988 May; 9(5):150-155. PubMed 3076770 Jacobson MA, Bacchetti P, Kolokathis A, et al. Surrogate markers for survival in patients with AIDS and AIDS related complex treated with zidovudine. BMJ. 1991 Jan 12; 302(6768):73-78. PubMed 1671651 Wachter H, Fuchs D, Hausen A, Reibnegger G, Werner ER. Neopterin as a marker for activation of cellular immunity: Immunologic basis and clinical application. Adv Clin Chem. 1989; 27:81-141. PubMed 2667296

RSCGP 618128 Nephrocalcinosis, Nephrolithiasis, and Renal Electrolyte Imbalance Gene Panel, Varies

Clinical Information: Dehydration, certain medications, diet, and digestive disorders are common factors that can increase the risk for electrolyte imbalances or the development of kidney stones. However, renal tubular loss of electrolytes or protein, or the development of kidney calculi can also signal underlying metabolic, endocrine, or renal tubular dysfunction that is genetic in origin, especially when symptoms present in utero, infancy, or adolescence. When the presence or severity of electrolyte imbalance or kidney stones observed in a patient cannot be explained by acquired causes or there are multiple cases clustered within a family, genetic testing for the inherited causes of kidney or extrarenal impairment of osmoregulation may be considered. This gene panel assesses 72 genes associated with heritable causes of electrolyte imbalance and kidney stones. A thorough clinical and laboratory evaluation prior to genetic testing is often essential for correct genetic diagnosis. While many symptoms associated with kidney stone formation and/or electrolyte imbalance may overlap, most disorders are identifiable by distinct clinical features and a biochemical "signature" established by plasma electrolyte profiles, blood volume status, urine biochemistries, and kidney stone analysis. Genes on this panel are associated with disorders of: 1) Renal salt wasting (Gitelman and Bartter syndromes, pseudohypoaldosteronism type 1, congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency, and glucocorticoid remediable aldosteronism) 2) Salt retention (pseudohypoaldosteronism type 2, Liddle syndrome, familial hyperaldosteronism types 1 and 3) 3) Acid-base homeostasis (proximal or distal renal tubular acidosis) 4) Water handling (nephrogenic diabetes insipidus, neurohypophyseal diabetes insipidus, and nephrogenic syndrome of inappropriate antidiuresis) 5) Calcium homeostasis (familial hypocalciuric hypercalcemia, autosomal dominant hypocalcemia), parathyroid function, and

vitamin D metabolism 6) Kidney crystallization inhibitors, such as magnesium, uromodulin, and pyrophosphate 7) Kidney crystallization promoters such as oxalate (calcium oxalate nephrolithiasis), phosphate (hypophosphatasia, Dent disease, familial tumoral calcinosis), urate (Lesch-Nyhan syndrome, xanthinuria), cystine (cystinuria), and 2,8-dihydroxyadenine (adenine phosphoribosyltransferase deficiency) This panel also includes genes associated with 3 syndromic disorders for which kidney stones or involvement have been reported: Wilson disease (low-molecular weight proteinuria, microscopic hematuria, and Fanconi syndrome that can result in kidney failure); amelogenesis imperfecta, type IG ("enamel-renal syndrome"; nephrocalcinosis); and Fanconi renotubular syndrome 4, with maturity-onset diabetes of the young (MODY; nephrocalcinosis).

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of a hereditary form of nephrocalcinosis, nephrolithiasis, or renal electrolyte imbalance Establishing a diagnosis for a variety of hereditary conditions associated with renal salt wasting or abnormal salt retention; impaired acid-base, water, and calcium homeostasis; or kidney crystallization

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 2. Singh P, Harris PC, Sas DJ, Lieske JC: The genetics of kidney stone disease and nephrocalcinosis. Nat Rev Nephrol. 2022 Apr;18(4):224-240

NETT
82734

Nettle, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to nettle Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased

likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

NEUN
70631

Neu-N Immunostain, Technical Component Only

Clinical Information: Neuronal-nuclei (Neu-N) protein is expressed in neurons in the brain and ganglia in the peripheral nervous system. Presence of Neu-N has been correlated with the withdrawal of the neuron from the cell cycle and with terminal differentiation of the neuron

Useful For: Identification of neuronal nuclei

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Kim KK, Kim YC, Adelstein RS, et al. Fox-3 and PSF interact to activate neural cell-specific alternative splicing. Nucleic Acids Res. 2011;39(8):3064-3078 2. Kim KK, Adelstein RS, Kawamoto S. Identification of neuronal nuclei (NeuN) as Fox-3, a new member of the Fox-1 gene family of splicing factors. J Biol Chem. 2009;284(45):31052-31061 3. Wolf HK, Buslei R, Schmidt-Kastner R, et al. NeuN: a useful neuronal marker for diagnostic histopathology. J Histochem Cytochem. 1996;44(10):1167-1171 4. Gusel'nikova VV, Korzhevskiy DE. NeuN As a neuronal nuclear antigen and neuron differentiation marker. Acta Naturae. 2015;7(2):42-47 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

NELL1
610585

Neural Epidermal Growth Factor-Like 1 Protein Immunostain, Technical Component Only

Clinical Information: Primary membranous nephropathy is an autoimmune disease of the kidney where antibodies target an antigen in the glomerular basement membrane resulting in kidney damage or failure. In up to 75% of primary membranous nephropathy cases PLA2R and THSD7A are the target antigens. Recently neural epidermal growth factor-like 1 (NELL-1) protein was identified as another target antigen for this pathology.

Useful For: Identification of neural epidermal growth factor-like 1 (NELL-1) protein primary membranous nephropathy

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. Granular glomerular basement membrane staining indicates a positive neural epidermal growth factor-like 1 (NELL-1) result. This must be distinguished from staining in podocytes. In Sethi et al, figure 3a provides images of positive staining for NELL-1 along the glomerular basement membranes of NELL-1-associated membranous nephropathy.(1) Figure 3b (F) in the same reference provides an image of podocyte staining for NELL-1 as seen on on-slide quality control and does not indicate a positive NELL-1 result.(1) The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Sethi S, Debiec H, Madden B, et al. Neural epidermal growth factor-like 1 protein (NELL-1) associated membranous nephropathy. Kidney Int. 2020;97(1):163-174 2. Nakamura R, Oyama T, Tajiri R, et al. Expression and regulatory effects on cancer cell behavior of NELL1 and NELL2 in human renal cell carcinoma. Cancer Sci. 2015;106(5):656-664 3. Aghaloo T, Jiang X, Soo C, et al. A study of the role of nell-1 gene modified goat bone marrow stromal cells in promoting new bone formation. Mol Ther. 2007;15(10):1872-1880 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

NONCP
603047

Neuro-Oncology Expanded Gene Panel with Rearrangement, Tumor

Clinical Information: Molecular biomarkers, including clinically relevant gene mutations (ie, sequence variants) and fusions, have been incorporated in the World Health Organization classification of central nervous system (CNS) tumors. This test evaluates targeted regions across 160 genes associated with a variety of adult and pediatric-type CNS tumors for the presence of somatic mutations and rearrangements (fusions and abnormal transcript variants) including, but not limited to, mutations in IDH1/2, TERT promoter, ATRX, TP53, H3-3A (previously H3F3A), H3C2/H3C3 (previously HIST1H3B/C), BRAF, FGFR1, NF1 and SMARCB1, and KIAA1549::BRAF and ZFTA::RELA (previously C11orf95::RELA) fusions, and EGFR transcript variants (eg, EGFR vIII). See Targeted DNA Gene Regions Interrogated by Neuro-Oncology Panel and RNA Targeted Gene Fusions and Abnormal Transcript Variants for details regarding the targeted gene regions identified by this test.

Useful For: Identifying mutations and rearrangements that may support a diagnosis or help determine prognosis for patients with CNS tumors Identifying specific mutations and rearrangements within genes known to be associated with response or resistance to specific cancer therapies This test is not intended

for use for hematological malignancies.

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Schwartzentruber J, Korshunov A, Liu XY, et al: Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature. 2012 Jan;482(7384):226-231 2. Zhang J, Wu G, Miller CP, et al: Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. Nat Genet. 2013 Jan;45(6):602-612 3. Jones DT, Hutter B, Jager N, et al: Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma. Nat Genet. 2013 Aug;45(8):927-932 4. Brennan CW, Verhaak RG, McKenna A, et al: The somatic genomic landscape of glioblastoma. Cell. 2013 Oct;155(2):462-477 5. Brastianos PK, Horowitz PM, Santagata S, et al: Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. Nat Genet. 2013 Mar;45(3):285-289 6. Clark VE, Erson-Omay EZ, Serin A, et al: Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science. 2013 Mar;339(6123):1077-1080 7. Wu G, Diaz AK, Paugh BS, et al: The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. Nat Genet. 2014 Mar;46(5):444-450 8. Cancer Genome Atlas Research Network, Brat DJ, Verhaak RG, et al: Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med. 2015 Jun;372(26):2481-2498 9. Eckel-Passow JE, Lachance DH, Molinaro AM, et al: Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med. 2015 25;372(26):2499-2508 10. Ceccarelli M, Barthel FP, Malta TM, et al: Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma. Cell. 2016 Jan;164(3):550-563 11. Pajtler KW, Mack SC, Ramaswamy V, et al: The current consensus on the clinical management of intracranial ependymoma and its distinct molecular variants. Acta Neuropathol. 2017 Jan;133(1):5-12 12. Northcott PA, Buchhalter I, Morrissy AS, et al: The whole-genome landscape of medulloblastoma subtypes. Nature. 2017;547(7663):311-317 13. WHO Classification of Tumours Editorial Board: Central Nervous System Tumours. 5th ed. World Health Organization; 2021. WHO Classification of Tumours. Vol 6. 14. Nabors LB, Portnow J, Ammirati M, et al: Central nervous system cancers version 1.2015. J Natl Compr Canc Netw. 2015 Oct;13(10);1191-1202

NONCM 622295 Neuro-Oncology Gene Panel, Mutations Only, Tumor

Clinical Information: Molecular biomarkers, including clinically relevant gene mutations (ie, sequence variants), have been incorporated in the World Health Organization classification of central nervous system (CNS) tumors. Additionally, there are clinically available targeted therapies for patients with certain CNS tumor types harboring specific mutations. This test evaluates targeted regions across 89 genes associated with a variety of adult and pediatric-type CNS tumors for the presence of somatic mutations including, but not limited to, mutations in IDH1/2, TERT promoter, ATRX, TP53, H3-3A (previously H3F3A), H3C2/H3C3 (previously HIST1H3B/C), BRAF, FGFR1, NF1 and SMARCB1. See Targeted DNA Gene Regions Interrogated by Neuro-Oncology Panel for details regarding the targeted gene regions identified by this test.

Useful For: Identifying mutations that may support a diagnosis or help determine prognosis for patients with central nervous system tumors Identifying specific mutations within genes known to be associated with response or resistance to specific cancer therapies This test is not intended for use for hematological malignancies.

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the

results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Schwartzentruber J, Korshunov A, Liu XY, et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature. 2012;482(7384):226-231 2. Zhang J, Wu G, Miller CP, et al. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. Nat Genet. 2013;45(6):602-612 3. Jones DT, Hutter B, Jager N, et al. Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma. Nat Genet. 2013;45(8):927-932 4. Brennan CW, Verhaak RG, McKenna A, et al. The somatic genomic landscape of glioblastoma. Cell. 2013;155(2):462-477 5. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. Nat Genet. 2013;45(3):285-289 6. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science. 2013;339(6123):1077-1080 7. Wu G, Diaz AK, Paugh BS, et al. The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. Nat Genet. 2014;46(5):444-450 8. Cancer Genome Atlas Research Network, Brat DJ, Verhaak RG, et al. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med. 2015;372(26):2481-2498 9. Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med. 2015 25;372(26):2499-2508 10. Ceccarelli M, Barthel FP, Malta TM, et al. Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma. Cell. 2016;164(3):550-563 11. Pajtler KW, Mack SC, Ramaswamy V, et al. The current consensus on the clinical management of intracranial ependymoma and its distinct molecular variants. Acta Neuropathol. 2017;133(1):5-12 12. Northcott PA, Buchhalter I, Morrissy AS, et al. The whole-genome landscape of medulloblastoma subtypes. Nature. 2017;547(7663):311-317 13. WHO Classification of Tumours Editorial Board: Central Nervous System Tumours. 5th ed. World Health Organization; 2021. WHO Classification of Tumours. Vol 6. 14. Nabors LB, Portnow J, Ammirati M, et al. Central nervous system cancers version 1.2015. J Natl Compr Canc Netw. 2015;13(10);1191-1202

NONCR 606322 Neuro-Oncology Gene Panel, Rearrangements Only, Tumor

Clinical Information: Molecular biomarkers, including clinically relevant gene fusions, have been incorporated in the World Health Organization classification of central nervous system (CNS) tumors. Additionally, there are clinically available targeted therapies for patients with certain CNS tumor types harboring specific fusions. This test evaluates targeted regions across 81 genes associated with a variety of adult and pediatric-type CNS tumors for the presence of somatic rearrangements (fusions and abnormal transcript variants) including, but not limited to, KIAA1549::BRAF and ZFTA::RELA (previously C11orf95::RELA) fusions, and EGFR transcript variants (eg, EGFR vIII). See RNA Targeted Gene Fusions and Abnormal Transcript Variants for details regarding the targeted gene regions identified by this test.

Useful For: Identifying rearrangements that may support a diagnosis or help determine prognosis for patients with central nervous system tumors Identifying rearrangements within genes known to be associated with response or resistance to specific cancer therapies This test is not intended for use for hematological malignancies.

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board: Central Nervous System Tumours. 5th ed. World Health Organization; 2021. WHO Classification of Tumours. Vol 6. 2. Nabors LB, Portnow J, Ammirati M, et al. Central nervous system cancers version 1.2015. J Natl Compr Canc Netw. 2015;13(10);1191-1202

NCDCS 615865 Neurochondrin Antibody, Cell-Binding Assay, Serum

Clinical Information: Neurochondrin is a neuronal target antigen in autoimmune cerebellar degeneration. Patients positive for neurochondrin-IgG present with a subacute to chronic cerebellar and brainstem syndrome. Patients respond to long-term immunosuppressive treatment with clinical stabilization or improvement.

Useful For: Evaluating neurochondrin-IgG by cell-binding assay using serum from patients presenting with cerebellar and brainstem syndrome

Interpretation: A positive result supports a diagnosis of central nervous system autoimmunity. Typical neurological phenotypes encountered include cerebellar ataxia and brainstem encephalitis. A paraneoplastic basis should be considered (uterine cancer in women) though cancers are, generally, not detected. Neurological stabilization or improvement may occur with immune therapy.

Reference Values:
Only orderable as a reflex. For more information see:
-DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
-ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
-MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
-PCDES / Pediatric Autoimmune Encephalopathy/CNS Disorder Evaluation, Serum

Negative

Clinical References: Shelly S, Kryzer TJ, Komorowski L, et al: Neurochondrin neurological autoimmunity. Neurol Neuroimmunol Neuroinflamm. 2019 Sep 11;6(6):e612. doi: 10.1212/NXI.0000000000000612

NCDCC 615864 Neurochondrin Antibody, Cell-Binding Assay, Spinal Fluid

Clinical Information: Neurochondrin is a neuronal target antigen in autoimmune cerebellar degeneration. Patients positive for neurochondrin-IgG present with a subacute to chronic cerebellar and brainstem syndrome. Patients respond to long-term immunosuppressive treatment with clinical stabilization or improvement.

Useful For: Evaluating neurochondrin-IgG by cell-binding assay using spinal fluid from patients presenting with cerebellar and brainstem syndrome

Interpretation: A positive result supports a diagnosis of central nervous system autoimmunity. Typical neurological phenotypes encountered include cerebellar ataxia and brainstem encephalitis. A paraneoplastic basis should be considered (uterine cancer in women) though cancers are generally not detected. Neurological stabilization or improvement may occur with immune therapy.

Reference Values:
Only orderable as a reflex. For more information see:
-DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-PCDEC / Pediatric Autoimmune Encephalopathy/CNS Disorder Evaluation, Spinal Fluid

Negative

Clinical References: Shelly S, Kryzer TJ, Komorowski L, et al: Neurochondrin neurological autoimmunity. Neurol Neuroimmunol Neuroinflamm. 2019 Sep 11;6(6):e612

NCDTS 616111 Neurochondrin Antibody, Tissue Immunofluorescence Titer, Serum

Clinical Information: Neurochondrin is a neuronal target antigen in autoimmune cerebellar degeneration. Patients positive for neurochondrin-IgG present with a subacute to chronic cerebellar and brainstem syndrome. Patients respond to long-term immunosuppressive treatment with clinical stabilization or improvement.

Useful For: Detecting neurochondrin-IgG in serum from patients presenting with cerebellar and brainstem syndrome Reporting an end titer result from serum specimens

Interpretation: A positive result supports a diagnosis of central nervous system autoimmunity. Typical neurological phenotypes encountered include cerebellar ataxia and brainstem encephalitis. A paraneoplastic basis should be considered (uterine cancer in women), although cancers are generally not detected. Neurological stabilization or improvement may occur with immune therapy.

Reference Values:
Only orderable as a reflex. For more information see:
-DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
-ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
-MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
-PCDES / Pediatric Autoimmune Encephalopathy/CNS Disorder Evaluation, Serum

<1:240

Clinical References: Shelly S, Kryzer TJ, Komorowski L, et al: Neurochondrin neurological autoimmunity. Neurol Neuroimmunol Neuroinflamm. 2019 Sep 11;6(6):e612

NCDTC 616112 Neurochondrin Antibody, Tissue Immunofluorescence Titer, Spinal Fluid

Clinical Information: Neurochondrin is a neuronal target antigen in autoimmune cerebellar degeneration. Patients positive for neurochondrin-IgG present with a subacute to chronic cerebellar and brainstem syndrome. Patients respond to long-term immunosuppressive treatment with clinical

stabilization or improvement.

Useful For: Detecting neurochondrin-IgG in spinal fluid (CSF) from patients presenting with cerebellar and brainstem syndrome Reporting an end titer result from CSF specimens

Interpretation: A positive result supports a diagnosis of central nervous system autoimmunity. Typical neurological phenotypes encountered include cerebellar ataxia and brainstem encephalitis. A paraneoplastic basis should be considered (uterine cancer in women), although cancers are generally not detected. Neurological stabilization or improvement may occur with immune therapy.

Reference Values:
Only orderable as a reflex. For more information see:
-DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-PCDEC / Pediatric Autoimmune Encephalopathy/CNS Disorder Evaluation, Spinal Fluid

<1:2

Clinical References: Shelly S, Kryzer TJ, Komorowski L, et al: Neurochondrin neurological autoimmunity. Neurol Neuroimmunol Neuroinflamm. 2019 Sep 11;6(6):e612. doi: 10.1212/NXI.0000000000000612

NF4FS
614591

Neurofascin-155 IgG4, Flow Cytometry, Serum

Clinical Information: Neurofascin-155 IgG4 antibodies are present in approximately 4% to 18% of patients with chronic inflammatory demyelinating neuropathy (CIDP) and, more rarely, in those with more acute forms of demyelinating neuropathy. This biomarker aids in the identification of a subset of these patients who are more likely to present with distal weakness, gait disturbance, tremor, and dysarthria as compared to classic CIDP. Most patients who are seropositive for neurofascin-155 IgG4 have been reported to be refractory to intravenous immune globulin (IVIG) therapy and often require second line treatment that includes B-cell depleting therapies such as rituximab. Studies in animal models, as well as the disease pathology indicate neurofascin-155 IgG4 antibodies directly disrupt the paranodal structure ultimately leading to demyelination. The presence of these antibodies, when detected, using flow cytometry is highly specific to CIDP and has not been reported in other disease mimics such as hereditary neuropathies, distal acquired demyelinating symmetric neuropathy, and motor neuron disease. This is test is useful in diagnostic work up of patients being evaluated for CIDP and related demyelinating peripheral neuropathies. This test should only be utilized in the appropriate clinical context.

Useful For: Evaluating patients with an underlying demyelinating neuropathy Diagnosis of a neurofascin-155 IgG4 mediated neuropathy

Interpretation: A positive result is consistent with a neurofascin-155 IgG4 mediated demyelinating neuropathy.

Reference Values:
Only orderable as part of a profile. For more information see:
-CIDP / Chronic Inflammatory Demyelinating Polyradiculoneuropathy/Nodopathy Evaluation, Serum
-DMNES / Peripheral Nervous System Demyelinating Neuropathy, Autoimmune Evaluation, Serum

Negative

Clinical References: 1. Ogata H, Yamasaki R, Hiwatashi A, et al. Characterization of IgG4 anti-neurofascin 155 antibody-positive polyneuropathy. Ann Clin Transl Neurol. 2015;2(10):960-971 2. Cortese A, Lombardi R, Briani C, et al. Antibodies to neurofascin, contactin-1, and contactin-associated protein 1 in CIDP: Clinical relevance of IgG isotype. Neurol Neuroimmunol Neuroinflamm. 2020;7(1):e639 3. Querol L, Nogales-Gadea G, Rojas-Garcia R, et al. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. Neurology. 2014;82(10):879-886

NF1Z
614585

Neurofibromatosis Type 1, NF1, Full Gene Analysis, Varies

Clinical Information: Germline variants in the NF1 gene are associated with neurofibromatosis type 1 (NF1), an autosomal dominant hereditary tumor syndrome.(1) NF1 is characterized by many manifestations beginning in childhood, including multiple cafe au lait macules, axillary and inguinal freckling, cutaneous and plexiform neurofibromas, iris hamartomas (known as Lisch nodules), and increased lifetime risk to develop optic glioma, other brain tumors, malignant peripheral nerve sheath tumors, and breast cancer.(1) NF1 has also been associated with learning disabilities, vasculopathy, and musculoskeletal features such as osteopenia, long bone dysplasia, and scoliosis.(1) Almost half of all individuals with NF1 have no family history as their variants arose de novo, during gamete formation or early embryogenesis.(1) Of note, some individuals may present with segmental/mosaic NF1, where an NF1 variant may be localized to only one segment or a few segments of the body. This test may not detect mosaic NF1.(1) The National Comprehensive Cancer Network provides recommendations regarding the breast cancer surveillance of adults with NF1.(2) Other medical management guidelines have been published by the American Academy of Pediatrics and the American College of Medical Genetics.(3,4)

Useful For: Evaluating patients with a personal or family history suggestive of neurofibromatosis type 1 (NF1) Establishing a diagnosis of a NF1 allowing for targeted cancer surveillance based on associated risks Identifying genetic variants associated with increased risk for NF1 allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Friedman JM. Neurofibromatosis 1. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated April 3, 2025. Accessed April 24, 2025. Available at: www.ncbi.nlm.nih.gov/books/NBK1109/ 2. Daly MB, Pal T, Berry MP, et al. Genetic/Familial high-risk assessment: Breast, ovarian, and pancreatic, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(1):77-102 3. Miller DT, Freedenberg D, Schorry E, et al. Health Supervision for Children With Neurofibromatosis Type 1. Pediatrics. 2019;143(5):e20190660 4. Stewart DR, Korf BR, Nathanson KL, Stevenson DA, Yohay K. Care of adults with neurofibromatosis type 1: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018;20(7):671-682 5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

NF2F
70520

Neurofilament (2F11) Immunostain, Technical Component Only

Clinical Information: Neurofilament (NF) constitutes the main structural elements of neuronal axons and dendrites. NF subunits are present in neurons, neuronal processes, peripheral nerves, and sympathetic ganglion cells. In brain parenchyma, NF labels the axons of the central nervous system. Within tumors, only neoplastic cells of neural origin or those exhibiting neuronal differentiation have been observed to express NF. Positive immunostaining has been observed in neuromas, gangliogliomas, neuroblastomas, and medulloblastomas. Other tumors that can stain for NF include pheochromocytoma, chemodectomas, and carcinoid tumors.

Useful For: Aiding in the identification of neoplastic cells of neural origin or those exhibiting neuronal differentiation

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Diepholder HM, Schwechheimer K, Mohadjer M, Knoth R, Volk B. A clinicopathologic and immunomorphologic study of 13 cases of ganglioglioma. Cancer. 1991;68(10):2192-2201 2. Franquemont DW, Mills SE, Lack EE. Immunohistochemical detection of neuroblastomatous foci in composite adrenal pheochromocytoma-neuroblastoma. Am J Clin Pathol. 1994;102(2):163-170 3. Matsunou H, Shimoda T, Kakimoto S, Yamashita H, Ishikawa E, Mukai M. Histopathologic and immunohistochemical study of malignant tumors of peripheral nerve sheath (malignant schwannoma). Cancer. 1985;56:2269-2279 4. Stockman DL, Miettinen M, Suster S, et al. Malignant gastrointestinal neuroectodermal tumor: clinicopathologic, immunohistochemical, ultrastructural, and molecular analysis of 16 cases with a reappraisal of clear cell sarcoma-like tumors of the gastrointestinal tract. Am J Surg Pathol. 2012;36(6):857 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

NFSMI
71354

Neurofilament (SMI31) Immunostain, Technical Component Only

Clinical Information: Neurofilament antibody clone SMI 31 reacts with a phosphorylated epitope on neurofilament H and, to a lesser degree, neurofilament M. Both of these proteins contain multiple tandemly repeated serine phosphorylation sites. Clone SMI 31 reacts with thick and thin axons and specific dendrites such as basket cell dendrites. SMI 31 may also stain neuronal cell bodies in pathological conditions.

Useful For: Differentiating neurons (neurofilament positive) from glia (neurofilament negative)

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Rudrabhatla P, Jaffe H, Pant HC. Direct evidence of phosphorylated

neuronal intermediate filament proteins in neurofibrillary tangles (NFTs): phosphoproteomics of Alzheimer's NFTs. FASEB J. 2011;25(11):3896-3905 2. Raina AK, Takeda A, Nunomura A, et al. Genetic evidence for oxidative stress in Alzheimer's disease. NeuroReport. 1999;10:1355-1357 3. Yang CC, Alvarez RB, Engel WK, et al. Nitric oxide-induced oxidative stress in autosomal recessive and dominant inclusion-body myopathies. Brain. 1998;121:1089-1097 4. Giasson BI, Mushynski WE. Aberrant stress-induced phosphorylation of perikaryal neurofilaments. J Biol Chem. 1996;271(48):30404-30409 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

NFLP
622765

Neurofilament Light Chain, Plasma

Clinical Information: Neurofilaments (NF) are exclusively located in the neuronal cytoskeleton and are released to the interstitial fluid upon axonal injury or neurodegeneration. NF concentrations in cerebrospinal fluid (CSF) and blood have been shown to correlate with the extent of axonal damage or neurodegeneration in various neurodegenerative diseases. Of the family of NF proteins, neurofilament light chain (NfL) has gained the most interest as a candidate marker of neurodegeneration. During axonal damage, NfL is released into the CSF, and eventually into the blood where concentrations are 40-fold lower than in the CSF. Concentrations of NfL in plasma have been shown to be approximately 5% to 10% lower than those measured in serum. Circulating NfL concentrations increase with age with at a rate approximately 2% to 3% per year of age in both male and female individuals. While the specific cause of this increase has not been elucidated, it is believed to be related to the aging process as well as to the development of subclinical ischemic events. NfL concentrations in blood (plasma or serum) reflect the extent of axonal damage, making them a generic marker of disease activity. Increases in NfL concentrations have been reported in individuals with traumatic brain injury, amyotrophic lateral sclerosis, multiple sclerosis, frontotemporal dementia, Alzheimer disease (AD), and other neurodegenerative diseases. Plasma neurofilament light chain (NfL) is a non-specific marker of neuro-axonal injury showing promising associations with outcomes in several neurological conditions. In neurodegenerative diseases, NfL may also serve as a prognostic marker of disease progression and drug efficacy biomarker of experimental therapies. In a meta-analysis of AD, frontotemporal dementia, and amyotrophic lateral sclerosis, plasma NfL concentrations were elevated in patients compared to controls with utility in differentiating neurodegenerative conditions from non-neurodegenerative mimics. However, due to a lack of specificity to a particular neurodegenerative disease, its role as a diagnostic marker may be limited.

Useful For: Assessing neuronal damage related to various neurodegenerative diseases

Interpretation:

Reference Values:
<2.5 years: < or =12.8 pg/mL
2.5 to 4 years: < or =11.8 pg/mL
5 to 9 years: < or =10.4 pg/mL
10 to 14 years: < or =8.8 pg/mL
15 to 19 years: < or =9.2 pg/mL
20 to 24 years: < or =10.4 pg/mL
25 to 29 years: < or =11.9 pg/mL
30 to 34 years: < or =13.5 pg/mL
35 to 39 years: < or =15.3 pg/mL
40 to 44 years: < or =17.3 pg/mL
45 to 49 years: < or =19.7 pg/mL
50 to 54 years: < or =22.4 pg/mL

55 to 59 years: < or =25.4 pg/mL
60 to 64 years: < or =28.8 pg/mL
65 to 69 years: < or =32.7 pg/mL
70 to 74 years: < or =37.1 pg/mL
75 to 79 years: < or =42.1 pg/mL
80 to 84 years: < or = 47.8 pg/mL
> or =85 years: < or =54.3 pg/mL

Clinical References: 1. Freedman MS, Gnanapavan S, Booth RA, et al. Guidance for use of neurofilament light chain as a cerebrospinal fluid and blood biomarker in multiple sclerosis management. EBioMedicine. 2024;101:104970. doi:10.1016/j.ebiom.2024.104970 2. Delcoigne B, Manouchehrinia A, Barro C, et al. Blood neurofilament light levels segregate treatment effects in multiple sclerosis. Neurology. 2020;94(11):e1201-e1212. doi:10.1212/WNL.0000000000009097 3. Pohl D, Waubant E, Banwell B, et al. Treatment of pediatric multiple sclerosis and variants. Neurology. 2007;68(16 Suppl 2):S54-65 4. Ghezzi A, Banwell B, Boyko A, et al. The management of multiple sclerosis in children: a European view. Mult Scler. 2010;16(10):1258-1267 5. Farragher CD, Ku Y, Powers JE. The potential role of neurofilament light in mild traumatic brain injury diagnosis: a systematic review. Cureus. 2022;14(11):e31301 6. Wang SL, Li N, Feng SY, Li Y. Serum neurofilament light chain as a predictive marker of neurologic outcome after cardiac arrest: a meta-analysis. BMC Cardiovasc. Disord. 2023;23(1):193 7. Khalil M, Teunissen CE, Lehmann S, et al. Neurofilaments as biomarkers in neurological disorders - towards clinical application. Nat Rev Neurol. 2024;20(5):269-287. doi:10.1038/s41582-024-00955-x 8. Ashton NJ, Janelidze S, Al Khleifat A, et al. A multicentre validation study of the diagnostic value of plasma neurofilament light. Nat Commun. 2021;12(1):3400 9. Wendel EM, Bertolini A, Kousoulos L, et al. Serum neurofilament light-chain levels in children with monophasic myelin oligodendrocyte glycoprotein-associated disease, multiple sclerosis, and other acquired demyelinating syndrome. Mult Scler. 2022;28(10):1553-1561 10. Karantali E, Kazis D, McKenna J, et al. Neurofilament light chain in patients with a concussion or head impacts: a systematic review and meta-analysis. Eur J Trauma Emerg Surg. 2022;48(3):1555-1567 11. Bornhorst JA, Figdore D, Campbell MR, et al. Plasma neurofilament light chain (NfL) reference interval determination in an age-stratified cognitively unimpaired cohort. Clin Chim Acta. 2022;535:153-156. doi:10.1016/j.cca.2022.08.017 12. Ashrafzadeh-Kian S, Figdore D, Larson B, et al. Head-to-head comparison of four plasma neurofilament light chain (NfL) immunoassays. Clin Chim Acta. 2024;561:119817. doi: 10.1016/j.cca.2024.119817 13. Figdore DJ, Ashrafzadeh-Kian S, Pazdernik VK, Algeciras-Schimnich A, Bornhorst JA. Determination of pediatric and adult reference intervals for neurofilament light chain (NfL) in blood and a comparison to other recent studies J Lab Precis Med. 2024;9:29. doi:10.21037/jlpm-24-33

PNEFS
84300

Neuroimmunology Antibody Follow-up, Serum

Clinical Information: Paraneoplastic autoimmune neurological disorders reflect a patient's humoral and cellular immune responses to cancer. The cancer may be new or recurrent, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeural proteins found in the plasma membrane, cytoplasm, and nucleus of neurons or muscle are generated in this immune response and serve as serological markers of paraneoplastic autoimmunity. The most recognized cancers in this context are small-cell lung carcinoma, thymoma, ovarian (or related mullerian) carcinoma, breast carcinoma, and Hodgkin lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin lymphoma, and chondroblastoma. An individual patient's autoantibody profile can predict a specific neoplasm with 90% certainty but not the neurological syndrome. Four classes of autoantibodies are recognized in serum analysis: -Neuronal nuclear (antineuronal nuclear antibody-type 1 [ANNA-1], ANNA-2, ANNA-3) -Neuronal and muscle cytoplasmic (Purkinje cell cytoplasmic antibody, type 1 [PCA-1], PCA-2, PCA-Tr, collapsin response-mediator protein-5 [CRMP-5], amphiphysin, and striational) -Glial nuclear (antiglial nuclear antibody: AGNA) -Plasma membrane cation channel antibodies (neuronal P/Q-type and muscle acetylcholine

receptor autoantibodies). These autoantibodies are potential effectors of neurological dysfunction. Patients who are seropositive usually present with subacute neurological signs and symptoms. The patient may present with encephalopathy, cerebellar ataxia, myelopathy, radiculopathy, plexopathy, sensory, sensorimotor, or autonomic neuropathy, with or without coexisting evidence of a neuromuscular transmission disorder: Lambert-Eaton syndrome, myasthenia gravis, or neuromuscular hyperexcitability. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Sensorimotor neuropathy and cerebellar ataxia are common presentations, but clinical pictures in some patients are dominated by striking gastrointestinal dysmotility, limbic encephalopathy, basal ganglionitis, or cranial neuropathy (especially loss of vision, hearing, smell, or taste). Cancer risk factors include past or family history of cancer, history of smoking, or social/environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favor less neurological morbidity and offer the best hope for survival.

Useful For: Monitoring patients who have previously tested positive for one or more antibodies within the past 5 years in a Mayo Clinic Laboratories serum evaluation

Interpretation: Antibodies directed at onconeural proteins shared by neurons, muscles, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects and are usually accompanied by subacute neurological signs and symptoms. Several autoantibodies have a syndromic association, but no known autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile result has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than one paraneoplastic autoantibody to be detected, each predictive of the same cancer.

Reference Values:

Test ID	Reporting Name	Methodology*	Reference Value
GANG	AChR Ganglionic Neuronal Ab, S	RIA	< or =0.02 nmol/L
ACMFS	AChR Modulating Flow Cytometry, S	FACS	Negative
AGNBS	AGNA-1 Immunoblot, S	IB	Negative
AINCS	Alpha Internexin CBA, S	CBA	Negative
AMPCS	AMPA-R Ab CBA, S	CBA	Negative
AMPHS	Amphiphysin Ab, S	IFA	Negative
AMIBS	Amphiphysin Immunoblot, S	IB	Negative
AN1BS	ANNA-1 Immunoblot, S	IB	Negative
AN2BS	ANNA-2 Immunoblot, S	IB	Negative
AGN1S	Anti-Glial Nuclear Ab, Type 1	IFA	Negative
ANN1S	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2S	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3S	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
APBCS	AP3B2 CBA, S	CBA	Negative

APBIS	AP3B2 IFA, S	IFA	Negative
CS2CS	CASPR2-IgG CBA, S	CBA	Negative
CRMS	CRMP-5-IgG, S	IFA	Negative
DPPCS	DPPX Ab CBA, S	CBA	Negative
DPPIS	DPPX Ab IFA, S	IFA	Negative
GABCS	GABA-B-R Ab CBA, S	CBA	Negative
GFACS	GFAP CBA, S	CBA	Negative
GFAIS	GFAP IFA, S	IFA	Negative
GRFCS	GRAF1 CBA, S	CBA	Negative
GRFIS	GRAF1 IFA, S	IFA	Negative
IGG_D	IgG Disialo. GD1b	ELISA	Negative
IG5CS	IgLON5 CBA, S	CBA	Negative
IG5IS	IgLON5 IFA, S	IFA	Negative
IGM_D	IgM Disialo. GD1b	ELISA	Negative
IGM_M	IgM Monos. GM1	ELISA	Negative
ITPCS	ITPR1 CBA, S	CBA	Negative
ITPIS	ITPR1 IFA, S	IFA	Negative
LG1CS	LGI1-IgG CBA, S	CBA	Negative
GL1CS	mGluR1 Ab CBA, S	CBA	Negative
GL1IS	mGluR1 Ab IFA, S	IFA	Negative
NCDCS	Neurochondrin CBA, S	CBA	Negative
NCDIS	Neurochondrin IFA, S	IFA	Negative
NFHCS	NIF Heavy Chain CBA, S	CBA	Negative
NIFIS	NIF IFA, S	IFA	Negative
NFLCS	NIF Light Chain CBA, S	CBA	Negative
NMDCS	NMDA-R Ab CBA, S	CBA	Negative
CCPQ	P/Q-Type Calcium Channel Ab	RIA	< or =0.02 nmol/L
PC1BS	PCA-1 Immunoblot, S	IB	Negative
PCTBS	PCA-Tr Immunoblot, S	IB	Negative
PCABP	Purkinje Cell Cytoplasmic Ab Type 1	IFA	Negative
PCAB2	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
PCATR	Purkinje Cell Cytoplasmic Ab Type Tr	IFA	Negative
SP5CS	Septin-5 CBA, S	CBA	Negative
SP5IS	Septin-5 IFA, S	IFA	Negative

SP7CS	Septin-7 CBA, S	CBA	Negative
SP7IS	Septin-7 IFA, S	IFA	Negative
SRPIS	SRP IFA Screen, S	IFA	Negative
SRPBS	SRP Immunoblot, S	IB	Negative
PDEIS	PDE10A Ab IFA, S	IFA	Negative
T46CS	TRIM46 Ab CBA, S	CBA	Negative
T46IS	TRIM46 Ab IFA, S	IFA	Negative

Clinical References: 1. Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology. 2011;77(2):179-189 2. Horta ES, Lennon VA, Lachance DH, et al. Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014;20(14):3862-3869 3. Gilligan M, McGuigan C, McKeon A. Paraneoplastic neurologic disorders. Curr Neurol Neurosci Rep. 2023;23(3):67-82. doi:10.1007/s11910-023-01250-w 4. Graus F, Vogrig A, Muniz-Castrillo S, et al. Updated diagnostic criteria for paraneoplastic neurologic syndromes. Neurol Neuroimmunol Neuroinflamm. 2021;8(4):e1014

PNEFC
84299

Neuroimmunology Antibody Follow-up, Spinal Fluid

Clinical Information: Paraneoplastic autoimmune neurological disorders reflect a patient's humoral and cellular immune responses to cancer. The cancer may be new or recurrent, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeural proteins found in the plasma membrane, cytoplasm, and nucleus of neurons or muscle are generated in this immune response and serve as serological markers of paraneoplastic autoimmunity. The most recognized cancers in this context are small-cell lung carcinoma, thymoma, ovarian (or related mullerian) carcinoma, breast carcinoma, and Hodgkin lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin lymphoma, and chondroblastoma. An individual patient's autoantibody profile can predict a specific neoplasm with 90% certainty but not the neurological syndrome. Three classes of autoantibodies are recognized in the spinal fluid analysis: -Neuronal nuclear (antineuronal nuclear antibody-type 1 [ANNA-1], ANNA-2, ANNA-3) -Neuronal and muscle cytoplasmic (Purkinje cell cytoplasmic antibody, type 1 [PCA-1]; PCA-2; PCA-Tr, collapsin response-mediator protein-5 [CRMP-5], and amphiphysin) -Glial nuclear (antiglial nuclear antibody: AGNA) Patients who are seropositive usually present with subacute neurological signs and symptoms. The patient may present with encephalopathy, cerebellar ataxia, myelopathy, radiculopathy, plexopathy, sensory, sensorimotor, or autonomic neuropathy, with or without coexisting evidence of a neuromuscular transmission disorder: Lambert-Eaton syndrome, myasthenia gravis, or neuromuscular hyperexcitability. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Sensorimotor neuropathy and cerebellar ataxia are common presentations, but the clinical picture in some patients is dominated by striking gastrointestinal dysmotility, limbic encephalopathy, basal ganglionitis, or cranial neuropathy (especially loss of vision, hearing, smell, or taste). Cancer risk factors include past or family history of cancer, history of smoking, or social/environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favor less neurological morbidity and offer the best hope for survival.

Useful For: Monitoring patients who have previously tested positive for 1 or more antibodies within the past 5 years in a Mayo Clinic Neuroimmunology Laboratory spinal fluid evaluation

Interpretation: Antibodies directed at onconeural proteins shared by neurons, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in

healthy subjects and are usually accompanied by subacute neurological signs and symptoms. Several autoantibodies have a syndromic association, but no known autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than one paraneoplastic autoantibodies to be detected, each predictive of the same cancer.

Reference Values:

Test ID	Reporting Name	Methodology*	Reference Value
AGNBC	AGNA-1 Immunoblot, CSF	IB	Negative
AINCC	Alpha Internexin CBA, CSF	CBA	Negative
AMPCC	AMPA-R Ab CBA, CSF	CBA	Negative
AMPHC	Amphiphysin Ab, CSF	IFA	Negative
AMIBC	Amphiphysin Immunoblot, CSF	IB	Negative
AN1BC	ANNA-1 Immunoblot, CSF	IB	Negative
AN2BC	ANNA-2 Immunoblot, CSF	IB	Negative
AGN1C	Anti-Glial Nuclear Ab Type 1	IFA	Negative
ANN1C	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2C	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3C	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
APBCC	AP3B2 CBA, CSF	CBA	Negative
APBIC	AP3B2 IFA, CSF	IFA	Negative
CS2CC	CASPR2-IgG CBA, CSF	CBA	Negative
CRMWC	CRMP-5-IgG Western Blot, CSF	WB	Negative
CRMC	CRMP-5-IgG, CSF	IFA	Negative
DPPCC	DPPX Ab CBA, CSF	CBA	Negative
DPPIC	DPPX Ab IFA, CSF	IFA	Negative
GABCC	GABA-B-R Ab CBA, CSF	CBA	Negative
GFACC	GFAP CBA, CSF	CBA	Negative
GFAIC	GFAP IFA, CSF	IFA	Negative
GRFCC	GRAF1 CBA, CSF	CBA	Negative
GRFIC	GRAF1 IFA, CSF	IFA	Negative
IG5CC	IgLON5 CBA, CSF	CBA	Negative

IG5IC	IgLON5 IFA, CSF	IFA	Negative
ITPCC	ITPR1 CBA, CSF	CBA	Negative
ITPIC	ITPR1 IFA, CSF	IFA	Negative
LG1CC	LGI1-IgG CBA, CSF	CBA	Negative
GL1CC	mGluR1 Ab CBA, CSF	CBA	Negative
GL1IC	mGluR1 Ab IFA, CSF	IFA	Negative
NCDCC	Neurochondrin CBA, CSF	CBA	Negative
NCDIC	Neurochondrin IFA, CSF	IFA	Negative
NFHCC	NIF Heavy Chain CBA, CSF	CBA	Negative
NIFIC	NIF IFA, CSF	IFA	Negative
NFLCC	NIF Light Chain CBA, CSF	CBA	Negative
NMDCC	NMDA-R Ab CBA, CSF	CBA	Negative
PC1BC	PCA-1 Immunoblot, CSF	IB	Negative
PCTBC	PCA-Tr Immunoblot, CSF	IB	Negative
PCTRC	Purkinje Cell Cytoplasmc Ab Type Tr	IFA	Negative
PCA1C	Purkinje Cell Cytoplasmic Ab Type 1	IFA	Negative
PCA2C	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
SP5CC	Septin-5 CBA, CSF	CBA	Negative
SP5IC	Septin-5 IFA, CSF	IFA	Negative
SP7CC	Septin-7 CBA, CSF	CBA	Negative
SP7IC	Septin-7 IFA, CSF	IFA	Negative
PDEIC	PDE10A Ab IFA, CSF	IFA	Negative
T46CC	TRIM46 Ab CBA, CSF	CBA	Negative
T46IC	TRIM46 Ab IFA, CSF	IFA	Negative

Clinical References: 1. Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology. 2011;77(2):179-189. doi:10.1212/WNL.0b013e318224afde 2. Horta ES, Lennon VA, Lachance DH, et al. Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014;20(14):3862-3869 3. Gilligan M, McGuigan C, McKeon A..Paraneoplastic neurologic Disorders. Curr Neurol Neurosci Rep. 2023;23(3):67-82. doi:10.1007/s11910-023-01250-w 4. Graus F, Vogrig A, Muniz-Castrillo S, et al. Updated diagnostic criteria for paraneoplastic neurologic syndromes. Neurol Neuroimmunol Neuroinflamm. 2021;8(4):e1014. doi:10.1212/NXI.0000000000001014

NMOFS
38324

Neuromyelitis Optica (NMO)/Aquaporin-4-IgG Fluorescence-Activated Cell Sorting (FACS) Assay, Serum

Clinical Information: Neuromyelitis optica (NMO), sometimes called Devic disease or opticospinal multiple sclerosis [MS]) is a severe, relapsing, autoimmune, inflammatory and demyelinating central nervous system disease that predominantly affects optic nerves and spinal cord.(1) The disorder is now recognized as a spectrum of autoimmunity (termed NMO spectrum disorders [NMOSD]) targeting the astrocytic water channel aquaporin-4 (AQP4).(1,2) Brain lesions are observed in >60% of patients with NMOSD and approximately 10% will be MS-like.(3) Children tend to have greater brain involvement than adults and brain lesions are more symptomatic than is typical for adult patients.(4) Extensive cerebral white matter signal abnormalities are sometimes encountered, most commonly in children, and are sometimes associated with encephalopathy. Circumventricular organs (CVO; eg, area postrema) are preferentially involved. Symptoms and signs attributable to area postrema involvement include intractable hiccups, nausea and vomiting, and these may occur in isolation, herald the onset of NMO or occur in association with the more classical optic neuritis or Longitudinally Extensive Transverse Myelitis (LETM).(5) Magnetic resonance imaging typically reveals large inflammatory spinal cord lesions involving 3 or more vertebral segments. During acute attacks, the cerebrospinal fluid contains inflammatory cells, but usually lacks evidence of intrathecal IgG synthesis. The clinical course is characterized by relapses of optic neuritis or transverse myelitis, or both. Many patients with NMOSD are misdiagnosed as having MS. Importantly, the prognosis and optimal treatments for the 2 diseases differ. NMOSD typically has a worse natural history than MS, with frequent and early relapses. NMOSD attacks are often severe resulting in a rapid accumulation of disability (blindness and paraplegia). More effective treatments combined with earlier and more accurate diagnosis has led to improved outcomes. Currently, in the AQP4-IgG era, 5 years after onset, approximately 30% of NMO patients will require a cane to walk and 10% will be wheelchair bound. Treatments for NMOSD include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Beta-interferon, a treatment promoted for MS, exacerbates NMOSD. Therefore, early diagnosis and initiation of NMO-appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. Skeletal muscle abnormalities with hyperCKemia have been reported in a few NMOSD patients. Recent reports indicate focal retinal vascular attenuation, inner nuclear layer thickening and microcystic edema in some NMO patients. The sensitivity and specificity of Fluorescence-Activated Cell Sorting (FACS) assay for NMO is >80% and >99%, respectively. Detection of NMO/APQ4-IgG allows distinction of NMOSD from MS and is indicative of a relapsing disease, mandating initiation of immunosuppression, even after the first attack, thereby reducing attack frequency and disability in the future.

Useful For: Diagnosis of a neuromyelitis optica spectrum disorder (NMOSD) Diagnosis of autoimmune AQP4 channelopathy Diagnosis of neuromyelitis optica (NMO) Distinguishing NMOSD from multiple sclerosis early in the course of disease

Interpretation: A positive value is consistent with a neuromyelitis optica spectrum disorder (NMOSD) and justifies initiation of appropriate immunosuppressive therapy at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 3 to 6 months if NMOSD is suspected. This autoantibody is not found in healthy subjects.

Reference Values:
Negative

Clinical References: 1. Wingerchuk DM, Lennon VA, Lucchinetti CF, et al: The spectrum of neuromyelitis optica. Lancet Neurol 2007;6:805-815 2. Lennon VA, Wingerchuk DM, Kryzer TJ, et al: A serum autoantibody marker of neuromyelitis optica; distinction from multiple sclerosis. Lancet 2004;364:2106-2112 3. Pittock SJ, Weinshenker BG, Lucchinetti CF, et al: Neuromyelitis optica brain

lesions localized at sites of high aquaporin 4 expression. Arch Neurol 2006 Jul;63(7):964-968 4. McKeon A, Lennon VA, Lotze T, et al: CNS aquaporin-4 autoimmunity in children. Neurology 2008 Jul 8;71(2):93-100 5. Apiwattanakul M, Popescu BF, Matiello M, et al: Intractable vomiting as the initial presentation of NMO. Ann Neurol 2010 Nov;68(5):757-761 6. Waters P, McKeon A, Leite MI, et al: Multicentre comparison of aquaporin-4 IgG assays in NMO spectrum disorders. Neurology 2012;78:665-671 7. Fryer JP, Lennon VA, Pittock SJ, et al: AQP4 autoantibody assay performance in clinical laboratory service. Neurol Neuroimmunol Neuroinflammation 2014;1:e11

NMOFC 38325 Neuromyelitis Optica (NMO)/Aquaporin-4-IgG Fluorescence-Activated Cell Sorting (FACS) Assay, Spinal Fluid

Clinical Information: Neuromyelitis optica (NMO), sometimes called Devic disease or opticospinal multiple sclerosis (MS) is a severe, relapsing, autoimmune, inflammatory and demyelinating central nervous system disease that predominantly affects optic nerves and spinal cord.(1) The disorder is now recognized as a spectrum of autoimmunity (termed NMO spectrum disorders: NMOSD) targeting the astrocytic water channel aquaporin-4 (AQP4).(1,2) Brain lesions are observed in >60% of patients with NMOSD and approximately 10% will be MS-like.(3) Children tend to have greater brain involvement than adults and brain lesions are more symptomatic than is typical for adult patients.(4) Extensive cerebral white matter signal abnormalities are sometimes encountered, most commonly in children, and are sometimes associated with encephalopathy. Circumventricular organs (CVO; eg, area postrema) are preferentially involved. Symptoms and signs attributable to area postrema involvement include intractable hiccups, nausea and vomiting, and these may occur in isolation, herald the onset of NMO, or occur in association with the more classical optic neuritis or Longitudinally Extensive Transverse Myelitis (LETM).(5) Magnetic resonance imaging typically reveals large inflammatory spinal cord lesions involving 3 or more vertebral segments. During acute attacks, the cerebrospinal fluid contains inflammatory cells, but usually lacks evidence of intrathecal IgG synthesis. The clinical course is characterized by relapses of optic neuritis or transverse myelitis, or both. Many patients with NMOSD are misdiagnosed as having MS. Importantly, the prognosis and optimal treatments for the 2 diseases differ. NMOSD typically has a worse natural history than MS, with frequent and early relapses. NMOSD attacks are often severe resulting in a rapid accumulation of disability (blindness and paraplegia). More effective treatments combined with earlier and more accurate diagnosis has led to improved outcomes. Currently, in the AQP4-IgG era, 5 years after onset, approximately 30% of NMO patients will require a cane to walk and 10% will be wheelchair bound. Treatments for NMOSD include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Beta-interferon, a treatment promoted for MS, exacerbates NMOSD. Therefore, early diagnosis and initiation of NMO-appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. Skeletal muscle abnormalities with hyerCKemia have been reported in a few NMOSD patients. Recent reports indicate focal retinal vascular attenuation, inner nuclear layer thickening and microcystic edema in some NMO patients. Detection of AQP4-IgG by NMO/AQP4 FACS in cerebrospinal fluid (CSF) allows distinction from MS and is indicative of an NMOSD. Though serum is optimal for AQP4-IgG testing, occasionally physicians submit only CSF for testing. A previous study, based on our first-generation indirect immunofluorescence assay compared the frequencies of AQP4-IgG in serum and CSF. The positivity rate was greater for serum alone than for CSF alone.(6) However, testing of CSF was helpful when the serum was negative. Detection of AQP4-IgG in CSF allowed unambiguous distinction of NMO from MS. CSF testing offered the additional advantage of generally lacking the nonorgan-specific IgG autoantibodies (eg, antinuclear, antimitochondrial, and smooth muscle) that are common in serum of patients with NMO and also with classic paraneoplastic autoimmune disorders. Recent AQP4 FACS analysis of paired CSF and serum samples from 66 patients submitted for AQP4-IgG testing reveals a slightly better detection rate in serum (n=59) compared with CSF (n=55). All 7 patients who tested negative in serum also tested negative in CSF.

Useful For: Diagnosis of a neuromyelitis optica spectrum disorder (NMOSD) Diagnosis of

autoimmune AQP4 channelopathy Distinguishing NMOSD from multiple sclerosis early in the course of disease

Interpretation: A positive value is consistent with a neuromyelitis optica spectrum disorder (NMOSD) and justifies initiation of appropriate immunosuppressive therapy at the earliest possible time. This allows early initiation and maintenance of optimal therapy. This autoantibody is not found in healthy subjects.

Reference Values:
Negative

Clinical References: 1. Wingerchuk DM, Lennon VA, Lucchinetti CF, et al: The spectrum of neuromyelitis optica. Lancet Neurol 2007;6:805-815 2. Lennon VA, Wingerchuk DM, Kryzer TJ, et al: A serum autoantibody marker of neuromyelitis optica; distinction from multiple sclerosis. Lancet 2004;364:2106-2112 3. Pittock SJ, Weinshenker BG, Lucchinetti CF, et al: Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. Arch Neurol 2006 Jul; 63(7):964-968 4. McKeon A, Lennon VA, Lotze T, et al: CNS aquaporin-4 autoimmunity in children. Neurology 2008 Jul 8;71(2):93-100 5. Apiwattanakul M, Popescu BF, Matiello M, et al: Intractable vomiting as the initial presentation of NMO. Ann Neurol 2010 Nov;68(5):757-761 6. McKeon A, Pittock SJ, Lennon VA: CSF complements serum for evaluating paraneoplastic antibodies and NMO-IgG. Neurology 2011 Mar 22;76(12):1108-1110

NSESF
81796

Neuron-Specific Enolase (NSE), Spinal Fluid

Clinical Information: Enolase is a glycolytic enzyme that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate. Enolase exists in the form of several tissue-specific isoenzymes, consisting of homo or heterodimers of 3 different monomer-isoforms (alpha, beta, and gamma). Neuron-specific enolase (NSE) is a 78 kDa gamma-homodimer and represents the dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues. Its levels in other tissues, except erythrocytes, are negligible. The biological half-life of NSE in body fluids is approximately 24 hours. Due to this organ specificity, concentrations of NSE in serum or, more commonly, cerebrospinal fluid (CSF) are often elevated in diseases that result in relative rapid (hours/days to weeks, rather than months to years) neuronal destruction. Measurement of NSE in serum or CSF can therefore assist in the differential diagnosis of a variety of neuron-destructive and neurodegenerative disorders. The most common application is in the differential diagnosis of dementias, where elevated CSF concentrations support the diagnosis of rapidly progressive dementias, such as Creutzfeldt-Jakob disease (CJD). NSE might also have utility as a prognostic marker in neuronal injury. For example, there is increasing evidence that elevated serum NSE levels correlate with a poor outcome in coma, particularly when caused by hypoxic insult.

Useful For: An auxiliary test in the diagnosis of Creutzfeldt-Jakob disease An auxiliary test in the diagnosis of small cell lung carcinoma metastasis to central nervous system or leptomeninges

Interpretation: The diagnosis of Creutzfeldt-Jakob disease (CJD) is highly complex and involves clinical history and neurologic examination; detection of characteristic periodic sharp and slow wave complexes on electroencephalographs; magnetic resonance imaging (hyperintense basal ganglia); and exclusion of other possible causes of dementia, in addition to cerebrospinal fluid (CSF) examination. Consequently, patients are often diagnosed as having possible, probable, or definite CJD based upon the constellation of clinical findings. Detection of elevated CSF levels of NSE protein in these patients assists in the final diagnosis. A CSF neuron-specific enolase (NSE) within the normal reference range makes sporadic CJD very unlikely but can be observed in less rapidly progressive forms of CJD, such as variant CJD related to infection with prions that cause bovine spongiform encephalopathy. With the

previous Mayo Clinic-developed assay, in a group of carefully pre-selected patients with a probable diagnosis of CJD and an indeterminate or elevated NSE concentration in CSF, the respective diagnostic sensitivities of approximately 87% and approximately 80%, and diagnostic specificities of approximately 66% and approximately 83% were observed. Small cell lung carcinoma central nervous system metastases, particularly if they involve the leptomeninges, will lead to, usually substantial, elevations in CSF NSE concentrations.

Reference Values:
Normal: < or =15 ng/mL

Indeterminate: 15-30 ng/mL

Elevated: >30 ng/mL
Elevated results may indicate the need for additional workup. Possible causes may be neuron-specific enolase-secreting central nervous system/leptomeningeal tumor or rapid neuronal destruction from a variety of causes. In the context of dementia, elevated results may be suggestive of Creutzfeldt-Jakob disease.

Clinical References:

NSEI
70630

Neuron-Specific Enolase Immunostain, Technical Component Only

Clinical Information: Neuron-specific enolase (NSE) is expressed in neuronal or neuroendocrine cells, such as neurons in the brain, ganglion cells in the wall of the gastrointestinal tract, nerves, and islet cells of the pancreas. It can be used to confirm neuroendocrine differentiation in tumors such as carcinoids.

Useful For: Characterization of neuroendocrine differentiation in tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Suhani, Ali S, Desai G, et al: Primary neuroendocrine carcinoma breast: our experience. Breast Dis. 2014;34(3):95-99 2. You H, Kim YI, Im SY, et al. Immunohistochemical study of central neurocytoma, subependymoma, and subependymal giant cell astrocytoma. J Neurooncol. 2005:74(1):1-8 3. Anstey A, Cerio R, Ramnarain N, et al. Desmoplastic malignant melanoma. An immunocytochemical study of 25 cases. Am J Dermatopathol. 1994;16:14-22 4. Cras P, Martin JJ, Gheuens J. Gamma-enolase and glial fibrillary acidic protein in nervous system tumors. An immunohistochemical study using specific monoclonal antibodies. Acta Neuropathol. 1988;75:377-384 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

NSE
80913

Neuron-Specific Enolase, Serum

Clinical Information: Enolase is a glycolytic enzyme that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate. Enolase exists in the form of several tissue-specific

isoenzymes, consisting of homo or heterodimers of 3 different monomer-isoforms (alpha, beta, and gamma). Neuron-specific enolase (NSE) is a 78 kDa gamma-homodimer and represents the dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues. Its levels in other tissues, except erythrocytes, are negligible. The biological half-life of NSE in body fluids is approximately 24 hours. Due to this organ-specificity, concentrations of NSE in serum or, more commonly, cerebrospinal fluid (CSF) are often elevated in diseases that result in relative rapid (hours/days to weeks rather than months to years) neuronal destruction. Measurement of NSE in serum or CSF can therefore assist in the differential diagnosis of a variety of neuron-destructive and neurodegenerative disorders. The most common application is in the differential diagnosis of dementias, where elevated CSF concentrations support the diagnosis of rapidly progressive dementias, such as Creutzfeldt-Jacob Disease. NSE may also have utility as a prognostic marker in neuronal injury. For example, there is increasing evidence that elevated serum NSE levels correlate with a poor outcome in coma, particularly when caused by hypoxic insult. Neuron-specific enolase is frequently overexpressed by neural crest-derived tumors. Up to 70% of patients with small cell lung carcinoma (SCLC) have elevated serum NSE concentrations at diagnosis. Approximately 90% of patients with advanced SCLC will have serum levels above the healthy reference range. Other neuroendocrine tumors with frequent expression of NSE include carcinoids (up to 66% of cases), islet cell tumors (typically <40% of cases), and neuroblastoma (exact frequency of NSE expression unknown). NSE levels in NSE-secreting neoplasms correlate with tumor mass and tumor metabolic activity. High levels have, therefore, some negative prognostic value. Falling or rising levels are often correlated with tumor shrinkage or recurrence, respectively.

Useful For: A follow-up marker in patients with neuron-specific enolase-secreting tumors of any type An auxiliary test in the diagnosis of small cell lung carcinoma An auxiliary test in the diagnosis of carcinoids, islet cell tumors, and neuroblastomas An auxiliary tool in the assessment of comatose patients

Interpretation: Serum neuron-specific enolase (NSE) measurement has its greatest utility in the follow-up of patients with tumors of any type that have been shown to secrete NSE. With successful treatment, serum concentrations should fall with a half-life of approximately 24 hours. Persistent NSE elevations in the absence of other possible causes (see Cautions) suggest persistent tumor. Rising levels indicate tumor spread or recurrence in patients who had previously become NSE negative. In the context of a patient with a lung mass, disseminated malignancy of unknown origin, or symptoms suggestive of paraneoplastic disease without identifiable tumor, elevated NSE levels suggest an underlying small cell lung carcinoma (SCLC). In patients with suspected carcinoid, islet cell tumor, or neuroblastoma, who have no clear elevations in the primary tumor markers used to diagnose these conditions, an elevated serum NSE level supports the clinical suspicion. -Carcinoid: chromogranin A, urinary 5-hydroxyindoleacetic acid, serum/blood 5-hydroxytryptamine (serotonin) -Islet cell tumors: variety of peptide and amine-derived hormones, chromogranin A -Neuroblastoma: vanillylmandelic acid and homovanillic acid When considered alongside established outcome predictors of coma, such as Glasgow coma scale and other clinical predictors (papillary light responses, corneal reflexes, motor responses to pain, myoclonus, status epilepticus), electroencephalogram, sensory evoked potentials, measurement of serum NSE concentrations provides additional information. Elevated levels are indicative of a poor outcome. Currently, no established algorithms exist to combine serum NSE concentrations and the various other predictors into a composite score that gives clear predictive outcome information. The NSE measurement, therefore, needs to be considered in a qualitative or semi-quantitative fashion and carefully weighed against other predictors by a physician experienced in examining and managing coma patients.

Reference Values:

< or =15 ng/mL

Serum markers are not specific for malignancy, and values may vary by method.

Clinical References:

NCLGP
608014

Neuronal Ceroid Lipofuscinosis (Batten Disease) Gene Panel, Varies

Clinical Information: Neuronal ceroid lipofuscinoses (NCL) are a subset of lysosomal storage diseases that involve defective cellular processing of lipids. NCL are clinically characterized by epilepsy, intellectual and motor decline, and blindness. Electron microscopy typically shows a characteristic accumulation of granular osmophilic deposits (GROD), curvilinear profiles (CVB), or fingerprint profiles (FP). Enzymatic testing may show deficiency in palmitoyl-protein thioesterase 1 (PPT1), tripeptidyl-peptidase 1 (TPP1), or cathepsin D (CTSD). Currently there are at least 14 genetically distinct forms. Age of onset and clinical features can be variable, from congenital to adult onset. NCL is typically inherited in an autosomal recessive manner, although one adult onset form (ANCL; DNAJC5 gene) has been shown to be autosomal dominant.

Useful For: Follow up for abnormal biochemical or electron microscopy results suspicious for neuronal ceroid lipofuscinoses (NCL) Establishing a molecular diagnosis for patients with NCL Identifying variations within genes known to be associated with NCL, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 2. Mole SE, Cotman SL: Genetics of the neuronal ceroid lipofuscinoses (Batten disease). Biochim Biophys Acta. 2015;1852(10PtB):2237-2241 3. Cooper JD, Tarczyluk MA, Nelvagal HR: Towards a new understanding of NCL pathogenesis. Biochim Biophys Acta. 2015;1852(10PtB):2256-2261 4. Williams RE, Mole SE: New nomenclature and classification scheme for the neuronal ceroid lipofuscinoses. Neurology. 2012;79(2):183-191 5. Mole SE, Williams RE: Neuronal ceroid-lipofuscinoses. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington. , Seattle; 2001. Updated August 1, 2013. Accessed October 28, 2020. Available at www.ncbi.nlm.nih.gov/books/NBK1428/

NCLBS
616838

Neuronal Ceroid Lipofuscinosis, Two-Enzyme Panel, Blood Spot

Clinical Information: The neuronal ceroid lipofuscinoses (NCL) comprise a group of recessively inherited neurodegenerative disorders involved in lysosomal protein catabolism. Clinically they are characterized by vision loss, seizures, developmental regression, behavioral changes, movement disorders, and distinguished from other neurodegenerative disorders by the accumulation of auto fluorescent storage material in the brain and tissues. Although at least 13 different genes have been identified, the NCL have traditionally been categorized based on the age of onset of symptoms: infantile, late-infantile, juvenile, and adult. Infantile (CLN1) and late-infantile NCL (CLN2) are caused by defects in palmitoyl-protein thioesterase 1 (PPT1) and tripeptidyl peptidase 1 (TPP1), respectively. Deficiency of tripeptidyl peptidase is also a cause of autosomal recessive spinocerebellar ataxia-7. Children affected by infantile NCL (CLN1) typically have normal growth and development until about 6 to 12 months of age. Slowed head

growth occurs at around 9 months followed by psychomotor degeneration, seizures, and progressive macular degeneration leading to blindness by the age 2 years. CLN1 is caused by a deficiency of the lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1), which cleaves long-chain fatty acids (usually palmitate) from cysteine residues. Electron microscopy shows granular osmophilic deposits in most cell types. PPT1 is thought to play an active role in various cell processes including apoptosis, endocytosis, and lipid metabolism. The late infantile form of NCL (CLN2) is primarily caused by deficiency of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1), which cleaves tripeptides from the N-terminus of polypeptides. Tissue damage results from the defective degradation and consequent accumulation of storage material with a curvilinear profile by electron microscopy. There is widespread loss of neuronal tissue especially in the cerebellum and hippocampal region. Disease onset occurs at 2 to 4 years of age with seizures, ataxia, myoclonus, psychomotor retardation, vision loss, and speech impairment. Diagnostic strategy depends on the age of onset of symptoms. In children presenting between the ages 0 to 4 years, enzyme assay of PPT1 and TPP1 is an appropriate first step. For other patients suspected of having an NCL, molecular genetic testing of CLN genes is available; see NCLGP / Neuronal Ceroid Lipofuscinosis (Batten Disease) Gene Panel, Varies.

Useful For: Supporting the biochemical diagnosis of two neuronal ceroid lipofuscinoses, CLN1 and CLN2 This test is not useful for carrier detection.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular genetic analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
Palmitoyl-protein thioesterase 1: >10.0 nmol/mL/h
Tripeptidyl peptidase 1: >27.0 nmol/mL/h

An interpretative report will be provided.

Clinical References: 1. Hofmann SL, Peltonen L. The neuronal ceroid lipofuscinoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 18, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225548100 2. Kohlschutter A, Schulz A, Bartsch U, Storch S. Current and emerging treatment strategies for neuronal ceroid lipofuscinoses. CNS Drugs. 2019;33(4):315-325. doi:10.1007/s40263-019-00620-8

NCLW
616839

Neuronal Ceroid Lipofuscinosis, Two-Enzyme Panel, Leukocytes

Clinical Information: The neuronal ceroid lipofuscinoses (NCL) comprise a group of recessively inherited neurodegenerative disorders involved in lysosomal protein catabolism. Clinically they are characterized by vision loss, seizures, developmental regression, behavioral changes, movement disorders, and distinguished from other neurodegenerative disorders by the accumulation of auto fluorescent storage material in the brain and tissues. Although at least 13 different genes have been identified, the CLN have traditionally been categorized based on the age of onset of symptoms: infantile, late-infantile, juvenile, and adult. Infantile (CLN1) and late-infantile NCL (CLN2) are caused by defects in palmitoyl-protein thioesterase 1 (PPT1) and tripeptidyl peptidase 1 (TPP1), respectively. Deficiency of tripeptidyl peptidase is also a cause of autosomal recessive spinocerebellar ataxia-7.

Children affected by infantile NCL (CLN1) typically have normal growth and development until about 6 to 12 months of age. Slowed head growth occurs at around 9 months followed by psychomotor degeneration, seizures, and progressive macular degeneration leading to blindness by the age 2 years. CLN1 is caused by a deficiency of the lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1), which cleaves long-chain fatty acids (usually palmitate) from cysteine residues. Electron microscopy shows granular osmophilic deposits in most cell types. PPT1 is thought to play an active role in various cell processes including apoptosis, endocytosis, and lipid metabolism. The late infantile form of NCL (CLN2) is primarily caused by deficiency of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1), which cleaves tripeptides from the N-terminus of polypeptides. Tissue damage results from the defective degradation and consequent accumulation of storage material with a curvilinear profile by electron microscopy. There is widespread loss of neuronal tissue especially in the cerebellum and hippocampal region. Disease onset occurs at 2 to 4 years of age with seizures, ataxia, myoclonus, psychomotor retardation, vision loss, and speech impairment. Diagnostic strategy depends on the age of onset of symptoms. In children presenting between the ages 0 to 4 years, enzyme assay of PPT1 and TPP1 is an appropriate first step. For other patients suspected of having an NCL, molecular genetic testing of CLN genes is available; see NCLGP / Neuronal Ceroid Lipofuscinosis (Batten Disease) Gene Panel, Varies.

Useful For: Supporting the biochemical diagnosis of two neuronal ceroid lipofuscinoses, CLN1 and CLN2 in whole blood specimens This test is not useful for carrier detection.

Interpretation: Abnormal results are not sufficient to establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on this assay, additional biochemical or molecular genetic analyses are required. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro, confirmatory studies (enzyme assay, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
Palmitoyl-protein thioesterase 1: >10.0 nmol/h/mg protein
Tripeptidyl peptidase 1: >20.0 nmol/h/mg protein

An interpretative report will be provided.

Clinical References: 1. Hofmann SL, Peltonen L. The neuronal ceroid lipofuscinoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; Accessed July 17, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225548100 2. Kohlschutter A, Schulz A, Bartsch U, Storch S. Current and emerging treatment strategies for neuronal ceroid lipofuscinoses. CNS Drugs. 2019;33(4):315-325. doi:10.1007/s40263-019-00620-8

NEUD1 622267 Neuronal Differentiation 1 (NeuroD1), Technical Component only

Clinical Information: Neuronal Differentiation 1 (NeuroD1) is expressed in a variety of cancers including but not limited to colorectal, pancreatic, small cell (of cervix and lung), and neuroendocrine lung carcinomas and may play a major role in neuroendocrine differentiation. There are four major subclasses of small cell carcinoma of lung and cervix, one of which dominantly expresses NeuroD1. The subclassification of small cell lung carcinomas could provide distinct therapeutic options.

Useful For: Subclassification of small cell lung carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Li Z, He Y, Li Y, et al. NeuroD1 promotes tumor cell proliferation and tumorigenesis by directly activating the pentose phosphate pathway in colorectal carcinoma. Oncogene 2021 40:6738-6747 2. Wang Y, Su D, Gao L, et al. Effect of NeuroD gene silencing on the migration and invasion of human pancreatic cancer cells PANC-1. Cell Biochem Biophys. 2014 69:487-494 3. Kim G, Kim M, Nam EJ, Lee JY, Park E. Application of Small Cell Lung Cancer Molecular Subtyping Markers to Small Cell Neuroendocrine Carcinoma of the Cervix: NEUROD1 as a Poor Prognostic Factor. Am J Surg Pathol. 2024;48(3):364-372 4. Osborne J, Larsen J, Shields M, et al. NeuroD1 regulates survival and migration of neuroendocrine lung carcinomas via signaling molecules TrkB and NCAM. Proc Natl Acad Sci USA. 2013 110:6524-6529 5. Gay C, Stewart C, Park E, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell 2021 39:3(3)46-60 6. Baine M, Hsieh M, Lai V, et al: SCLC subtypes defined by ASCL1, NEUROD1, POU2F3, and YAP1: A comprehensive immunohistochemical and histopathologic characterization. J Thorc Oncol. 2020;15(12):1823-1835

NSAIP
621136

Neurosyphilis IgG Antibody Index with VDRL, Serum and Spinal Fluid

Clinical Information: Neurosyphilis (NS) caused by the spirochete Treponema pallidum can occur at any stage of syphilis. Currently the Centers for Disease Control and Prevention estimates that approximately 2% of patients with syphilis will develop neuroinvasive syphilis if untreated. Early stages of NS may be asymptomatic or symptomatic, with patients typically exhibiting classic meningitis symptoms. Patients with late-stage NS patients may present with dementia paralytica or tabes dorsalis. Other manifestations of neuroinvasive syphilis include ocular or otologic syphilis, which can occur at any stage, however are more common during early NS. The diagnosis of NS is challenging due to a number of factors, including the lack of consensus on the relevance of abnormal cerebrospinal fluid (CSF) findings in patients who are seropositive for syphilis but neurologically asymptomatic. With respect to diagnostic testing, numerous treponemal and non-treponemal (lipoidal) assays have been evaluated, alongside CSF protein and pleocytosis findings, however direct comparisons of these assays are limited. The VDRL assay is currently the only assay with US Food and Drug Administration (FDA) clearance as an aid in the diagnosis of NS, however the sensitivity and specificity of this non-treponemal (lipoidal) assay is highly variable, ranging from 66.7% to 85.7% and 78.2% to 86.7%, respectively. Although no treponemal assay has FDA clearance as an aid for diagnosis of NS, studies evaluating the fluorescent treponemal antibody absorption (FTA-ABS) assay performed in CSF from patients with definitive NS was associated with a sensitivity of 90.9% to 100%. Specificity of this approach ranged from 55% to 100% however, primarily due to the issue of passive diffusion of serum antibodies across the blood-brain barrier. The NS antibody index assay corrects for passive diffusion across an inflamed blood-brain barrier by measuring quantitative levels of anti-T pallidum antibodies in serum and CSF and normalizing those to total IgG and albumin in both specimen sources. A positive NS antibody index indicates true intrathecal antibody synthesis of antibodies to T. pallidum, which alongside clinical and exposure history can be used to establish a diagnosis of NS. All NS antibody index positive samples are also reflexed for testing by the VDRL assay to acquire a semi-quantitative titer. The NS antibody index should only be ordered in patients who are seropositive for antibodies to T pallidum in blood, who also present with neurologic manifestations suspicious for NS or who are at risk for asymptomatic NS.

Useful For: Aid in the diagnosis of neuroinvasive syphilis

Interpretation: Negative: No antibodies to syphilis (Treponema pallidum) detected in cerebrospinal fluid (CSF). A negative result in a patient with appropriate exposure history and symptoms consistent with neurosyphilis should not solely be used to exclude infection. If not already performed, testing for antibodies to T pallidum in serum should be ordered. Reactive: Supplemental testing to determine a syphilis IgG Ab Index in CSF has been ordered. Diagnosis of neurosyphilis should not be established solely based on a reactive screening result.

Reference Values:

NEUROSYPHILIS SCREEN, IgG, SPINAL FLUID:
Negative
Reference values apply to all ages.

NEUROSYPHILIS IgG ANTIBODY INDEX:
Antibody Index: 0.6-1.2

Reference values apply to all ages.

VDRL TITER, SPINAL FLUID:
Negative

Reference values apply to all ages.

Clinical References: 1. Alberto C, Deffert C, Lambeng N, et al. Intrathecal synthesis index of specific anti-Treponema IgG: A new tool for the diagnosis of syphilis. Microbiol Spectr. 2022;10(1):e01477-21 2. Papp JR, Park IU, Fakile Y, Pereira L, Pillay A, Bolan GA. CDC Laboratory Recommendations for Syphilis Testing, United States, 2024. MMWR Recomm Rep. 2024;73(1):1-32 3. Klein M, Angstwurm K, Esser S, et al. German guidelines on the diagnosis and treatment of neurosyphilis. Neurol Res Pract. 2020;2:33 4. We S, Ye F, Wang Y, Li D. Neurosyphilis: insights into its pathogenesis, susceptibility, diagnosis, treatment and prevention. Front Neuro. 2024;14:1340321 5. Reiber H, Lange P. Quantification of virus-specific antibodies in cerebrospinal fluid and serum: sensitive and specific detection of antibody synthesis in brain. Clin Chem. 1991;37(7):1153-1160

NSAI
621141

Neurosyphilis IgG, Antibody Index, Spinal Fluid

Clinical Information: Neurosyphilis (NS) caused by the spirochete Treponema pallidum can occur at any stage of syphilis. Currently the Centers for Disease Control and Prevention estimates that approximately 2% of patients with syphilis will develop neuroinvasive syphilis if untreated. Early stages of NS may be asymptomatic or symptomatic, with patients typically exhibiting classic meningitis symptoms. Patients with late-stage NS may present with dementia paralytica or tabes dorsalis. Other manifestations of neuroinvasive syphilis include ocular or otologic syphilis, which can occur at any stage, however are more common during early NS. The diagnosis of NS is challenging due to a number of factors, including the lack of consensus on the relevance of abnormal cerebrospinal fluid (CSF) findings in patients who are seropositive for syphilis but neurologically asymptomatic. With respect to diagnostic testing, numerous treponemal and non-treponemal (lipoidal) assays have been evaluated, alongside CSF protein and pleocytosis findings, however direct comparisons of these assays are limited. The Venereal Diseases Research Laboratory (VDRL) assay is currently the only assay with US Food and Drug Administration (FDA) clearance as an aid in the diagnosis of NS, however the sensitivity and specificity of this non-treponemal (lipoidal) assay is highly variable, ranging from 66.7% to 85.7% and 78.2% to 86.7%, respectively. Although no treponemal assay has FDA clearance as an aid for diagnosis of NS, studies evaluating the fluorescent treponemal antibody absorption (FTA-ABS) assay performed in CSF from patients with definitive NS was associated with a sensitivity of 90.9% to 100%. Specificity of this approach ranged from 55% to 100% however, primarily due to the issue of passive diffusion of serum antibodies across the blood-brain barrier. The NS antibody index assay corrects for passive diffusion

across an inflamed blood-brain barrier by measuring quantitative levels of anti-T pallidum antibodies in serum and CSF and normalizing those to total IgG and albumin in both specimen sources. A positive NS antibody index indicates true intrathecal antibody synthesis of antibodies to T pallidum, which alongside clinical and exposure history can be used to establish a diagnosis of NS. All NS antibody index positive samples are also reflexed for testing by the VDRL assay to acquire a semi-quantitative titer. The NS antibody index should only be ordered in patients who are seropositive for antibodies to T pallidum in blood, who also present with neurologic manifestations suspicious for NS or who are at risk for asymptomatic NS.

Useful For: Aid in the diagnosis of neuroinvasive syphilis as part of a profile

Interpretation: Negative: Results indicate lack of intrathecal antibody synthesis to syphilis (Treponema pallidum). This suggests the absence of neurosyphilis. The initial screen reactive result may be due to anti-syphilis antibodies present in the cerebrospinal fluid (CSF) due to increased permeability of the blood-brain barrier or transient introduction during lumbar puncture. Equivocal: Possible intrathecal antibody synthesis to syphilis (T pallidum) detected. Results should be correlated with exposure history and clinical presentation to establish a diagnosis of neurosyphilis. Sample has been reflexed for VDRL testing to establish a titer. False positive results may occur in patients with other spirochete infections (eg, Borrelia, Leptospira). Positive: Results indicate the presence of intrathecal antibody synthesis to syphilis (T pallidum), suggesting neurosyphilis. Results should be correlated with exposure history and clinical presentation to establish the diagnosis. Sample has been reflexed to VDRL testing to establish a titer. False positive results may occur in patients with other spirochete infections (eg, Borrelia, Leptospira). Invalid: Result is due to abnormally elevated total IgG levels in CSF. This may be due to passive diffusion through the blood-brain barrier or contamination of the CSF with blood during a traumatic lumbar puncture. Consider repeat testing if clinically indicated.

Reference Values:
Only orderable as part of a profile. For more information see NSAIP / Neurosyphilis IgG Antibody Index with VDRL, Serum and Spinal Fluid.

Antibody Index: 0.6-1.2

Reference values apply to all ages.

Clinical References: 1. Alberto C, Deffert C, Lambeng N, et al. Intrathecal Synthesis Index of Specific Anti-Treponema IgG: A New Tool for the Diagnosis of Syphilis. Microbiol Spectr. 2022;10(1):e01477-21 2. Papp JR, Park IU, Fakile Y, Pereira L, Pillay A, Blan GA. CDC Laboratory Recommendations for Syphilis Testing, United States. MMWR Recomm Rep. 2024;73(1):1-32 3. Klein M, Angstwurm K, Esser S, et al. German guidelines on the diagnosis and treatment of neurosyphilis. Neuro Res Pract. 2020;2(33):1-9 4. Wu S, Ye F, Wang Y, Li D. Neurosyphilis: insights into its pathogenesis, susceptibility, diagnosis, treatment and prevention. Front Neurol. 2024;14:1340321 5. Reiber H, Lange P. Quantification of virus-specific antibodies in cerebrospinal fluid and serum:sensitive and specific detection of antibody synthesis in brain. Clin Chem. 1991;37(7):1153-1160

FNEU2
75905

Neurotensin

Clinical Information: Neurotensin is a 13 amino acid peptide produced primarily by endocrine cells of the ileal mucosa. Physiological actions of Neurotensin include hypertension, vasodilation, hyperglycemia, and inhibition of gastric motility. Its C-terminus is similar to Angiotensin I. It is a potent analgesic affecting hypothermia, muscle relaxation, and decreased motor activity. Pancreatic Polypeptide secretion is strongly stimulated by Neurotensin. Neurotensin appears to cause the release of Luteinizing Hormone-Releasing Hormone and Corticotropin Releasing Hormone effecting the release

of Luteinizing Hormone, Follicle Stimulating Hormone, and ACTH but not Thyroid Stimulating Hormone or Growth Hormone. Neurotensin also stimulates pancreatic bicarbonate and intestinal secretion. Neurotensin levels are stimulated by food and Bombesin. Elevated levels have been found in pancreatic endocrine tumors, Oat Cell, Squamous, and Adeno Carcinomas. Elevated levels have been found to cause watery diarrhea.

Reference Values:
50-100 pg/mL

FNEU
91688

Neurotransmitter Metabolites (5HIAA, HVA, 3OMD) (CSF)

Clinical Information: CSF Neurotransmitter Metabolites (5HIAA, HVA, 3OMD) (NC04) is useful for diagnosis of certain disorders of neurotransmitter metabolism. This testing may also be used for assessment of Variants of Uncertain Significance (VUS) identified during genetic testing (e.g. Next Generation Sequencing or Capillary Sequencing Testing). CLINICAL Monoamine metabolite testing includes homovanillic acid (HVA), 3-O-methyl-Dopa (3-OMD), and 5-hydroxyindole acetic acid (5-HIAA). This test is useful in diagnosing pediatric neurotransmitter diseases affecting dopamine and serotonin metabolism in the brain. Inborn errors of metabolism and various drugs may lead to severe imbalances and disturbances in these neurotransmitter systems that are reflected by changes in the concentration of monoamines metabolites in CSF. Primary inherited defects involve deficiencies in tyrosine and tryptophan hydroxylase, aromatic amino acid decarboxylase, monoamine oxidase, dopamine beta hydroxylase and the dopamine transwporter. Other defects in the biopterin synthesis pathway may also affect dopamine and serotonin metabolism. These disorders are characterized by a wide range of symptoms that may include developmental delay, mental disability, behavioral disturbances, dystonia, seizures, encephalopathy, athetosis and ptosis.

Interpretation:

Reference Values:

Age (years)	5HIAA (nmol/L)	HVA (nmol/L)	3-O-MD (nmol/L)
0-0.2	208-1159	337-1299	<300
0.2-0.5	179-711	450-1132	<300
0.5-2.0	129-520	294-1115	<300
2.0-5.0	74-345	233-928	<150
5.0-10	66-338	218-852	<100
10-15	67-189	167-563	<100
Adults	67-140	145-324	<100

Interpretation performed by Keith Hyland, Ph.D.

Note: If test results are inconsistent with the clinical presentation, please call our laboratory to discuss the case and/or submit a second sample for confirmatory testing.

FNTSM
91940

Neurotransmitter Profile 3

Reference Values:

5-Methyltetrahydrofolate Age (years)	5MTHF (nmol/L)
0-0.2	40-240
0.2-0.5	40-240
0.5-2.0	40-187
2.0-5.0	40-150
10-15	40-128
Adults	40-120
Neurotransmitter Metabolites/Amines Age (years)	5HIAA (nmol/L)
0-0.2	208-1159
0.2-0.5	179-711
0.5-2.0	129-520
2.0-5.0	74-345
5.0-10	66-338
10-15	67-189
Adults	67-140
Neurotransmitter Metabolites/Amines Age (years)	5HIAA (nmol/L)
0-0.2	208-1159
0.2-0.5	179-711
0.5-2.0	129-520
2.0-5.0	74-345
5.0-10	66-338
10-15	67-189
Adults	67-140
Tetrahydrobiopterin/Neopterin Profile Age (years)	BH4 (nmol/L)
0-0.2	40-105
0.2-0.5	23-98
0.5-2.0	18-58
2.0-5.0	18-50
5.0-10	9-40
10-15	9-32
Adults	10-30

NADF
35312

Newborn Aneuploidy Detection, FISH, Blood

Clinical Information: Up to 95% of chromosomal abnormalities diagnosed prenatally involve aneuploidy (gain or loss of whole chromosome) of chromosomes 13, 18, 21, X, and Y. In liveborn infants, about 8 in 1000 have a major chromosome anomaly, of which 6.5 in 1000 involve aneuploidy of 1 of these 5 chromosomes. Diagnosis of chromosomal disorders can be performed by chromosome analysis of uncultured blood, standard chromosome study, and the technique utilizing fluorescence in situ hybridization (FISH) based on interphase cells. Standard chromosome analysis takes 3 to 10 days and analysis from uncultured newborn blood is often unsatisfactory and labor-intensive. FISH-based methods facilitate rapid diagnosis of aneuploidy and may be helpful in medically urgent evaluations of newborn infants suspected to have aneuploidy of any of these chromosomes. This test does not detect chromosomal aneuploidies other than 13, 18, 21, X, and Y or any structural anomaly that does not result in gain of these chromosomes. Low levels of mosaicism involving chromosomes 13, 18, 21, X, or Y may not be detected by this assay.

Useful For: Screening for chromosomal aneuploidies of chromosomes 13, 18, 21, X, and Y in newborn peripheral blood specimens

Interpretation: When no significant abnormalities are detected by the targeted fluorescence in situ hybridization (FISH) probes, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, recommendations for additional testing, and contact information for the laboratory if there are additional questions.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Jalal SM, Law ME. Detection of newborn aneuploidy by interphase fluorescence in situ hybridization. Mayo Clin Proc. 1997;72(8):705-710 2. Cassidy SB, Allanson JE: Management of Genetic Syndromes. 2nd ed. John Wiley and Sons; 2005:557 3. Sheets KB, Crissman BG, Feist CD, et al. Practice guidelines for communicating a prenatal or postnatal diagnosis of Down syndrome: recommendations of the national society of genetic counselors. J Genet Couns. 2011;20(5):432-444 4. Carroll J, Wigby K, Murray S. Genetic testing strategies in the newborn. J Perinatol. 2020:40(7):1007-1016

NIU
8626

Nickel, 24 Hour, Urine

Clinical Information: Nickel (Ni) is a highly abundant element with a silvery-white appearance. Nickel is frequently combined with other metals to form alloys and is essential for the catalytic activity of some plant and bacterial enzymes (including in several pathogenic and symbiotic species in humans) but has no known role in humans. Most nickel is used to make stainless steel. Nickel and its compounds have no characteristic odor or taste. Ni compounds are used for Ni plating, to color ceramics, to make some batteries, and as catalysts that increase the rate of chemical reactions. One of the most toxic nickel compounds is nickel carbonyl, Ni(CO)4, which is used as a catalyst in petroleum refining and in the plastics industry, is frequently employed in the production of metal alloys (which are popular for their anticorrosive and hardness properties), in nickel-cadmium rechargeable batteries, and is used as a catalyst in hydrogenation of oils. Ni(CO)4 is very toxic and is lipid-soluble, allowing it to cross cell membranes. Occupational exposure to Ni occurs primarily via inhalation of Ni compounds. Inhalation of dust high in Ni content has been associated with development of lung and nasal cancer. Food is the major source of exposure to Ni. Foods naturally high in Ni concentrations include chocolate, soybeans, nuts, and oatmeal. Individuals may also be exposed to Ni by breathing air, drinking water, or smoking tobacco containing Ni. Stainless steel and coins contain Ni. Some jewelry is plated with Ni or made from Ni alloys. Patients

may be exposed to Ni in implanted devices including joint prostheses, sutures, clips, and screws made from Ni-containing alloys. The most common harmful health effect of Ni in humans is an allergic reaction. Approximately 10% to 20% of the population is sensitive to Ni. The most serious harmful health effects from exposure to Ni, such as chronic bronchitis, reduced lung function, and cancer of the lung and nasal sinus, have occurred in people who have breathed dust containing certain Ni compounds while working in Ni refineries or nickel-processing plants. Urine is the specimen of choice for the determination of Ni exposure, but serum concentrations can be used to verify an elevated urine concentration. Patients undergoing dialysis are exposed to Ni and accumulate Ni in blood and other organs; there appear to be no adverse health effects from this exposure. Hypernickelemia has been observed in patients undergoing kidney dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended.

Useful For: Preferred test for biomonitoring patients for nickel exposure to minimize any potential diurnal variation

Interpretation: Values of 6.0 mcg/24-hour specimen and higher represent possible environmental or occupational exposure. Hypernickelemia, in the absence of exposure, may be an incidental finding or could be due to specimen contamination.

Reference Values:
0-17 years: Not established
> or =18 years: <6.0 mcg/24h

Clinical References: 1. Moreno ME, Acosta-Saavedra LC, Mez-Figueroa D, et al. Biomonitoring of metal in children living in a mine tailings zone in Southern Mexico: A pilot study. Int J Hyg Environ Health. 2010;213(4):252-258. doi:10.1016/j.ijheh.2010.03.005 2. Schulz C, Angerer J, Ewers U, Heudorf U, Wilhelm M. Human Biomonitoring Commission of the German Federal Environment Agency: Revised and new reference values for environmental pollutants in urine or blood of children in Germany derived from the German Environmental Survey on Children 2003-2006 (GerES IV). Int J Hyg Environ Health. 2009;212(6):637-647. doi:10.1016/j.ijheh.2009.05.003 3. US Department of Health and Human Services: Toxicological profile for nickel. Agency for Toxic Substances and Disease Registry; 2005. Accessed March 2020. Available at www.atsdr.cdc.gov/ToxProfiles/tp15.pdf 4. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018 5. Zambelli B, Ciurli S. Nickel and human health. In: Sigel A, Sigel H, Sigel R, eds. Interrelations between Essential Metal Ions and Human Diseases. Springer; 2013:321-357. Metal Ions in Life Sciences. Vol 13

NIS
8622

Nickel, Serum

Clinical Information: Nickel (Ni) is a highly abundant element with a silvery-white appearance. Nickel is frequently combined with other metals to form alloys and is essential for the catalytic activity of some plant and bacterial enzymes (including in several pathogenic and symbiotic species in humans) but has no known role in humans. Nickel and its compounds have no characteristic odor or taste. Ni compounds are used for Ni plating, to color ceramics, to make some batteries, and as substances known as catalysts that increase the rate of chemical reactions. One of the most toxic Ni compounds is nickel carbonyl, Ni(CO)4, which is used as a catalyst in petroleum refining and in the plastics industry, is frequently employed in the production of metal alloys such as stainless steel (which are popular for their anticorrosive and hardness properties), in nickel-cadmium rechargeable batteries, and is used as a catalyst in hydrogenation of oils. Ni(CO)4 is very toxic and is lipid-soluble, allowing it to cross cell membranes. Occupational exposure to Ni occurs primarily via inhalation of Ni compounds. Inhalation of dust high in Ni content has been associated with development of lung and nasal cancer. Food is the

major source of exposure to Ni. Foods naturally high in Ni include chocolate, soybeans, nuts, and oatmeal. Individuals may also be exposed to nickel by breathing air, drinking water, or smoking tobacco containing Ni. Stainless steel and coins contain Ni. Some jewelry is plated with Ni or made from Ni alloys. Patients may be exposed to Ni in artificial body parts made from Ni-containing alloys. The most common harmful health effect of Ni in humans is an allergic reaction. Approximately 10% to 20% of the population is sensitive to Ni. The most serious harmful health effects from exposure to Ni, such as chronic bronchitis, reduced lung function, and cancer of the lung and nasal sinus, have occurred in people who have breathed dust containing certain Ni compounds while working in Ni refineries or nickel-processing plants. Urine is the specimen of choice for the determination of Ni exposure, but serum concentrations can be used to verify an elevated urine concentration. Patients undergoing dialysis are exposed to Ni and accumulate Ni in blood and other organs; there appear to be no adverse health effects from this exposure. Hypernickelemia has been observed in patients undergoing kidney dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended.

Useful For: Confirmation of an elevated urinary nickel concentration This test is not useful for the investigation of nickel hypersensitivity.

Interpretation: Values 2.0 ng/mL and higher represent possible environmental or occupational exposure to nickel (Ni). Toxic Ni concentrations are greater or equal to 10 ng/mL. Normal Ni values are based on a Mayo Clinic study using healthy volunteers. Toxic values have been deduced from observation and unpublished internal study. Clinical concern about Ni toxicity should be limited to patients with potential for exposure to toxic Ni compounds. Hypernickelemia, in the absence of exposure, may be an incidental finding or could be due to specimen contamination.

Reference Values:
<2.0 ng/mL

Clinical References: 1. Moreno ME, Acosta-Saavedra LC, Mez-Figueroa D, et al. Biomonitoring of metal in children living in a mine tailings zone in Southern Mexico: A pilot study. Int J Hyg Environ Health. 2010;213(4):252-258. doi:10.1016/j.ijheh.2010.03.005 2. Schulz C, Angerer J, Ewers U, Heudorf U, Wilhelm M, Human Biomonitoring Commission of the German Federal Environment Agency. Revised and new reference values for environmental pollutants in urine or blood of children in Germany derived from the German Environmental Survey on Children 2003-2006 (GerES IV). Int J Hyg Environ Health. 2009;212(6):637-647. doi:10.1016/j.ijheh.2009.05.003 3. US Department of Health and Human Services: Toxicological profile for nickel. Agency for Toxic Substances and Disease Registry. HHS; 2005. Accessed September 6, 2023. Available at www.atsdr.cdc.gov/ToxProfiles/tp15.pdf 4. Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 5. Zambelli B, Ciurli S: Nickel and human health. In: Sigel A, Sigel H, Sigel R, eds. Interrelations between Essential Metal Ions and Human Diseases. Metal Ions in Life Sciences. Vol 13. Springer, Dordrecht; 2013:321-357 6. Begum W, Rai S, Banerjee S, et al. A comprehensive review on the sources, essentiality and toxicological profile of nickel. RSC Adv. 2022;12(15):9139-9153doi:10.1039/d2ra00378c

NIUCR
614552

Nickel/Creatinine Ratio, Random, Urine

Clinical Information: Nickel (Ni) is a highly abundant element with a silvery-white appearance. Nickel is frequently combined with other metals to form alloys and is essential for the catalytic activity of some plant and bacterial enzymes (including in several pathogenic and symbiotic species in humans) but has no known role in humans. Most nickel is used to make stainless steel. Nickel and its compounds have no characteristic odor or taste. Ni compounds are used for Ni plating, to color ceramics, to make some batteries, and as catalysts that increase the rate of chemical reactions. One of the most toxic Ni

compounds is nickel carbonyl, Ni(CO)4, which is used as a catalyst in petroleum refining and in the plastics industry, is frequently employed in the production of metal alloys (which are popular for their anticorrosive and hardness properties), in nickel-cadmium rechargeable batteries, and is used as a catalyst in hydrogenation of oils. Ni(CO)4 is very toxic and is lipid-soluble, allowing it to cross cell membranes. Occupational exposure to Ni occurs primarily via inhalation of Ni compounds. Inhalation of dust high in Ni content has been associated with development of lung and nasal cancer. Food is the major source of exposure to Ni. Foods naturally high in Ni include chocolate, soybeans, nuts, and oatmeal. Individuals may also be exposed to Ni by breathing air, drinking water, or smoking tobacco containing nickel. Stainless steel and coins contain Ni. Some jewelry is plated with Ni or made from Ni alloys. Patients may be exposed to Ni in implanted devices including joint prostheses, sutures, clips, and screws made from Ni-containing alloys. The most common harmful health effect of Ni in humans is an allergic reaction. Approximately 10% to 20% of the population is sensitive to it. The most serious harmful health effects from exposure to Ni, such as chronic bronchitis, reduced lung function, and cancer of the lung and nasal sinus, have occurred in people who have breathed dust containing certain Ni compounds while working in Ni refineries or Ni-processing plants. Urine is the specimen of choice for the determination of Ni exposure, but serum concentrations can be used to verify an elevated urine concentration. Patients undergoing dialysis are exposed to Ni and accumulate Ni in blood and other organs; there appear to be no adverse health effects from this exposure. Hypernickelemia has been observed in patients undergoing kidney dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended.

Useful For: Preferred specimen type for biomonitoring nickel exposure

Interpretation: Values of 3.8 mcg/g creatinine and higher for male patients or 4.3 mcg/g creatinine and higher for female patients represent possible environmental or occupational exposure to nickel (Ni). Ni concentrations above 50 mcg/g creatinine are of concern, suggesting excessive exposure. Hypernickelemia, in the absence of exposure, may be an incidental finding or could be due to specimen contamination.

Reference Values:

NICKEL:
0-17 years: Not established
Males > or =18 years: <3.8 mcg/g creatinine
Females > or =18 years: <4.3 mcg/g creatinine

CREATININE:
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients younger than 18 years of age.

Clinical References: 1. Moreno ME, Acosta-Saavedra LC, Mez-Figueroa D, et al. Biomonitoring of metal in children living in a mine tailings zone in Southern Mexico: A pilot study. Int J Hyg Environ Health. 2010;213(4):252-258. doi:10.1016/j.ijheh.2010.03.005 2. Schulz C, Angerer J, Ewers U, Heudorf U, Wilhelm M, Human Biomonitoring Commission of the German Federal Environment Agency. Revised and new reference values for environmental pollutants in urine or blood of children in Germany derived from the German Environmental Survey on Children 2003-2006 (GerES IV). Int J Hyg Environ Health. 2009;212(6):637-647. doi:10.1016/j.ijheh.2009.05.003 3. US Department of Health and Human Services: Toxicological profile for nickel. Agency for Toxic Substances and Disease Registry. HHS; 2005. Accessed September 6, 2023. Available at www.atsdr.cdc.gov/ToxProfiles/tp15.pdf 4. Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 5. Zambelli B, Ciurli S: Nickel and human health. In: Sigel A, Sigel H, Sigel R, eds. Interrelations between Essential Metal Ions and Human Diseases. Metal Ions in Life Sciences. Vol 13. Springer, Dordrecht; 2013:321-357 6. Begum W, Rai S, Banerjee S, et al. A comprehensive review on the sources, essentiality and toxicological profile

of nickel. RSC Adv. 2022;12(15):9139-9153. doi:10.1039/d2ra00378c

NIUC
614553

Nickel/Creatinine Ratio, Random, Urine

Clinical Information: Nickel (Ni) is a highly abundant element with a silvery-white appearance. Nickel is frequently combined with other metals to form alloys and is essential for the catalytic activity of some plant and bacterial enzymes but has no known role in humans. Most nickel is used to make stainless steel. Nickel and its compounds have no characteristic odor or taste. Ni compounds are used for Ni plating, to color ceramics, to make some batteries, and as catalysts that increase the rate of chemical reactions. One of the most toxic Ni compounds is nickel carbonyl, Ni(CO)4, which is used as a catalyst in petroleum refining and in the plastics industry, is frequently employed in the production of metal alloys (which are popular for their anticorrosive and hardness properties), in nickel-cadmium rechargeable batteries, and is used as a catalyst in hydrogenation of oils. Ni(CO)4 is very toxic. Occupational exposure to Ni occurs primarily via inhalation of Ni compounds. Inhalation of dust high in Ni content has been associated with development of lung and nasal cancer. Food is the major source of exposure to Ni. Foods naturally high in Ni include chocolate, soybeans, nuts, and oatmeal. Individuals may also be exposed to Ni by breathing air, drinking water, or smoking tobacco containing nickel. Stainless steel and coins contain Ni. Some jewelry is plated with Ni or made from Ni alloys. Patients may be exposed to Ni in implanted devices including joint prostheses, sutures, clips, and screws made from Ni-containing alloys. The most common harmful health effect of Ni in humans is an allergic reaction. Approximately 10% to 20% of the population is sensitive to it. The most serious harmful health effects from exposure to Ni, such as chronic bronchitis, reduced lung function, and cancer of the lung and nasal sinus, have occurred in people who have breathed dust containing certain Ni compounds while working in Ni refineries or Ni-processing plants. Urine is the specimen of choice for the determination of Ni exposure, but serum concentrations can be used to verify an elevated urine concentration. Patients undergoing dialysis are exposed to Ni and accumulate Ni in blood and other organs; there appear to be no adverse health effects from this exposure. Hypernickelemia has been observed in patients undergoing renal dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended.

Useful For: Measurement of nickel concentration for biomonitoring nickel exposure

Interpretation: Values of 3.8 mcg/g creatinine and higher for male patients, or 4.3 mcg/g creatinine and higher for female patients, represent possible environmental or occupational exposure to nickel (Ni). Ni concentrations above 50 mcg/g creatinine are of concern, suggesting excessive exposure. Hypernickelemia, in the absence of exposure, may be an incidental finding or could be due to specimen contamination.

Reference Values:
Only orderable as part of a profile. For more information see NIUCR / Nickel/Creatinine Ratio, Random, Urine.

0-17 years: Not established
Males > or =18 years: <3.8 mcg/g creatinine
Females > or =18 years: <4.3 mcg/g creatinine

Clinical References: 1. Moreno ME, Acosta-Saavedra LC, Mez-Figueroa D, et al. Biomonitoring of metal in children living in a mine tailings zone in Southern Mexico: A pilot study. Int J Hyg Environ Health. 2010;213(4):252-258. doi:10.1016/j.ijheh.2010.03.005 2. Schulz C, Angerer J, Ewers U, Heudorf U, Wilhelm M, Human Biomonitoring Commission of the German Federal Environment Agency. Revised and new reference values for environmental pollutants in urine or blood of children in Germany derived from the German Environmental Survey on Children 2003-2006 (GerES IV). Int J Hyg Environ Health.

2009;212(6):637-647. doi:10.1016/j.ijheh.2009.05.003 3. US Department of Health and Human Services: Toxicological profile for nickel. Agency for Toxic Substances and Disease Registry. HHS; 2005. Accessed September 6, 2023. Available at www.atsdr.cdc.gov/ToxProfiles/tp15.pdf 4. Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds: Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023 5. Zambelli B, Ciurli S: Nickel and human health. In: Sigel A, Sigel H, Sigel R, eds. Interrelations between Essential Metal Ions and Human Diseases. Metal Ions in Life Sciences. Vol 13. Springer, Dordrecht; 2013:321-357 6. Begum W, Rai S, Banerjee S, et al. A comprehensive review on the sources, essentiality and toxicological profile of nickel. RSC Adv. 2022;12(15):9139-9153.

NICOU
82510

Nicotine and Metabolites, Random, Urine

Clinical Information: Tabacco use remains the leading cause of preventable disease, disability, and death in the United States. Nicotine, coadministered in tobacco products such as cigarettes, pipes, cigars, or chew, is an addictive substance that causes individuals to continue use of tobacco despite concerted efforts to quit. Nicotine stimulates dopamine release and increases dopamine concentration in the nucleus accumbens, a mechanism that is thought to be the basis for addiction to drugs of abuse. Nicotine is rapidly metabolized in the liver to cotinine, exhibiting an elimination half-life of 2 hours. Cotinine exhibits an apparent elimination half-life of 15 hours. Patients using tobacco products excrete nicotine in urine in the concentration range of 1000 to 5000 ng/mL. Cotinine accumulates in urine in proportion to dose and hepatic metabolism (which is genetically determined); most tobacco users excrete cotinine in the range of 1000 to 8000 ng/mL. Urine concentrations of nicotine and metabolites in these ranges indicate the subject is using tobacco or is receiving high-dose nicotine patch therapy. In addition to nicotine and metabolites, tobacco products contain other alkaloids that can serve as unique markers of tobacco use. Two such markers are anabasine and nornicotine. Anabasine is present in tobacco products but not in nicotine replacement therapies. Nornicotine is present as an alkaloid in tobacco products and as a metabolite of nicotine. The presence of anabasine (>10 ng/mL) or nornicotine (>30 ng/mL) in urine indicates current tobacco use, irrespective of whether the subject is on nicotine replacement therapy. The presence of nornicotine without anabasine is consistent with use of nicotine replacement products. Heavy tobacco users who abstain from tobacco for 2 weeks exhibit urine nicotine values below 30 ng/mL, cotinine values below 50 ng/mL, anabasine levels below 2 ng/mL, and nornicotine levels below 2 ng/mL. Passive exposure to tobacco smoke can cause accumulation of nicotine metabolites in nontobacco users. Urine cotinine has been observed to accumulate up to 20 ng/mL from passive exposure. Neither anabasine nor nornicotine accumulates from passive exposure. Tobacco users engaged in programs to abstain from tobacco require support in the form of counseling, pharmacotherapy, and continuous encouragement. Occasionally, counselors may elect to monitor abstinence by biochemical measurement of nicotine and metabolites in a random urine specimen to verify abstinence. If results of biologic testing indicate the patient is actively using a tobacco product during therapy, additional counseling or intervention may be appropriate. Quantification of urine nicotine and metabolites, while a patient is actively using a tobacco product, is useful to define the concentrations that a patient achieves through self-administration of tobacco. Nicotine replacement dose can then be tailored to achieve the same concentrations early in treatment to assure adequate nicotine replacement so the patient may avoid the strong craving they may experience early in the withdrawal phase. This can be confirmed by measurement of urine nicotine and metabolite concentrations at a steady state (2-3 days after replacement therapy is started). Once the patient is stabilized on the dose necessary to achieve complete replacement and responding well to therapy, the replacement dose can be slowly tapered to achieve complete withdrawal.

Useful For: Monitoring tobacco use Monitoring patients on nicotine-replacement therapy for concurrent use of tobacco products

Interpretation: Urine nicotine in the range of 1000 to 5000 ng/mL with cotinine in the range of 1000 to 8000 ng/mL indicates the subject is either actively using a tobacco product or on high-dose nicotine patch therapy. The presence of anabasine and nornicotine indicates a subject on patch therapy who is

actively using a tobacco product. Typical findings are as follows: While using a tobacco product: -Peak nicotine concentration: 1000 to 5000 ng/mL -Peak cotinine concentration: 1000 to 8000 ng/mL -Anabasine concentration: 10 to 500 ng/mL -Nornicotine concentration: 30 to 900 ng/mL Tobacco user after 2 weeks complete abstinence: -Nicotine concentration: <30 ng/mL -Cotinine concentration: <50 ng/mL -Anabasine concentration: <2.0 ng/mL -Nornicotine concentration: <2.0 ng/mL Nontobacco user with passive exposure: -Nicotine concentration: <20 ng/mL -Cotinine concentration: <20 ng/mL -Anabasine concentration: <2.0 ng/mL -Nornicotine concentration: <2.0 ng/mL Nontobacco user with no passive exposure: -Nicotine concentration: <5.0 ng/mL -Cotinine concentration: <5.0 ng/mL -Anabasine concentration: <2.0 ng/mL -Nornicotine concentration: <2.0 ng/mL

Reference Values:

Non-tobacco user with no passive exposure:

NICOTINE
<5.0 ng/mL

COTININE
<5.0 ng/mL

ANABASINE
<2.0 ng/mL

NORNICOTINE
<2.0 ng/mL

Clinical References: 1. Dale LC, Hurt RD, Hays JT. Drug therapy to aid in smoking cessation. Tips on maximizing patients' chances for success. Postgrad Med. 1998;104(6):75-78, 83-84 2. Rudasingwa G, Kim Y, Lee C, Lee J, Kim S, Kim S. Comparison of nicotine dependence and biomarker levels among traditional cigarette, heat-not-burn cigarette, and liquid e-cigarette users: Results from the Think Study. Int J Environ Res Public Health. 2021;18(9):4777. doi:10.3390/ijerph18094777 3. Sharma P, Sane N, Anand SD, Marimutthu P, Benegal V. Assessment of cotinine in urine and saliva of smokers, passive smokers, and nonsmokers: Method validation using liquid chromatography and mass spectrometry. Indian J Psychiatry. 2019;61(3):270-276. doi:10.4103/psychiatry.IndianJPsychiatry_61_18

NICOS
82509

Nicotine and Metabolites, Serum

Clinical Information: Tobacco use remains the leading cause of preventable disease, disability, and death in the United States. Nicotine, coadministered in tobacco products such as cigarettes, pipe tobacco, cigars, or chew, is an addicting substance that causes individuals to continue use of tobacco despite concerted efforts to quit. Nicotine stimulates dopamine release and increases dopamine concentration in the nucleus accumbens, a mechanism that is thought to be the basis for addiction for drugs of abuse. Nicotine-dependent patients use tobacco products to achieve a peak serum nicotine value of 30 to 50 ng/mL, the concentration at which the nicotine high is maximized. Nicotine is metabolized in the liver to cotinine. Cotinine accumulates in serum in proportion to dose and hepatic metabolism (which is genetically determined); most tobacco users accumulate cotinine in the range of 200 to 800 ng/mL. Serum concentrations of nicotine and metabolites in these ranges indicate the patient is using tobacco or is receiving high-dose nicotine patch therapy. Nicotine is rapidly metabolized, exhibiting an elimination half-life of approximately 2 hours. Cotinine exhibits an apparent elimination half-life of approximately 24 hours. Heavy tobacco users who abstain from tobacco for 2 weeks exhibit serum nicotine values less than 3.0 ng/mL and cotinine less than 3.0 ng/mL. Passive exposure to tobacco smoke can cause accumulation of nicotine metabolites in nontobacco users. Serum cotinine has been observed to accumulate up to 8 ng/mL from passive exposure. Tobacco users engaged in programs to abstain from tobacco require support in the form of counseling, pharmacotherapy, and continuous encouragement. Occasionally, counselors may elect to monitor abstinence by biochemical measurement of nicotine and metabolites in

serum to verify abstinence. If results of biologic testing indicate the patient is actively using a tobacco product during therapy, additional counseling or intervention may be appropriate.

Useful For: Monitoring tobacco use in a clinical setting

Interpretation: Serum nicotine concentration in the range of 30 to 50 ng/mL with cotinine in the range of 200 to 800 ng/mL indicates the subject is either actively using a tobacco product or on nicotine replacement therapy. To discriminate if a patient on nicotine replacement therapy is also actively using a tobacco product, see NICOU / Nicotine and Metabolites, Random, Urine analysis; the presence of anabasine in urine, a tobacco alkaloid not present in nicotine replacement products, indicates recent tobacco use. Typical findings are as follows: While using a tobacco product: -Peak nicotine concentration: 30 to 50 ng/mL -Peak cotinine concentration: 200 to 800 ng/mL* *Higher values may be seen in subjects with high cytochrome P450 2D6 activity Tobacco user after 2 weeks complete abstinence: -Nicotine concentration: <3.0 ng/mL -Cotinine concentration: <3.0 ng/mL Nontobacco user with passive exposure: -Nicotine concentration: <3.0 ng/mL -Cotinine concentration: <8.0 ng/mL Nontobacco user with no passive exposure: -Nicotine concentration: <3.0 ng/mL -Cotinine concentration: <3.0 ng/mL

Reference Values:

NICOTINE
<3.0 ng/mL

COTININE
<3.0 ng/mL

Clinical References: 1. Dale LC, Hurt RD, Hays JT. Drug therapy to aid in smoking cessation. Tips on maximizing patients' chances for success. Postgrad Med. 1998;104(6):75-78, 83-84 2. Moyer TP, Charlson JR, Enger RJ, et al. Simultaneous analysis of nicotine, nicotine metabolites, and tobacco alkaloids in serum or urine by tandem mass spectrometry, with clinically relevant metabolic profiles. Clin Chem. 2002;48(9):1460-1471 3. Nicotine and cotinine. Testing.com; Updated February 2, 2023. Accessed February 16, 2024. Available at www.testing.com/tests/nicotine-and-cotinine/ 4. McGrath-Morrow SA, Gorzkowski J, Groner JA, et al. The effects of nicotine on development. Pediatrics. 2020;145(3):e20191346. doi:10.1542/peds.2019-1346

NCSRY
46918

Nicotine Survey, Serum

Clinical Information: Tobacco use remains the leading cause of preventable disease, disability, and death in the United States. Nicotine, coadministered in tobacco products such as cigarettes, pipe tobacco, cigars, or chew, is an addicting substance that causes individuals to continue use of tobacco despite concerted efforts to quit. Nicotine stimulates dopamine release and increases dopamine concentration in the nucleus accumbens, a mechanism that is thought to be the basis for addiction for drugs of abuse. Nicotine-dependent patients use tobacco products to achieve a peak serum nicotine value of 30 to 50 ng/mL, the concentration at which the nicotine high is maximized. Nicotine is metabolized in the liver to cotinine. Cotinine accumulates in serum in proportion to dose and hepatic metabolism (which is genetically determined); most tobacco users accumulate cotinine in the range of 200 to 800 ng/mL. Serum concentrations of nicotine and metabolites in these ranges indicate the patient is using tobacco or is receiving high-dose nicotine patch therapy. Nicotine is rapidly metabolized, exhibiting an elimination half-life of approximately 2 hours. Cotinine exhibits an apparent elimination half-life of approximately 24 hours. Heavy tobacco users who abstain from tobacco for 2 weeks exhibit serum nicotine values less than 3.0 ng/mL and cotinine less than 3.0 ng/mL. Passive exposure to tobacco smoke can cause accumulation of nicotine metabolites in nontobacco users. Serum cotinine has been observed to accumulate up to 8 ng/mL from passive exposure. Tobacco users engaged in programs

to abstain from tobacco require support in the form of counseling, pharmacotherapy, and continuous encouragement. Occasionally, counselors may elect to monitor abstinence by biochemical measurement of nicotine and metabolites in serum to verify abstinence. If results of biologic testing indicate the patient is actively using a tobacco product during therapy, additional counseling or intervention may be appropriate.

Useful For: Monitoring tobacco use in a health fair setting

Interpretation: Serum nicotine concentration in the range of 30 to 50 ng/mL with cotinine in the range of 200 to 800 ng/mL indicates the subject is either actively using a tobacco product or on nicotine replacement therapy. To discriminate if a patient on nicotine replacement therapy is also actively using tobacco products, see NICOU / Nicotine and Metabolites, Random, Urine analysis; the presence of anabasine in urine, a tobacco alkaloid not present in nicotine replacement products, indicates recent tobacco use. Typical findings are as follows: While using a tobacco product: -Peak nicotine concentration: 30 to 50 ng/mL -Peak cotinine concentration: 200 to 800 ng/mL* *Higher values may be seen in subjects with high cytochrome P450 2D6 activity Tobacco user after 2 weeks complete abstinence: -Nicotine concentration: <3.0 ng/mL -Cotinine concentration: <3.0 ng/mL Nontobacco user with passive exposure: -Nicotine concentration: <3.0 ng/mL -Cotinine concentration: <8.0 ng/mL Nontobacco user with no passive exposure: -Nicotine concentration: <3.0 ng/mL -Cotinine concentration: <3.0 ng/mL

Reference Values:
NICOTINE
<3.0 ng/mL

COTININE
<3.0 ng/mL

Clinical References: 1. Dale LC, Hurt RD, Hays JT. Drug therapy to aid in smoking cessation. Tips on maximizing patients' chances for success. Postgrad Med 1998;104(6):75-78, 83-84 2. Moyer TP, Charlson JR, Enger RJ, et al. Simultaneous analysis of nicotine, nicotine metabolites, and tobacco alkaloids in serum or urine by tandem mass spectrometry, with clinically relevant metabolic profiles. Clin Chem 2002;48(9):1460-1471 3. Nicotine and cotinine. Testing.com; Updated February 2, 2023. Accessed February 16, 2024. Available at www.testing.com/tests/nicotine-and-cotinine/ 4. McGrath-Morrow SA, Gorzkowski J, Groner JA, et al. The effects of nicotine on development. Pediatrics. 2020;145(3):e20191346. doi:10.1542/peds.2019-1346

NITU
607705

Nitrogen, Total, 24 Hour, Urine

Clinical Information: Nitrogen is a key component of proteins. Nitrogen balance is the difference between the amount of nitrogen ingested and the amount excreted in the urine and feces. A majority of nitrogen is excreted as urea in the urine; however, fecal nitrogen can account for 30% to 50% of total nitrogen excretion. A patient who is in negative nitrogen balance is catabolizing muscle protein to meet the metabolic requirements of protein catabolism; therefore, urine and fecal nitrogen concentrations may be increased due to stress, physical trauma, surgery, infections, burns, and 11-oxysteroid or thyroxine use. Testosterone and growth hormone have anabolic effects on protein synthesis and may decrease urine and fecal nitrogen levels. In the course of chronic progressive pancreatitis, as the pancreas is destroyed, serum amylase and lipase may revert to normal. However, excessive fecal nitrogen levels persist and are used as an indicator of pancreatic atrophy.

Useful For: Assessing nutritional status (protein malnutrition) Assessment of protein nutrition and nitrogen balance in hospitalized patients Evaluating protein catabolism Determining nitrogen balance, when used in conjunction with 24-hour fecal nitrogen measurement

Interpretation: Urinary nitrogen excretion levels within the normal range are indicative of adequate nutrition. Slightly abnormal excretion rates may be a result of moderate stress or complications, such as infection or trauma. Significantly abnormal excretion rates may be associated with severe stress due to multiple traumas, head injury, sepsis, or extensive burns. The goal with therapy for a depleted person is a positive nitrogen balance of 4 to 6 g nitrogen/24 hours.

Reference Values:

<16 years: Not established
> or =16 years: 4-20 g/24 hours

Clinical References: 1. Morse MH, Haub MD, Evans WJ, Campbell WW. Protein requirement of elderly women: nitrogen balance responses to three levels of protein intake. J Gerontol A Biol Sci Med Sci. 2001;56(11):M724-730 2. Phinney SD: The assessment of protein nutrition in the hospitalized patient. Clin Lab Med. 1981;1:767-774 3. Konstantinides FN, Kostantinides NN, Li JC, Myaya ME, Cerra FB. Urinary urea nitrogen: too insensitive for calculating nitrogen balance studies in surgical clinical nutrition. J Parenter Enteral Nutr. 1991;15(2):189-193 4. Borowitz D, Konstan MW, O'Rourke A, Cohen M, Hendeles L, Murray FT. Coefficients of fat and nitrogen absorption in healthy subjects and individuals with cystic fibrosis. J Pediatr Pharmacol Ther. 2007;12(1):47-52. doi:10.5863/1551-6776-12.1.47 5. Dickerson RN: Nitrogen balance and protein requirements for critically ill older patients. Nutrients. 2016;8(4):226. doi:10.3390/nu8040226

NITF
607704

Nitrogen, Total, Feces

Clinical Information: Nitrogen is a key component of proteins. Nitrogen balance is the difference between the amount of nitrogen ingested and the amount excreted in the urine and feces. A majority of nitrogen is excreted as urea in the urine; however, fecal nitrogen can account for 30% to 50% of total nitrogen excretion. A patient who is in negative nitrogen balance is catabolizing muscle protein to meet the metabolic requirements of protein catabolism; therefore, urine and fecal nitrogen concentrations may be increased due to stress, physical trauma, surgery, infections, burns, and 11-oxysteroid or thyroxine use. Testosterone and growth hormone have anabolic effects on protein synthesis and may decrease urine and fecal nitrogen levels. In the course of chronic progressive pancreatitis, as the pancreas is destroyed, serum amylase and lipase may revert to normal. However, excessive fecal nitrogen levels persist and are used as an indicator of pancreatic atrophy.

Useful For: Determining nitrogen balance, when used in conjunction with 24-hour urine nitrogen measurement Assessing nutritional status (protein malnutrition) Evaluating protein catabolism

Interpretation: Average fecal nitrogen (N) excretion is approximately 1 to 2 g N/24 hours. Significantly abnormal excretion rates, resulting in negative nitrogen balance, may be associated with severe stress due to multiple traumas, head injury, sepsis, or extensive burns. Elevated values above 2.5 g N/24 hours may be consistent with chronic progressive pancreatitis. The goal with therapy for a depleted person is a positive nitrogen balance of 4 to 6 g N/24 hours.

Reference Values:

<16 years: Not established
> or =16 years: 1-2 g/24 hours

Clinical References: 1. Morse MH, Haub MD, Evans WJ, Campbell WW. Protein requirement of elderly women: nitrogen balance responses to three levels of protein intake. J Gerontol A Biol Sci Med Sci. 2001;56(11):M724-730 2. Phinney SD. The assessment of protein nutrition in the hospitalized patient. Clin Lab Med. 1981;1:767-774 3. Konstantinides FN, Kostantinides NN, Li JC, Myaya ME, Cerra FB. Urinary urea nitrogen: too insensitive for calculating nitrogen balance studies in surgical

clinical nutrition. J Parenter Enteral Nutr. 1991;15(2):189-193 4. Borowitz D, Konstan MW, O'Rourke A, Cohen M, Hendeles L, Murray FT. Coefficients of fat and nitrogen absorption in healthy subjects and individuals with cystic fibrosis. J Pediatr Pharmacol Ther. 2007;12(1):47-52. doi:10.5863/1551-6776-12.1.47 5. Dickerson RN. Nitrogen balance and protein requirements for critically ill older patients. Nutrients. 2016;8(4):226. doi:10.3390/nu8040226

NKX3
606692

NKX3.1 Immunostain, Technical Component Only

Clinical Information: Homeobox NKX3.1 (NKX3.1) is a prostate-specific protein. Expression of NKX3.1 is used in the diagnosis of metastatic adenocarcinoma or ambiguous tumors that are from the prostatic origin.

Useful For: Identifying tumors of prostatic origin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Gurel B, Ali TZ, Montgomery EA, et al. NKX3.1 as a marker of prostatic origin in metastatic tumors. Am J Surg Pathol. 2010;34(8):1097-1105 2. Huang H, Guma SR, Melamed J, Zhou M, Lee P, Deng FM. NKX3.1 and PSMA are sensitive diagnostic markers for prostatic carcinoma in bone metastasis after decalcification of specimens. Am J Clin Exp Urol. 2018;6(5):182-188 3. Gary B, Azuero R, Mohanty GS, Bell WC, Eltoum IE, Abdulkadir SA. Interaction of Nkx3.1 and p27kip1 in prostate tumor initiation. Am J Pathol. 2004;164(5):1607-1614 4. Mohanty SK, Smith SC, Chang E, et al. Evaluation of contemporary prostate and urothelial lineage biomarkers in a consecutive cohort of poorly differentiated bladder neck carcinomas. Am J Clin Pathol. 2014;142(2):173-183 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

SSF1
87294

Nocardia Stain, Varies

Clinical Information: Nocardia species and other aerobic actinomycetes can cause significant disease in immunocompromised patients. Clinical presentations can include, but are not limited to, pneumonia, skin abscess, bacteremia, brain abscess, eye infection, and joint infection. The modified acid-fast stain can detect Nocardia species and other partially-acid fast aerobic actinomycetes directly from clinical specimens.

Useful For: Detecting Nocardia species and other partially-acid fast aerobic actinomycetes in clinical specimens

Interpretation: Patients whose specimens are reported as partially acid-fast positive should be considered potentially infected with Nocardia species or other aerobic actinomycetes, pending definitive diagnosis by molecular methods or culture.

Reference Values:
Reported as positive or negative

Clinical References: Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ. Clinical and

laboratory features of the Nocardia spp. based on current molecular taxonomy. Clin Microbiol Rev. 2006;19(2):259-282

NDSPC
113339

Non-Gynecologic Direct Smear (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test

NTPPC
113337

Non-Gynecologic, ThinPrep (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

NSIP
31769

Non-Seasonal Inhalant Allergen Profile, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years of age due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to non-seasonal inhalant allergen profile Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive

4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070

NSFIB
604200

Nonalcoholic Steatohepatitis (NASH)-FibroTest, Serum and Plasma

Clinical Information: This test estimates the 3 elementary features of metabolic liver disease: steatosis, activity, and fibrosis. The estimation is made by measuring 10 standard serum biomarkers (gamma-glutamyl transferase, total bilirubin, alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, alanine aminotransferase, aspartate aminotransferase, cholesterol, triglycerides, and fasting plasma glucose). Results from these tests are combined with the patient's age and sex to estimate hepatic fibrosis (FibroTest), steatosis (SteatoTest 2), and activity (NashTest 2) scores.

Useful For: Diagnosis and the follow-up of liver fibrosis, steatosis, and inflammation Estimating hepatic fibrosis Assessing inflammation for metabolic diseases Assessing severity of nonalcoholic steatohepatitis (NASH) in patients with nonalcoholic fatty liver disease with steatosis (NAFLD) Assessing steatosis or fatty liver Reassuring patients with steatosis only, without fibrosis Managing patients with severe injuries such as advanced fibrosis and NASH

Interpretation: This test provides numeric scores that assess hepatic fibrosis (FibroTest), hepatic inflammation (NashTest 2), and steatosis (SteatoTest 2). Interpretation of the scores is provided in the report. Individual results from the 10 component tests are also provided with institution-specific reference intervals. FibroTest is reported relative to a scale ranging from F0-F4 (F0=no fibrosis, F1=minimal fibrosis, F2=moderate fibrosis, F3=advanced fibrosis, F4=severe fibrosis [cirrhosis]). Fibrosis scores may overlap (eg, F0/F1, F1/F2). NashTest 2 is reported relative to a scale ranging from N0-N3 (N0=no nonalcoholic steatohepatitis [NASH], N1=mild NASH, N2=moderate NASH, N3=severe NASH). Steatosis is reported relative to a scale ranging from S0-S2S3 (S0=no steatosis [<5%], S1=mild steatosis [5-33%], S2/S3=moderate/severe steatosis [34-100%]). A stage of S1 or S2S3 is considered clinically significant.

Reference Values:

NASHTEST 2 INTERPRETATION NashTest 2 score	**Grade**	**Interpretation**
0.00-0.25*	N0	No NASH
0.25-0.50*	N1	Mild NASH
0.50-0.75*	N2	Moderate NASH
0.75-1.00*	N3	Severe NASH
*Boundary values can apply to 2 stages based on rounding. For example, a	Grade	Interpretation

NashTest 2 score of 0.245 will round up to 0.25 and be staged N0. A NashTest 2 score of 0.254 will round down to 0.25 and be staged N2. STEATOTEST 2 INTERPRETATION SteatoTest 2 score

0.00-0.40*	S0	No steatosis (
0.40-0.55*	S1	Mild steatosis (5-33%)
0.55-1.00*	S2	Moderate/severe steatosis (34-100%)
*Boundary values can apply to 2 stages based on rounding. For example, a SteatoTest 2 score of 0.395 will round up to 0.40 and be staged S0. A SteatoTest 2 score of 0.404 will round down to 0.40 and be staged S1. FIBROTEST INTERPRETATION FibroTest score	Stage	Interpretation
0.00-0.21*	F0	No fibrosis
0.21-0.27*	F0-F1	No fibrosis
0.27-0.31*	F1	Minimal fibrosis
0.31-0.48*	F1-F2	Minimal fibrosis
0.48-0.58*	F2	Moderate fibrosis
0.58-0.72*	F3	Advanced fibrosis
0.72-0.74*	F3-F4	Advanced fibrosis
0.74-1.00	F4	Severe fibrosis (Cirrhosis)

Clinical References:

NSRGG
617393

Noonan Syndrome and Related Conditions Gene Panel, Varies

Clinical Information: Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphology, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. Heart defects observed in NS include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward-slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. The incidence of NS is estimated to be between 1 in 1000 and 1 in 2500, although subtle expression in adulthood may cause this number to be an underestimate. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Variants in other genes on this panel have been associated with a smaller percentage of NS and related phenotypes, including Noonan syndrome with multiple lentigines (formerly known as LEOPARD syndrome), Noonan syndrome with loose anagen hair, cardiofaciocutaneous syndrome, Costello syndrome, Baraitser-Winter syndrome, and Legius syndrome.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of Noonan syndrome, Noonan syndrome with multiple lentigines, Noonan syndrome with loose anagen hair, cardiofaciocutaneous syndrome, Costello syndrome, Baraitser-Winter syndrome, Legius syndrome, and related conditions Establishing a diagnosis of Noonan syndrome, Noonan syndrome with multiple lentigines, Noonan syndrome with loose anagen hair, cardiofaciocutaneous syndrome, Costello syndrome, Baraitser-Winter syndrome, Legius syndrome, and related conditions

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

LNORO
65170

Norovirus PCR, Molecular Detection, Feces

Clinical Information: Noroviruses, previously known as Norwalk-like viruses, are highly contagious RNA viruses that cause acute gastroenteritis (diarrhea, vomiting). Although 6 genogroups of norovirus have been identified, only 3 genogroups (genogroup: G1, G2, and G4) cause disease in humans. Furthermore, the majority of outbreaks have been associated with G1 and G2, with G2 being most common.(1) Noroviruses are transmitted through close, personal contact with an infected individual or via the fecal-oral route in which the virus becomes ingested in contaminated food or water. These viruses are extremely contagious, with fewer than 20 virions being able to cause disease.(1) Once infected, the incubation period is typically short, between 24 and 72 hours. The onset of symptoms is abrupt, with vomiting and watery nonbloody diarrhea being common. Patients may also experience a low-grade fever, as well as headache and mild body aches.(1) The diagnosis of norovirus infection can often be made on clinical grounds, and symptoms generally resolve in 24 to 48 hours. However, in certain patients, especially those who are immunocompromised or hospitalized, laboratory testing may be indicated for infection control purposes and to limit the use of antibiotics. Testing of diarrheal feces by real-time polymerase chain reaction allows for a rapid and sensitive means of detecting and differentiating norovirus G1 and G2 in clinical stool samples.

Useful For: Diagnosing gastrointestinal disease (diarrhea or vomiting) caused by norovirus genogroups 1 and 2 This test should not be used as a test-of-cure.

Interpretation: A positive result indicates that RNA from norovirus genogroups 1 and/or 2 was present in the clinical specimen. A negative result suggests that RNA from norovirus genogroups 1 and 2 was absent in the clinical specimen.

Reference Values:
Negative

Clinical References: 1. National Center for Immunization and Respiratory Diseases, Division of Viral Diseases: Norovirus. Center for Disease Control and Prevention; 2013. Updated February 23, 2023. Accessed March 28, 2023. Available at www.cdc.gov/norovirus/index.html 2. Echenique IA, Stosor V, Gallon L, Kaufman D, Qi C, Zembower TR: Prolonged norovirus infection after pancreas transplantation: a case report and review of chronic norovirus. Transpl Infect Dis. 2016 Feb;18(1):98-104

NEREG
31767

Northeast Regional Allergen Profile, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years of age due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to northeast regional allergen profile Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070

NOTRP
37119

Nortriptyline, Serum

Clinical Information: Nortriptyline is a tricyclic antidepressant used for treatment of endogenous depression. It also is a metabolite of the antidepressant amitriptyline. Nortriptyline is used when its stimulatory side effect is considered to be of clinical advantage; amitriptyline is used when the side

effect of mild sedation is desirable. Nortriptyline is unique among the antidepressants in that its blood level exhibits the classical therapeutic window effect, as blood concentrations above or below the therapeutic window correlate with poor clinical response. Thus, therapeutic monitoring to ensure that the blood level is within the therapeutic window is critical to accomplish successful treatment with this drug. Like amitriptyline, nortriptyline can cause major cardiac toxicity when the concentration is above 500 ng/mL, characterized by QRS widening (intraventricular conduction delay), which leads to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations.

Useful For: Monitoring nortriptyline concentration during therapy Evaluating potential nortriptyline toxicity May aid in evaluating patient compliance

Interpretation: Most individuals display optimal response to nortriptyline with serum levels of 70 to 170 ng/mL. Risk of toxicity is increased with nortriptyline levels above 500 ng/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimens collected at trough (ie, immediately before the next dose).

Reference Values:
Therapeutic concentration: 70-170 ng/mL
Note: Therapeutic ranges are for specimens collected at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

Clinical References: 1. Wille SM, Cooreman SG, Neels HM, Lambert WE. Relevant issues in the monitoring and the toxicology of antidepressants. Crit Rev Clin Lab Sci. 2008;45(1):25-89 2. Thanacoody HK, Thomas SHL. Antidepressant poisoning. Clin Med (Lond). 2003;3(2):114-118 3. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-01):9-62 4. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

NTC3Z
616563

NOTCH3 Gene, Full Gene Analysis, Varies

Clinical Information: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary small vessel disorder and common genetic cause of stroke and dementia in adults. Onset of clinical symptoms typically occurs in mid-adulthood and may include recurrent ischemic stroke and transient ischemic attacks, cognitive decline that progresses to dementia, migraine with aura, and psychiatric disturbances. Symmetric and progressive white matter hyperintensities, lacunes of presumed vascular origin, and subcortical infarcts are characteristic neuroimaging findings. Granular osmophilic material (GOM) detected by electron microscopy on skin fibroblasts is considered a pathognomonic finding for CADASIL. Disease-causing variants in the NOTCH3 gene cause CADASIL. Most individuals with CADASIL inherit the condition from a parent, but rare de novo variants have been reported. The family history may appear negative due to variable expressivity of the condition and failure to recognize symptoms in other affected family members. Further, NOTCH3 is comprised of repetitive epidermal growth-factor like repeat (EGFr) domains. Reported pathogenic variants typically result in either loss of or gain of cysteine residues within EGFr domains; those impacting EGFr domains 1-6 are fully penetrant, while those impacting EGRr domains 7-34 may be associated with mild disease or incomplete penetrance. Heterozygous pathogenic variants in NOTCH3 also cause autosomal dominant lateral meningocele syndrome (LMS). LMS is a rare condition associated with multiple lateral meningoceles, hearing loss, developmental delay, hypotonia, joint hyperlaxity, and variable additional congenital malformations. LMS typically occurs due to a de novo disease-causing variant, but rare instances of inheritance from an affected parent have been reported.

Useful For: Establishing a molecular diagnosis in individuals with features of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and NOTCH3-related disorders Identifying disease-causing variants within the NOTCH3 gene known to be associated with CADASIL and NOTCH3-related disorders, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424 2. Ferrante E, Cudrici C, Boehm M: CADASIL: new advances in basic science and clinical perspectives. Curr Opin Hematol. 2019 May; 26(3):193-198 3. Rutten J, Van Eijsden B, Duering M et al: The effect of NOTCH3 pathogenic variant position on CADASIL disease severity: NOTCH3 EGFr 1-6 pathogenic variant are associated with a more severe phenotype and lower survival compared with EGFr 7-34 pathogenic variant. Genet Med. 2019 Mar; 21(3):676-682 4. Canalis E: The skeleton of lateral meningocele syndrome. Front Genet. 2021 Jan 14;11620334

FCDU4 Novel Psychoactives, Umbilical Cord Tissue
75779

Reference Values:
Reporting limit determined each analysis.

Units: ng/g

Only orderable as part of a profile-see FCDSU.

NR4A3 NR4A3 (9q22.33) Rearrangement, FISH, Tissue
64940

Clinical Information: The gene NR4A3 is often altered in extraskeletal myxoid chondrosarcomas (EMC) and acinic cell carcinoma of the salivary gland.(1,2) Rearrangement of the NR4A3 gene region may be involved with up to 4 partner genes as a pathway to EMC. Fluorescence in situ hybridization analysis allows for the detection of rearrangement of the NR4A3 gene region.

Useful For: Identifying NR4A3 gene rearrangements Supporting the diagnosis of extraskeletal myxoid chondrosarcoma or acinic cell carcinoma when used in conjunction with an anatomic pathology consultation

Interpretation: A positive result with the NR4A3 probe is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result of NR4A3 suggests inactivating structural alterations of the NR4A3 gene region at 9q22.33. A negative result suggests no structural alterations of the locus. NR4A3 will be clinically interpreted as positive or negative. A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the NR4A3 probe set. A positive result is consistent with rearrangement of the NR4A3 gene and likely reflects NR4A3 fusion with a partner gene. A positive result may support a diagnosis of extraskeletal

myxoid chondrosarcoma or acinic cell carcinoma of salivary gland. The significance of this finding is dependent on the clinical and pathologic features. A negative result suggests a NR4A3 gene rearrangement is not present. A negative result does not exclude the diagnosis of extraskeletal myxoid chondrosarcoma or acinic cell carcinoma of salivary gland.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Benini S, Cocchi S, Gamberi G, Magagnoli G, et al. Diagnostic utility of molecular investigation in extraskeletal myxoid chondrosarcoma. J Mol Diagn. 2014;16(3):314-323 2. Haller F, Bieg M, Will R, et al. Enhancer hijacking activates oncogenic transcription factor NR4A3 in acinic cell carcinomas of the salivary glands. Nat Commun. 2019;10(1):368

PBNP1
615897

NT-Pro B-Type Natriuretic Peptide, Serum

Clinical Information: B-type natriuretic peptide (formerly brain natriuretic peptide: BNP) is a small, ringed peptide secreted by the heart to regulate blood pressure and fluid balance.(1) This peptide is stored in, and secreted predominantly from, membrane granules in the heart ventricles in a pro form (proBNP). Once released from the heart in response to ventricle volume expansion or pressure overload, the N-terminal (NT) piece of 76 amino acids (NT-proBNP) is rapidly cleaved by the enzymes corin and furin to release the active 32-amino acid peptide (BNP).(2) Both BNP and NT-proBNP are markers of atrial and ventricular distension due to increased intracardiac pressure. The New York Heart Association (NYHA) developed a 4-stage functional classification system for congestive heart failure (CHF) based on the severity of the symptoms. Studies have demonstrated that the measured concentrations of circulating BNP and NT-proBNP increase with the severity of CHF based on the NYHA classification.

Useful For: Aiding in the diagnosis of congestive heart failure using serum specimens

Interpretation: Under 50 years of age: N-terminal pro B-type natriuretic peptide (NT-proBNP) values below 300 pg/mL have a 99% negative predictive value for excluding acute congestive heart failure (CHF). A cutoff of 1200 pg/mL for patients with an estimated glomerular filtration rate (eGFR) below 60 yields a diagnostic sensitivity and specificity of 89% and 72% for acute CHF. NT-proBNP values greater than 450 pg/mL are consistent with CHF in adults under 50 years of age. 50-75 years of age: NT-proBNP values below 300 pg/mL have a 99% negative predictive value for excluding acute CHF. A cutoff of 1200 pg/mL for patients with an eGFR below 60 yields a diagnostic sensitivity and specificity of 89% and 72% for acute CHF. A diagnostic NT-proBNP cutoff of 900 pg/mL has been suggested for adults 50 to 75 years of age in the absence of kidney failure. Over 75 years of age: NT-proBNP values below 300 pg/mL have a 99% negative predictive value for excluding acute CHF. A cutoff of 1200 pg/mL for patients with an eGFR below 60 yields a diagnostic sensitivity and specificity of 89% and 72% for acute CHF. A diagnostic NT-proBNP cutoff of 1800 pg/mL has been suggested for adults over 75 years of age in the absence of kidney failure. NT-Pro BNP levels are loosely correlated with New York Heart Association (NYHA) functional class (see Table). Table. Interpretive Levels for CHF Functional class 5th to 95th percentile Median I 31-1110 pg/mL 377 pg/mL II 55-4975 pg/mL 1223 pg/mL III 77-26,916 pg/mL 3130 pg/mL IV * * *In a Mayo Clinic study of 75 patients with CHF, only 4 were characterized as class IV. Accordingly, range and median are not provided.

Reference Values:
Males
0-2 day: 321-11,987 pg/mL
3-11 day: 263-5918 pg/mL
12 day-1 month: Not applicable
2 month-1 year: 37-646 pg/mL

2 years: 39-413 pg/mL
3 years-6 years: 23-289 pg/mL
7 years-14 years: < or =157 pg/mL
15 years-18 years: < or =158 pg/mL
19-39 years: <79 pg/mL
40-44 years: < or =72 pg/mL
45-54 years: < or =87 pg/mL
55-64 years: < or =88 pg/mL
> or =65 years: < or =540 pg/mL

Females
0-2 day: 321-11,987 pg/mL
3-11 day: 263-5918 pg/mL
12 day-1 month: Not applicable
2 month-1 year: 37-646 pg/mL
2 years: 39-413 pg/mL
3 years-6 years: 23-289 pg/mL
7 years-14 years: < or=157 pg/mL
15 years-18 years: < or =158 pg/mL
19-39 years: <160 pg/mL
40-44 years: < or =162 pg/mL
45-54 years: < or =141 pg/mL
55-64 years: < or =226 pg/mL
> or =65 years: < or =540 pg/mL

Clinical References: 1. Januzzi JL, van Kimmenade RR, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the international collaborative of NT-proBNP study. Eur Heart J. 2006;27(3):330-337. doi:10.1093/eurheartj/ehi631 2. van Kimmenade RR, Pinto YM, Bayes-Genis A, et al. Usefulness of intermediate amino-terminal pro-brain natriuretic peptide concentrations for diagnosis and prognosis of acute heart failure. Am J Cardiol. 2006;98(3):386-390. doi:10.1016/j.amjcard.2006.02.043 3. DeFilippi C, van Kimmenade R, Pinto YM. Amino-terminal pro-B-type natriuretic peptide testing in renal disease. Am J Cardiol. 2008;101(3A):82- 88. doi:10.1016/j.amjcard.2007.11.029 4. Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

NTRK
606377

NTRK Gene Fusion Panel, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Fusions involving the NTRK1, NTRK2, and NTRK3 genes (ie, NTRK gene fusions) are oncogenic drivers of multiple types of pediatric and adult solid tumors. In solid tumors, the presence of an NTRK gene fusion is a biomarker for response to tropomyosin receptor kinase (TRK) inhibitor therapies. This test assesses for fusions involving targeted regions of NTRK1, NTRK2, and NTRK3 genes. The results of this test can be useful in guiding treatment of individuals with advanced solid tumors. See Method Description for details regarding the targeted gene regions evaluated by this test.

Useful For: Identifying solid tumors that may respond to targeted therapies by simultaneously assessing for fusions involving targeted regions of the NTRK1, NTRK2, and NTRK3 genes resulting in fusion transcripts. This test is not useful for hematologic malignancies.

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Drilon A, Laetsch TW, Kummar S. Efficacy of Larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 2018;378(8):731-739. doi:10.1056/NEJMoa1714448 2. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol. 2018;15(12):731-747. doi:10.1038/s41571-018-0113-0

NTRKM 619703 NTRK Genes Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information: The NTRK1, NTRK2, and NTRK3 genes encode the tropomyosin receptor kinases TrkA, TrkB, and TrkC, respectively. Fusions of the NTRK genes with a variety of 5' (upstream) partner genes upregulate Trk kinase activity and contribute to tumorigenesis. NTRK gene fusions have been reported in diverse tumor types. Numerous US Food and Drug Administration approved pan-Trk inhibitors have been developed for the treatment of tumors with NTRK gene fusions. However, resistance to Trk inhibition can occur through the development of NTRK gene mutations. This test can be used to identify NTRK resistance mutations to aid in the management of these patients. Second generation Trk inhibitors have been developed to overcome resistance to the first-generation inhibitors.

Useful For: Identifying NTRK mutations that may predict resistance to Trk inhibitors

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. WHO Classification of Tumours Editorial Board: Central nervous system tumours. 5th ed. World Health Organization; 2021. WHO Classification of Tumours. Vol 6. 4. Killela PJ, Reitman ZJ, Jiao Y, et al. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. Proc Natl Acad Sci USA. 2013;110(15):6021-6026 5. Koelsche C, Sahm F, Capper D, et al. Distribution of TERT promoter mutations in pediatric and adult tumors of the nervous system. Acta Neuropathol. 2013;126(6):907-915 6. Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med. 2015;372(26):2499-2508 7. Cancer Genome Atlas Research Network, Brat DJ, et al. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med. 2015;372(26):2481-2498 8. Huang FW, Hodis E, Xu MJ, Kryukov GV, Chin L, Garraway LAl. Highly recurrent TERT promoter mutations in human melanoma. Science. 2013;339(6122):957-959 9. Schulze K, Imbeaud S,Letouze E, et al. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. Nat Genet. 2015;47(5):505-511

NMRLP 603839 Nuclear Magnetic Resonance Lipoprotein Profile, Serum

Clinical Information: Low-density lipoprotein particle (LDL-P) concentration is positively associated with increased risk of atherosclerotic cardiovascular disease (ASCVD). LDL-P is heterogeneous and contains many lipids and proteins, including phospholipids, triglycerides, and cholesterol. LDL cholesterol is a surrogate biomarker of LDL-P. LDL cholesterol is the historical measure of atherogenic lipid burden. There is a large variance in the relative amount of cholesterol carried by each LDL-P. Consequently, subjects with similar LDL cholesterol values can have markedly different serum concentrations of LDL-P. Multiple studies have shown that serum concentrations of LDL-P more accurately reflect actual risk of ASCVD when LDL cholesterol values are discrepant. High-density lipoprotein particle (HDL-P) concentration is inversely associated with risk of ASCVD. HDL cholesterol is also inversely associated with ASCVD, since it is a surrogate marker for HDL-P. Like other lipoproteins, HDL-P is heterogeneous, and particles contain highly variable proportions of proteins and lipids, including phospholipids, sphingolipids, and cholesterol. Several large clinical studies have shown that HDL-P is more significantly associated with ASCVD risk than HDL cholesterol. Furthermore, HDL-P remains significantly associated with ASCVD even among subjects taking cholesterol-lowering medications. HDL-P more accurately reflects actual risk of ASCVD when HDL cholesterol values are discrepant.

Useful For: Assessment and management of a patient's risk for atherosclerotic cardiovascular disease
Identifying residual risk that may be present in some patients on cholesterol targeting treatment

Interpretation: Elevated concentrations of low-density lipoprotein particle (LDL-P) are associated with increased risk of atherosclerotic cardiovascular disease. LDL-P is a more accurate indicator of risk when LDL cholesterol is discordantly low. Lower concentrations of high-density lipoprotein particle are associated with increased risk of atherosclerotic cardiovascular disease.

Reference Values:
> or =18 years:

LDL Particles:
Desirable: <1,000 nmol/L
Above Desirable: 1,000-1,299 nmol/L
Borderline high: 1,300-1,599 nmol/L
High: 1,600-2,000 nmol/L
Very high: > or =2,000 nmol/L

HDL Particles:
Male: >30 mcmol/L
Female: >35 mcmol/L

LDL Cholesterol (NMR):
Desirable: <100 mg/dL
Above Desirable: 100-129 mg/dL
Borderline high: 130-159 mg/dL
High: 160-189 mg/dL
Very high: > or =190 mg/dL

Reference values have not been established for patients younger than 18 years of age.

Clinical References: 1. Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. Circulation. 2013;128(11):1189-1197. doi:10.1161/CIRCULATIONAHA.113.002671 2. Lawler PR, Akinkuolie AO, Ridker PM, et al. Discordance between circulating atherogenic cholesterol mass and lipoprotein particle concentration in relation to future coronary events in women. Clin Chem. 2017;63(4):870-879. doi:10.1373/clinchem.2016.264515 3. Akinkuolie AO, Paynter NP, Padmanabhan L, Mora S: High-

density lipoprotein particle subclass heterogeneity and incident coronary heart disease. Circ Cardiovasc Qual Outcomes. 2014;Jan;7(1):55-63. doi:10.1161/CIRCOUTCOMES.113.000675 4. Tehrani DM, Zhao Y, Blaha MJ, et al. Discordance of ow-density lipoprotein and high-density lipoprotein cholesterol particle versus cholesterol concentration for the prediction of cardiovascular disease in patients with metabolic syndrome and diabetes mellitus. Am J Cardiol. 2016;117(12):1921-1927. doi:10.1016/j.amjcard.2016.03.040 5. Mackey RH, Greenland P, Goff DC, Lloyd-Jones D, Sibley CT, Mora S. High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events. J Am Coll Cardiol. 2012;60(6):508-516. doi:10.1016/j.jacc.2012.03.060 6. Otvos JD, Shalaurova I, Freedman DS, Rosenson RS. Effects of pravastatin treatment on lipoprotein subclass profiles and particle size in the PLAC-I trial. Atherosclerosis. 2002;160:41-48 7. Khera AV, Demler OV, Adelman SJ, et al. Cholesterol efflux capacity, high-density lipoprotein particle number, and incident cardiovascular events: an analysis from the JUPITER trial (Justification for the use of statins in prevention: An intervention trial evaluating rosuvastatin). Circulation. 2017;135(25):2494-2504. doi:10.1161/CIRCULATIONAHA.116.025678

NMITO
617090

Nuclear Mitochondrial Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: The mitochondrion occupies a unique position in eukaryotic biology. It is the site of energy metabolism, and it is the sole subcellular organelle that is composed of proteins derived from 2 genomes, mitochondrial and nuclear. A group of hereditary disorders due to variants in either the mitochondrial genome or nuclear mitochondrial genes has been well characterized. The diagnosis of mitochondrial disease can be particularly challenging as the presentation can occur at any age, involve virtually any organ system, and be associated with widely varying severities. Due to the considerable overlap in the clinical phenotypes of various mitochondrial disorders, it is often difficult to distinguish these specific inherited disorders without genetic testing. This test utilizes massively parallel sequencing, also termed next-generation sequencing, to analyze 221 nuclear-encoded genes implicated in mitochondrial disease. The utility of this test is to assist in the diagnosis of the subset of mitochondrial diseases that result from variants in the nuclear genes encoding mitochondrial proteins. This includes disorders of mitochondrial protein synthesis, disorders of coenzyme Q10 biosynthesis, disorders of the respiratory chain complexes and disorders of mitochondrial DNA (mtDNA) maintenance (ie, mtDNA depletion disorders).

Useful For: Diagnosing the subset of mitochondrial disease that results from variants in the nuclear-encoded genes A second-tier test for patients in whom previous targeted gene variant analyses for specific mitochondrial disease-related genes were negative Identifying variants within genes of the nuclear genome that are known to be associated with mitochondrial disease, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Munnich A, Rotig A, Cormier-Daire V, Rustin P. Clinical presentation of respiratory chain deficiency. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The

Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill; 2019. Accessed March 8, 2024. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225086827 3. Wong LJ. Molecular genetics of mitochondrial disorders. Dev Disabil Res Rev. 2010;16(2):154-162 4. Barca E, Long Y, Cooley V, et al. Mitochondrial disease in North America: An analysis of the NAMDC Registry. Neurol Genet. 2020;6(2):e402

NPMFM 620654 Nucleophosmin (NPM1) Mutation Analysis, Bone Marrow

Clinical Information: Acute myeloid leukemia (AML) is a heterogeneous disease of the blood and bone marrow, characterized by clonal expansion of hematopoietic stem and progenitor cells with impaired differentiation capacity, leading to bone marrow failure. Nucleophosmin (NPM1) mutated AML represents a distinct entity in the World Health Organization classification. NPM1 mutation occurs in 20% to 30% of AML cases. Most of these patients have a normal karyotype. Detection of an NPM1 mutation without coexisting FLT3-ITD (FMS-like tyrosine kinase-3 internal tandem duplication) suggests a more favorable prognosis. More than 50 different heterozygous mutations have been identified in NPM1 in exon 12. Three mutation types, A, B, and D, account for about 95% of the NPM1 mutations. NPM1 mutation detection has been utilized in monitoring measurable residual disease.

Useful For: Detection of nucleophosmin (NPM1) mutation provides information for prognosis in patients with newly diagnosed acute myeloid leukemia. NPM1 mutation with absence of FLT3-ITD (FMS-like tyrosine kinase-3 internal tandem duplication) is associated with a better prognosis. This RNA based quantitative test detects about 95% of NPM1 mutations and can be used for monitoring measurable residual disease.

Interpretation: Nucleophosmin (NPM1) mutation occurs in 20% to 30% of acute myeloid leukemia (AML) cases. AML with NPM1 mutation is a subtype of AML classification. Detection of an NPM1 mutation with absence of FLT3-ITD (FMS-like tyrosine kinase-3 internal tandem duplication) is associated with better outcomes, increased complete remission, and improved overall survival in AML. Concurrent NPM1 and FLT3-ITD mutations confer intermediate risk in AML. Three mutation types, A, B, and D account for about 95% of the NPM1 mutations in AML. This RNA based quantitative test detects the transcripts of the type A, B, and D mutations and provides a useful target for measurable residual disease (MRD) monitoring. The continued presence of NPM1 mutant transcripts is associated with a higher chance of relapse than those with non-detectable NPM1 mutant transcripts. MRD status prior to allogeneic hematopoietic stem cell transplant has been shown to be a good predictor of outcome.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Heath EM, Chan SM, Minden MD, Murphy T, Shlush LI, Schimmer AD. Biological and clinical consequences of NPM1 mutations in AML. Leukemia. 2017;31(4):798-807 2. Falini B, Sciabolacci S, Falini L, Brunetti L, Martelli MP. Diagnostic and therapeutic pitfalls in NPM1-mutated AML: notes from the field. Leukemia. 2021;35(11):3113-3126 3. Hindley A, Catherwood MA, McMullin MF, Mills KI. Significance of NPM1 Gene Mutations in AML. Int J Mol Sci. 2021;22(18):10040 4. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-1719

NPM1Q 604418 Nucleophosmin (NPM1) Mutation Analysis, Varies

Clinical Information: Acute myeloid leukemia (AML) is a genetically heterogeneous group of

neoplasms. While cytogenetic aberrations detected at the time of diagnosis are the most used prognostic feature, approximately 50% of AML cases show a normal karyotype, which is considered an intermediate-risk feature. Within this group, FLT3 variants are considered indicators of poor prognosis. However, in the absence of a FLT3 variant, the presence of a NPM1 variant is associated with a more favorable prognosis. A NPM1 alteration is a common finding in de novo AML (25%-30% of cases) and consists of small insertion (typically 4 base pairs) or deletion/insertion events involving exon 12. Three variants are highly recurrent, termed types A, B, and D, and together account for approximately 90% of NPM1 alterations in de novo AML. Thus, in patients with newly diagnosed AML, those with normal karyotype, no FLT3 variant, and a NPM1 alteration are considered to have a better prognosis than patients in the same group with neoplasms lacking a NPM1 alteration. Furthermore, the presence of a NPM1 alteration serves as a sensitive marker for evaluating minimal disease and therapeutic response following treatment.

Useful For: As a prognostic indicator in patients with newly diagnosed acute myelogenous leukemia with normal karyotype and no FLT3 variant and as a leukemia-specific marker of minimal residual disease

Interpretation: The assay incorporates 2 parts: a qualitative screen for exon 12 NPM1 alterations and a quantitative reverse transcription polymerase chain reaction (RT-PCR) assay to determine the copy number of NPM1 transcripts (relative to ABL1 reference messenger RNA [mRNA]). This strategy will allow for identification of the NPM1 alteration at diagnosis, as well as a high sensitivity method to monitor patients who are post-therapy for minimal residual disease. Results will therefore be interpreted with integration of the quantitative and qualitative test results in the context of NPM1 alteration type identified at the time of AML diagnosis if available. Because the quantitative RT-PCR component only reliably detects and quantifies the 3 most common variant types (A, B, D), there is a very small possibility that the qualitative assay may indicate the presence of an NPM1 alteration, but the quantitative assay will be (falsely) negative. In patients with newly diagnosed acute myeloid leukemia, a normal karyotype, and no FLT3 variant, the presence of an NPM1 alteration is an indicator of a more favorable prognosis. Similarly, following chemotherapy, the presence, relative quantity, and trend of change of NPM1 mRNA transcript is associated with risk of disease relapse.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Heath EM, Chan SM, Minden MD, Murphy T, Shlush LI, Schimmer AD. Biological and clinical consequences of NPM1 mutations in AML. Leukemia. 2017;31(4):798-807. doi:10.1038/leu.2017.30 2. Kronke J, Schlenck RF, Jensen KO, et al. Monitoring of minimal residual disease in NPM1-mutated acute myeloid leukemia: a study from the German-Austrian acute myeloid leukemia study group. J Clin Oncol. 2011;29(19):2709-2716. doi:10.1200/JCO.2011.35.0371 3. Ivey A, Hills RK, Simpson MA, et al. Assessment of minimal residual disease in standard-risk AML. N Engl J Med. 2016;374(5):422-433. doi:10.1056/NEJMoa1507471 4. Shayegi N, Kramer M, Bornhauser M, et al. The level of residual disease based on mutant NPM1 is an independent prognostic factor for relapse and survival in AML. Blood. 2013;122(1):83-92. doi:10.1182/blood-2012-10-461749

NUT
70521

NUT Immunostain, Technical Component Only

Clinical Information: Nuclear protein in testis (NUT) is normally confined to the germ cells of the testis and ovary. A recently recognized cancer is NUT midline carcinoma (NMC), defined by the presence of chromosomal rearrangements involving the NUT gene on chromosome 15q14. NMCs are aggressive and highly lethal carcinomas that are very difficult to discern from other poorly differentiated carcinomas by morphology alone.

Useful For: Aiding in the diagnosis of nuclear protein in testis midline carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Davis BN, Karabakhtsian RG, Pettigrew AL, Arnold SM, French CA, Brill YM. Nuclear protein in testis midline carcinomas: a lethal and underrecognized entity. Arch Pathol Lab Med. 2011;135(11):1494-1498 2. Evans AG, French CA, Cameron MJ, et al. Pathologic characteristics of NUT midline carcinoma arising in the mediastinum. Am J Surg Pathol. 2012;36(8):1222-1227 3. French CA. NUT midline carcinoma. Cancer Genet Cytogenet. 2010;203(1):16-20 4. Haack H, Johnson LA, Fry CJ, et al. Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. Am J Surg Pathol. 2009;33(7):984-991 5. Stelow EB. A review of NUT midline carcinoma. Head Neck Pathol. 2011;5:31-35 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

NUT1F
63431

NUTM1 (15q14) Rearrangement, FISH, Tissue

Clinical Information: Nuclear protein in testis (NUT) midline carcinomas (NMC) are rare aggressive tumors with rapid onset. Although NMC has been described in several anatomic sites, it is commonly observed in the head, neck, or thorax. These tumors are poorly differentiated and defined by rearrangement of the NUTM1 gene on chromosome 15q14. In the majority of cases, NUTM1 is rearranged in an apparently balanced translocation with the BRD4 gene on chromosome 19p13.1; however, other partners for NUTM1 rearrangement have been reported. NUTM1 rearrangement has not been identified in other midline malignancies. Therefore, a separation of NUTM1, in the proper clinical and histologic context, is diagnostic for NMC and can be confirmed by fluorescence in situ hybridization with NUT break-apart probes.

Useful For: Identifying NUTM1 gene rearrangements in patients with nuclear protein in testis midline carcinoma to aid in confirming or excluding the diagnosis

Interpretation: The presence of NUTM1 rearrangement confirms the diagnosis of nuclear protein in testis midline carcinomas (NMC) in the proper clinical and histologic context. The absence of NUTM1 rearrangement rules out the diagnosis of NMC in the proper clinical and histologic context. A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the NUTM1 locus which, in conjunction with the proper clinical and histologic features, is diagnostic of NMC. A negative result suggests no rearrangement of the NUTM1 gene region at 15q14. A confirmed diagnosis of NMC results in specific clinical management that may be distinct from the management of other carcinomas.

Reference Values:
An interpretive report will be provided.

Clinical References: 11. Bauer DE, Mitchell CM, Strait KM, et al: Clinicopathologic features and long-term outcomes of NUT midline carcinoma. Clin Cancer Res. 2012 Oct;18(20):5773-5779 2. Ziai J, French CA, Zambrano E: NUT gene rearrangement in a poorly-differentiated carcinoma of the submandibular gland. Head Neck Pathol. 2010 June;4(2):163-168 3. Herbert H, Johnson LA, Fry CJ, et al: Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. Am J Surg Pathol. 2009 July;33(7):984-991 4. Stelow EB, Bellizzi AM, Taneja K, et al: NUT rearrangement in undifferentiated carcinomas of the upper aerodigestive tract. Am J Surg Pathol. 2008 Jun;32(6):828-834 5. French CA: NUT midline carcinoma. NatRev Cancer. 2014 Jan;14:149-150

NMEG
82497

Nutmeg, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to nutmeg Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

NUTSP
31771

Nuts Allergen Profile, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to nuts Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/Equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070

FNGPG
57930

Nuts and Grains Panel IgG

Reference Values:

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should

only be ordered by physicians who recognize the limitations of the test.

FOAKE
57999

Oak Live (Quercus virginiana) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal/Borderline 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 49.99 Very High Positive 5 50.00 – 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

FROE
57907

Oak Red (Quercus rubra) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >=50 Very Strong Positive

Reference Values:
<0.35 kU/L

OAK
82673

Oak, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to oak Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FOATG
57576

Oat IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

OATS
82688

Oat, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to oat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE

antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

OCT2
70522

OCT-2 Immunostain, Technical Component Only

Clinical Information: OCT-2 is a transcription factor that binds to the octamer motif of the immunoglobulin gene promoter, recruits the coactivator BOB.1, and activates immunoglobulin gene transcription. OCT-2 is variably expressed in germinal center B cells, weakly expressed in mantle zone B cells, and weakly to moderately expressed in plasma cells. The protein is localized to the nuclear compartment. Expression of BOB.1, OCT-2, and PU.1 transcription factors are often downregulated in classical Hodgkin lymphoma. OCT-2 is overexpressed in lymphocyte-predominant (LP) cells of nodular LP Hodgkin lymphoma. These properties can be useful in the diagnosis of lymphoma.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. McCune RC, Syrbu SE, Vasef MA. Expression profiling of transcription factors Pax-5, Oct-1, Oct-2, BOB.1, and PU.1 in Hodgkin's and non-Hodgkin's lymphomas: a

comparative study using high throughput tissue microarrays. Mod Pathol. 2006;19(7):1010-1018 2. Loddenkemper C, Anagnostopoulos I, Hummell M, et al. Differential Emu enhancer activity and expression of BOB.1/OBF.1, Oct2, PU.1, and immunoglobulin in reactive B-cell populations, B-cell non Hodgkin lymphomas and Hodgkin lymphomas. J Pathol. 2004;202(1):60-69 3. Marafioti T, Ascani S, PulfordK, et al. Expression of B-lymphocyte-associated transcription factors in human T-cell neoplasm. Am J Pathol. 2003;162(3):861-871 4. O'Malley DP, Fedoriw Y, Weiss LM. Distinguishing classical Hodgkin lymphoma, gray zone lymphoma, and large B-cell lymphoma: A proposed scoring system. Appl Immunohistochem Mol Morphol. 2016;24(8):535-540. doi: 10.1097/PAI.0000000000000236 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

OCT4
70523

OCT3/4 Immunostain, Technical Component Only

Clinical Information: Octamer-binding transcription factor 3/4 (OCT4), also known as POU5F1, is a transcription factor expressed by embryonal stem cells and germ cells. Staining for OCT4 can aid in the diagnosis of testicular or ovarian germ cell tumors; it is highly specific for germ cell neoplasia, especially seminomas.

Useful For: Identification of germ cell tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Zhao FQ. Octamer-binding transcription factors: genomics and functions. Front Biosci. 2013;18:1051-1071 2. Cheng L, Sung MT, Cossu-rocca P, et al. OCT4: biological functions and clinical applications as a marker of germ cell neoplasia. J Pathol. 2007;211(1):1-9 3. Jung SM, Chu PH, Shiu TF, et al. Expression of OCT4 in the primary germ cell tumors and thymoma in the mediastinum. Appl Immunohistochem Mol Morphol. 2006;14(3):273-275 4. Lau SK, Chang KL. OCT4: a sensitive and specific immunohistochemical marker for metastatic germ cell tumors. Adv Anat Pathol. 2006;13(2):76-79 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

OCTO
82820

Octopus, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to octopus Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FLNZ
91129

Olanzapine (Zyprexa)

Reference Values:
Reference Range: 10.0 – 80.0 ng/mL

Expected steady state concentrations in patients on recommended daily dosages:
10 – 80.0 ng/mL
Plasma concentrations of olanzapine greater than 9.0 ng/mL have been associated with therapeutic effect.

Toxic range has not been established.

OLIG2
71357

OLIG2 Immunostain, Technical Component Only

Clinical Information: Oligodendrocyte transcription factor 2 (OLIG2) is a transcription factor that

participates in oligodendrocyte and motor neuron differentiation. During embryogenesis OLIG2 promotes the growth of motor neuron progenitor cells. OLIG2 expression decreases upon further neuronal differentiation. OLIG2 is also involved in oligodendrocyte differentiation where expression remains present in mature glial cells. In gliomas, OLIG2 represses the p53 tumor suppressor pathway, thereby contributing to glioma progression.

Useful For: Distinguishing gliomas from neurocytomas and ependymomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Suzuki A, Nobusawa S, Natsume A, et al. Olig2 labeling index is correlated with histological and molecular classifications in low-grade diffuse gliomas. J Neurooncol. 2014;120(2):283-291 2. Popova SN, Bergqvist M, Dimberg A, et al. Subtyping of gliomas of various WHO grades by the application of immunohistochemistry. Histopathology. 2014;64(3):365-379 3. Ballester LY, Wang Z, Shandilya S, et al. Morphologic characteristics and immunohistochemical profile of diffuse intrinsic pontine gliomas. Am J Surg Pathol. 2013;37(9):1357-1364 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

OLIGS
2783

Oligoclonal Banding, Serum

Clinical Information: The diagnosis of multiple sclerosis (MS) is dependent on clinical, radiological, and laboratory findings. The detection of increased intrathecal immunoglobulin (Ig) synthesis is the basis for current diagnostic laboratory tests for MS. These tests include kappa free light chains in the cerebrospinal fluid (CSF) and CSF oligoclonal band (OCB) detection. Abnormal CSF OCB patterns have been reported in 70% to 80% of MS patients. Increased intrathecal Ig synthesis may occur in other inflammatory CSF diseases, and therefore, this assay is not specific for MS.

Useful For: Diagnosis of multiple sclerosis; especially useful in patients with equivocal clinical presentation and radiological findings Determining number of serum oligoclonal bands in order to calculate the number of cerebrospinal fluid-specific bands present

Interpretation: When the oligoclonal band assay detects 2 or more unique IgG bands in the cerebrospinal fluid (CSF), the result is positive. Cerebrospinal fluid is used in the diagnosis of multiple sclerosis (MS) by identifying increased intrathecal IgG synthesis qualitatively (oligoclonal bands). The presence of 2 or more unique CSF oligoclonal bands was reintroduced as one of the diagnostic criteria for MS in the 2017 revised McDonald criteria. These findings, however, are not specific for MS as CSF-specific IgG synthesis may also be found in patients with other neurologic diseases including infectious, inflammatory, cerebrovascular, and paraneoplastic disorders. Clinical correlation recommended.

Reference Values:
Only orderable as part of a profile. For more information see:
-OLIG / Oligoclonal Banding, Serum and Spinal Fluid
-MSP3 / Multiple Sclerosis (MS) Cascade, Serum and Spinal Fluid

CSF Oligoclonal Bands Interpretation: <2 bands

Clinical References: 1. Andersson M, Alvarez-Cermeno J, Bernardi G, et al. Cerebrospinal fluid

in the diagnosis of multiple sclerosis: a consensus report. J Neurol Neurosurg Psychiatry. 1994;57(8):897-902 2. Fortini AS, Sanders EL, Weinshenker BG, Katzmann JA. Cerebrospinal fluid oligoclonal bands in the diagnosis of multiple sclerosis. Isoelectric focusing with IgG immunoblotting compared with high-resolution agarose gel electrophoresis and cerebrospinal fluid IgG index. Am J Clin Pathol. 2003;120(5):672-675 3. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-173 4. Gurtner KM, Shosha E, Bryant SC, et al. CSF free light chain identification of demyelinating disease: comparison with oligoclonal banding and other CSF indexes. Clin Chem Lab Med. 2018;56(7):1071-1080 5. Saadeh R, Pittock S, Bryant S, et al. CSF kappa free light chains as a potential quantitative alternative to oligoclonal bands in multiple sclerosis. Neurology. 2019;92(15_supplement). doi:10.1212/WNL.92.15_supplement.S37.001

OLIG 8017 Oligoclonal Banding, Serum and Spinal Fluid

Clinical Information: The diagnosis of multiple sclerosis (MS) is dependent on clinical, radiological, and laboratory findings. The detection of increased intrathecal immunoglobulin synthesis is the basis for current diagnostic laboratory tests for MS. These tests include the measurement of kappa free light chains in cerebrospinal fluid (CSF) and CSF oligoclonal band (OCB) detection. Abnormal CSF OCB patterns have been reported in 70% to 80% of MS patients. Increased intrathecal Ig synthesis may occur in other inflammatory CSF diseases and, therefore this assay is not specific for MS.

Useful For: Diagnosis of multiple sclerosis; especially useful in patients with equivocal clinical presentation and radiological findings

Interpretation: When the oligoclonal band assay detects 2 or more unique IgG bands in the cerebrospinal fluid (CSF), the result is positive. Cerebrospinal fluid is used in the diagnosis of multiple sclerosis (MS) by identifying increased intrathecal IgG synthesis qualitatively (oligoclonal bands). The presence of 2 or more unique CSF oligoclonal bands was reintroduced as one of the diagnostic criteria for MS in the 2017 revised McDonald criteria. These findings, however, are not specific for MS as CSF-specific IgG synthesis may also be found in patients with other neurologic diseases including infectious, inflammatory, cerebrovascular, and paraneoplastic disorders. Clinical correlation recommended.

Reference Values:
CSF Oligoclonal Bands Interpretation: <2 bands

Clinical References: 1. Andersson M, Alvarez-Cermeno J, Bernardi G, et al. Cerebrospinal fluid in the diagnosis of multiple sclerosis: a consensus report. J Neurol Neurosurg Psychiatry. 1994;57(8):897-902 2. Fortini AS, Sanders EL, Weinshenker BG, Katzmann JA. Cerebrospinal fluid oligoclonal bands in the diagnosis of multiple sclerosis. Isoelectric focusing with the IgG immunoblotting compared with high resolution agarose gel electrophoresis and cerebrospinal fluid IgG index. Am J Clin Pathol. 2003:120(5):672-675 3. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-173 4. Gurtner KM, Shosha E, Bryant SC, et al. CSF free light chain identification of demyelinating disease: comparison with oligoclonal banding and other CSF indexes. Clin Chem Lab Med. 2018;56(7):1071-1080 5. Saadeh R, Pittock S, Bryant S, et al. CSF kappa free light chains as a potential quantitative alternative to oligoclonal bands in multiple sclerosis. Neurology. 2019;92(15_supplement). doi:10.1212/WNL.92.15_supplement.S37.001

OLIGC 3484 Oligoclonal Banding, Spinal Fluid

Clinical Information: The diagnosis of multiple sclerosis (MS) is dependent on clinical, radiological,

and laboratory findings. The detection of increased intrathecal immunoglobulin (Ig) synthesis is the basis for current diagnostic laboratory tests for MS. These tests include the cerebrospinal fluid (CSF) IgG index and CSF oligoclonal band (OCB) detection. Abnormal CSF IgG indexes and OCB patterns have been reported in 70% to 80% of MS patients. Increased intrathecal Ig synthesis may occur in other inflammatory CSF diseases and, therefore, this assay is not specific for MS.

Useful For: Diagnosis of multiple sclerosis; especially useful in patients with equivocal clinical presentation and radiological findings

Interpretation: When the oligoclonal band assay detects 2 or more unique IgG bands in the cerebrospinal fluid (CSF), the result is positive. Cerebrospinal fluid is used in the diagnosis of multiple sclerosis (MS) by identifying increased intrathecal IgG synthesis qualitatively (oligoclonal bands). The presence of 2 or more unique CSF oligoclonal bands was reintroduced as one of the diagnostic criteria for MS in the 2017 revised McDonald criteria. These findings however, are not specific for MS as CSF-specific IgG synthesis may also be found in patients with other neurologic diseases including infectious, inflammatory, cerebrovascular, and paraneoplastic disorders. Clinical correlation recommended.

Reference Values:
Only orderable as part of a profile. For more information, see:
-OLIG / Oligoclonal Banding, Serum and Spinal Fluid
-MSP3 / Multiple Sclerosis (MS) Cascade, Serum and Spinal Fluid

Cerebrospinal fluid Oligoclonal Bands Interpretation: <2 bands

Clinical References: 1. Andersson M, Alvarez-Cermeno J, Bernardi G, et al. Cerebrospinal fluid in the diagnosis of multiple sclerosis: a consensus report. J Neurol Neurosurg Psychiatry. 1994;57(8):897-902 2. Fortini AS, Sanders EL, Weinshenker BG, Katzmann JA. Cerebrospinal fluid oligoclonal bands in the diagnosis of multiple sclerosis. Isoelectric focusing with the IgG immunoblotting compared with high resolution agarose gel electrophoresis and cerebrospinal fluid IgG index. Am J Clin Pathol. 2003:120(5):672-675 3. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-173 4. Gurtner KM, Shosha E, Bryant SC, et al. CSF free light chain identification of demyelinating disease: comparison with oligoclonal banding and other CSF indexes. Clin Chem Lab Med. 2018;56(7):1071-1080 5. Saadeh R, Pittock S, Bryant S, et al. CSF kappa free light chains as a potential quantitative alternative to oligoclonal bands in multiple sclerosis. Neurology. 2019;92(15_supplement). doi:10.1212/WNL.92.15_supplement.S37.001

OLIGU
64889

Oligosaccharide Screen, Random, Urine

Clinical Information:

Useful For: Screening for selected oligosaccharidosis

Interpretation: This is a screening test; not all oligosaccharidoses are detected. The resulting excretion profile may be characteristic of a specific disorder; however, abnormal results require confirmation by enzyme assay or molecular genetic testing. When abnormal results are detected with characteristic patterns, a detailed interpretation is given, including an overview of results and significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional confirmatory studies (enzyme assay, molecular genetic analysis).

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed June 9, 2025. Available at https://ommbid.mhmedical.com/content.aspx?bookId=2709&sectionId=225544161 2. Thomas GH. Disorders of glycoprotein degradation: Alpha-mannosidosis, beta-mannosidosis, fucosidosis, and sialidosis. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed June 9, 2025. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225545029 3. Leslie N, Bailey L. Pompe Disease. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1993-2025. Updated November 21, 2019. Accessed June 9, 2025. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1261/ 4. Raas-Rothschild A, Spiegel R. Mucolipidosis III Gamma. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1993-2025. Updated November 21,2019. Accessed June 9, 2025. Available at: www.ncbi.nlm.nih.gov/books/NBK24701/ 5. Leroy JG, Cathey SS, Friez MJ. GNPTAB-Related Disorders.]. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1993-2025. Updated August 29, 2019.Accessed June 9, 2025. Available at: www.ncbi.nlm.nih.gov/books/NBK1828/

FOLBG
57671

Olive Black IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

OLIV
82733

Olive Tree, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to olive tree Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

OLIVF
86306

Olive-Food, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to olive-food Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with

the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FONG
57636

Onion IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

ONIN
82806

Onion, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to onion Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

OPTMX
62736

Opiate Confirmation, Chain of Custody, Meconium

Clinical Information: Opiates are naturally occurring alkaloids that are derived from the opium poppy and demonstrate analgesic effects. Opioids are derived from natural and semisynthetic alkaloids of opium or synthetic compounds(1): -Codeine is a naturally occurring opioid agonist often incorporated into formulations along with acetaminophen or aspirin to increase its analgesic effect.(2) Codeine is metabolized to morphine and subsequently undergoes glucuronidation and sulfation. -Morphine is an opioid receptor agonist used for major pain analgesia.(2) It has been shown to distribute widely into many fetal tissues(3) and has been detected in meconium. -Hydrocodone is a semisynthetic analgesic derived from codeine. Hydrocodone is 6 times more potent than codeine and is prescribed for treatment of moderate-to-moderately severe pain.(2) Hydrocodone undergoes O-demethylation in vivo, forming hydromorphone. -Hydromorphone, a semisynthetic derivative of morphine, is an opioid analgesic. It is 7 to 10 times more potent than morphine, its addiction liability is similar to morphine.(2) -Oxycodone, a semisynthetic narcotic derived from thebaine. It is metabolized by O-demethylation, forming oxymorphone.(2) -Oxymorphone is a semisynthetic opioid derivative of thebaine and is indicated for moderate-to-severe pain.(2) -Heroin, a semisynthetic derivative of morphine, is rapidly deacetylated in vivo to the active metabolite 6-monoacetylmorphine (6-MAM), which is further

hydrolyzed to morphine.(2) Opiates have been shown to readily cross the placenta and distribute widely into many fetal tissues. Opiate use by the mother during pregnancy increases the risk of prematurity and small size for gestational age. Furthermore, heroin-exposed infants exhibit an early onset of withdrawal symptoms compared to methadone-exposed infants. These infants demonstrate a variety of symptoms including irritability, hypertonia, wakefulness, diarrhea, yawning, sneezing, increased hiccups, jitteriness, excessive sucking, and seizures. Long-term intrauterine drug exposure may lead to abnormal neurocognitive and behavioral development as well as an increased risk of sudden infant death syndrome. The disposition of opiates and opioids in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and it slowly moves into the colon by the 16th week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis. Chain of custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting maternal prenatal opiate/opioid use up to 5 months before birth Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

Interpretation: The presence of any of the following opiates (codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone) at 20 ng/g or more or 6-monoacetylmorphine at 10 ng/g or more indicates the newborn was exposed to opiates/opioids during gestation.

Reference Values:
Negative

Positives are reported with a quantitative liquid chromatography tandem mass spectrometry (LC-MS/MS) result.
Cutoff concentrations for LC-MS/MS testing:
Codeine: 20 ng/mL
Hydrocodone: 20 ng/mL
Hydromorphone: 20 ng/mL
Morphine: 20 ng/mL
Oxycodone: 20 ng/mL
Oxymorphone: 20 ng/mL

Clinical References: 1. Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill; 2006 2. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020 3. Szeto HH. Kinetics of drug transfer to the fetus. Clin Obstet Gynecol. 1993;36:246-254 4. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero: mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60:45-56 5. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:454-454: chap 43

OPATM
84326

Opiate Confirmation, Meconium

Clinical Information: Opiates are naturally occurring alkaloids that are derived from the opium poppy and demonstrate analgesic effects. Opioids are derived from natural and semisynthetic alkaloids of opium or synthetic compounds(1): -Codeine is a naturally occurring opioid agonist often incorporated into formulations along with acetaminophen or aspirin to increase its analgesic effect.(2) Codeine is metabolized to morphine and subsequently undergoes glucuronidation and sulfation. -Morphine is an opioid receptor agonist used for major pain analgesia.(2) It has been shown to distribute widely into many fetal tissues(3) and has been detected in meconium. -Hydrocodone is a semisynthetic analgesic derived from codeine. Hydrocodone is 6 times more potent than codeine and is prescribed for treatment of moderate-to-moderately severe pain.(2) Hydrocodone undergoes O-demethylation in vivo, forming hydromorphone. -Hydromorphone, a semisynthetic derivative of morphine, is an opioid analgesic. It is 7 to 10 times more potent than morphine, its addiction liability is similar to morphine.(2) -Oxycodone, a semisynthetic narcotic derived from thebaine. It is metabolized by O-demethylation, forming oxymorphone.(2) -Oxymorphone is a semisynthetic opioid derivative of thebaine and is indicated for moderate-to-severe pain.(2) -Heroin, a semisynthetic derivative of morphine, is rapidly deacetylated in vivo to the active metabolite 6-monoacetylmorphine (6-MAM), which is further hydrolyzed to morphine.(2) Opiates have been shown to readily cross the placenta and distribute widely into many fetal tissues. Opiate use by the mother during pregnancy increases the risk of prematurity and small size for gestational age. Furthermore, heroin-exposed infants exhibit an early onset of withdrawal symptoms compared to methadone-exposed infants. These infants demonstrate a variety of symptoms, including irritability, hypertonia, wakefulness, diarrhea, yawning, sneezing, increased hiccups, jitteriness, excessive sucking, and seizures. Long-term intrauterine drug exposure may lead to abnormal neurocognitive and behavioral development as well as an increased risk of sudden infant death syndrome. The disposition of opiates and opioids in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and it slowly moves into the colon by the 16th week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.

Useful For: Detecting maternal prenatal opiate/opioid use up to 5 months before birth

Interpretation: The presence of any of the following opiates (codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone) at 20 ng/g or greater or 6-monoacetylmorphine at 10 ng/g or greater indicates the newborn was exposed to opiates/opioids during gestation.

Reference Values:
Negative

Positives are reported with a quantitative liquid chromatography tandem mass spectrometry (LC-MS/MS) result.

Cutoff concentrations for LC-MS/MS testing:
Codeine: 20 ng/g
Hydrocodone: 20 ng/g
Hydromorphone: 20 ng/g
Morphine: 20 ng/g
Oxycodone: 20 ng/g
Oxymorphone: 20 ng/g

Clinical References: 1. Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill; 2006 2. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020 3. Szeto HH. Kinetics of drug transfer to the fetus. Clin Obstet Gynecol. 1993;36(2):246-254 4. Ahanya SN, Lakshmanan J, Morgan BLG, Ross MG. Meconium passage in utero: mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-56 5. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:454-454: chap 43

OPATX
62735

Opiates Confirmation, Chain of Custody, Random, Urine

Clinical Information: Codeine is converted by hepatic metabolism to morphine and norcodeine with a half-life of 2 to 4 hours. If codeine is ingested, the ratio of codeine to morphine generally exceeds 1.0 in urine during the first 24 hours. The ratio may fall below 1.0 after 24 hours; and after 30 hours, only morphine may be detected. Morphine is a naturally occurring narcotic analgesic obtained from the poppy plant, Papaver somniferum. Morphine is converted by hepatic metabolism to normorphine with a half-life of 2 to 4 hours. The presence of morphine in urine can indicate exposure to morphine, heroin, or codeine within 2 to 3 days. Ingestion of bakery products containing poppy seeds can also cause morphine to be excreted in urine. If excessively large amounts are consumed, this can result in urine morphine concentrations up to 2000 ng/mL for a period of 6 to 12 hours after ingestion. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the 6-beta hydroxymetabolites. Hydromorphone and norhydrocodone are both metabolites of hydrocodone. Dihydrocodeine is also a minor metabolite. Trace amounts of hydrocodone can also be found in the presence of approximately 100-fold higher concentrations of oxycodone or hydromorphone since it can be a pharmaceutical impurity in these medications. The presence of hydrocodone indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The presence of hydromorphone indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone; therefore, the presence of hydromorphone could also indicate exposure to hydrocodone. Dihydrocodeine is a semisynthetic narcotic analgesic prepared by the hydrogenation of codeine. It is also a minor metabolite of hydrocodone. It is metabolized to dihydromorphine and has a half-life of 3.4 to 4.5 hours. Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone. Naloxone is a synthetic narcotic antagonist and used for partial or complete reversal of opioid depression induced by natural or synthetic opioids. It has also been incorporated into oral tablets of opioids to discourage abuse. The duration of action is dependent on the dose and route of administration. The half-life in adults is approximately 30 to 81 minutes. The detection interval for the opiates is generally 2 to 3 days after last ingestion. Chain of custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detection and quantification of codeine, hydrocodone, oxycodone, morphine, hydromorphone, oxymorphone, noroxycodone, noroxymorphone, norhydrocodone, dihydrocodeine, and naloxone in urine Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: This procedure reports the total urine concentration; this is the sum of the

unconjugated and conjugated forms of the parent drug.

Reference Values:
Negative
Positive results are reported with a quantitative result.

Cutoff concentrations:

Immunoassay screen: 300 ng/mL

Liquid chromatography tandem mass spectrometry:
Codeine: 25 ng/mL
Dihydrocodeine: 25 ng/mL
Hydrocodone: 25 ng/mL
Norhydrocodone: 25 ng/mL
Hydromorphone: 25 ng/mL
Oxycodone: 25 ng/mL
Noroxycodone: 25 ng/mL
Oxymorphone: 25 ng/mL
Noroxymorphone: 25 ng/mL
Naloxone: 25 ng/mL
Morphine: 25 ng/mL

Clinical References: 1. Jutkiewicz EM, Traynor JR. Opioid analgesics. In: Brunton LL, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 14th ed. McGraw-Hill Companies, Inc; 2023:chap 23 2. Baselt, RC. Disposition of Toxic Drugs and Chemical in Man. 10th ed. Biomedical Publications; 2014 3. Hackett LP, Dusci LJ, Ilett KF, Chiswell GM. Optimizing the hydrolysis of codeine and morphine glucuronides in urine. Ther Drug Monit. 2002;24(5):652-657 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

OPATU
8473

Opiates Confirmation, Random, Urine

Clinical Information: Codeine is converted by hepatic metabolism to morphine and norcodeine with a half-life of 2 to 4 hours. If codeine is ingested, the ratio of codeine to morphine generally exceeds 1.0 in urine during the first 24 hours. The ratio may fall below 1.0 after 24 hours, and after 30 hours, only morphine may be detected. Morphine is a naturally occurring narcotic analgesic obtained from the poppy plant, Papaver somniferum. Morphine is converted by hepatic metabolism to normorphine with a half-life of 2 to 4 hours. The presence of morphine in urine can indicate exposure to morphine, heroin, or codeine within 2 to 3 days. Ingestion of bakery products containing poppy seeds can also cause morphine to be excreted in urine. If excessively large amounts are consumed, this can result in urine morphine concentrations up to 2000 ng/mL for a period of 6 to 12 hours after ingestion. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the 6-beta hydroxymetabolites. Hydromorphone and norhydrocodone are both metabolites of hydrocodone. Dihydrocodeine is also a minor metabolite. Trace amounts of hydrocodone can also be found in the presence of approximately 100-fold higher concentrations of oxycodone or hydromorphone since it can be a pharmaceutical impurity in these medications. The presence of hydrocodone indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The presence of hydromorphone indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone; therefore, the presence of hydromorphone could also indicate exposure to hydrocodone.

Dihydrocodeine is a semisynthetic narcotic analgesic prepared by the hydrogenation of codeine. It is also a minor metabolite of hydrocodone. It is metabolized to dihydromorphine and has a half-life of 3.4 to 4.5 hours. Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides, and is excreted primarily via the kidney. The presence of oxycodone indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone. Naloxone is a synthetic narcotic antagonist and used for partial or complete reversal of opioid depression induced by natural or synthetic opioids. It has also been incorporated into oral tablets of opioids to discourage abuse. The duration of action is dependent on the dose and route of administration. The half-life in adults is approximately 30 to 81 minutes. The detection interval for opiates is generally 2 to 3 days after last ingestion.

Useful For: Detection and quantification of codeine, hydrocodone, oxycodone, morphine, hydromorphone, oxymorphone, noroxycodone, noroxymorphone, norhydrocodone, dihydrocodeine, and naloxone in urine

Interpretation: This test reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

Reference Values:

Negative

Positive results are reported with a quantitative result.

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Codeine: 25 ng/mL
Dihydrocodeine: 25 ng/mL
Hydrocodone: 25 ng/mL
Norhydrocodone: 25 ng/mL
Hydromorphone: 25 ng/mL
Oxycodone: 25 ng/mL
Noroxycodone: 25 ng/mL
Oxymorphone: 25 ng/mL
Noroxymorphone: 25 ng/mL
Naloxone: 25 ng/mL
Morphine: 25 ng/mL

Clinical References: 1. Jutkiewicz EM, Traynor JR. Opioid analgesics. In: Brunton LL, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 14th ed. McGraw-Hill Companies, Inc; 2023:chap 23 2. Baselt, RC. Disposition of Toxic Drugs and Chemical in Man. 10th ed. Biomedical Publications; 2014 3. Hackett LP, Dusci LJ, Ilett KF, Chiswell GM. Optimizing the hydrolysis of codeine and morphine glucuronides in urine. Ther Drug Monit. 2002;24(5):652-657 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

FOPIA
75030

Opiates, Serum or Plasma, Quantitative

Interpretation:

Reference Values:

Drugs covered: codeine, morphine, 6-acetylmorphine, hydrocodone, hydromorphone, oxycodone, and oxymorphone. All drugs covered and the non-glucuronidated (free) form.

Positive cutoff: 2 ng/mL

For medical purposes only; not valid for forensic use.

FCDU1
75776

Opiates, Umbilical Cord Tissue

Reference Values:
Reporting limit determined each analysis.

Units: ng/g

Only orderable as part of a profile-see FCDSU.

FORNG
57632

Orange IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

ORNG
82740

Orange, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to orange Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased

likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ORCH
82907

Orchard Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to orchard grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FORGG
57661

Oregano IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

OREG
82496

Oregano, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to oregano Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or

anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ORXNA
604230

Orexin-A/Hypocretin-1, Spinal Fluid

Clinical Information: Narcolepsy affects 0.02% to 0.05% of the population and the onset of symptoms often occurs in adolescence. Orexin (also known as orexin-A or hypocretin-1) is a neuropeptide produced in the hypothalamus and is involved in the sleep/wake cycle in humans. Impairment of orexin production and orexin-modulated neurotransmission is associated with narcolepsy with cataplexy (episodes of muscle weakness in response to emotional stimuli). An abnormally low concentration of orexin-A/hypocretin-1 in cerebrospinal fluid (CSF) is indicative of what is termed type 1 narcolepsy. Survey of the literature reveals that approximately 85% to 95% of randomly selected individuals with type 1 narcolepsy and typical cataplexy, exhibit low (<110 pg/mL) CSF orexin (hypocretin-1) concentrations.(1) In one large study, the sensitivity of this cutoff was found to be 87% with a specificity of 99%.(2) Orexin deficiency and type 1 narcolepsy are closely associated with HLA (human leukocyte antigen) complex DQB1 *0602. However, while almost all individuals with narcolepsy exhibit this particular HLA complex, it is not specific for the presence of narcolepsy type 1. CSF concentrations have been found to almost always be above 200 pg/mL in healthy individuals and those with non-type 1-narcoleptic sleep disorders such as narcolepsy type 2 and idiopathic hypersomnia.

Useful For: Aiding in the diagnosis and differentiation of type 1 narcolepsy from other causes of hypersomnolence This assay is not intended for use as a screening test.

Interpretation: The diagnostic criteria for type 1 narcolepsy in the International Classification of Sleep Disorders (3) include the presence of hypersomnia, cataplexy (episodes of muscle weakness in response to emotional stimuli) and measured cerebrospinal fluid (CSF) orexin (hypocretin-1) concentrations less than or equal to 110 pg/mL. Orexin (hypocretin-1) CSF concentrations have been classified into 3 categories in the literature. They include low (< or =110 pg/mL), which is indicative of type 1 narcolepsy; intermediate (ranges between 111-200 pg/mL); and normal (>200 pg/mL). Previous studies have shown that 106 of 113 patients with clinically defined type 1 narcolepsy exhibited low (<110 pg/mL) orexin concentrations. In another study, all 48 healthy individuals exhibited orexin (hypocretin-1) CSF concentrations above 200 pg/mL.

Reference Values:
Normal individuals: >200 pg/mL

Previous literature has defined cerebrospinal fluid orexin-A/hypocretin-1 concentrations of 110 pg/mL or below as being consistent with narcolepsy type 1-(Mignot E. Arch Neurol. 2002:59;1553-1562). Concentrations between 111 pg/mL and 200 pg/mL are considered intermediate and have limited diagnostic utility for narcolepsy, as they may be representative of other neurological disorders. Concentrations above 200 pg/mL are considered normal.

Clinical References: 1. Bourgin P, Zeitzer JM, Mignot E. CSF hypocretin-1 assessment in sleep and neurological disorders. Lancet Neurol. 2008;7(7):649-662. doi:10.1016/S1474-4422(08)70140-6 2. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol. 2002;59(10):155-162. doi:10.1001/archneur.59.10.1553 3. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387-1394. doi:10.1378/chest.14-0970 4. Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. Lancet. 2007;369(9560):499-511. doi:10.1016/S0140-6736(07)60237-2 5. Ripley B, Overeem S, Fujiki N, et al. CSF hypocretin/orexin levels in narcolepsy and other neurological conditions. Neurology. 2001;57(12):2253-2258. doi:10.1212/wnl.57.12.2253 6. Liblau RS, Vassalli A, Seifinejad A, Tafti M. Hypocretin (orexin) biology and the pathophysiology of narcolepsy with cataplexy. Lancet Neurol. 2015;14(3):318-328. doi:10.1016/S1474-4422(14)70218-2 7. Keating G, Bliwise DL, Saini P, Rye DB, Trotti LM. Hypocretin measurement: shelf age of radioimmunoassay kit, but not freezer time, influences assay variability. Scand J Clin Lab Invest. 2017;77(5):390-393. doi:10.1080/00365513.2017.1325928 8. Sahni AS, Carlucci M, Malik M, Prasad B. Management of excessive sleepiness in patients with narcolepsy and OSA: Current challenges and future prospects. Nat Sci Sleep. 2019;11:241-252. Published 2019 Oct 23. doi:10.2147/NSS.S218402

OAU
80619

Organic Acids Screen, Random, Urine

Clinical Information: Organic acids occur as physiologic intermediates in a variety of metabolic pathways. Organic acidurias are a group of disorders in which one or more of these pathways are blocked, resulting in a deficiency of normal products and an abnormal accumulation of intermediate metabolites (organic acids) in the body. These excess metabolites are excreted in the urine. The incidence of individual inborn errors of organic acid metabolism varies from 1 in 10,000 to greater than 1 in 1,000,000 live births. Collectively, their incidence approximates 1 in 3000 live births. This estimate, however, does not include other inborn errors of metabolism (ie, amino acid disorders, urea cycle disorders, congenital lactic acidemias) for which diagnosis and monitoring may require organic acid analysis. If all possible disease entities were included, the incidence of conditions where informative organic acid profiles could be detected in urine is likely to approach 1 in 1000 live births. Organic acidurias typically present with either an acute life-threatening illness in early infancy or unexplained developmental delay with intercurrent episodes of metabolic decompensations in later childhood. A situation of severe and persistent metabolic acidosis of unexplained origin, elevated anion gap, and severe neurologic manifestations, such as seizures, should be considered strong diagnostic

indicators of one of these diseases. The presence of ketonuria, occasionally massive, provides an important clue toward the recognition of disorders, especially in the neonatal period. Hyperammonemia, hypoglycemia, and lactic acidemia are frequent findings, especially during acute episodes of metabolic decompensations.

Useful For: Diagnosis of inborn errors of metabolism

Interpretation: When no significant abnormalities are detected, the organic acid analysis is reported and interpreted in qualitative terms only. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis).

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Lehotay DC, Clarke JT. Organic acidurias and related abnormalities. Crit Rev Clin Lab Sci. 1995;32(4):377-429 2. Ferreira CR, van Karnebeek CDM. Inborn errors of metabolism. In: de Vries LS, Glass HC, eds. Neonatal Neurology. Elsevier; 2019:449-481. Handbook of Clinical Neurology. Vol 162 3. Chapman KA. Practical management of organic acidemias. Trans Sc Rare Dis. 2019;1-12. doi:10.3233/TRD-190039

OAUS
610707

Organic Acids Screen, Urine Spot

Clinical Information: Organic acids occur as physiologic intermediates in a variety of metabolic pathways. Organic acidurias are a group of disorders in which one or more of these pathways are blocked, resulting in a deficiency of normal products and an abnormal accumulation of intermediate metabolites (organic acids) in the body. These excess metabolites are excreted in the urine. The incidence of individual inborn errors of organic acid metabolism varies from 1 in 10,000 to greater than 1 in 1,000,000 live births. Collectively, their incidence approximates 1 in 3000 live births. This estimate, however, does not include other inborn errors of metabolism (ie, amino acid disorders, urea cycle disorders, congenital lactic acidemias) for which diagnosis and monitoring may require organic acid analysis. If all possible disease entities were included, the incidence of conditions where informative organic acid profiles could be detected in urine is likely to approach 1 in 1000 live births. Organic acidurias typically present with either an acute life-threatening illness in early infancy or unexplained developmental delay with intercurrent episodes of metabolic decompensations in later childhood. A situation of severe and persistent metabolic acidosis of unexplained origin, elevated anion gap, and severe neurologic manifestations, such as seizures, should be considered strong diagnostic indicators of one of these diseases. The presence of ketonuria, occasionally massive, provides an important clue toward the recognition of disorders, especially in the neonatal period. Hyperammonemia, hypoglycemia, and lactic acidemia are frequent findings, especially during acute episodes of metabolic decompensations.

Useful For: Diagnosis of inborn errors of metabolism using dried urine specimens

Interpretation: When no significant abnormalities are detected, the organic acid analysis is reported and interpreted in qualitative terms only. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis).

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Lehotay DC, Clarke JT. Organic acidurias and related abnormalities. Crit Rev Clin Lab Sci. 1995;32(4):377-429 2. Ferreira CR, van Karnebeek CDM. Inborn errors of metabolism. In: de Vries LS, Glass HC, eds. Neonatal Neurology. Elsevier; 2019:449-481. Handbook of Clinical Neurology. Vol 162 3. Chapman KA. Practical management of organic acidemias. Trans Sc Rare Dis. 2019;1-12. doi:10.3233/TRD-190039

IDENT
9221

Organism Referred for Identification, Aerobic Bacteria

Clinical Information: Organisms are referred to confirm identification or when the identity is unknown. This may provide helpful information regarding the significance of the organism, its role in the disease process, and its possible origin. Techniques employed may include conventional biochemical analysis, commercial identification strips or panels, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry or sequencing nucleic acid of the 16S ribosomal RNA gene.

Useful For: Identification of pure isolates of aerobic bacteria Differentiation of members of the Staphylococcus aureus complex (S aureus, Staphylococcus argenteus, Staphylococcus schweitzeri)

Interpretation: Genus and species are reported on aerobic bacterial isolates, whenever possible. Bacillus species will be reported out as "Large spore-forming aerobic gram-positive Bacillus, not Bacillus cereus or Bacillus anthracis," unless species identification is specifically requested on the request form.

Reference Values:
Identification of organism

Clinical References: 1. Carroll KC, Pfaller MA, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019 2. Procop GW, Church DL, Hall GD, et al, eds. Koneman's Color Atlas and Textbook of Diagnostic Microbiology. 7th ed. Lippincott Williams and Wilkins; 2017

ANIDE
8114

Organism Referred for Identification, Anaerobic Bacteria

Clinical Information: Anaerobic bacteria are the greatest component of the human body's normal bacterial microbiota colonizing the skin, oral cavity, and genitourinary and lower gastrointestinal tracts. Their presence is important in promoting vitamin and other nutrient absorption and in preventing infection with disease-causing bacteria. Anaerobes generally are of low pathogenicity but may possess virulence factors, such as endotoxin or polysaccharide capsules, or produce extracellular toxins. Disease occurs when a large inoculum develops in an area lacking oxygen or with a poor blood supply. Typical anaerobic infections include peritonitis, abdominal or pelvic abscesses, endometritis, pelvic inflammatory disease, aspiration pneumonia, empyema, lung abscesses, sinusitis, brain abscesses, gas gangrene, and other soft tissue infections. Many Bacteroides produce beta-lactamase and are resistant to penicillins and cephalosporins. Imipenem, metronidazole, and clindamycin are effective agents, although resistance to clindamycin is increasing.

Useful For: Identifying anaerobic bacteria involved in human infections

Interpretation: Isolation of anaerobes in significant numbers from well-collected specimens from blood, other normally sterile body fluids, or closed collections of purulent fluid indicates infection with the identified organism.

Reference Values:
Identification of organism

Clinical References: 1. Jousimies-Somer HR, Summanen P, Citron DM, et al: Wadsworth Anaerobic Bacteriology Manual. 6th ed. Star Publishing Co; 2002 2. Baron EJ: Approaches to identification of anaerobic bacteria. In: Jorgensen JH, Carroll KC. Funke G, et al, eds. Manual of Clinical Microbiology. 11th ed. ASM Press; 2015:905-908 3. Hall GS: Anaerobic bacteriology. In: Garcia LS, ed. Clinical Microbiology Procedures Handbook. Vol 1. 3rd ed. ASM Press; 2010:section 4 4. Song Y, Finegold SM: Peptostreptococcus, Finegoldia, Anaerococcus, Peptoniphilus, Veillonella, and other anaerobic cocci. In: Jorgensen JH, Carroll KC. Funke G, et al, eds. Manual of Clinical Microbiology. 11th ed. ASM Press; 2015:909-919 5. Hall V, Copsey SD: Propionibacterium, Lactobacillus, Actinomyces, and other non-spore-forming anaerobic gram-positive rods. In: Jorgensen JH, Carroll KC. Funke G, et al, eds. Manual of Clinical Microbiology. 11th ed. ASM Press; 2015:920-939 6. Stevens DL, Bryant AE, Carroll K: Clostridium. In: Jorgensen JH, Carroll KC. Funke G, et al, eds. Manual of Clinical Microbiology. 11th ed. ASM Press; 2015:940-966 7. Kononen E, Conrads G, Nagy E: Bacteroides, Porphyromonas, Prevotella, Fusobacterium, and other anaerobic gram-negative rods. In: Jorgensen JH, Carroll KC. Funke G, et al, eds. Manual of Clinical Microbiology. 11th ed. ASM Press; 2015:967-993

OROT
8905

Orotic Acid, Random, Urine

Clinical Information: Urinary excretion of orotic acid, an intermediate in pyrimidine biosynthesis, is increased in many urea cycle disorders and in a number of other disorders involving the metabolism of arginine. The determination of orotic acid can be useful to distinguish between various causes of elevated ammonia (hyperammonemia). Hyperammonemia is characteristic of all urea cycle disorders, but orotic acid is only elevated in some, including ornithine transcarbamylase (OTC) deficiency, citrullinemia, and argininosuccinic aciduria. Orotic acid is also elevated in the transport defects of dibasic amino acids (lysinuric protein intolerance and hyperornithinemia, hyperammonemia, and homocitrullinuria [HHH] syndrome) and is greatly elevated in patients with hereditary orotic aciduria (uridine monophosphate synthase [UMPS] deficiency). Ornithine transcarbamylase deficiency is an X-linked urea cycle disorder that affects patients to varying degrees based on their sex and severity of molecular OTC variant. It is thought to be the most common urea cycle disorder, with an estimated incidence of 1:56,000. In OTC deficiency, carbamoyl phosphate accumulates and is alternatively metabolized to orotic acid. Allopurinol inhibits orotidine monophosphate decarboxylase and, when given to OTC carriers (who may have normal orotic acid excretion), can cause increased excretion of orotic acid. When orotic acid is measured after a protein load or administration of allopurinol, its excretion is a very sensitive indicator of OTC activity. A carefully monitored allopurinol challenge followed by several determinations of a patient's orotic acid excretion can be useful to identify OTC carriers, as approximately 5% to 10% of OTC variant are not detectable by current molecular genetic testing methods.

Useful For: Evaluation of the differential diagnosis of hyperammonemia and hereditary orotic aciduria
Sensitive indicator of ornithine transcarbamylase (OTC) activity after administration of allopurinol or a protein load to identify OTC carriers

Interpretation: The value for the orotic acid concentration is reported. The interpretation of the result must be correlated with clinical and other laboratory findings.

Reference Values:
< or =6 years: < or =4 mmol/mol creatinine
7-18 years: < or =3 mmol/mol creatinine
> or =19 years: 5 mmol/mol creatinine

Clinical References: 1. Singh RH, Rhead WJ, Smith W, et al. Nutritional management of urea cycle

disorders. Crit Care Clin. 2005;21(4 Suppl):S27-35 2. Lee B, Singh RH, Rhead WJ, et al. Considerations in the difficult-to-manage urea cycle disorder patient. Crit Care Clin. 2005;21(4 Suppl):S19-25 3. Brusilow SW, Horwich AL. Urea cycle enzymes. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed February 25, 2025. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225084071 4. Webster DR, Becroft DO, van Gennip AH, Van Kuilenburg AP. Hereditary orotic aciduria and other disorders of pyrimidine metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease., McGraw-Hill; 2019. Accessed February 25, 2025. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225090376 5. Ah Mew N, Simpson KL, Gropman AL, Lanpher BC, Chapman KA, Summar, ML. Urea cycle disorders overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated May 26, 2022. Accessed February 25, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1217

FORRT
57968

Orris Root (Iris florentina) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

OTP
620710

Orthopedia Homeobox Protein (OTP) Immunostain, Technical Component Only

Clinical Information: Orthopedia homeobox protein (OTP) is a nuclear transcription factor which may serve as a novel prognostic factor associated with pulmonary carcinoid tumors. Negative or weak expression of OTP is associated with poor prognosis. Nuclear staining for OTP is reported to have high sensitivity and specificity for the diagnosis of lung carcinoid tumors. Cytoplasmic granular staining does not reflect OTP expression and should not be regarded as positive.

Useful For: Distinguishing lung carcinoid tumors from metastatic neuroendocrine tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Moonen L, Derks J, Dingemans AM, Speel EJ, Al. Orthopedia homeobox (OTP) in pulmonary neuroendocrine tumors: The diagnostic value and possible molecular interactions. Cancers. 2019;11(10),1508 2. Viswanathan K, Borczuk AC, Siddiqui MT, Orthopedia homebox protein (OTP) is a sensitive and specific marker for primary pulmonary carcinoid tumors in cytologic and surgical specimens. J Am Soc Cytopathol. 2019;8(1):39-46 3. Hanley KZ, Dureau ZJ, Cohen C, et al. Orthopedia homeobox is preferentially expressed in typical carcinoids of the lung. Cancer Cytopathol. 2018;126(4):236-242

OPTU
614360

Orthostatic Protein, Timed Collection, Urine

Clinical Information: Orthostatic proteinuria refers to the development of increased proteinuria that develops only when the person is upright and resolves when recumbent or supine. This condition is usually seen in children, adolescents, or young adults, and accounts for the majority of cases of proteinuria in childhood. Orthostatic proteinuria usually does not indicate significant underlying renal pathology, and is usually not associated with other urine abnormalities such as hypoalbuminemia, hematuria, red blood cell casts, fatty casts, etc. Orthostatic proteinuria typically resolves over time. This test characterizes this condition by obtaining 2 urine collections within a 24-hour time frame, one collection obtained while the person is recumbent or supine, the other when upright.

Useful For: Diagnosis of orthostatic proteinuria As a second-order test for additional characterization of proteinuria of less than 3 grams/24 hours, particularly in children or adolescents

Interpretation: A supine 8-hour urine protein excretion of less than 68 mg/8 hours together with either 1) an elevated upright (16-hour) excretion of greater than 197 mg/16 hours, or 2) a 24-hour urine protein excretion of greater than 228 mg/24 hours is considered consistent with orthostatic proteinuria.

Reference Values:
Nighttime (supine) collection: <68 mg/8 hours
Reference values have not been established for patients <18 years of age.

Daytime collection: <197 mg/16 hours
Reference values have not been established for patients <18 years of age

Clinical References: 1. Rinehart BK, Terrone DA, Larmon JE, et al: A 12-hour urine collection accurately assesses proteinuria in hospitalized hypertensive gravida. J Perinatol. 1999;19:556-558 2. Adelberg AM, Miller J, Doerzbacher M, Lambers DS: Correlation of quantitative protein measurements in 8-, 12-, and 24-hour urine samples for diagnosis of preeclampsia. Am J Obstet Gynecol. 2001 Oct;185(4):804-807 3. Rytand DA, Spreiter S: Prognosis in postural (orthostatic) proteinuria: forty to fifty-year follow-up of six patients after diagnosis by Thomas Addis. N Engl J Med. 1981;305(11):618-621 4. Robinson RR: Isolated proteinuria in asymptomatic patients. Kidney Int. 1980;18:395-406 5. Dube J, Girouard J, Leclerc P et al: Problems with the estimation of urine protein by automated assays. Clin Biochem. 2005:38(5) 479-485 6. Koumantakis G, Wyndham, L: Fluorescein interference with urinary creatinine and protein measurements. Clin Chem. 1991;37(10):1799 7. Lamb EJ, Jones GRD: Kidney function tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:479-517

ORTHP
617766

Orthostatic Proteinuria, Random, Urine

Clinical Information: Orthostatic proteinuria refers to the development of increased proteinuria that develops only when the person is upright and resolves when recumbent or supine. This condition is usually seen in children, adolescents, or young adults, and accounts for the majority of cases of proteinuria in childhood. Orthostatic proteinuria usually does not indicate significant underlying renal pathology, and is usually not associated with other urine abnormalities such as hypoalbuminemia, hematuria, red blood cell casts, fatty casts, etc. Orthostatic proteinuria typically resolves over time. This test evaluates for this condition by demonstrating either significant proteinuria, even while supine, or normal protein excretion. Significant proteinuria, even while supine, suggests that the patient does not have orthostatic proteinuria while normal protein excretion supports the diagnosis. This test is typically done on three consecutive mornings to provide more robust support for the diagnosis.

Useful For: Diagnosis of orthostatic proteinuria

Interpretation: First-morning urine protein-to-creatinine ratio below 0.20 mg/mg creatinine supports the diagnosis of orthostatic proteinuria, while a result above 0.20 mg/mg creatinine does not support this diagnosis. Further investigation into other etiologies for proteinuria may be warranted.

Reference Values:
PROTEIN/CREATININE RATIO:
> or =18 years: <0.18 mg/mg creatinine

CREATININE:> or =18 years = 16-326 mg/dL
Reference values have not been established for patients younger than 18 years of age.

Clinical References: 1. Brunzel N: Chemical examination of urine. In: Fundamentals of Urine and Body Fluids. 4th ed. Saunders; 2018:92-94 2. Wilson DM, Anderson RL: Protein-osmolality ratio for the quantitative assessment of proteinuria from a random urinalysis sample. Am J Clin Pathol. 1993 Oct;100(4):419-424 3. Morgenstern BZ, Butani L, Wollan P, Wilson DM, Larson TS: Validity of protein-osmolality versus protein-creatinine ratios in the estimation of quantitative proteinuria from random samples of urine in children. Am J Kidney Dis. 2003 Apr;41(4):760-766 4. Rinehart BK, Terrone DA, Larmon JE, Perry KG Jr, Martin RW, Martin JN Jr: A 12-hour urine collection accurately assesses proteinuria in hospitalized hypertensive gravida. J Perinatol. 1999 Dec;19(8 Pt 1):556-558 5. Adelberg AM, Miller J, Doerzbacher M, Lambers DS: Correlation of quantitative protein measurements in 8-, 12-, and 24-hour urine samples for diagnosis of preeclampsia. Am J Obstet Gynecol. 2001 Oct;185(4):804-807 6. Robinson RR: Isolated proteinuria in asymptomatic patients. Kidney Int. 1980 Sep;18(3):395-406 7. Dube J, Girouard J, Leclerc P, Douville P: Problems with the estimation of urine protein by automated assays. Clin Biochem. 2005 May;(38):479-485 8. Koumantakis G, Wyndham L: Fluorescein interference with urinary creatinine and protein measurements. Clin Chem. 1991 Oct;37(10 Pt 1):1799 9. Lamb EJ, Jones GRD: Kidney function tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:479-517

OSM24
622326

Osmolality, 24 Hour, Urine

Clinical Information: Osmolality is an index of the solute concentration. Urine osmolality is a measure of the concentration of osmotically active particles, principally sodium, chloride, potassium, and urea; glucose can contribute significantly to the osmolality when present in substantial amounts in urine. Urinary osmolality corresponds to urine specific gravity in nondisease states. The ability of the kidney to maintain both tonicity and water balance of the extracellular fluid can be evaluated by measuring the osmolality of the urine either routinely or under artificial conditions. More information concerning the state of renal water handling or abnormalities of urine dilution or concentration can be obtained if urinary osmolality is compared to serum osmolality and urine electrolyte studies are performed. Normally, the ratio of urine osmolality to serum osmolality is 1.0 to 3.0, reflecting a wide range of urine osmolality.

Useful For: Assessing the concentrating and diluting ability of the kidney using a 24-hour urine collection

Interpretation: With normal fluid intake and normal diet, a patient will produce urine of about 500 to 850 mosmol/kg water. Above the age of 20 years, there is an age dependent decline in the upper reference range of approximately 5 mOsm/kg/year. The normal kidney can concentrate urine to 800 to 1400 mosmol/kg and with excess fluid intake, a minimal osmolality of 40 to 80 mosmol/kg can be reached. With dehydration, the urine osmolality should be 3 to 4 times the plasma osmolality When a patient is drinking relatively large amounts of fluid the urine can be maximally diluted to approximately 100 mosmol/kg water. A 24-hour urine osmolality will reflect the average urine osmolality over the day. Thus, a 24-hour urine osmolality will provide information regarding patient's ability to either dilute or

concentrate the urine, and also their habitual water intake throughout the day in relation to their osmole intake. This information is most commonly used to determine if a patient with a risk of kidney stone disease is ingesting enough fluid to maintain a relatively dilute urine. Rough guidelines would suggest a treatment target of less than 400 mosmol/ kg water in a stone forming individual, which correlates with a total urine volume of greater than 2 L in an average individual.

Reference Values:
0-11 months: 50-750 mOsm/kg
> or =12 months: 150-1,150 mOsm/kg

Clinical References: 1. Newman D, Price C. Renal function and nitrogen metabolites. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 4th ed. WB Saunders Company; 2006 2. Delaney MP, Lamb EJ. Kidney disease. In. Rifai NF, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1306

OSMOF 606758 Osmolality, Feces

Clinical Information: The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors: -Normal daily dietary intake of electrolytes -Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure -Electrolyte transport into fecal water due to exogenous substances and rare toxins (eg, cholera toxin) Fecal osmolality is normally in equilibrium with vascular osmolality, and sodium is the major effector of this equilibrium. Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or drugs inducing secretions, such as phenolphthalein or bisacodyl. Differentiating osmotic from non-osmotic causes of diarrhea is the goal of liquid stool testing.(1,2) The primary way this is accomplished is through the measurement of sodium and chloride and calculation of the osmotic gap, which uses an assumed normal osmolality of 290 mOsm/kg rather than direct measurement of the osmolality. Measurement of osmolality can be useful in the evaluation of chronic diarrhea to help identify whether a specimen has been diluted with hypotonic fluid to simulate diarrhea.(1,3)

Useful For: Measurement of osmolality for the workup of cases of chronic diarrhea Diagnosis of factitious diarrhea (where patient adds fluid to stool to simulate diarrhea)

Interpretation: Stool osmolality below 220 mOsm/kg indicates dilution with a hypotonic fluid.(1)

Reference Values:
An interpretive report will be provided

Clinical References: 1. Steffer KJ, Santa Ana CA, Cole JA, Fordtran JS: The practical value of comprehensive stool analysis in detecting the cause of idiopathic chronic diarrhea. Gastroenterol Clin North Am. 2012;41:539-560 2. Sweetser S: Evaluating the patient with diarrhea: A case-based approach. Mayo Clin Proc. 2012;87:596-602 3. Phillips S, Donaldson L, Geisler K, Pera A, Kochar R: Stool composition in factitial diarrhea: a 6-year experience with stool analysis. Ann Intern Med. 1995;123:97-100

UOSMU 606520 Osmolality, Random, Urine

Clinical Information: Osmolality is an index of the solute concentration. Urine osmolality is a measure of the concentration of osmotically active particles, principally sodium, chloride, potassium, and

urea; glucose can contribute significantly to the osmolality when present in substantial amounts in urine. Urinary osmolality corresponds to urine specific gravity in nondisease states. The ability of the kidney to maintain both tonicity and water balance of the extracellular fluid can be evaluated by measuring the osmolality of the urine either routinely or under artificial conditions. More information concerning the state of renal water handling or abnormalities of urine dilution or concentration can be obtained if urinary osmolality is compared to serum osmolality and if urine electrolyte studies are performed. Normally, the ratio of urine osmolality to serum osmolality is 1.0 to 3.0, reflecting a wide range of urine osmolality.

Useful For: Assessing the concentrating and diluting ability of the kidney

Interpretation: With normal fluid intake and normal diet, a patient will produce urine of about 500 to 850 mosmol/kg water. Above age of 20 years, there is an age dependent decline in the upper reference range of approximately 5 mOsm/kg/year. The normal kidney can concentrate urine to 800 to 1400 mosmol/kg and with excess fluid intake, a minimal osmolality of 40 to 80 mosmol/kg can be reached. With dehydration, the urine osmolality should be 3 to 4 times the plasma osmolality.

Reference Values:
0-11 months: 50-750 mOsm/kg
> or =12 months: 150-1,150 mOsm/kg

Clinical References: 1. Newman D, Price C: Renal function and nitrogen metabolites. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 4th ed. WB Saunders Company; 2006 2. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1306

UOSMS
614057

Osmolality, Serum

Clinical Information: Osmolality is a measure of the number of dissolved solute particles in solution. It is determined by the number and not by the nature of the particles in solution. Dissolved solutes change the physical properties of solutions, increasing the osmotic pressure and boiling point and decreasing the vapor pressure and freezing point. Serum osmolality increases with dehydration and decreases with overhydration. The patient receiving intravenous fluids should have a normal osmolality. If the osmolality rises, the fluids contain relatively more electrolytes than water. If the osmolality falls, relatively more water than electrolytes is being administered. Normally, the ratio of serum sodium, in mEq/L, to serum osmolality, in mOsm/kg, is between 0.43 and 0.5. The ratio may be distorted in drug intoxication. Generally, the same conditions that decrease or increase the serum sodium concentration affect the osmolality. A comparison of measured and calculated serum osmolality produces a delta-osmolality. If this is above 40 mOsm/kg H2O in a critically ill patient, the prognosis is poor. An easy formula to calculate osmolality is: Osmolality (mOsm/kg H2O)=2 Na+ Glucose + BUN 20 3

Useful For: Evaluating acutely ill or comatose patients

Interpretation: An increased gap between measured and calculated osmolality may indicate ingestion of poison, ethylene glycol, methanol, or isopropanol.

Reference Values:
275-295 mOsm/kg

Clinical References: 1. Murphy JE, Henry JB: Evaluation of renal function, and water, and electrolyte, and acid base balance. In: Henry JB, ed: Todd-Sanford-Davidsohn Clinical Diagnosis and

Management by Laboratory Methods. 19th ed. WB Saunders Company; 2006 2. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1306

FRAG
9064

Osmotic Fragility, Erythrocytes

Clinical Information: Spherocytes are osmotically fragile cells that rupture more easily in a hypotonic solution than do normal red blood cells . Because they have a low surface area:volume ratio, they lyse at a higher osmolarity than do normal discocytes (ie, RBC). Cells that have a larger surface area:volume ratio, such as target cells or hypochromic cells, are more resistant to lysing. After incubation, an increase in hemolysis is seen in spherocytes. Hereditary spherocytosis typically has a greater number of spherocytes than other causes of spherocytosis. Therefore, the degree of lysis is usually more pronounced, but this is not always the case. Some rare disorders can also cause marked fragility, and hereditary spherocytosis cases can display moderate fragility.

Useful For: Evaluating suspected hereditary spherocytosis-associated hemolytic anemia Confirming or detecting mild spherocytosis

Interpretation: An interpretive report will be provided.

Reference Values:
> or =12 months:
0.50 g/dL NaCl (unincubated): 3-53% hemolysis
0.60 g/dL NaCl (incubated): 14-74% hemolysis
0.65 g/dL NaCl (incubated): 4-40% hemolysis
0.75 g/dL NaCl (incubated): 1-11% hemolysis

NaCl = sodium chloride
Reference values have not been established for patients who are younger than 12 months of age.

Clinical References: 1. Palek J, Jarolin P: Hereditary spherocytosis. In: Williams WJ, Beutler E, Erslev AJ, Lichtman MA, eds. Hematology. 4th ed. McGraw-Hill Book Company; 1990:558-569 2. King MJ, Garcon L, Hoyer JD, et al: International Council for Standardization in Haematology. ICSH guidelines for the laboratory diagnosis of nonimmune hereditary red cell membrane disorders. Int J Lab Hematol. 2015 Jun;37(3):304-325

OSG_F
610305

Osmotic Gap, Feces

Clinical Information: The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors: -Normal daily dietary intake of electrolytes -Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure -Electrolyte transport into fecal water due to exogenous substances and rare toxins (eg, cholera toxin) Fecal osmolality is normally in equilibrium with vascular osmolality, and sodium is the major effector of this equilibrium.(1) Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or drugs inducing secretions, such as phenolphthalein or bisacodyl. Osmotic diarrhea is caused by ingestion of poorly absorbed ions or sugars and can be characterized by the following: -Stool volume typically decreased by fasting -Fecal fluid usually has an elevated osmotic gap -Osmotic agents such as magnesium, sorbitol, or polyethylene glycol may be the cause through the intentional or inadvertent use of laxatives -Carbohydrate malabsorption due most commonly to lactose intolerance -Carbohydrate malabsorption can be differentiated from other osmotic causes by a low stool pH (<6) Non-

osmotic causes of diarrhea include bile acid malabsorption, inflammatory bowel disease, endocrine tumors, and neoplasia.(1) Secretory diarrhea is classified as non-osmotic and is caused by disruption of epithelial electrolyte transport when secretory agents such as anthraquinones, phenolphthalein, bisacodyl, or cholera toxin are present. The fecal fluid usually has elevated electrolytes (primarily sodium and chloride) and a low osmotic gap (<50 mOsm/kg). Infection is a common secretory process; however, it does not typically cause chronic diarrhea (defined as symptoms >4 weeks).

Useful For: Workup of cases of chronic diarrhea Differentiating osmotic from non-osmotic causes of chronic diarrhea.

Interpretation: Osmotic Gap: -Osmotic gap is calculated as 290 mOsm/kg-(2[Na]+2[K]). Typically, stool osmolality is similar to serum since the gastrointestinal (GI) tract does not secrete water.(1) -An osmotic gap above 50 mOsm/kg is suggestive of an osmotic component contributing to the symptoms of diarrhea.(1-3) -Magnesium-induced diarrhea should be considered if the osmotic gap is above 75 mOsm/kg and is likely if the magnesium concentration is over 110 mg/dL.(1) -An osmotic gap of 50 mOsm/kg or less is suggestive of secretory causes of diarrhea.(1-3) -A highly negative osmotic gap or a fecal sodium concentration greater than plasma or serum sodium concentrations suggests the possibility of either sodium phosphate or sodium sulfate ingestion by the patient.(4) Sodium: -Sodium is typically found at lower concentrations (mean 30 +/- 5 mmol/L) in patients with osmotic diarrhea caused by magnesium-containing laxatives, while typically at higher concentrations (mean 104 +/- 5 mmol/L) in patients known to be taking secretory laxatives.(5) Sodium and Potassium: -High sodium and potassium in the absence of an osmotic gap indicate active electrolyte transport in the GI tract that might be induced by agents such as cholera toxin or hypersecretion of vasointestinal peptide.(1)

Reference Values:
An interpretive report will be provided

Clinical References: 1. Steffer KJ, Santa Ana CA, Cole JA, Fordtran JS: The practical value of comprehensive stool analysis in detecting the cause of idiopathic chronic diarrhea. Gastroenterol Clin North Am. 2012 Sep;41(3):539-560 2. Sweetser S: Evaluating the patient with diarrhea: A case-based approach. Mayo Clin Proc. 2012 Jun;87 (6):596-602 3. Eherer AJ, Fordtran JS: Fecal osmotic gap and pH in experimental diarrhea of various causes. Gastroenterology. 1992 Aug;103(2):545-551 4. Fine KD, Ogunji F, Florio R, Porter J, Ana C: Investigation and diagnosis of diarrhea caused by sodium phosphate. Dig Dis Sci. 1998 Dec; 43(12):2708-2714 5. Phillips S, Donaldson L, Geisler K, Pera A, Kochar R: Stool composition in factitial diarrhea: a 6-year experience with stool analysis. Ann Intern Med. 1995 Jun 30;123(2):97-100 6. Casprary WF: Diarrhea associated with carbohydrate malabsorption. Clin Gastroenterol. 1986;15:631-655

OSCAL
80579

Osteocalcin, Serum

Clinical Information: Osteocalcin, the most important noncollagen protein in bone matrix, accounts for approximately 1% of the total protein in human bone. It is a 49-amino acid protein with a molecular weight of approximately 5800 Da. Osteocalcin contains up to 3 gamma-carboxyglutamic acid residues as a result of posttranslational, vitamin K-dependent enzymatic carboxylation. Its production is dependent upon vitamin K and is stimulated by 1,25 dihydroxy vitamin D. Osteocalcin is produced by osteoblasts and is widely accepted as a marker of bone osteoblastic activity. Osteocalcin, incorporated into the bone matrix, is released into the circulation from the matrix during bone resorption and, hence, is considered a marker of bone turnover rather than a specific marker of bone formation. Osteocalcin levels are increased in metabolic bone diseases with increased bone or osteoid formation, including osteoporosis, osteomalacia, rickets, hyperparathyroidism, renal osteodystrophy, thyrotoxicosis, and in individuals with fractures, acromegaly, and bone metastasis. By means of osteocalcin measurements, it is possible to monitor therapy with antiresorptive agents (bisphosphonates or hormone replacement

therapy) in, for example, patients with osteoporosis or hypercalcemia.(1) Decrease in osteocalcin is also observed in some disorders (eg, hypoparathyroidism, hypothyroidism, and growth hormone deficiency). Immunochemical and chromatographic studies have demonstrated considerable heterogeneity for concentrations of circulating osteocalcin in normal individuals and in patients with osteoporosis, chronic kidney failure, and Paget disease. Both intact osteocalcin (amino acids 1-49) and the large N-terminal/midregion (N-MID) fragment (amino acids 1-43) are present in blood. Intact osteocalcin is unstable due to protease cleavage between amino acids 43 and 44. The N-MID fragment, resulting from cleavage, is considerably more stable. This assay detects both the stable N-MID fragment and intact osteocalcin.

Useful For: Monitoring and assessing effectiveness of antiresorptive therapy in patients treated for osteopenia, osteoporosis, Paget disease, or other disorders in which osteocalcin levels are elevated As an adjunct in the diagnosis of medical conditions associated with increased bone turnover, including Paget disease, cancer accompanied by bone metastases, primary hyperparathyroidism, and renal osteodystrophy This test is not useful for the diagnosis of osteoporosis.

Interpretation: Elevated levels of osteocalcin indicate increased bone turnover. In patients taking antiresorptive agents (bisphosphonates or hormone replacement therapy), a decrease of 20% or less from baseline osteocalcin level (ie, prior to the start of therapy) after 3 to 6 months of therapy suggests effective response to treatment.(2) Patients with diseases, such as hyperparathyroidism, which can be cured, should have a return of osteocalcin levels to the reference range within 3 to 6 months after complete cure.(3)

Reference Values:

Males
<5 years: 19-75 ng/mL
5-9 years: 21-108 ng/mL
10-15 years: 19-159 ng/mL
16-17 years: 12-114 ng/mL
> or =18 years: 9-42 ng/mL

Females
<5 years: 14-126 ng/mL
5-9 years: 16-152 ng/mL
10-15 years: 15-151 ng/mL
16-17 years: 9-70 ng/mL
> or =18 years: 9-42 ng/mL

Clinical References: 1. Chen JT, Hosoda K, Hasumi K, Ogata E, Shiraki M: Serum N-terminal osteocalcin is a good indicator for estimating responders to hormone replacement therapy in postmenopausal women. J Bone Miner Res. 1996 Nov;11(11):1784-1792 2. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J, Committee of Scientific Advisors of the International Osteoporosis Foundation: The use of biochemical markers of bone turnover in osteoporosis. Committee of Scientific Advisors of the International Osteoporosis Foundation. Osteoporos Int. 2000;11(6):S2-S17 3. Harris SS, Soteriades E, Dawson-Hughes B, Framingham Heart Study, Boston Low-Income Elderly Osteoporosis Study: Secondary hyperparathyroidism and bone turnover in elderly blacks and whites. J Clin Endocrinol Metab. 2001 Aug;86(8):3801-3804 4. Fraser W: Bone and mineral metabolism. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1422-1491

OIBFG
617407

Osteogenesis Imperfecta and Bone Fragility Gene Panel, Varies

Clinical Information:

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive osteogenesis imperfecta and other hereditary conditions associated with bone fragility

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(4) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Marom R, Rabenhorst BM, Morello R: Osteogenesis imperfecta: an update on clinical features and therapies. Eur J Endocrinol. 2020 Oct;183(4):R95-R106. doi:10.1530/EJE-20-0299 2. Steiner RD, Basel D: COL1A1/2 osteogenesis imperfecta. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2005. Updated May 6, 2021. Accessed August 1, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1295/ 3. Marini JC, Forlino A, Bachinger HP, et al: Osteogenesis imperfecta. Nat Rev Dis Primers. 2017 Aug 18;3:17052. doi: 10.1038/nrdp.2017.52 4. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

OAPNS 39855 Ova and Parasite, Microscopy, Varies

Clinical Information: A variety of different parasites may be found in specimens other than stool (eg, colonic washings, duodenal aspirates, other anatomical site washings or aspirates, respiratory specimens, liver cyst aspirates or abscesses, and tissues). These parasites may include protozoa (microscopic unicellular eukaryotes) and helminths (worms). Infection is often asymptomatic but possible signs and symptoms of infection may include cough, fever, bloody sputum, skin lesions, and abdominal pain.

Useful For: Detecting and identifying parasitic protozoa and eggs and larvae of parasitic helminths

Interpretation: A positive result indicates the presence of the parasite but does not necessarily indicate that it is the cause of the patient's symptoms. Some strains of protozoa are nonpathogenic, and some helminths cause little or no illness.

Reference Values:
Negative
If positive, organism identified.

Clinical References: 1. Garcia LS. Diagnostic Medical Parasitology. 6th ed. ASM Press; 2016 2. Pritt BS. Parasitology Benchtop Reference Guide. 2nd ed. CAP; 2017

OPE 619736 Ova and Parasite, Travel History or Immunocompromised, Feces

Clinical Information: A variety of different parasites may be found in fecal specimens, duodenal aspirates, and other intestinal specimens. These parasites may include protozoa (microscopic unicellular eukaryotes) and helminths (aka worms). Infection is often asymptomatic, but symptoms range from

diarrhea and malnutrition, intestinal obstruction, and rarely, death. The most common intestinal reported parasites in fecal specimens are Giardia intestinalis (aka Giardia duodenalis, Giardia lamblia) and Cryptosporidium species. Both parasites may cause watery diarrhea and are endemic in the United States. The best tests for these 2 common parasites are parasite-specific fecal antigen tests (GIAR / Giardia Antigen, Feces and CRYPS / Cryptosporidium Antigen, Feces). Other parasites are less commonly seen in the United States, and this test is the appropriate test for their detection. See Parasitic Investigation of Stool Specimens Algorithm for determining which test should be ordered based on the patient's exposure history and risk factors. If evaluating a patient for diarrhea, see Laboratory Testing for Infectious Causes of Diarrhea Algorithm.

Useful For: Detecting and identifying parasitic protozoa and eggs and larvae of parasitic helminths in stool specimens

Interpretation: A positive result indicates the presence of the parasite but does not necessarily indicate that it is the cause of any symptoms. Some strains of protozoa are nonpathogenic, and some helminths cause little or no illness.

Reference Values:
Negative
If positive, organism identified

Clinical References: 1. Garcia LS. Diagnostic Medical Parasitology. 6th ed. AMS Press; 2016 2. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea. Clin Infect Dis. 2017;65(12):e45-e80. doi:10.1093/cid/cix669

OVAL
82826

Ovalbumin, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to ovalbumin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FOVAS
57836

Ovarian Antibody Screen with Reflex to Titer, IFA

Reference Values:
Anti-Ovary Antibody: Negative
Anti-Ovary Ab Titer: <1:5

OVMU
82825

Ovomucoid, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to ovomucoid Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

OXI
82679

Ox-Eye Daisy, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to ox-eye daisy Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the

concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

DOXA1
606473

Oxalate Analysis, Hemodialysate

Clinical Information: Oxalate is a dicarboxylic acid, an end product of glyoxalate and glycerate metabolism that is excreted in the urine where it is a common component of kidney stones (up to 85%). Hyperoxaluria can be either genetic (eg, primary hyperoxaluria) or acquired/secondary (eg, enteric hyperoxaluria), and can lead to nephrocalcinosis and renal failure. Monitoring the adequacy of oxalate removal during hemodialysis can be useful in the management of patients with hyperoxaluria and renal failure, particularly following transplantation.

Useful For: Determining the amount of oxalate removed during a dialysis session Individualizing the dialysis prescription of hyperoxaluric patients

Interpretation: An exponential decrease in oxalate signal is expected through dialysis procedure. Signals below 2 mcM at any point during dialysis suggest that the plasma has been effectively cleared, although there can be rebound after dialysis ceases. Total oxalate removed during a dialysis session can be estimated by multiplying the concentration of oxalate in the dialysate by the oxalate flow rate for each time period that the oxalate is measured.

Reference Values:
Not applicable

Clinical References: 1. Perinpam M, Enders FT, Mara KC, et al: Plasma oxalate in relation to eGFR in patients with primary hyperoxaluria, enteric hyperoxaluria and urinary stone disease. Clin Biochem 2017;50(18):1014-1019 2. Tang X, Voskoboev NV, Wannarka SL, et al: Oxalate quantification in hemodialysate to assess dialysis adequacy for primary hyperoxaluria. Am J Nephrol 2014;39(5):376-382 3. Marangella M, Petrarulo M, Mandolfo S, et al: Plasma profiles and dialysis kinetics of oxalate in patients receiving hemodialysis. Nephron 1992;60(1):74-80 4. Marangella M,

Vitale C, Petrarulo M, et al: Bony content of oxalate in patients with primary hyperoxaluria or oxalosis-unrelated renal failure. Kidney Int 1995;48(1):182-187

OXU
606737

Oxalate, 24 Hour, Urine

Clinical Information: Oxalate is an end product of glyoxalate and glycerate metabolism. Humans do not have an enzyme capable of degrading oxalate, therefore it must be eliminated by the kidney. In tubular fluid, oxalate can combine with calcium to form calcium oxalate stones. In addition, high concentrations of oxalate may be toxic to kidney cells. Increased urinary oxalate excretion results from inherited enzyme deficiencies (primary hyperoxaluria), gastrointestinal disorders associated with fat malabsorption (secondary hyperoxaluria), or increased oral intake of oxalate-rich foods or vitamin C (ascorbic acid). Since increased urinary oxalate excretion promotes calcium oxalate stone formation, various strategies are employed to lower oxalate excretion.

Useful For: Monitoring therapy for kidney stones using 24-hour urine collections Identifying increased urinary oxalate as a risk factor for stone formation Diagnosis of primary or secondary hyperoxaluria

Interpretation: An elevated urine oxalate (>0.46 mmol/24 hours) may suggest disease states such as secondary hyperoxaluria (fat malabsorption), primary hyperoxaluria (alanine glyoxalate transferase enzyme deficiency, glyceric dehydrogenase deficiency), idiopathic hyperoxaluria, or excess dietary oxalate or vitamin C intake. In stone-forming patients, high urinary oxalate values, sometimes even in the upper limit of the normal range, are treated to reduce the risk of stone formation.

Reference Values:
0.11-0.46 mmol/24 h
9.7-40.5 mg/24 h
The reference value is for a 24-hour collection. Specimens collected for other than a 24-hour period are reported in unit of mmol/L for which reference values are not established.

Reference values have not been established for patients who are younger than 16 years.

Clinical References: 1. Wilson DM, Liedtke RR. Modified enzyme-based colorimetric assay of urinary and plasma oxalate with improved sensitivity and no ascorbate interference: reference values and sample handling procedures. Clin Chem. 1991;37(7):1229-1235 2. Lieske JC, Wang X. Heritable traits that contribute to nephrolithiasis. Urolithiasis. 2019;47(1):5-10 3. Lieske JC, Turner ST, Edeh SN, Smith JA, Kardia SLR. Heritability of urinary traits that contribute to nephrolithiasis. Clin J Am Soc Nephrol. 2014;9(5):943-950 4. Zhao F, Bergstralh EJ, Mehta, RA, et al. Predictors of incident ESRD among patients with primary hyperoxaluria presenting prior to kidney failure. Clin J Am Soc Nephrol. 2016;11(1):119-126

POXA1
606472

Oxalate, Plasma

Clinical Information: Oxalate is an insoluble dicarboxylic acid, which is an end product of liver metabolism of glyoxalate and glycerate. Humans lack an enzyme to degrade oxalate, and thus it must be eliminated by the kidney. Oxalate is a strong anion and tends to precipitate with calcium, especially in the urinary tract. Consequently, about 75% of all kidney stones contain calcium oxalate in some proportion. In renal failure oxalate is retained in the body, and it can precipitate in tissues causing tissue toxicity, a condition called oxalosis. In the absence of disease, up to 90% of the body pool of oxalate is produced by hepatic metabolism and the other 10% is provided by oxalate contained in various foods. However, in the presence of gastrointestinal diseases that cause fat malabsorption, the percentage of oxalate absorbed from food can be much greater. The oxalate content of fruits and vegetables is quite variable, some being quite

high and others virtually zero. Oxalate is freely filtered by the glomerulus. A smaller amount is also secreted in the proximal tubule. If the glomerular filtration rate (GFR) is decreased, oxalate begins to be retained in the body. However, in persons without primary hyperoxaluria (PH) or enteric hyperoxaluria (EH), plasma levels do not exceed the normal range until the GFR decreases below 10-20 mL/min/1.73 m(2). Plasma oxalate concentration is a reflection of the body pool size. When the pool increases, oxalate may precipitate in tissues and cause toxicity. Plasma oxalate pool size can be increased in various situations: Increased production and accumulation results from an abnormality in at least 3 different enzymes: Alanine glyoxalate transferase is necessary for the conversion of glycolate to alanine. A deficiency or intracellular mistargeting of this hepatic enzyme results in increased oxalate production (primary hyperoxaluria type1). Glycolate reductase/hydroxypyruvate reductase deficiency in the liver and elsewhere in the body results in increased glyceric acid formation, which leads to increased oxalate production (primary hyperoxaluria type 2). A third type of PH was recently shown to be due to variants of HOGA1 that encodes the enzyme 4-hydroxy-2-oxaloglutarate aldolase that is found in hepatic mitochondria (primary hyperoxaluria type 3). Increased oxalate load can be caused by increased absorption from the intestines after consuming large amounts of oxalate-rich foods such as rhubarb, spinach, or nuts. Certain abnormalities of the gastrointestinal tract can cause fat malabsorption including short bowel syndromes, inflammatory bowel disease, gastric bypass for obesity, and pancreatic insufficiency. All of these gastrointestinal abnormalities result in increased oxalate absorption from the intestinal tract. This condition referred to as EH is due to saponification of calcium by fatty acids in the colon, which in turn frees up oxalate anions for absorption. Decreased urinary oxalate excretion in chronic kidney disease (CKD) also causes oxalate retention in the body. Management of patients with PH and renal failure is difficult. Intensive dialyses are undertaken in an attempt to keep plasma levels below the level at which supersaturation and crystallization can occur in body tissues such as heart and bones (called oxalosis). PH is typically diagnosed by measuring oxalate levels in urine. However, as kidney function decreases, the renal excretion of oxalate also decreases. In such situations, plasma oxalate levels are often be informative. Although plasma oxalate increases in CKD patients without PH, values are much higher in those CKD patients who do have PH or EH. Plasma oxalate is often used to monitor these patients during critical periods in and around kidney transplantation, dialysis, or liver transplantation. Oxalate concentration in dialysate fluid is a reflection of the oxalate removed during dialysis.

Useful For: Assessing the body pool size of oxalate in patients with enzyme deficiencies, such as primary hyperoxaluria (PH), or patients with enteric hyperoxaluria Aiding in the diagnosis of PH in a patient with chronic kidney disease of indeterminate cause when urinary oxalate is not available Monitoring patients with renal failure and primary or enteric hyperoxaluria in order to be sure they are receiving enough dialysis Aiding in maintaining plasma oxalate levels below supersaturation (25-30 mcmol/L)

Interpretation: In patients with normal renal function, the presence of increased plasma oxalate concentration is good evidence for overproduction of oxalate (primary hyperoxaluria: PH). In the presence of renal insufficiency, plasma oxalate levels can be markedly elevated in patients with PH or enteric hyperoxaluria (EH). Increased levels of plasma oxalate can be found in dialysis patients without EH or PH, but the degree of elevation is less.(1) In patients with possible primary hyperoxaluria and renal insufficiency, the diagnosis often can be presumptively made by knowing the plasma level of oxalate. However, ancillary tests, such as the demonstration of oxalate crystals in tissues (other than the kidney) or increased glycolate in dialysate (for patients on dialysis) are frequently necessary to make an accurate diagnosis.

Reference Values:

< or =2.0 mcmol/L

Reference values have not been established for patients younger than 18 years of age or older than 87 years of age.

Clinical References: 1. Perinpam M, Enders FT, Mara KC, et al: Plasma oxalate in relation to

eGFR in patients with primary hyperoxaluria, enteric hyperoxaluria and urinary stone disease. Clin Biochem. 2017 Dec;50(18):1014-1019 2. Edvardsson VO, Goldfarb DS, Lieske JC, et al: Hereditary causes of kidney stones and chronic kidney disease. Pediatr Nephrol. 2013 Oct;28(10):1923-1942

ROXUR
606747

Oxalate, Random, Urine

Clinical Information: Oxalate is an end product of glyoxalate and glycerate metabolism. Humans have no enzyme capable of degrading oxalate, therefore it must be eliminated by the kidney. In tubular fluid, oxalate can combine with calcium to form calcium oxalate stones. In addition, high concentrations of oxalate may be toxic to kidney cells. Increased urinary oxalate excretion results from inherited enzyme deficiencies (primary hyperoxaluria), gastrointestinal disorders associated with fat malabsorption (secondary hyperoxaluria), or increased oral intake of oxalate-rich foods or vitamin C. Since increased urinary oxalate excretion promotes calcium oxalate stone formation, various strategies are employed to lower oxalate excretion.

Useful For: Monitoring therapy for kidney stones using random urine specimens Identifying increased urinary oxalate as a risk factor for stone formation Diagnosis of primary or secondary hyperoxaluria

Interpretation: An elevated urine oxalate (>0.46 mmol/day) may suggest disease states such as secondary hyperoxaluria (fat malabsorption), primary hyperoxaluria (alanine glyoxalate transferase enzyme deficiency, glyceric dehydrogenase deficiency), idiopathic hyperoxaluria, or excess dietary oxalate or vitamin C intake. In stone-forming patients, high urinary oxalate values, sometimes even in the upper limit of the normal range, are treated to reduce the risk of stone formation. The urinary oxalate creatinine ratio varies widely in young children from below 0.35 mmol/mL at birth, to below 0.15 mmol/mL at 1 year of age, to below 0.10 mmol/mL at 10 years of age, and below 0.05 mmol/mL at 20 years of age (see table below).(1) Table. Oxalate/Creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 <0.175 0.5-1 <0.139 1-2 <0.103 2-3 <0.08 3-5 <0.064 5-7 <0.056 7-17 <0.048

Reference Values:
No established reference values

Clinical References: 1. Matos V, Van Melle G, Werner D, Bardy D, Guignard JP. Urinary oxalate and urate to creatinine ratios in a healthy pediatric population. Am J Kidney Dis. 1999;34(2):e1. doi:10.1053/AJKD034000e6 2. Wilson DM, Liedtke RR. Modified enzyme-based colorimetric assay of urinary and plasma oxalate with improved sensitivity and no ascorbate interference: reference values and sample handling procedures. Clin Chem. 1991;37(7):1229-1235 3. Lieske JC, Wang X. Heritable traits that contribute to nephrolithiasis. Urolithiasis. 2019;47(1):5-10 4. Lieske JC, Turner ST, Edeh SN, Smith JA, Kardia SLR. Heritability of urinary traits that contribute to nephrolithiasis. Clin J Am Soc Nephrol. 2014;9(5):943-950 5. Zhao F, Bergstralh EJ, Mehta RA, et al. Predictors of Incident ESRD among Patients with Primary Hyperoxaluria Presenting Prior to Kidney Failure. Clin J Am Soc Nephrol. 2016;11(1):119-126. doi:10.2215/CJN.02810315

OXCO1
606748

Oxalate, Random, Urine

Clinical Information: Oxalate is an end product of glyoxalate and glycerate metabolism. Humans have no enzyme capable of degrading oxalate so it must be eliminated by the kidney. In tubular fluid, oxalate can combine with calcium to form calcium oxalate stones. In addition, high concentrations of oxalate may be toxic for renal cells. Increased urinary oxalate excretion results from inherited enzyme deficiencies (primary hyperoxaluria), gastrointestinal disorders associated with fat malabsorption (secondary hyperoxaluria), or increased oral intake of oxalate-rich foods or vitamin C. Since increased urinary oxalate excretion promotes calcium oxalate stone formation, various strategies are employed to

lower oxalate excretion.

Useful For: Monitoring therapy for kidney stones Identifying increased urinary oxalate as a risk factor for stone formation Diagnosis of primary or secondary hyperoxaluria

Interpretation: An elevated urine oxalate (>0.46 mmol/day) may suggest disease states such as secondary hyperoxaluria (fat malabsorption), primary hyperoxaluria (alanine glyoxalate transferase enzyme deficiency, glyceric dehydrogenase deficiency), idiopathic hyperoxaluria, or excess dietary oxalate or vitamin C intake. In stone-forming patients high urinary oxalate values, sometimes even in the upper limit of the normal range, are treated to reduce the risk of stone formation. The urinary oxalate creatinine ratio varies widely in young children from <0.35 mmol/mL at birth, to <0.15 mmol/mL at 1 year, to <0.10 mmol/mL at 10 years, and <0.05 mmol/mL at 20 years of age (see table below).(1) Oxalate/Creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 <0.175 0.5-1 <0.139 1-2 <0.103 2-3 <0.08 3-5 <0.064 5-7 <0.056 7-17 <0.048

Reference Values:
Only orderable as part of a profile. For more information see ROXUR / Oxalate, Random, Urine.

No established reference values

Clinical References: 1. Matos V, Van Melle G, Werner D, Bardy D, Guignard JP: Urinary oxalate and urate to creatinine ratios in a healthy pediatric population. Am J Kidney Dis. 1999;34:e1 2. Wilson DM, Liedtke RR: Modified enzyme-based colorimetric assay of urinary and plasma oxalate with improved sensitivity and no ascorbate interference: reference values and sample handling procedures. Clin Chem. 1991;37:1229-1235 3. Lieske JC, Wang X: Heritable traits that contribute to nephrolithiasis. Urolithiasis. 2019 Feb;47(1):5-10 4. Lieske JC, Turner ST, Edeh SN, Smith JA, Kardia SLR: Heritability of urinary traits that contribute to nephrolithiasis. Clin J Am Soc Nephrol. 2014 May;9(5):943-950. doi: 10.2215/CJN.08210813 5. Zhao F, Bergstralh EJ, Mehta RA, et al: Predictors of incident ESRD among patients with primary hyperoxaluria presenting prior to kidney failure. Clin J Am Soc Nephrol. 2016 Jan 7;11(1):119-126. doi: 10.2215/CJN.02810315

RAT11
606751

Oxalate/Creatinine Ratio, Urine

Clinical Information: Oxalate is an end product of glyoxalate and glycerate metabolism. Humans have no enzyme capable of degrading oxalate so it must be eliminated by the kidney. In tubular fluid, oxalate can combine with calcium to form calcium oxalate stones. In addition, high concentrations of oxalate may be toxic for renal cells. Increased urinary oxalate excretion results from inherited enzyme deficiencies (primary hyperoxaluria), gastrointestinal disorders associated with fat malabsorption (secondary hyperoxaluria), or increased oral intake of oxalate-rich foods or vitamin C. Since increased urinary oxalate excretion promotes calcium oxalate stone formation, various strategies are employed to lower oxalate excretion.

Useful For: Calculating the oxalate concentration per creatinine

Interpretation: An elevated urine oxalate (>0.46 mmol/day) may suggest disease states such as secondary hyperoxaluria (fat malabsorption), primary hyperoxaluria (alanine glyoxalate transferase enzyme deficiency, glyceric dehydrogenase deficiency), idiopathic hyperoxaluria, or excess dietary oxalate or vitamin C intake. In stone-forming patients high urinary oxalate values, sometimes even in the upper limit of the normal range, are treated to reduce the risk of stone formation. The urinary oxalate creatinine ratio varies widely in young children from <0.35 mmol/mL at birth to <0.15 mmol/mL at 1 year to <0.10 mmol/mL at 10 years and <0.05 mmol/mL at 20 years of age (see table below).(1) Oxalate/Creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 <0.175 0.5-1 <0.139 1-2 <0.103 2-3 <0.08

3-5 <0.064 5-7 <0.056 7-17 <0.048

Reference Values:
Only orderable as part of a profile. For more information see ROXUR / Oxalate, Random, Urine.

No established reference values.

Clinical References: 1. Matos V, Van Melle G, Werner D, Bardy D, Guignard JP: Urinary oxalate and urate to creatinine ratios in a healthy pediatric population. Am J Kidney Dis. 1999;34:e1 2. Wilson DM, Liedtke RR: Modified enzyme-based colorimetric assay of urinary and plasma oxalate with improved sensitivity and no ascorbate interference: reference values and sample handling procedures. Clin Chem. 1991;37:1229-1235 3. Lieske JC, Wang X: Heritable traits that contribute to nephrolithiasis. Urolithiasis. 2019 Feb;47(1):5-10 4. Lieske JC, Turner ST, Edeh SN, Smith JA, Kardia SLR: Heritability of urinary traits that contribute to nephrolithiasis. Clin J Am Soc Nephrol. 2014 May;9(5):943-950. doi: 10.2215/CJN.08210813 5. Zhao F, Bergstralh EJ, Mehta RA, et al: Predictors of incident ESRD among patients with primary hyperoxaluria presenting prior to kidney failure. Clin J Am Soc Nephrol. 2016 Jan 7;11(1):119-126. doi: 10.2215/CJN.02810315

FOXAZ
90108

Oxazepam (Serax), Serum

Reference Values:
Reference Range: 200 - 500 ng/mL

OMHC
81030

Oxcarbazepine Metabolite, Serum

Clinical Information: Oxcarbazepine (OCBZ) is approved as monotherapy and adjunctive therapy for partial seizures with and without secondary generalized seizures in adults and as adjunctive therapy for partial seizures in children. In humans, OCBZ is a prodrug that is almost immediately and completely metabolized to 10-hydroxy-10,11-dihydrocarbamazepine, known as monohydroxy carbamazepine (MHC), an active metabolite that is responsible for OCBZ's therapeutic effect. The elimination half-life is approximately 2 hours for OCBZ and 7 to 11 hours for MHC. The therapeutic range (10-35 mcg/mL) is based on concentrations of the metabolite, not the parent drug; this assay measures the metabolite only. In clinical practice, the OCBZ dosage should be individually adjusted for each patient to achieve the desired therapeutic response. Toxicity associated with OCBZ includes hyponatremia, dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, and abnormal gait. These toxicities may be observed when blood concentrations are in the therapeutic range.

Useful For: Monitoring serum concentration during oxcarbazepine therapy Assessing compliance Assessing potential toxicity

Interpretation: Therapeutic ranges are based on specimens collected at trough (ie, immediately before the next dose). Most individuals display optimal response to oxcarbazepine therapy when serum levels of the metabolite (measured in this assay) are between 10 and 35 mcg/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range. Thus, interpretation should include clinical evaluation.

Reference Values:
Oxcarbazepine metabolite: 10-35 mcg/mL

Clinical References: 1. Hiemke C, Bergemann N, Clement HW, et al: Consensus guidelines for

therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62 2. Perucca E. Clinical pharmacology and therapeutic use of the new antiepileptic drugs. Fundam Clin Pharmacol. 2001;15(6):405-417 3. Lloyd P, Flesch G, Dieterle W. Clinical pharmacology and pharmacokinetics of oxcarbazepine. Epilepsia. 1994;35(Suppl 3):S10-S13 4. Gonzalez-Esquivel DF, Ortega-Gavilan M, Alcantara-Lopez G, Jung-Cook H. Plasma level monitoring of oxcarbazepine in epileptic patients. Arch Med Res. 2000;31(2):202-205 5. Johannessen SI, Tomson T. Pharmacokinetic variability of newer antiepileptic drugs: when is monitoring needed? Clin Pharmacokinet. 2006;45(11):1061-1075 6. Patsalos PN, Berry DJ, Bourgeois BFD, et al. Antiepileptic drugs-best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239-1276

FOXFU
75390

Oxycodone - Free (Unconjugated), Serum

Reference Values:

OXYSX
61727

Oxycodone Screen, Chain of Custody, Random, Urine

Clinical Information: Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (eg, codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone). Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone greater than 100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and therefore the presence of oxymorphone could also indicate exposure to oxycodone. Chain of custody is a record of the disposition of a specimen to document the individuals who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detection of oxycodone and oxymorphone in urine following chain-of-custody procedures This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. For information about drug testing, including estimated detection times, see Drug Class Testing on MayoClinicLabs.com.

Reference Values:
Negative
Screening cutoff concentration:
Oxycodone: 100 ng/mL

Clinical References: 1. Anderson DT, Fritz KL, Muto JJ. Oxycontin: the concept of a "ghost pill" and the postmortem tissue distribution of oxycodone in 36 cases. J Anal Toxicol. 2002;26(7):448-459 2. Jannetto PJ, Gock SG. Oxycodone: Recognition and Pharmacogenomics. Clinical and Forensic Toxicology News 2003 March 3. Cone EJ, Fant RV, Rohay JM, et al. Oxycodone involvement in drug

abuse deaths: a DAWN-based classification scheme applied to an oxycodone postmortem database containing over 1000 cases. J Anal Toxicol. 2003;27(2):57-67. doi:10.1093/jat/27.2.57 4. Baselt RC, Cravey RH. Oxycodone. In: Disposition of Toxic Drugs and Chemicals in Man. 4th ed. Chemical Toxicology Institute. 1995;572-574 5. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

OXYSU 62623 Oxycodone Screen, Random, Urine

Clinical Information: Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (eg, codeine). Oxycodone is metabolized to noroxycodone, oxymorphone and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone.

Useful For: Detection of oxycodone and oxymorphone in urine

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. For more information see individual tests (eg, OXYCU / Oxycodone with Metabolite Confirmation, Random, Urine). For information about drug testing, including estimated detection times, see Optimize Urine Drug Monitoring for Opioids.

Reference Values:
Negative
Screening cutoff concentration:
Oxycodone: 100 ng/mL

Clinical References: 1. Anderson DT, Fritz KL, Muto JJ. Oxycontin: the concept of a "ghost pill" and the postmortem tissue distribution of oxycodone in 36 cases. J Anal Toxicol. 2002;26(7):448-459. doi:10.1093/jat/26.7.448 2. Jannetto PJ, Gock SG. Oxycodone: Recognition and Pharmacogenomics. Clinical and Forensic Toxicology News, 2003 March 3. Cone EJ, Fant RV, Rohay JM, et al. Oxycodone involvement in drug abuse deaths: A DAWN-based classification scheme applied to an oxycodone postmortem database containing over 1000 cases. J Anal Toxicol. 2003;27(2):57-67. doi:10.1093/jat/27.2.57 4. Baselt RC, Cravey RH. Oxycodone. In: Disposition of Toxic Drugs and Chemicals in Man. 4th ed. Chemical Toxicology Institute; 1995:572-574 5. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

OXYCX 61728 Oxycodone with Metabolite Confirmation, Chain of Custody, Random, Urine

Clinical Information: Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone, and therefore, the presence of oxymorphone could also indicate exposure to oxycodone. The detection interval for opiates is generally 2 to 3 days after last ingestion. Chain of

custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detection and quantification of oxycodone, oxymorphone, noroxycodone, and noroxymorphone in urine Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

Reference Values:
Negative
Positive results are reported with a quantitative result.

Cutoff concentrations:

Immunoassay screen: 100 ng/mL

Liquid chromatography tandem mass spectrometry:
Oxycodone: 25 ng/mL
Noroxycodone: 25 ng/mL
Oxymorphone: 25 ng/mL
Noroxymorphone: 25 ng/mL

Clinical References: 1. Jutkiewicz EM, Traynor JR. Opioid analgesics. In: Brunton LL, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 14th ed. McGraw-Hill, Inc; 2023:chap 23 2. Baselt, RC. Disposition of Toxic Drugs and Chemical in Man. 10th ed. Biomedical Publications; 2014 3. Hackett LP, Dusci LJ, Ilett KF, Chiswell GM. Optimizing the hydrolysis of codeine and morphine glucuronides in urine. Ther Drug Monit. 2002;24(5):652-657 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

OXYCU
62616

Oxycodone with Metabolite Confirmation, Random, Urine

Clinical Information: Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone. The detection interval for opiates is generally 2 to 3 days after last ingestion.

Useful For: Detection and quantification of oxycodone, oxymorphone, noroxycodone, and noroxymorphone in urine

Interpretation: This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

Reference Values:
Negative

Positive results are reported with a quantitative result.

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Oxycodone: 25 ng/mL
Noroxycodone: 25 ng/mL
Oxymorphone: 25 ng/mL
Noroxymorphone: 25 ng/mL

Clinical References: 1. Jutkiewicz EM, Traynor JR. Opioid analgesics. In: Brunton LL, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 14th ed. McGraw-Hill, Inc; 2023:chap 23 2. Baselt, RC. Disposition of Toxic Drugs and Chemical in Man. 10th ed. Biomedical Publications; 2014 3. Hackett LP, Dusci LJ, Ilett KF, Chiswell GM. Optimizing the hydrolysis of codeine and morphine glucuronides in urine. Ther Drug Monit. 2002;24(5):652-657 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

OXYMU
62622

Oxymorphone Confirmation, Random, Urine

Clinical Information: Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone. The detection interval for opiates is generally 2 to 3 days after last ingestion.

Useful For: Detection and quantification of oxymorphone and noroxymorphone in urine

Interpretation: This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

Reference Values:
Negative

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Oxymorphone: 25 ng/mL
Noroxymorphone: 25 ng/mL

Clinical References: 1. Jutkiewicz EM, Traynor JR. Opioid analgesics. In: Brunton LL, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 14th ed. McGraw-Hill Companies, Inc; 2023:chap 23 2. Baselt, RC. Disposition of Toxic Drugs and Chemical in Man. 10th ed. Biomedical Publications; 2014 3. Hackett LP, Dusci LJ, Ilett KF, Chiswell GM. Optimizing the hydrolysis of codeine and morphine glucuronides in urine. Ther Drug Monit. 2002;24(5):652-657 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

OXYWB
113429

Oxysterols, Blood

Clinical Information: Niemann-Pick disease types A, B, and C (NPA, NPB, and NPC, respectively) are a group of autosomal recessive lysosomal storage disorders affecting metabolism of specific lipids within cells. Niemann-Pick disease types A and B, also known as acid sphingomyelinase deficiency, result in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and may also affect the brain. NPA disease is more severe than NPB, and it is characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration,

deafness, and blindness leading to death by 3 years of age. NPB disease is limited to visceral symptoms, such as hepatosplenomegaly, with survival into adulthood. Some patients have been described with intermediary clinical phenotypes. Large, lipid-laden foam cells are characteristic of the disease. Approximately 50% of patients with this condition have cherry-red spots in the macula. Treatment is available in the form of enzyme replacement therapy, which helps to reduce the accumulation of sphingomyelin; however, it is not effective in treating the central nervous system. The combined prevalence of NPA and NPB is estimated to be 1 in 250,000 individuals. NPA and NPB are inherited in an autosomal recessive manner and are caused by biallelic disease-causing variants in the SMPD1 gene. Although there is a higher frequency of type A among the Ashkenazi Jewish population, both types are panethnic. Individuals with NPA and NPB typically have elevations of lyso-sphingomyelin (LSM) and LSM 509 combined with potential elevations in cholestane-3-beta, 5-alpha, 6-beta-triol (COT) and 7-ketocholesterol (7-KC). Molecular genetic testing for NPA and NPB disease is also available (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify gene list ID: IEMCP-W6S9XD). Niemann-Pick disease type C is caused by a defect in cellular cholesterol trafficking, which results in the progressive accumulation of unesterified cholesterol in late endosomes/lysosomes. NPC is considered a lipid storage disorder with variable age of onset, from the neonatal period to adulthood, and highly variable clinical presentation. Most individuals are diagnosed during childhood with symptoms that include ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures. Infants may present with or without hepatosplenomegaly and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Adult-onset NPC is associated with a slower progression and is characterized by psychiatric illness, ataxia, dystonia, and speech difficulties. New treatments are available for patients with NPC that help improve both the neurological and functional symptoms. The incidence of NPC is approximately 1 in 120,000 to 150,000 live births. NPC is an autosomal recessive condition and is caused by biallelic disease-causing variants in either the NPC1 or NPC2 genes. Individuals with NPC exhibit elevated levels of oxysterol COT; LSM 509 and 7-KC may also be elevated. The diagnosis of NPC can be confirmed by demonstration of impaired cholesterol esterification and positive filipin staining in cultured fibroblasts. For molecular confirmation, genetic testing for NPC disease can be performed (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify gene list ID: IEMCP-H683JG).

Useful For: Investigating a possible diagnosis of Niemann-Pick disease type A, B, or C using whole blood specimens Monitoring of individuals with Niemann-Pick type C disease This test is not useful for the identification of carriers.

Interpretation: An elevation of cholestane-3-beta, 5-alpha, 6-beta-triol is highly suggestive of Niemann-Pick disease type C (NPC) disease. An elevation of lyso-sphingomyelin is highly suggestive of Niemann-Pick disease type A or B (NPA or NPB) disease.

Reference Values:

Cholestane-3-beta,5-alpha,6-beta-triol
Cutoff: < or =0.800 nmol/mL

Lyso-sphingomyelin
Cutoff: < or =0.100 nmol/mL

Clinical References: 1. Newborn Screening ACT Sheet [Decreased acid sphingomyelinase] Acid Sphingomyelinase Deficiency (ASMD). American College of Medical Genetics and Genomics; 2022. Revised May 2022. Accessed December 2, 2024. Available at www.acmg.net/PDFLibrary/Niemann-Pick.pdf 2. Wasserstein MP, Schuchman EH. Acid sphingomyelinase deficiency. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated April 27, 2023. Accessed December 2, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1370/ 3. Patterson M: Niemann-Pick disease type C. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000.

Updated December 10, 2020. Accessed December 2, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1296/ 4. Schuchman EH. The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann-Pick disease. Int J Clin Pharmacol Ther. 2009;47Suppl 1:S48-S57. doi:10.5414/cpp47048 5. Hollack CEM, de Sonnaville ESV, Cassiman D, et al. Acid sphingomyelinase (Asm) deficiency patients in The Netherlands and Belgium: disease spectrum and natural course in attenuated patients. Mol Genet Metab. 2012;107(3):526-533 6. Wasserstein M, Dionisi-Vici C, Giugliani Ret al. Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD). Mol Genet Metab. 2019;126(2):98-105 7. Geberhiwot T, Moro A, Dardis A, et al. International Niemann-Pick Disease Registry (INPDR): Consensus clinical management guidelines for Niemann-Pick disease type C. Orphanet J Rare Dis. 2018;13(1):50 8. Bremova-Ertl T, Claassen J, Foltan T, et al. Efficacy and safety of N-acetyl-L-leucine in Niemann-Pick disease type C. J Neurol. 2022;269(3):1651-1662. doi:10.1007/s00415-021-10717-0 9. Mengel E, Patterson MC, Da Riol RM, et al. Efficacy and safety of arimoclomol in Niemann-Pick disease type C: Results from a double-blind, randomised, placebo-controlled, multinational phase 2/3 trial of a novel treatment. J Inherit Metab Dis. 2021;44(6):1463-1480. doi:10.1002/jimd.12428

OXYBS
63147

Oxysterols, Blood Spot

Clinical Information: Niemann-Pick disease types A, B, and C (NPA, NPB, and NPC, respectively) are a group of autosomal recessive lysosomal storage disorders affecting metabolism of specific lipids within cells. Niemann-Pick disease types A and B, also known as acid sphingomyelinase deficiency, result in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and may also affect the brain. NPA disease is more severe than NPB, and it is characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness leading to death by 3 years of age. NPB disease is limited to visceral symptoms, such as hepatosplenomegaly, with survival into adulthood. Some patients have been described with intermediary clinical phenotypes. Large, lipid-laden foam cells are characteristic of the disease. Approximately 50% of patient with this condition have cherry-red spots in the macula. Treatment is available in the form of enzyme replacement therapy, which helps to reduce the accumulation of sphingomyelin; however, it is not effective in treating the central nervous system. The combined prevalence of NPA and NPB is estimated to be 1 in 250,000 individuals. NPA and NPB are inherited in an autosomal recessive manner and are caused by biallelic disease-causing variants in the SMPD1 gene. Although there is a higher frequency of type A among the Ashkenazi Jewish population, both types are panethnic. Individuals with NPA and NPB typically have elevations of lyso-sphingomyelin (LSM) and LSM 509 combined with potential elevations in cholestane-3 beta, 5 alpha, 6 beta-triol (COT) or 7-ketocholesterol (7-KC). Molecular genetic testing for NPA and NPB disease is also available (see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify gene list ID: IEMCP-W6S9XD). Niemann-Pick disease type C is caused by a defect in cellular cholesterol trafficking, which results in the progressive accumulation of unesterified cholesterol in late endosomes/lysosomes. NPC is considered a lipid storage disorder with variable age of onset, from the neonatal period to adulthood, and highly variable clinical presentation. Most individuals are diagnosed during childhood with symptoms that include ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures. Infants may present with or without hepatosplenomegaly and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Adult-onset NPC is associated with a slower progression and is characterized by psychiatric illness, ataxia, dystonia, and speech difficulties. New treatments are available for patients with NPC that help improve both the neurological and functional symptoms. The incidence of NPC is approximately 1 in 120,000 to 150,000 live births. NPC is an autosomal recessive condition and is caused by biallelic disease-causing variants in either the NPC1 or NPC2 genes. Most individuals with NPC exhibit elevated levels of oxysterol COT in dried blood spots, however, testing in plasma (OXNP / Oxysterols, Plasma) is more sensitive, particularly in patients with an atypical presentation. Elevations may also be seen in LSM 509 and 7-KC. The diagnosis of NPC can be confirmed by demonstration of impaired cholesterol esterification and positive filipin staining in cultured fibroblasts or by molecular genetic analysis of the

NPC1 and NPC2 genes (see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify gene list ID: IEMCP-H683JG).

Useful For: Investigating a possible diagnosis of Niemann-Pick disease types A, B, or C using blood spot specimens Monitoring of individuals with Niemann-Pick disease type C This test is not useful for the identification of carriers.

Interpretation: An elevation of cholestane-3-beta, 5-alpha, 6-beta-triol is highly suggestive of Niemann-Pick disease type C (NPC) disease. An elevation of lyso-sphingomyelin is highly suggestive of Niemann-Pick disease type A or B (NPA or NPB) disease.

Reference Values:
Cholestane-3-beta,5-alpha,6-beta-triol
Cutoff: < or =0.800 nmol/mL

Lyso-sphingomyelin
Cutoff: < or =0.100 nmol/mL

Clinical References: 1. Newborn Screening ACT Sheet [Decreased acid sphingomyelinase] Acid Sphingomyelinase Deficiency (ASMD). American College of Medical Genetics and Genomics; 2022. Revised May 2022. Accessed December 2, 2024. Available at www.acmg.net/PDFLibrary/Niemann-Pick.pdf 2. Wasserstein MP, Schuchman EH. Acid sphingomyelinase deficiency. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated April 27, 2023. Accessed December 2, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1370/ 3.. Patterson M. Niemann-Pick disease type C. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated December 10, 2020. Accessed December 2, 2024.. Available at www.ncbi.nlm.nih.gov/books/NBK1296/ 4.Schuchman EH. The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann-Pick disease. Int J Clin Pharmacol Ther. 2009;47(Suppl 1):S48-S57. doi:10.5414/cpp47048. 5. Hollack CEM, de Sonnaville ESV, Cassiman D et al. Acid sphingomyelinase (Asm) deficiency patients in The Netherlands and Belgium: disease spectrum and natural course in attenuated patients. Mol Genet Metab. 2012;107(3):526-533 6. Wasserstein M, Dionisi-Vici C, Giugliani R, et al. Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD). Mol Genet Metab. 2019;126(2):98-105 7. Geberhiwot T, Moro A, Dardis A, et al. International Niemann-Pick Disease Registry (INPDR): Consensus clinical management guidelines for Niemann-Pick disease type C. Orphanet J Rare Dis. 2018;13(1):50 8. Bremova-Ertl T, Claassen J, Foltan T, et al. Efficacy and safety of N-acetyl-L-leucine in Niemann-Pick disease type C. J Neurol. 2022;269(3):1651-1662. doi:10.1007/s00415-021-10717-0 9. Mengel E, Patterson MC, Da Riol RM, et al. Efficacy and safety of arimoclomol in Niemann-Pick disease type C: Results from a double-blind, randomised, placebo-controlled, multinational phase 2/3 trial of a novel treatment. J Inherit Metab Dis. 2021;44(6):1463-1480. doi:10.1002/jimd.12428

OXNP
62988

Oxysterols, Plasma

Clinical Information: Niemann-Pick disease types A, B, and C (NPA, NPB, and NPC, respectively) are a group of autosomal recessive lysosomal storage disorders affecting metabolism of specific lipids within cells. Niemann-Pick disease types A and B, also known as acid sphingomyelinase deficiency, result in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and may also affect the brain. NPA disease is more severe than NPB, and it is characterized by early onset with feeding problems, dystrophy, persistent jaundice, hepatosplenomegaly, neurological deterioration, deafness, and blindness leading to death by 3 years of age. NPB disease is limited to visceral symptoms, such as hepatosplenomegaly, with survival into adulthood. Some patients have been described with

intermediary clinical phenotypes. Large, lipid-laden foam cells are characteristic of the disease. Approximately 50% of patients with this condition have cherry-red spots in the macula. Treatment is available in the form of enzyme replacement therapy, which helps to reduce the accumulation of sphingomyelin; however, it is not effective in treating the central nervous system. The combined prevalence of NPA and NPB is estimated to be 1 in 250,000 individuals. NPA and NPB are inherited in an autosomal recessive manner and are caused by biallelic disease-causing variants in the SMPD1 gene. Although there is a higher frequency of type A among the Ashkenazi Jewish population, both types are panethnic. Individuals with NPA and NPB typically have elevations of lyso-sphingomyelin (LSM) and LSM 509 combined with potential elevations in cholestane-3 beta, 5 alpha, 6 beta-triol (COT) or 7-ketocholesterol (7-KC). Molecular genetic testing for NPA and NPB disease is also available (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify gene list ID: IEMCP-W6S9XD). Niemann-Pick disease type C is caused by a defect in cellular cholesterol trafficking, which results in the progressive accumulation of unesterified cholesterol in late endosomes/lysosomes. NPC is considered a lipid storage disorder with variable age of onset, from neonates to adulthood, and highly variable clinical presentation. Most individuals are diagnosed during childhood with symptoms that include ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures. Infants may present with or without hepatosplenomegaly and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Adult-onset NPC is associated with a slower progression and is characterized by psychiatric illness, ataxia, dystonia, and speech difficulties. New treatments are available for patients with NPC that help improve both the neurological and functional symptoms. The incidence of NPC is approximately 1 in 120,000 to 150,000 live births. NPC is an autosomal recessive condition and is caused by biallelic disease-causing variants in either the NPC1 or NPC2 genes. Individuals with NPC exhibit elevated levels of oxysterol COT; LSM 509 and7-KC may also be elevated. The diagnosis of NPC can be confirmed by demonstration of impaired cholesterol esterification and positive filipin staining in cultured fibroblasts. For molecular confirmation, genetic testing for NPC disease can be performed (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify gene list ID: IEMCP-H683JG).

Useful For: Investigating a possible diagnosis of Niemann-Pick disease types A, B, or C using plasma specimens Monitoring of individuals with Niemann-Pick type C disease This test is not useful for the identification of carriers.

Interpretation: An elevation of cholestane-3-beta, 5-alpha, 6-beta-triol is highly suggestive of Niemann-Pick disease type C (NPC). An elevation of lyso-sphingomyelin is highly suggestive of Niemann-Pick type A or B (NPA or NPB) disease.

Reference Values:

Cholestane-3-beta,5-alpha,6-beta-triol
Cutoff: < or =0.070 nmol/mL

7-Ketocholesterol
Cutoff: < or =0.100 nmol/mL

Lyso-sphingomyelin
Cutoff :< or = 0.100 nmol/mL

Clinical References: 1. Newborn Screening ACT Sheet [Decreased acid sphingomyelinase] Acid Sphingomyelinase Deficiency (ASMD). American College of Medical Genetics and Genomics; 2022. Revised May 2022. Accessed December 2, 2024. Available at www.acmg.net/PDFLibrary/Niemann-Pick.pdf 2. Wasserstein MP, Schuchman EH. Acid sphingomyelinase deficiency. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews. [Internet]. University of Washington, Seattle; 2006. Updated April 27, 2023. Accessed December 2, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1370/ 3. Patterson M. Niemann-Pick disease type C. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated December 10, 2020. Accessed

December 2, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1296/ 4. Schuchman EH. The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann-Pick disease. Int J Clin Pharmacol Ther. 2009;47(Suppl 1):S48-S57. doi:10.5414/cpp47048 5.. Hollack CEM, de Sonnaville ESV, Cassiman D et al. Acid sphingomyelinase (Asm) deficiency patients in The Netherlands and Belgium: disease spectrum and natural course in attenuated patients. Mol Genet Metab. 2012;107(3):526-533 6. Wasserstein M, Dionisi-Vici C, Giugliani R, et al. Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD). Mol Genet Metab. 2019;126(2):98-105 7. Geberhiwot T, Moro A, Dardis A, et al. International Niemann-Pick Disease Registry (INPDR): Consensus clinical management guidelines for Niemann-Pick disease type C. Orphanet J Rare Dis. 2018;13(1):50 8. Bremova-Ertl T, Claassen J, Foltan T, et al. Efficacy and safety of N-acetyl-L-leucine in Niemann-Pick disease type C. J Neurol. 2022;269(3):1651-1662. doi:10.1007/s00415-021-10717-0 9. Mengel E, Patterson MC, Da Riol RM, et al. Efficacy and safety of arimoclomol in Niemann-Pick disease type C: Results from a double-blind, randomised, placebo-controlled, multinational phase 2/3 trial of a novel treatment. J Inherit Metab Dis. 2021;44(6):1463-1480. doi:10.1002/jimd.12428

OYST
82883

Oyster, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to oyster Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive

3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CCPQ
81185

P/Q-Type Calcium Channel Antibody, Serum

Clinical Information: This test is not offered as a standalone test but is included in the following test procedures as an aid for diagnosis of neurological autoimmunity, usually in a paraneoplastic context. -MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum -MGLE / Myasthenia Gravis/Lambert-Eaton Myasthenic Syndrome Evaluation, Serum P/Q-type calcium channels regulate neurotransmitter release at motor nerve terminals and are involved in central neurotransmission. A snail venom toxin, omega conopeptide MVIIC, is a specific high-affinity antagonist for P/Q-type channels. Autoantibodies directed against extracellular epitopes of P/Q-type calcium channels are implicated as the effectors of the Lambert-Eaton myasthenic syndrome (LES). These antibodies generally reflect an immune response against cancer. P/Q-type calcium channel binding antibodies are found in 95% of nonimmunosuppressed patients with LES (100% of those with cancer) and in 20% of patients who have encephalomyeloneuropathies related to carcinoma of lung, breast, or ovary.

Useful For: Confirming a diagnosis of Lambert-Eaton syndrome Implicating autoimmunity as a disease-causing mechanism in patients with complex neurologic presentations, particularly in those with a history of cancer Implicating autoimmunity as the basis of limbic encephalitis, cerebellar ataxia, myelopathy, peripheral neuropathy, or autonomic neuropathy This test is not useful as a general screening test for cancer.

Interpretation: Values greater than 0.02 nmol/L are consistent with neurologic autoimmunity and suggest a paraneoplastic basis. Values in nonimmunosuppressed patients with Lambert-Eaton syndrome are usually greater than 0.1 nmol/L.

Reference Values:
Only orderable as part of a profile. For more information see:
MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
MGLE / Myasthenia Gravis/Lambert-Eaton Myasthenic Syndrome Evaluation, Serum
PNEFS / Neuroimmunology Antibody Follow-Up, Serum

< or =0.02 nmol/L

Clinical References: 1. Lennon VA, Kryzer TJ, Griesmann GE, et al. Calcium-channel antibodies in the Lambert-Eaton myasthenic syndrome and other paraneoplastic syndromes. N Engl J Med. 1995;332(22):1467-1474 2. Lennon VA. Serological profile of myasthenia gravis and distinction from the lambert-eaton myasthenic syndrome. Neurology. 1997;48(Suppl 5):S23-S27 3. Zalewski NL, Lennon VA, Lachance DH, Klein CJ, Pittock SJ, Mckeon A. P/Q- and N-type calcium-channel antibodies: Oncological, neurological, and serological accompaniments. Muscle Nerve. 2016;54(2):220-227. doi:10.1002/mus.25027

P16
70524

p16 (INK4a/CDKN2A) Immunostain, Technical Component Only

Clinical Information: p16 (INK4a/CDKN2A) is a cell cycle regulatory protein that is overexpressed in cervical dysplasia related to human papilloma virus (HPV) infection. Nuclear and cytoplasmic staining is seen in dysplastic squamous cervical epithelial cells infected with HPV but not in normal cells. A subset of pancreatic islet cells and dendritic cells show expression of p16 and can serve as positive control.

Useful For: Aids in the identification of human papilloma virus infection

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Castle PE. A LASTing impression: incorporating p16 immunohistochemistry into routine diagnosis of cervical neoplasia. Pathol Case Rev. 2013;18:154-157 2. Doxtader EE, Katzenstein AL. The relationship between p16 expression and high-risk human papillomavirus infection in squamous cell carcinomas from sites other than uterine cervix: a study of 137 cases. Hum Pathol. 2012;43(3):327-332 3. El-Naggar AK, Westra WH. p16 expression as a surrogate marker for HPV-related oropharyngeal carcinoma: a guide for interpretative relevance and consistency. Head Neck. 2012;34(4):459-461 4. Klaes R, Benner A, Friedrich T, et al. p16INK4a immunohistochemistry improves interobserver agreement in the diagnosis of cervical intraepithelial neoplasia. Am J Surg Pathol. 2002;26(11):1389-1399 5. Singhi AD, Westra WH. Comparison of human papillomavirus in situ hybridization and p16 immunohistochemistry in the detection of human papillomavirus-associated head and neck cancer based on a prospective clinical experience. Cancer. 2010;116(9):2166-2173 6. Abdelhakam DA, Huenerberg KA, Nassar A. Utility of p16 and HPV testing in oropharyngeal squamous cell carcinoma: An institutional review. Diagn Cytopathol. 2021;49(1):54-59 7. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

P40NA
70526

p40 + Napsin A Immunostain, Technical Component Only

Clinical Information: p40 is an antibody (detected by the chromogen 3,3'-diaminobenzidine) that recognizes the deltaNp63 isoform of p63. This isoform may exert an oncogenic effect and is selectively expressed in squamous cell carcinoma. Napsin A is an aspartic proteinase involved in the proteolytic processing of surfactant precursors in the normal alveolar epithelium. In normal tissues, napsin A is expressed in the cytoplasm of alveolar macrophages, type II pneumocytes, pancreatic ducts and acini, and in renal tubules (detected by the chromogen fast red). Napsin A has clinical utility for the identification of primary lung adenocarcinomas. Napsin A is also positive in a subset of thyroid and renal cell carcinomas (especially papillary types).

Useful For: p40 aids in the classification of carcinomas and lymphomas Napsin A aids in the identification of primary lung adenocarcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the

patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Whithaus K, Fukuoka J, Prihoda TJ, Jagirdar J. Evaluation of napsin A, cytokeratin 5/6, p63, and thyroid transcription factor 1 in adenocarcinoma versus squamous cell carcinoma of the lung. Arch Pathol Lab Med. 2012;136(2):155-162 2. Sterlacci W, Savic S, Schmid T, et al. Tissue-sparing application of the newly proposed IASLC/ATS/ERS classification of adenocarcinoma of the lung shows practical diagnostic and prognostic impact. Am J Clin Pathol. 2012;137(6):946-956 3. Nonaka D. A study of deltaNp63 expression in lung non-small cell carcinomas. Am J Surg Pathol. 2012;36(6):895-899 4. Kargi A, Gurel D, Tuna B. The diagnostic value of TTF-1, CK 5/6, and p63 immunostaining in classification of lung carcinomas. Appl Immunohistochem Mol Morphol. 2007;15(4):415-420 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298

P40
70527

p40 Immunostain, Technical Component Only

Clinical Information: p40 is an antibody that recognizes the deltaNp63 isoform of p63. This isoform may exert an oncogenic effect and is selectively expressed in squamous cell carcinoma.

Useful For: Diagnosis and classification of carcinomas and lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Travis WD, Brambilla E, Noguchi M, et al. Diagnosis of lung cancer in small biopsies and cytology: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. Arch Pathol Lab Med. 2013;137(5):668-684 2. Nonaka D. A study of deltaNp63 expression in lung non-small cell carcinomas. Am J Surg Pathol. 2012;36(6):895-899 3. Pelosi G, Fabbri A, Bianchi F, et al. DeltaNp63 (p40) and thyroid transcription factor-1 immunoreactivity on small biopsies or cellblocks for typing non-small cell lung cancer: a novel two-hit, sparing-material approach. J Thorac Oncol. 2012;7(2):281-290 4. Bishop JA, Teruya-Feldstein J, Westra WH, Pelosi G, Travis WD, Rekhtman N. p40 (deltaNp63) is superior to p63 for the diagnosis of pulmonary squamous cell carcinoma. Mod Pathol. 2012;25(3):405-415 5. Geddert H, Kiel S, Heep HJ, Gabbert HE, Sarbia M. The role of p63 and deltaNp63 (p40) protein expression and gene amplification in esophageal carcinogenesis. Hum Pathol. 2003;34(9):850-856 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

P504S
610458

P504S Immunostain, Technical Component Only

Clinical Information: Alpha-methylacyl coenzyme A racemase, also known as p504S, is a peroxisomal and mitochondrial enzyme that exhibits a granular expression in the cytoplasm (detected by the chromogen Fast Red). P504S expression is useful in the differentiation between benign prostate glands and prostatic adenocarcinoma as well as in characterizing primary and metastatic renal cell carcinomas.

Useful For: Characterization of renal cell carcinoma and the identification of high-grade prostatic intraepithelial neoplasia and prostate carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Strojan Flezar M, Gutnik H, Jeruc J, Kirbis IS. Typing of renal tumors by morphological and immunocytochemical evaluation of fine needle aspirates. Virchows Arch. 2011;459(6):607-614 2. Molinie V, Balaton A, Rotman S, et al. Alpha-methyl CoA racemase expression in renal cell carcinomas. Hum Pathol. 2006;37(6):698-703 3. Lin F, Brown RE, Shen T, Yang XJ, Schuerch C. Immunohistochemical detection of P504S in primary and metastatic renal cell carcinomas. Appl Immunohistochem Mol Morphol. 2004;12(2):153-159 4. Jiang Z, Fanger GR, Woda BA, et al. Expression of alpha-methylacyl-CoA racemase (P504s) in various malignant neoplasms and normal tissues: astudy of 761 cases. Hum Pathol. 2003;34(8):792-796 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298

P53
70528

p53 Immunostain, Technical Component Only

Clinical Information: p53 is a tumor-suppressor protein. Genetic events (variant and deletion) that affect both P53 alleles can lead to loss of cell cycle control in the setting of DNA damage, resulting in genetic instability and neoplastic transformation. Altered p53 also has a prolonged half-life compared to wildtype p53 and, thus, accumulates in the nucleus and can be detected by immunohistochemistry. Abnormalities of the P53 gene are one of the most common genetic changes associated with cancer and can be found in a wide variety of tumor types, where they are generally associated with a worse prognosis. The p53 protein can be readily detected in a subset of cancers of the colon, stomach, bladder, breast, lung, and testes and in melanoma and lymphoma.

Useful For: Aiding in the identification of neoplastic cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298 2. Camelo-Piragua S, Jansen M, Ganguly A, et al. A sensitive and specific diagnostic panel to distinguish diffuse astrocytoma from astrocytosis: chromosome 7 gain with mutant isocitrate dehydrogenase 1 and p53. J Neuropathol Exp Neurol. 2011;70(2):110-115 3. Klemi PJ, Pylkkanen L, Kiilholma P, Kurvinen K, Joensuu H. p53 protein detected by immunohistochemistry as a prognostic factor in patients with epithelial ovarian carcinoma. Cancer. 1995;76(7):1201-12084. Mayall FG, Goddard H, Gibbs AR. p53 immunostaining in the distinction between benign and malignant mesothelial proliferations using formalin-fixed paraffin sections. J Pathol. 1992;168(4):377-3815. van den Berg FM, Baas IO, Polak MM, Offerhaus GJ. Detection of p53 overexpression in routinely paraffin-embedded tissue of human carcinomas using a novel target unmasking fluid. Am J Pathol. 1993;142(2):381-385 6. Zarei S, Wang Y, Jenkins SM, Voss JS, Kerr SE, Bell DA. Clinicopathologic, Immunohistochemical, and Molecular Characteristics of Ovarian Serous Carcinoma With Mixed Morphologic Features of High-grade and Low-grade Serous Carcinoma. Am J Surg Pathol. 2020;44(3):316-328 7. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

P57I
70529

p57 (KIP2/CDKN1C) Immunostain, Technical Component Only

Clinical Information: p57 (KIP2/CDKN1C) is a cell cycle regulatory protein that acts as a tumor-suppressor gene by inhibiting the activity of cyclin dependent kinases. p57 is expressed in the cytotrophoblasts, intermediate trophoblasts, and villous stromal cells in normal placenta. Loss of p57 expression is associated with complete hydatidiform moles and can help distinguish them from partial hydatidiform moles and hydropic abortions.

Useful For: Aids in the identification of cytotrophoblasts, intermediate trophoblasts, and villous stromal cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Banet N, DeScipio C, Murphy KM, et al. Characteristics of hydatidiform moles: analysis of a prospective series with p57 immunohistochemistry and molecular genotyping. Mod Pathol. 2014;27(2):238-254 2. Marjoniemi VM. Immunohistochemistry in gynaecological pathology: a review. Pathology. 2004;36(2):109-119 3. McConnell TG, Murphy KM, Hafez M, Vang R, Ronnett BM. Diagnosis and subclassification of hydatidiform moles using p57 immunohistochemistry and molecular genotyping: validation and prospective analysis in routine and consultation practice settings with development of an algorithmic approach. Am J Surg Pathol. 2009;33(6):805-817 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

P62
70629

p62 Immunostain, Technical Component Only

Clinical Information: Argyrophilic grain disease (AGD) is a common, late-onset dementia characterized by the presence of argyrophilic grains and coiled bodies. AGD is a frequent pathologic finding in patients who have been diagnosed with amnestic-type mild cognitive impairment. Immunohistochemical detection of ubiquitin-binding protein p62 is a sensitive and reproducible method to identify grain pathology in AGD.

Useful For: Aids in diagnosing argyrophilic grain disease

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Scott IS, Lowe JS. The ubiquitin-binding protein p62 identifies argyrophilic grain pathology with greater sensitivity than conventional silver stains. Acta Neuropathol 2006;113(4):417-420 2. Ferrer I, Santpere G, van Leeuwen FW. Argyrophilic grain disease. Brain. 2008;131(Pt 6):1416-1432 3. Kuusisto E, Kauppinen T, Alafuzoff I. Use of p62/SQSTM1 antibodies for neuropathological diagnosis. Neuropathol Appl Neurobiol. 2008;34(2):169-180 4. Jicha GA, Petersen RC, et al: Argyrophilic grain disease in demented subjects presenting initially with amnestic mild cognitive impairment. J Neuropathol Exp Neurol 2006;65:602-609 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

P63
70530

p63 Immunostain, Technical Component Only

Clinical Information: The p63 protein is a member of the p53 family of tumor-suppressor proteins. The predominant localization of p63 protein is in the basal layer of stratified squamous and transitional epithelia. p63 is negative in malignant tumors of the prostate. Striated muscle staining may be observed with p63.

Useful For: Aiding in identifying squamous, urothelial, or myoepithelial differentiation in tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Livasy CA, Karaca G, Nanda R, et al. Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. Mod Pathol. 2006;19(2):264-271 2. Ueo T, Kashima K, Daa T, Kondo Y, Sasaki A, Yokoyama S. Immunohistochemical analysis of morules in colonic neoplasma: morules are morphologically and qualitatively different from squamous metaplasia. Pathobiology. 2005;72(5):269-278 3. Varma M, Jasani B. Diagnostic utility of immunohistochemistry in morphologically difficult prostate cancer: review of current literature. Histopathology. 2005;47(1):1-16 4. Weinstein MH, Signoretti S, Loda M. Diagnostic utility of immunohistochemical staining for p63, a sensitive marker of prostatic basal cells. Mod Pathol. 2002;15(12):1302-1308 5. Hu WM, Jin JT, Wu CY, et al. Expression of P63 and its correlation with prognosis in diffuse large B-cell lymphoma: a single center experience. Diagn Pathol. 2019;14(1):128. doi:10.1186/s13000-019-0880-7 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

SQUI
82821

Pacific Squid, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pacific squid Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be

responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PN10X
62911

Pain Clinic Survey 10, Chain of Custody, Random, Urine

Clinical Information: This assay was designed to test for and confirm by gas chromatography mass spectrometry the following: -Barbiturates -Cocaine -Methadone -Phencyclidine This assay was designed to test for and confirm by liquid chromatography tandem mass spectrometry the following -Opiates -Benzodiazepines -Carboxy-tetrahydrocannabinol -Amphetamines Chain of custody is a record of the disposition of a specimen to document the individuals who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting drug use involving amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, and carboxy-tetrahydrocannabinol This chain-of-custody test is intended to be used in a setting where the test results can be used to make a definitive diagnosis. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited. This test is not intended for use in employment-related testing.

Interpretation: A positive result derived by this testing indicates that the patient has used one of the drugs detected by these techniques in the recent past. For information about drug testing, including estimated detection times, see Drug Class Testing on MayoClinicLabs.com.

Reference Values:
Only orderable as part of a profile. For more information see PANOX / Pain Clinic Survey 10, Chain of Custody, Urine.

Negative
Screening cutoff concentrations:
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 100 ng/mL
Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
Methadone metabolite: 300 ng/mL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

Clinical References: 1. Physician's Desk Reference (PDR). 60th edition. Medical Economics Company; 2006 2. Bruntman LL. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Book Company; 2006 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

PANOX
62737

Pain Clinic Survey 10, Chain of Custody, Random, Urine

Clinical Information: This assay was designed to test for and confirm by gas chromatography mass spectrometry (GC-MS) the following: -Barbiturates -Cocaine -Methadone -Phencyclidine This assay was designed to test for and confirm by liquid chromatography tandem mass spectrometry (LC-MS/MS) the following: -Opiates -Benzodiazepines -Carboxy-tetrahydrocannabinol -Amphetamines This test uses the simple screening technique which involves immunoassay testing for drugs by class. Oxycodone is not detected well with the opiate screening assay; therefore, confirmation testing is included to detect this drug. All positive screening results are confirmed by either GC-MS or LC-MS/MS and quantitated before a positive result is reported. Chain of custody is a record of the disposition of a specimen to document the individuals who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting drug use involving amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, and tetrahydrocannabinol This chain-of-custody test is intended to be used in a setting where the test results can be used to make a definitive diagnosis. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited. This test is not intended for use in employment-related testing.

Interpretation: A positive result derived by this testing indicates that the patient has used one of the drugs detected by these techniques in the recent past. For information about drug testing, including estimated detection times, see Drug Class Testing on MayoClinicLabs.com.

Reference Values:
Negative
Screening cutoff concentrations
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 100 ng/mL

Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
Methadone metabolite: 300 ng/mL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL
This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

Clinical References: 1. Physician's Desk Reference (PDR). 60th ed. Medical Economics Company; 2006 2. Bruntman LL. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Book Company; 2006 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

FPALI
75392

Paliperidone, Serum

Interpretation: Paliperidone is an atypically-structured antipsychotic agent and the main pharmacologically active metabolite of Risperidone (commonly referred to as 9-hydroxyrisperidone). The following mean plasma paliperidone concentrations have been reported: 3 mg single extended release oral dose: 4.9 ng/mL at 24 hours 6 mg single extended release oral dose: 10 ng/mL at 24 hours 12 mg single extended release oral dose: 20 ng/mL at 24 hours 3 mg extended release oral dose for 7 days: 11 ng/mL at 22 hours after last dose 78-156 mg IM once monthly for 6 months: 10-20 ng/mL (median trough concentration) Acute ingestion of 180 and 504 mg extended release paliperidone resulted in serum concentrations of 170 and 883 ng/mL, respectively, approximately 40 hours after ingestion and the reported serum concentration following acute ingestion of 270 mg was 100 ng/mL 16 hours post-ingestion. A femoral blood paliperidone concentration of 240 ng/mL was the only finding in an individual who died 2 weeks after a 525 depot IM injection. The blood/plasma ratio of paliperidone is 0.7-0.8.

Reference Values:
None Detected ng/mL

Units: ng/mL

FPAN2
75907

Pancreastatin, Plasma

Clinical Information:

Reference Values:
10-135 pg/mL

Clinical References: 1. Raines D, Chester M, Diebold AE, et al. A prospective evaluation of the effect of chronic proton pump inhibitor use on plasma biomarker levels in humans. Pancreas. 2012;41(4):508-511 2. O'Dorisio TM, Krutzik SR, Woltering EA, et al. Development of a highly sensitive and specific carboxy-terminal human Pancreastatin assay to monitor neuroendocrine tumor behavior. Pancreas. 201;39(5):611-616 3. Piero E, Mirelles P, Silvestre RA, et al. Pancreastatin inhibits insulin secretion as induced by glucagon, vasoactive intestinal polypeptide, gastric inhibiting peptide, and 8-cholecystokinin in the perfused rat pancreas. Metabolism. 1989;38(7):679-682 4. Tatemoto K, Efendic S, Mutt S, et al. Pancreastatin, a novel pancreatic peptide that inhibits insulin secretion. Nature. 1986;324(6096):476-478 5. Calhoun K, Toth-Fejel S, Chee J, et al. Serum peptide profiles in patients with carcinoid tumors. Am J Surg. 2003;186(1):28-31 6. Syverson U, Jacobsen MB, O'Connor DT, et al. Immunoassays for measurement of chromogranin A and pancreastatin-like immunoreactivity in humans:

correspondence in patients with neuroendocrine neoplasia. Neuropeptides. 1994;26(3):201-206 7. Kogner P, Bjellerup P, Svensson T, et al. Pancreastatin immunoreactivity in favourable childhood neuroblastoma and ganglioneuroma. Eur J Cancer. 1995;31A(4):557-560 8. Desai DC, O'Dorisio TM, Schirmer WJ, et al. Serum pancreastatin levels predict response to hepatic artery chemoembolization and somatostatin analog therapy in metastatic neuroendocrine tumors. Regul Pept. 2001;96(3):113-117

ELASF
609492

Pancreatic Elastase, Feces

Clinical Information: Pancreatic elastase (PE) is a proteolytic enzyme produced in the pancreatic acinar cells. It is released as a zymogen, which is then converted to an active enzyme in the duodenum by trypsin. PE has an important role in digestion and proteolytically degrades proteins preferentially at alanine residues. Exocrine pancreatic insufficiency (EPI) is a condition in which the pancreas does not produce sufficient digestive enzymes required to breakdown ingested food, leading to maldigestion and malabsorption.(1) Clinical symptoms of EPI include steatorrhea, bloating, abdominal discomfort, and weight loss.(2) EPI is most commonly caused by chronic pancreatitis but can also be associated with pancreatic cancer, pancreatic surgery, necrotizing acute pancreatitis, cystic fibrosis, inflammatory bowel disease (both Crohn disease and ulcerative colitis), diabetes (types I and II), gastric surgery, short bowel syndrome, and Zollinger-Ellison syndrome.(2,3) If left untreated, patients with EPI can experience weight loss and significant nutrient deficiencies. Treatment for EPI centers on administration of pancreatic enzyme replacement therapy. Stool testing is a critical component for the diagnosis of EPI. The 72-hour fecal fat test is useful for evaluating for the presence of steatorrhea.(4) However, this testing is cumbersome for the patient and not easily tolerated due to the requirement of consuming 100 g fat/day. An alternate to the 72-hour fecal fat test is the measurement of PE in stool. The amount of PE in stool is representative of pancreatic enzyme production; patients with EPI may have reduced concentrations of PE in feces. Current guidelines from the American Gastroenterological Association identify PE in stool as the most appropriate initial test for evaluation of patients with a high probability of pancreatic disease and clinical signs consistent with malabsorption (5). However, the guidelines acknowledge that this testing can be prone to false-positive results, especially in patients with a low pre-test probability for EPI. In a meta-analysis, PE in stool demonstrated a pooled sensitivity of 77% and a specificity of 88%, when compared to secretin stimulation testing. In patients with a low-pretest probability for EPI, the false-positive rate was estimated to by 11%. In addition, the sensitivity of fecal PE is higher in patients with severe EPI compared to patients with moderate or mild disease.(6)

Useful For: Evaluating patients with suspected exocrine pancreatic insufficiency, with symptoms of unexplained diarrhea, constipation, steatorrhea, flatulence, weight loss, upper abdominal pain, and food intolerances Monitoring of exocrine pancreatic function in cystic fibrosis, diabetes mellitus, or chronic pancreatitis

Interpretation: Pancreatic elastase concentrations above 200 mcg/g are normal and are not indicative of exocrine pancreatic insufficiency. Pancreatic elastase concentrations from 100 to 200 mcg/g are suggestive for moderate exocrine pancreatic insufficiency. Pancreatic elastase concentrations below 100 mcg/g are consistent with exocrine pancreatic insufficiency.

Reference Values:
<100 mcg/g (Severe Pancreatic Insufficiency)
100-200 mcg/g (Moderate Pancreatic Insufficiency)
>200 mcg/g (Normal)

Reference values apply to all ages.

Clinical References: 1. Phillips ME, Hopper AD, Leeds JS, et al. Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines. 2021;8(1):e000643 2. Capurso G, Traini

M, Piciucchi M, Signoretti M, Arcidiacono PG. Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. Clin Exp Gastroenterol. 2019;12:129-139 3. Leeds JS, Oppong K, Sanders DS. The role of fecal elastase-1 in detecting exocrine pancreatic disease. Nat Rev Gastroenterol Hepatol. 2011;8(7):405-415 4. Chowdhury SD, Kurien RT, Ramachandran A, et al. Pancreatic exocrine insufficiency: Comparing fecal elastase 1 with 72-h stool for fecal fat estimation. Indian J Gastroenterol. 2016;35(6):441-444 5. Whitcomb DC, Buchner AM, Forsmark CE. AGA clinical practice update o the epidemiology, evaluation, and management of exocrine pancreatic insufficiency: Expert review. Gastroenterology. 2023;165(5):1292-1301 6. Vanga RR, Tansil A, Sidiq S, et al. Diagnostic performance of measurement of fecal elastase-1 in detection of exocrine pancreatic insufficiency: Systemic review and meta-analysis. 2018;16(8):1220-1228

HPP
8014

Pancreatic Polypeptide, Plasma

Clinical Information: Pancreatic polypeptide (PP) is secreted by the pancreas in response to hypoglycemia, ingestion of food, or "sham" feeding (food is chewed, but not swallowed) secondary to vagal nerve stimulation. Secretion is blocked by vagotomy or atropine. The exact physiologic role of PP is undetermined, although the hormone is thought to be involved in exocrine pancreatic secretion and gallbladder emptying. Markedly elevated levels are often associated with endocrine tumors of the pancreas (eg, insulinoma, glucagonoma, pancreatic polypeptide-secreting tumor of the pancreas). Patients with diabetes may also have elevated PP levels. A lack of response to sham feeding may indicate vagal nerve damage (eg, surgery-related nerve damage, autonomic nerve disorders). Extensive pancreatic destruction (eg, chronic pancreatitis, pancreatic cancer) may also result in low basal PP levels and a lack of response to sham feeding.

Useful For: Detecting pancreatic endocrine tumors Assessing vagal nerve function after meal or sham feeding

Interpretation: High levels of pancreatic polypeptide may be seen in pancreatic endocrine tumors, diabetes, and a nonfasting state. Markedly elevated levels may be seen in some pancreatic exocrine tumors. A normal response to a sham feeding consists of a rapid pancreatic polypeptide rise over baseline followed by a return to baseline. With vagal damage, no increase over baseline is seen.

Reference Values:
0-19 years: Not established
20-29 years: <228 pg/mL
30-39 years: <249 pg/mL
40-49 years: <270 pg/mL
50-59 years: <291 pg/mL
60-69 years: <312 pg/mL
70-79 years: <332 pg/mL
> or =80 years: Not established

Clinical References: 1. Panzuto F, Severi C, Cannizzaro R, et al. Utility of combined use of plasma levels of chromogranin A and pancreatic polypeptide in the diagnosis of gastrointestinal and pancreatic endocrine tumors. J Endocrinol Invest. 2004;27(1):6-11 2. Brimnes Damholt M, Rasmussen BK, Hilsted L, et al. Basal serum pancreatic polypeptide is dependent on age and gender in an adult population. Scand J Clin Lab Invest. 1997;57(8):695-702 3. Escobar H, Jushnir M, Ray J, et al. Measurement of pancreatic polypeptide and its peptide variant in human serum and plasma by immunocapture-liquid-chromatography-tandem mass spectrometry. Reference intervals and practical assay considerations. Biochem Physiol. 2014;3:140. doi:10.4172/2168-9652.1000140 4. Balaji N, Crookes P, Banki F, et al. A Safe and Noninvasive Test for Vagal Integrity Revisited. Arch Surg. 2002;137(8):954-959 5. Maus A, Fatica EM, Taylor R, et al. Identification, measurement, and assessment of the clinical utility of human

pancreatic polypeptide by liquid chromatography-tandem mass spectrometry. J Proteome Res. 2023;22(4):1322-1330. doi:10.1021/acs.jproteome.2c00829

WESPR
621326

Panel to Whole Exome Sequencing Reflex Test, Varies

Clinical Information:

Useful For:

Interpretation: Variants of interest are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(4) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants are reported in one of the following categories: -Likely Causative: variants with a high degree of suspicion for causing the patient's reported clinical features -Possibly Relevant: variants that may be related to the patient's clinical features or variants in genes of uncertain significance -Secondary Findings: medically actionable variants unrelated to the indication for testing (see below for additional information) -Previously Reported: variants that were reported on the original panel test report but do not reach the reporting criteria to be included in the above categories. It is possible that a variant may not be recognized as the underlying cause of disease due to incomplete scientific knowledge about the function of all genes in the human genome or the impact of variants in those genes. Secondary Findings: Patients are evaluated for medically actionable secondary findings and these findings are reported in accordance with the most current ACMG recommendations, including the most up-to-date gene list.(5) Variants in these genes will not be evaluated or reported if the patient opts out of this evaluation unless they overlap with the patient's reported clinical phenotype. The presence of a variant in family member comparator specimens is stated on the patient's (proband's) report unless family members opt out of secondary findings. If the patient (proband) opts out, secondary findings will not be reported for any family member. Variants that are present in family members comparators but absent from the patient (proband) are not evaluated. The absence of a reportable secondary finding does not guarantee that there are no disease-causing or likely disease-causing variants in these genes, as portions of the genes may not be adequately covered by this testing methodology. Reanalysis and Raw Data Requests: Patient data is not guaranteed to be stored indefinitely. Requests for reanalysis or release of raw data may not be possible, and a new whole exome sequencing order may be required if the original patient data is no longer available or no longer compatible with current bioinformatics processes or analysis tools. Reanalysis of the patient's exome due to new patient clinical features, advances in genetic knowledge, or changes in testing methodology is available. See test WESR/ Whole Exome Sequencing Reanalysis, Varies or contact the laboratory at 800-533-1710 for more information. Requests for the raw data obtained from whole exome sequencing should be directed to the laboratory. A separate fee may apply. Raw data will be released for individuals who complete a Mayo Clinic release of information form. If raw data for family member comparators is requested, it will only be released with an accompanying request for the proband's raw data. Contact the laboratory for instructions on completing the release of information form. The laboratory is not responsible for providing software or other tools needed to visualize, filter, or interpret this data.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Clark MM, Stark Z, Farnaes L, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. NPJ Genom Med. 2018;3:16. doi:10.1038/s41525-018-0053-8 2. Deignan JL, Chung WK, Kearney HM, et al. Points to consider in the reevaluation and reanalysis of genomic test results: A statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2019;21(6):1267-1270 3. Tan NB, Stapleton R, Stark Z, et al. Evaluating systematic reanalysis of

clinical genomic data in rare disease from single center experience and literature review. Mol Genet Genomic Med. 2020;8(11):e1508 4. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 5. Miller DT, Lee K, Gordon AS, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(8):1391-1398. doi:10.1038/s41436-021-01171-4

PAPY
82356

Papaya, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to papaya Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PAPR
82810

Paprika, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to paprika Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PFIB
601950

Parafibromin, Immunostain, Technical Component Only

Clinical Information: Parafibromin is a protein encoded by the HRPT2 oncosuppressor gene, and the expression is reported to be decreased or absent in parathyroid carcinomas. Parafibromin is expressed in the nucleus of benign parathyroids, parathyroid adenomas, and other normal tissues but shows loss of expression in parathyroid carcinomas, making it a good diagnostic tool to identify parathyroid carcinomas and distinguish them from parathyroid adenomas.

Useful For:

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Gill A, Clarkson A, Gimm O, et al. Loss of nuclear rxpression of parafibromin distinguishes parathyroid carcinomas and hyperparathyroidism-jaw tumor (HPT-JT) syndrome-related adenomas from sporadic parathyroid adenomas and hyperplasias. Am J Surg Pathol. 2006:30(9):1140-1149 2. Juhlin C, Hoog A. Parafibromin as a diagnostic instrument for parathyroid carcinoma-lone ranger or part of the posse? Int J Endocrinol 2010;2010:324964 3. Kim HK, Oh YL, Kim SH, et al. Parafibromin immunohistochemical staining to differentiate parathyroid carcinoma from parathyroid adenoma. Head and Neck. 2012;34(2):201-206. doi:10.1002/hed.21716 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PNPAB
61881

Paraneoplastic Pemphigus Antibody, IgG, Serum

Clinical Information: Paraneoplastic pemphigus (PNP) (also paraneoplastic autoimmune multiorgan syndrome [PAMS] to denote the systemic nature of the syndrome) is an autoimmune mucocutaneous blistering disease affecting adults or, rarely, children that generally heralds the presence of an underlying malignancy. PNP/PAMS can be defined and identified by a combination of the following features: 1. Painful stomatitis and a polymorphous cutaneous eruption with lesions that may be blistering, lichenoid, erythema multiforme-like, or morbilliform 2. Variable histopathologic findings, including acantholysis, lichenoid, or interface change 3. Variable direct immunofluorescence findings from a perilesional biopsy, often demonstrating deposition of IgG and complement in the epidermal intercellular spaces, granular/linear complement deposition along the epidermal basement membrane zone, or a lichenoid tissue reaction 4. Indirect immunofluorescence evidence of cell surface deposition on primate esophagus or rat bladder epithelium 5. Enzyme-linked immunosorbent assay evidence of serum autoantibodies against desmogleins 1 or 3 and, possibly, against bullous pemphigoid 180 and 230 antigens The incidence of the disease is unknown, but it is less common than pemphigus vulgaris or foliaceus. Clinical features of the disease can mimic those seen in a drug reaction, erythema multiforme, Stevens-Johnson syndrome, pemphigus, lichen planus, or toxic epidermal necrolysis. In the majority of cases, PNP/PAMS is associated with non-Hodgkin lymphoma, chronic lymphocytic leukemia, thymoma, or Castleman disease. A serious complication includes bronchiolitis obliterans, which may lead to respiratory failure.

Useful For: Diagnosis of paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome in the setting of erosive or lichenoid mucocutaneous disease

Interpretation: In the appropriate clinical setting, a positive result can support a diagnosis of paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome (PNP/PAMS). However, correlation with clinical features, histopathologic findings, results of serum studies (such as indirect

immunofluorescence on primate esophagus substrate and enzyme-linked immunosorbent assay for Dsg1/3) is required for a final diagnosis. As the test is not entirely sensitive, a negative test result does not exclude the possibility of PNP/PAMS.

Reference Values:
Negative

Clinical References: 1. Anhalt GJ, Kim SC, Stanley JR, et al. Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. N Engl J Med. 1990;323(25):1729-1735. doi:10.1056/NEJM199012203232503 2. Anhalt GJ, Aris-Abdo L, Bonitz P, Labib RS. Antigen specificity of paraneoplastic pemphigus: predictive value of diagnostic techniques based on the study of 17 patients and 135 control subjects. J Invest Dermatol. 1992(4);98:580. Abstract 172 3. Liu AY, Valenzuela R, Helm TN, Camisa C, Melton AL, Bergfeld WF. Indirect immunofluorescence on rat bladder transitional epithelium: a test with high specificity for paraneoplastic pemphigus. J Am Acad Dermatol. 1993;28(5 Pt 1):696-699. doi: 10.1016/0190-9622(93)70095-b 4. Camisa C, Helm TN. Paraneoplastic pemphigus is a distinct neoplasia-induced autoimmune disease. Arch Dermatol. 1993;129(7):883-886 5. Montagnon CM, Tolkachjov SN, Murrell DF, et al. Intraepithelial autoimmune blistering dermatoses: Clinical features and diagnosis. J Am Acad Dermatol. 2021;84(6): 1507-1519. doi:10.1016/j.jaad.2020.11.075 6. Montagnon CM, Lehman JS, Murrell DF, et al. Intraepithelial autoimmune bullous dermatoses: disease activity assessment and therapy. J Am Acad Dermatol. 2021;84(6);1523-1537. doi:10.1016/j.jaad.2021.02.073

PVLE
607409

Paraneoplastic Vision Loss Evaluation, Serum

Clinical Information: There are 2 recognized forms of paraneoplastic vision loss: paraneoplastic autoimmune optic neuropathy with retinopathy accompanying collapsin response-mediator protein-5 (CRMP-5)-IgG and cancer associated retinopathy (CAR) accompanying recoverin antibody. Both occur in the setting of occult small-cell carcinoma of the lung or other body region. Patients with CRMP-5-IgG associated optic neuropathy commonly present with painless bilateral visual loss over weeks to months. At onset, there is typically bilateral optic disc edema without evidence of enhancement of the optic nerve on magnetic resonance imaging or elevated opening pressure on lumbar puncture. Visual acuity can range from 20/20 to hand motion. In most cases, patients have coexisting vitritis or retinitis. In addition, patients can have diplopia, usually from cerebellar involvement. The majority of patients with CRMP-5 associated optic neuropathy will have other neurologic deficits from CRMP-5 autoimmunity, such as asymmetric axonal polyradiculoneuropathy. CAR presents with subacute painless progressive bilateral (although asymmetry has been described) progressive vision loss over weeks to months, reflecting both rod and cone retinal dysfunction in most patients. Accordingly, symptoms often include nyctalopia (inability to see in dim light or at night), impaired dark adaptation, photopsia (flashes of light in the field of vision), photosensitivity, dyschromatopsia, and, ultimately, severe visual acuity loss. Patients with CRMP-5-IgG-related ophthalmitis may have improvements with intra-ocular or systemic corticosteroid treatment. Patients with recoverin-related retinopathy are unlikely to have vision improvement with treatment.

Useful For: Evaluating patients with rapidly progressive vision loss where a paraneoplastic cause for vision loss (retinopathy or optic neuritis with other findings [eg, retinitis] is suspected) Evaluating patients with small-cell carcinoma who develop vision loss

Interpretation: Recoverin IgG: Seropositivity is consistent with a diagnosis of paraneoplastic retinopathy. Considerations include small-cell carcinoma, pulmonary, or extrapulmonary. Collapsin response-mediator protein-5 IgG: Seropositivity is consistent with a diagnosis of paraneoplastic retinitis or ophthalmitis. Considerations include small-cell carcinoma, pulmonary, or extrapulmonary.

Reference Values:
COLLAPSIN RESPONSE-MEDIATOR PROTEIN-5-IgGNegative

RECOVERIN IMMUNOBLOT
Negative

COLLAPSIN RESPONSE-MEDIATOR PROTEIN-5 TITER
<1:240

COLLAPSIN RESPONSE-MEDIATOR PROTEIN-5 WESTERN BLOT
Negative
Titers lower than 1:240 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored serum (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call 1-800-533-1710 to request CRMP-5 Western blot. Neuron-restricted patterns of IgG staining that do not fulfill criteria for CRMP-5-IgG may be reported as "unclassified antineuronal IgG." Complex patterns that include non-neuronal elements may be reported as "uninterpretable."

Clinical References: 1. Cross SA, Salomao DR, Parisi JE, et al: Paraneoplastic autoimmune optic neuritis with retinitis defined by CRMP-5-IgG. Ann Neurol. 2003 Jul;54(1):38-50 doi: 10.1002/ana.10587 2. Lopez A, McKeon A, Lachance D, et al: Recoverin antibody: Ophthalmologic and oncologic significance. Neurology. 2016 Apr 5;86(16 Supplement)P6.131

PAVAL
83380

Paraneoplastic, Autoantibody Evaluation, Serum

Clinical Information: Paraneoplastic autoimmune neurological disorders reflect a patient's humoral and cellular immune responses to cancer. The cancer may be new or recurrent, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeural proteins found in the plasma membrane, cytoplasm, and nucleus of neurons, glia, or muscle are generated in this immune response and serve as serological markers of paraneoplastic autoimmunity. Cancers recognized in this context most commonly are small-cell lung carcinoma, thymoma, ovarian (or related Mullerian) carcinoma, breast carcinoma, and Hodgkin lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin lymphoma, and chondroblastoma. An individual patient's autoantibody profile can predict a specific neoplasm with 90% certainty but not the neurological syndrome. It should be noted that this evaluation is considered to be limited and not comprehensive (see Cautions). Three classes of autoantibodies are recognized in this evaluation: -Antineuronal nuclear antibodies (ANNA-1, ANNA-2, ANNA-3) -Anti-glial/neuronal nuclear antibodies (AGNA-1; also known as Sox1) -Neuronal and glial cytoplasmic antibodies (Purkinje cytoplasmic antibody [PCA]-1, PCA-2, PCA-Tr, collapsin response-mediator protein [CRMP]-5, and amphiphysin) Patients who are seropositive usually present with subacute neurological signs and symptoms such as encephalopathy, cerebellar ataxia, myelopathy, nerve (including radiculopathy, plexopathy, sensory/sensorimotor, or autonomic) or neuromuscular junction disorders. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Cancer risk factors include previous or family history of cancer, history of smoking, or social or environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favor less neurological morbidity and offer the best hope for survival.

Useful For: Serological evaluation of patients who present with a subacute neurological disorder of undetermined etiology, especially those with known risk factors for cancer Directing a focused search for cancer Investigating neurological symptoms that appear during, or after, cancer therapy and are not explainable by metastasis Differentiating autoimmune neuropathies from neurotoxic effects of chemotherapy Monitoring the immune response of seropositive patients during cancer therapy Detecting early evidence of cancer recurrence in previously seropositive patients

Interpretation: Antibodies directed at onconeural proteins shared by neurons, glia, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects and are usually accompanied by subacute neurological signs and symptoms. Several autoantibodies have a syndromic association, but no autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than one paraneoplastic autoantibody to be detected, each predictive of the same cancer.

Reference Values:

Test ID	Reporting name	Methodology*	Reference value
PAINT	Interpretive Comments	Medical interpretation	Not applicable
AMPHS	Amphiphysin Ab, S	IFA	Negative
AGN1S	Anti-Glial Nuclear Ab, Type 1	IFA	Negative
ANN1S	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2S	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3S	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
CRMS	CRMP-5-IgG, S	IFA	Negative
PCABP	Purkinje Cell Cytoplasmic Ab Type 1	IFA	Negative
PCAB2	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
PCATR	Purkinje Cell Cytoplasmic Ab Type Tr	IFA	Negative
Reflex Tests: Test ID	Reporting name	Methodology*	Reference value
AGNBS	AGNA-1 Immunoblot, S	IB	Negative
AGNTS	AGNA-1 Titer, S	IFA	
AMIBS	Amphiphysin Immunoblot, S	IB	Negative
AN1BS	ANNA-1 Immunoblot, S	IB	Negative
AN1TS	ANNA-1 Titer, S	IFA	
AN2BS	ANNA-2 Immunoblot, S	IB	Negative
AN2TS	ANNA-2 Titer, S	IFA	
AN3TS	ANNA-3 Titer, S	IFA	
APHTS	Amphiphysin Ab Titer, S	IFA	
CRMTS	CRMP-5-IgG Titer, S	IFA	
CRMWS	CRMP-5-IgG Western Blot, S	WB	Negative
PC1BS	PCA-1 Immunoblot, S	IB	Negative

PC1TS	PCA-1 Titer, S	IFA	
PC2TS	PCA-2 Titer, S	IFA	
PCTBS	PCA-Tr Immunoblot, S	IB	Negative
PCTTS	PCA-Tr Titer, S	IFA	

Clinical References: 1. McKeon A, Pittock SJ. Overview and diagnostic approach in autoimmune neurology. Continuum (Minneap, Minn). 2024;30(4):960-994. doi:10.1212/CON.0000000000001447 2. Zekeridou A. Paraneoplastic neurologic disorders. Continuum (Minneap, Minn). 2024;30(4):1021-1051. doi:10.1212/CON.0000000000001449

PAC1
37430

Paraneoplastic, Autoantibody Evaluation, Spinal Fluid

Clinical Information: Several antineuronal and glial autoantibodies are recognized clinically as markers of a patient's immune response to specific cancers (paraneoplastic autoantibodies). Seropositive patients present with neurologic signs and symptoms in more than 90% of cases. The cancers are most commonly small-cell lung carcinoma, ovarian (or related mullerian) carcinoma, breast carcinoma, thymoma, or Hodgkin lymphoma. The cancers may be new or recurrent, are usually limited in metastatic volume, and are often occult by standard imaging procedures. Detection of the informative marker autoantibodies allows early diagnosis and treatment of the cancer, which may lessen neurological morbidity and improve survival. Serum is the preferred specimen for paraneoplastic autoantibodies. However, cerebrospinal fluid (CSF) results are sometimes positive when serum results are negative (especially for collapsin response-mediator protein-5-IgG [CRMP-5] and other inflammatory central nervous system autoimmunity). Additionally, CSF is more readily interpretable because it generally lacks the interfering nonorgan-specific antibodies that are common in the serum of patients with cancer. Because neurologists typically perform spinal taps in these patients, the recommendation is to submit CSF specimens with serum specimens, either for simultaneous testing or to be held for testing only if serum is negative. CRMP-5-IgG western blot is also performed by specific request for more sensitive detection of CRMP-5-IgG. Testing should be requested in cases of subacute basal ganglionic disorders (chorea, parkinsonism), cranial neuropathies (especially loss of vision, taste, or smell), and myelopathies.

Useful For: Aiding in the diagnosis of paraneoplastic neurological autoimmune disorders related to carcinoma of lung, breast, ovary, thymoma, or Hodgkin lymphoma using spinal fluid specimens

Interpretation: Antibodies directed at onconeural proteins shared by neurons, glia, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects and are usually accompanied by subacute neurological signs and symptoms. Several autoantibodies have a syndromic association, but no autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than one paraneoplastic autoantibody to be detected, each predictive of the same cancer.

Reference Values:

Test ID	Reporting name	Methodology	Reference value
AMPHC	Amphiphysin Ab, CSF	IFA	Negative
AGN1C	Anti-Glial Nuclear Ab, Type 1	IFA	Negative
ANN1C	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
ANN2C	Anti-Neuronal Nuclear Ab, Type 2	IFA	Negative
ANN3C	Anti-Neuronal Nuclear Ab, Type 3	IFA	Negative
CRMC	CRMP-5-IgG, CSF	IFA	Negative
PCTRC	Purkinje Cell Cytoplasmc Ab Type Tr	IFA	Negative
PCA1C	Purkinje Cell Cytoplasmic Ab Type 1	IFA	Negative
PCA2C	Purkinje Cell Cytoplasmic Ab Type 2	IFA	Negative
Reflex Information: Test ID	Reporting name	Methodology	Reference value
AGNBC	AGNA-1 Immunoblot, CSF	IB	Negative
AGNTC	AGNA-1 Titer, CSF	IFA	
AMIBC	Amphiphysin Immunoblot, CSF	IB	Negative
AN1BC	ANNA-1 Immunoblot, CSF	IB	Negative
AN1TC	ANNA-1 Titer, CSF	IFA	
AN2BC	ANNA-2 Immunoblot, CSF	IB	Negative
AN2TC	ANNA-2 Titer, CSF	IFA	
AN3TC	ANNA-3 Titer, CSF	IFA	
APHTC	Amphiphysin Ab Titer, CSF	IFA	
CRMTC	CRMP-5-IgG Titer, CSF	IFA	
CRMWC	CRMP-5-IgG Western Blot, CSF	WB	Negative
PC1BC	PCA-1 Immunoblot, CSF	IB	Negative
PC1TC	PCA-1 Titer, CSF	IFA	
PC2TC	PCA-2 Titer, CSF	IFA	
PCTBC	PCA-Tr Immunoblot, CSF	IB	Negative
PCTTC	PCA-Tr Titer, CSF	IFA	

Clinical References: 1. Lucchinetti CF, Kimmel DW, Lennon VA: Paraneoplastic and oncological profiles of patients seropositive for type 1 anti-neuronal nuclear antibody. Neurology. 1998 Mar;50(3):652-657 2. Graus F, Vincent A, Pozo-Rosich P, et al: Anti-glial nuclear antibody: marker of lung cancer-related paraneoplastic neurological syndromes. J Neuroimmunol. 2005 Aug;165(1-2):166-171 3. Pittock SJ, Lucchinetti CF, Lennon VA: Anti-neuronal nuclear autoantibody type 2: paraneoplastic accompaniments. Ann Neurol. 2003 May;53(5):580-587 4. Chan KH, Vernino S, Lennon VA: ANNA-3 anti-neuronal nuclear antibody: marker of lung cancer-related autoimmunity. Ann Neurol. 2001 Sep;50(3):301-311 5. Hetzel DJ, Stanhope CR, O'Neill BP, Lennon VA: Gynecologic cancer in patients with subacute cerebellar degeneration predicted by anti-Purkinje cell antibodies and limited in metastatic volume. Mayo Clin Proc. 1990 Dec;65(12):1558-1563 6. Pittock SJ, Lucchinetti CF, Parisi JE, et al: Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol. 2005 Jul;58(1):96-107 7. McKeon A, Pittock SJ: Paraneoplastic encephalomyelopathies: pathology and mechanisms. Acta Neuropathol. 2011 Oct;122(4):381-400 8. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul 15;20(14):3862-3869

PARID
9202

Parasite Identification, Varies

Clinical Information: Infectious diseases are spread and caused by a variety of macroscopic vectors. A wide array of macroscopic parasites (worms and ectoparasites) and parasite mimics or artifacts may be submitted for examination and identification. It is important to promptly and accurately identify these specimens so that the ordering physician can appropriately treat and counsel the patient.

Useful For: Gross identification of parasites (eg, worms) and arthropods (eg, ticks, bed bugs, lice, mites) Detecting or eliminating the suspicion of parasitic infection by identifying suspect material passed in stool or found on the body Supporting the diagnosis of delusional parasitosis Identifying ticks, including Ixodes species (the vector for Lyme disease)

Interpretation: A descriptive report is provided identifying the worm or arthropod. Worms and hard ticks are identified to the species level, when possible, while other parasitic arthropods are identified to the genus level. Arthropods that do not cause human disease and parasite mimics resembling worms are reported as nonparasites or free-living insects.

Reference Values:
A descriptive report is provided.

Clinical References: Mathison BA, Pritt BS. Laboratory Identification of Arthropod Ectoparasites. Clin Microbiol Rev. 2014;27(1):48-67

PTH
70544

Parathyroid Hormone (PTH) Immunostain, Technical Component Only

Clinical Information: Parathyroid hormone staining is useful in identifying parathyroid glands in cases of hyperparathyroidism. Hyperproduction of parathyroid-like hormone may occur in association with lung tumors; such tumors may have reactivity with parathyroid hormone antibodies.

Useful For: Identification of parathyroid glands

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate

immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Matsushita H, Usui M, Hara Y, et al. Co-secretion of parathyroid hormone and parathyroid-hormone-related protein via a regulated pathway in human parathyroid adenoma cells. Am J Pathol. 1997;150(3):661-871 2. Oka T, Yoshioka T, Shrestha GR, et al. Immunohistochemical study of nodular hyperplastic parathyroid glands in patients with secondary hyperparathyroidism. Virchows Arch A Pathol Anat Histopathol. 1988;413(1):53-60 3. Wick MR, Ritter JH, Humphrey PA, Nappi O. Clear cell neoplasms of the endocrine system and thymus. Semin Diagn Pathol. 1997;14(3):183-202 4. Sass MR, Wewer Albrechtsen NJ, Pedersen J, et al. Secretion of parathyroid hormone may be coupled to insulin secretion in humans. Endocr Connect. 2020;9(7):747-754. doi:10.1530/EC-20-0092 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PTHFN
61526

Parathyroid Hormone, Fine-Needle Aspiration Biopsy (FNAB)-Needle Wash

Clinical Information: Parathyroid hormone (PTH) is produced and secreted by the parathyroid glands, which are located along the posterior aspect of the thyroid gland. PTH analysis in rinse material obtained from fine-needle aspiration (FNA) biopsies has gained popularity to discriminate thyroid tissues from enlarged parathyroid glands as well as facilitate parathyroid localization prior to surgery. Various groups have reported on the utility of this technique with specificity of 91% to100% and sensitivity of 82% to 100%. Measuring PTH in the rinse material proves to be very useful in cases of nondiagnostic cytology. Comparing the results of the PTH rinse material with serum PTH is highly recommended. An elevated PTH in the serum could falsely elevate PTH in the washings if the rinse is contaminated with blood. In these cases, only PTH values significantly higher than the serum should be considered as true positive results. Cytologic examination and measurement of PTH can be performed on the same specimen. To measure PTH, the FNA needle is rinsed with a small volume of normal saline solution immediately after a specimen for cytological examination has been expelled from the needle for a smear or CytoTrap preparation. Specimen collection is critical for the performance of the assay, and the needle should be rinsed with a minimal volume. Each FNA needle from a single biopsied area is washed with 0.1 to 0.5 mL of normal saline. The washes from a single area are pooled (final volume 0.5-1.5 mL). PTH levels are measured in the saline wash.

Useful For: Discriminating thyroid tissue from enlarged parathyroid glands Facilitating parathyroid localization prior to surgery An adjunct to cytology examination of fine-needle aspiration specimens to confirm or exclude presence of parathyroid tissue in the biopsied area.

Interpretation: Parathyroid hormone (PTH) values less than 100 pg/mL suggest the biopsied site does not contain PTH-secreting tissue. PTH values greater than or equal to 100 pg/mL are suggestive of the presence PTH-secreting tissue at the site biopsied or along the needle track. This result is dependent on accurate sampling and a total needle wash volume between 0.5 and 1.5 mL. This test should be interpreted in the context of the clinical presentation, imaging, and cytology findings. If the results are discordant with the clinical presentation, a sampling error at the time of the biopsy should be considered.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Bancos I, Grant CS, Nadeem S, et al. Risks and benefits of parathyroid fine-needle aspiration with parathyroid hormone washout. Endocr Pract. 2012;18(4):441-449 2. Ketha

H, Lasho MA, Algeciras-Schimnich A. Analytical and clinical validation of parathyroid hormone (PTH) measurement in fine-needle aspiration biopsy (FNAB) washings. Clin Biochem. 2016;49(1-2):16-21 3. Trimboli P, D'Aurizio F, Tozzoli R, Giovanella L. Measurement of thyroglobulin, calcitonin, and PTH in FNA washout fluids. Clin Chem Lab Med. 2017;55(7):914-925

PTH2
28379

Parathyroid Hormone, Serum

Clinical Information: Parathyroid hormone (PTH) is produced and secreted by the parathyroid glands, which are located along the posterior aspect of the thyroid gland. The hormone is synthesized as a 115-amino acid precursor (pre-pro-PTH), cleaved to pro-PTH, and then to the 84-amino acid molecule, PTH (numbering, by universal convention, starting at the amino terminus). The precursor forms generally remain within the parathyroid cells. Secreted PTH undergoes cleavage and metabolism to form carboxyl-terminal fragments (PTH-C), amino-terminal fragments (PTH-N), and mid-molecule fragments (PTH-M). Only those portions of the molecule that carry the amino terminus (ie, the whole molecule and PTH-N) are biologically active. The active forms have half-lives of approximately 5 minutes. The inactive PTH-C fragments, with half-lives of 24 to 36 hours, make up more than 90% of the total circulating PTH and are primarily cleared by the kidneys. In patients with kidney failure, PTH-C fragments can accumulate to very high levels. PTH 184 is also elevated in these patients, with mild elevations being considered a beneficial compensatory response to end organ PTH resistance, which is observed in kidney failure. The serum calcium level regulates PTH secretion via negative feedback through the parathyroid calcium sensing receptor (CASR). Decreased calcium levels stimulate PTH release. Secreted PTH interacts with its specific type II G-protein receptor, causing rapid increases in renal tubular reabsorption of calcium and decreased phosphorus reabsorption. It also participates in long-term calciostatic functions by enhancing mobilization of calcium from bone and increasing kidney synthesis of 1,25-dihydroxy vitamin D, which, in turn, increases intestinal calcium absorption. In rare inherited syndromes of parathyroid hormone resistance or unresponsiveness, and in kidney failure, PTH release may not increase serum calcium levels. Hyperparathyroidism causes hypercalcemia, hypophosphatemia, hypercalcuria, and hyperphosphaturia. Long-term consequences are dehydration, kidney stones, hypertension, gastrointestinal disturbances, osteoporosis, and sometimes neuropsychiatric and neuromuscular problems. Hyperparathyroidism is most commonly primary and caused by parathyroid adenomas. It can also be secondary in response to hypocalcemia or hyperphosphatemia. This is most commonly observed in kidney failure. Long-standing secondary hyperparathyroidism can result in tertiary hyperparathyroidism, which represents the secondary development of autonomous parathyroid hypersecretion. Rare cases of mild, benign hyperparathyroidism can be caused by inactivating CASR genetic variants. Hypoparathyroidism is most commonly secondary to thyroid surgery but can also occur on an autoimmune basis or due to activating CASR genetic variants. The symptoms of hypoparathyroidism are primarily those of hypocalcemia with weakness, tetany, and possible optic nerve atrophy.

Useful For: Diagnosis and differential diagnosis of hypercalcemia Diagnosis of primary, secondary, and tertiary hyperparathyroidism Diagnosis of hypoparathyroidism Monitoring kidney failure patients for possible renal osteodystrophy

Interpretation: Approximately 90% of the patients with primary hyperparathyroidism have elevated parathyroid hormone (PTH) levels. The remaining patients have normal (inappropriate for the elevated calcium level) PTH levels. Approximately 40% of the patients with primary hyperparathyroidism have serum phosphorus levels below 2.5 mg/dL, and about 80% have serum phosphorus levels below 3.0 mg/dL. A (appropriately) low PTH level and high phosphorus level in a patient with hypercalcemic suggests that the hypercalcemia is not caused by PTH or PTH-like substances. A (appropriately) low PTH level with a low phosphorus level in a patient with hypercalcemia suggests the diagnosis of paraneoplastic hypercalcemia caused by parathyroid-related peptide (PTHRP). PTHRP shares N-terminal homology with PTH and can transactivate the PTH receptor. It can be produced by many different tumor types. A low or normal PTH in a patient with hypocalcemia suggests hypoparathyroidism, provided the serum magnesium level is normal. Low magnesium levels inhibit PTH release and action and can mimic

hypoparathyroidism. Low serum calcium and high PTH levels in a patient with normal kidney function suggest resistance to PTH action (pseudohypoparathyroidism type 1a, 1b, 1c, or 2) or, very rarely, bio-ineffective PTH. A limited number of the PTH-C fragments, which accumulate in kidney failure, chiefly PTH 7-84, cross-react in this and other intact PTH assays. PTH 1-84 is also elevated in kidney failure, with mild elevations being considered beneficial. Consequently, when measured with an intact PTH assay, concentrations of 1.5 to 3 times the upper limit of the healthy reference range appear to represent the optimal range for patients with kidney failure. Lower concentrations may be associated with adynamic renal bone disease, while higher levels suggest possible secondary or tertiary hyperparathyroidism, which can result in high-turnover renal osteodystrophy. Some patients with moderate hypercalcemia and equivocal phosphate levels, who have either mild elevations in PTH or (inappropriately) normal PTH levels, may be suffering from familial hypocalciuric hypercalcemia, which is due to inactivating CASR genetic variants. The molar renal calcium to creatinine clearance is typically less than 0.01 in these individuals. The condition can be confirmed by CASR gene sequencing; see CASRG / CASR Full Gene Sequencing with Deletion/Duplication, Varies.

Reference Values:

<1 month: 7.0-59 pg/mL
4 weeks-11 months: 8.0-61 pg/mL
12 months-10 years: 11-59 pg/mL
11 years-17 years: 15-68 pg/mL
18 years and older: 15-65 pg/mL

Clinical References: 1. Boudou P, Ibrahim F, Cormier C, Chabas A, Sarfati E, Souberbielle JC. Third- or second-generation parathyroid hormone assays: a remaining debate in the diagnosis of primary hyperparathyroidism. J Clin Endocrinol Metab. 2005;90(12):6370-6372 2. Silverberg SJ, Bilezikian JP. The diagnosis and management of asymptomatic primary hyperparathyroidism. Nat Clin Pract Endocrinol Metab. 20062(9):494-503 3. Brossard JH, Cloutier M, Roy L, Lepage R, Gascon-Barre M, D'Amour P. Accumulation of a non-(1-84) molecular form of parathyroid hormone (PTH) detected by intact PTH assay in renal failure: importance in the interpretation of PTH values. J Clin Endocrinol Metab. 1996;81(11):3923-3929 4. Garfield N, Karaplis AC. Genetics and animal models of hypoparathyroidism. Trends Endocrinol Metab. 2001;12(7):288-294 5. Sakhaee K. Is there an optimal parathyroid hormone level in end-stage renal failure: the lower the better? Curr Opin Nephrol Hypertens. 2001;10(3):421-427 6. Vetter T, Lohse MJ. Magnesium and the parathyroid. Curr Opin Nephrol Hypertens. 2002;11(4):403-410 7. Bilezikian JP, Potts JT Jr, Fuleihan GEH, et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Clin Endocrinol Metab. 2002;87(12):5353-5361 8. Minisola S, Pepe J, Piemonte S, Cipriani C. The diagnosis and management of hypercalcaemia. BMJ. 2015;350:h2723 9. Cooper MS. Disorders of calcium metabolism and parathyroid disease. Best Pract Res Clin Endocrinol Metab. 2011;25(6):975-983. doi: 10.1016/j.beem.2011.07.001 10. De Sanctis V, Soliman A, Fiscina B. Hypoparathyroidism: from diagnosis to treatment. Curr Opin Endocrinol Diabetes Obes. 2012;19(6):435-442. doi:10.1097/MED.0b013e3283591502

PTHRP
81774

Parathyroid Hormone-Related Peptide, Plasma

Clinical Information: Parathyroid hormone-related peptide (PTHrP) exists in several isoforms, ranging in size from 60 to 173 amino acids, which are created by differential splicing and posttranslational processing by prohormone convertases. PTHrP is produced in low concentrations by virtually all tissues. The N-terminus and the secondary structure of multiple isoforms of PTHrP resemble parathyroid hormone (PTH), allowing PTHrP to bind to the same receptor as PTH. The physiological role of PTHrP can be divided into 5 categories: 1) Transepithelial calcium transport, particularly in the kidney and mammary gland 2) Smooth muscle relaxation in the uterus, bladder, gastrointestinal tract, and arterial wall 3) Regulation of cellular proliferation 4) Cellular differentiation and apoptosis of multiple tissues 5) As an indispensable component of successful pregnancy and fetal

development (embryonic gene deletion is lethal in mammals) Humoral hypercalcemia of malignancy (HHM) is a common complication of cancer. Elevations of PTHrP are the most common cause of malignancy-associated hypercalcemia. PTHrP leads to hypercalcemia by stimulating calcium resorption from bone and reabsorption in the kidneys. It also plays a significant function in osteolysis in bony metastases, particularly in breast cancer, and has been postulated to play a role in malignancy-associated cachexia through induction of orexigenic peptides. Various malignancies secrete PTHrP resulting in HHM. PTHrP production is most commonly seen in carcinomas of breast, lung (squamous), head and neck (squamous), kidney, bladder, cervix, uterus, and ovary. Neuroendocrine tumors may also occasionally produce PTHrP. Most other carcinomas, sarcomas, and hematolymphoid malignancies only sporadically produce PTHrP, with the exception of T-cell lymphomas and myeloma. In HHM, the typical laboratory presentation includes elevated calcium and PTHrP, decreased PTH, and suppressed serum 1,25 dihydroxyvitamin D3 levels. Patients with HHM may have increased PTHrP values before treatment. PTHrP level decreases and PTH level increases, accompanied by decreased serum calcium values, are observed with successful treatment.

Useful For: Aiding in the evaluation of individuals with hypercalcemia of unknown origin Aiding in the evaluation of individuals with suspected humoral hypercalcemia of malignancy The test should not be used to exclude cancer or screen individuals with tumors for humoral hypercalcemia of malignancy.

Interpretation: Depending on the patient population, up to 80% of individuals with malignant tumors and hypercalcemia will be suffering from humoral hypercalcemia of malignancy (HHM). Of these, 50% to 70% might have an elevated parathyroid hormone-related peptide (PTHrP) level. These patients will also usually show typical biochemical changes of excess parathyroid hormone (PTH)-receptor activation, namely, besides the hypercalcemia, they might have hypophosphatemia, hypercalcuria, hyperphosphaturia, and elevated serum alkaline phosphatase. Their PTH levels will typically be less than 30 pg/mL or undetectable. In patients with biochemical findings that suggest, but do not prove, primary hyperparathyroidism (eg, hypercalcemia, but normal or near-normal serum phosphate, and a PTH level that is within the population reference range but above 30 pg/mL), HHM should be considered as a diagnostic possibility, particularly if the patient is an older adult, has a history of malignancy, or has risk factors for malignancy. An elevated PTHrP level in such a patient is highly suggestive of HHM as the cause for the hypercalcemia.

Reference Values:
< or =4.2 pmol/L

Reference values have not been established for patients younger than 1 year.

Clinical References: 1. Donovan PJ, Achong N, Griffin K, Galligan J, Pretorius CJ, McLeod DS. PTHrP-mediated hypercalcemia: causes and survival in 138 patients. J Clin Endocrinol Metab. 2015;100(5):2024-2029 2. Goltzman D. Nonparathyroid hypercalcemia. Front Horm Res. 2019;51:77-90 3. Jacobs TP, Bilezikian JP. Clinical Review: Rare causes of hypercalcemia. J Clin Endocrinol Metab. 2005;90(11):6316-6322 4. Mundy GR, Edwards JR. PTH-related peptide (PTHrP) in hypercalcemia. J Am Soc Nephrol. 2008;19(4):672-675

PPAP
52964

Parental Sample Prep for Prenatal Microarray Testing, Blood

Clinical Information: In order to interpret equivocal array results on a prenatal sample (amniotic fluid or chorionic villus), parental studies are performed to determine if the abnormality detected on the prenatal array is inherited or de novo. Maternal cell contamination testing is performed on the maternal blood and prenatal specimen to detect the presence of maternal cells in the fetal sample.

Useful For: Preparing parental blood specimen for possible confirmation testing if an abnormality is

detected on the prenatal array sample DNA extraction of the maternal blood specimen used for maternal cell contamination testing

Interpretation: No interpretation will be provided. This test is for specimen processing only.

Reference Values:
An interpretive report will be provided.

PCAB
83728

Parietal Cell Antibodies, IgG, Serum

Clinical Information: Pernicious anemia (PA) is a common form of cobalamin (vitamin B12) deficiency anemia.(1) The disorder is characterized by abnormally large (megaloblastic) red blood cells and atrophic body gastritis (ABG) resulting from autoimmune-mediated destruction of parietal cells that line the stomach wall. The destruction of parietal cells leads to impaired production of intrinsic factor (IF) required for the absorption of vitamin B12. PA is frequently associated with other autoimmune conditions, such as autoimmune thyroid disease, type 1 diabetes mellitus, and vitiligo.(2-5) Diagnosis of PA relies on histologically proven ABG, peripheral blood examination showing megaloblastic anemia, vitamin B12 deficiency, parietal cell antibodies (PCA) with or without intrinsic factor antibodies (IFA), and elevated serum gastrin from loss of acid secretion.(2-4) PCA bind to the alpha- and beta-subunits of the membrane-bound H(+)/K(+)-ATPase while IFA bind directly to intrinsic factor, blocking its ability to bind vitamin B12.(1,4) Both PCA and IFA are useful diagnostic tests for PA, however, compared to PCA, IFA are more specific and lack diagnostic sensitivity.(2,4,5)

Useful For: Evaluating patients suspected of having pernicious anemia or autoimmune-mediated deficiency of vitamin B12 with or without megaloblastic anemia

Interpretation: A positive result indicates the presence of IgG antibodies to H(+)/K(+) ATPase and maybe suggestive of pernicious anemia (PA) or a related autoimmune disease. A negative result indicates no detectable IgG antibodies to H(+)/K(+) ATPase; it does not rule out PA. An equivocal result is inconclusive for the presence of IgG antibodies to H(+)/K(+)ATPase. Consider re-testing in 4-6 weeks if clinical suspicion for PA is high.

Reference Values:
Negative: < or =20.0 Units
Equivocal: 20.1-24.9 Units
Positive: > or =25.0 Units
Reference values apply to all ages.

Clinical References: 1. Toh BH, Van Driel IR, Gleeson PA. Pernicious anemia. N Eng J Med. 1997;337(20):1441-1448 2. Bizzaro N, Antico A. Diagnosis and classification of pernicious anemia. Autoimmun Rev. 2014;13(4-5):565-568 3. Toh BH: Pathophysiology and laboratory diagnosis of pernicious anemia. Immunol Res. 2017;65(1):326-330 4. Lenti MV, Rugge M, Lahner E, et al. Autoimmune gastritis. Nat Rev Dis Primers. 2020;6(1):56 5. Oo TH: Diagnostic difficulties in pernicious anemia. Discov Med. 2019;28(155):247-253

PJUD
82877

Parietaria judaica, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an

allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Parietaria judaica Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

POFF
82549

Parietaria officinalis, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In

individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Parietaria officinalis Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PLINK
62139

Paroxysmal Nocturnal Hemoglobinuria, PI-Linked Antigen, Blood

Clinical Information: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disorder characterized by nocturnal hemoglobinuria, chronic hemolytic anemia, thrombosis, pancytopenia, and, in some patients, acute or chronic myeloid malignancies. Paroxysmal nocturnal hemoglobinuria appears to be a hematopoietic stem cell disorder that affects erythroid, granulocytic, and megakaryocytic cell lines. The abnormal cells in PNH have been shown to lack glycosylphosphatidylinositol (GPI)-linked proteins in erythroid, granulocytic, megakaryocytic, and, in some instances, lymphoid cells. Variants in the phosphatidylinositol glycan A gene, PIGA, have been

identified consistently in patients with PNH, thus confirming the biological defect in this disorder. A flow cytometric-based assay can detect the presence or absence of these GPI-linked proteins in granulocytes, monocytes, erythrocytes, and lymphocytes, thus avoiding the problems associated with red blood cell (RBC)-based diagnostic methods (Ham test) in which recent hemolytic episodes or recent transfusions can give false-negative results. A partial list of known GPI-linked proteins includes CD14, CD16, CD24, CD55, CD56, CD58, CD59, C8-binding protein, alkaline phosphatase, acetylcholine esterase, and a variety of high frequency human blood antigens. In addition, fluorescent aerolysin binds directly to the GPI anchor and can be used to evaluate the expression of the GPI linkage. In-house studies, as well as others in the literature, have shown that flow cytometry-based assays will detect all Ham-positive PNH cases, as well as some Ham-negative PNH cases. This assay replaces the sugar water test and the Ham test for the evaluation of patients with possible PNH. Patients with PNH should be transfused with ABO-specific reb blood cells (RBCs), which do not need to be washed. If, for some reason, they need to receive non-ABO type-specific (type O) cells, these RBC units should be washed. Since recipient antibodies to granulocyte antigens can trigger hemolytic episodes in PNH, if they have such antibodies these patients should receive leukoreduced RBCs and platelets.

Useful For: Screening for and confirming the diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) Monitoring patients with PNH

Interpretation: Individuals with paroxysmal nocturnal hemoglobinuria (PNH) have absent or decreased expression of all the glycosylphosphatidylinositol (GPI)-linked antigens and fluorescent aerolysin (FLAER) on peripheral blood cells derived from the PNH clone. Recent data showed that small PNH clones can be detected in a relatively high percentage of cases of aplastic anemia and myelodysplastic syndrome. While the significance of this finding is still uncertain, it appears that these patients may benefit from immunosuppressive therapy. This test incorporates a sophisticated technique of separating different cell populations using gating on antigen-positive cells, as well as the sensitivity to enable detection of small PNH clones. In addition, this test detects a partial loss of CD59 on type II red blood cells (RBC). Patients with large proportion of type II RBC are unlikely to show high levels of hemolysis, unlike patients with complete loss of GPI-linked proteins (predominantly type III cells). While PNH is a disorder of hematopoietic stem cells and all lineages are affected, the percentage of affected cells can differ between lineages, most commonly due to hemolysis and/or transfusion. Individuals without PNH have normal expression of FLAER (neutrophils and monocytes) and normal expression of all GPI-linked antigens-CD14 (monocytes), CD16 (neutrophils and NK cells), CD24 (neutrophils), and CD59 (RBC).

Reference Values:
An interpretive report will be provided.

RED BLOOD CELLS:
PNH RBC-Partial Antigen loss: 0.00-0.99%
PNH RBC-Complete Antigen loss: 0.00-0.01%
PNH Granulocytes: 0.00-0.01%
PNH Monocytes: 0.00-0.05%

Clinical References: 1. Richards SJ, Hill A, Hillman P. Recent advances in the diagnosis, monitoring and management of patients with paroxysmal nocturnal hemoglobinuria. Cytometry B Clin Cytom. 2007;72(5):291-298 2. Sutherland DR, Illingworth A, Marinov I, et al. ICCS/ESCCA consensus guidelines to detect GPI-deficient cells in paroxysmal nocturnal hemoglobinuria (PNH) and related disorders part 2 - reagent selection and assay optimization for high-sensitivity testing. Cytometry B Clin Cytom. 2018;94(1):23-48. doi:10.1002/cyto.b.21610 3. Illingworth A, Marinov I, Sutherland DR, Wagner-Ballon O, DelVecchio L. ICCS/ESCCA consensus guidelines to detect GPI-deficient cells in paroxysmal nocturnal hemoglobinuria (PNH) and related disorders part 3 - data analysis, reporting and case studies. Cytometry B Clin Cytom. 2018;94(1):49-66. doi:10.1002/cyto.b.21609 4. Oldaker T, Whitby L, Saber M, Holden J, Wallace PK, Litwin V. ICCS/ESCCA consensus guidelines to detect GPI-deficient cells in

paroxysmal nocturnal hemoglobinuria (PNH) and related disorders part 4 - assay validation and quality assurance. Cytometry B Clin Cytom. 2018;94(1):67-81. doi:10.1002/cyto.b.21615 5. Dezern AE, Borowitz MJ: ICCS/ESCCA consensus guidelines to detect GPI-deficient cells in paroxysmal nocturnal hemoglobinuria (PNH) and related disorders part 1 - clinical utility. Cytometry B Clin Cytom. 2018;94(1):16-22. doi:10.1002/cyto.b.21608 6. Illingworth AJ, Marinov I, Sutherland DR. Sensitive and accurate identification of PNH clones based on ICCS/ESCCA PNH Consensus Guidelines-A summary. Int J Lab Hematol. 2019;41 Suppl 1:73-81. doi:10.1111/ijlh.13011 7. Seth N, Mahajan V, Kedia S, Sutar A, Sehgal K. Utility of FLAER and CD157 in a five-color single-tube high sensitivity assay, for diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH)-A standalone flow cytometry laboratory experience. Int J Lab Hematol. 2021;43(2):259-265. doi:10.1111/ijlh.13366 8. Payne D, Johansson U, Bloxham D, et al. Inter-laboratory validation of a harmonized PNH flow cytometry assay. Cytometry B Clin Cytom. 2018;94(5):580-587. doi:10.1002/cyto.b.21726 9. Sutherland DR, Ortiz F, Quest G, et al. High-sensitivity 5-, 6-, and 7-color PNH WBC assays for both Canto II and Navios platforms. Cytometry B Clin Cytom. 2018;94(4):637-651. doi:10.1002/cyto.b.21626

FPRTF
57967

Parrot Australian (Budgerigar) Feathers IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.5 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

FPARG
57686

Parsley IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

PSLY
82765

Parsley, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to parsley Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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0		Negative
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1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PARVS
48395

Parvovirus B19 Antibodies, IgG and IgM, Serum

Clinical Information: Parvovirus B19 is the causative agent of fifth disease (ie, erythema infectiosum, slapped cheek syndrome), which usually produces a mild illness characterized by an intensive erythematous maculopapular facial rash. Most outbreaks of parvovirus infection are acquired by direct contact with respiratory secretions and primarily occur in the spring. Close contact between individuals is responsible for infection in schools, daycare centers, and hospitals. The virus has also been associated with fetal damage (hydrops fetalis), aplastic crisis, and arthralgia. Infection during pregnancy presents the risk of transmission to the fetus that may cause intrauterine death. The rate of fetal death following maternal infection ranges between 1% and 9%. Parvovirus B19 preferentially replicates in erythroid progenitor cells.(1) Infection with parvovirus B19 occurs early in life, and the virus is transmitted by respiratory secretion and occasionally by blood products. The prevalence of parvovirus B19 IgG antibodies increases with age. The age-specific prevalence of antibodies to parvovirus is 2% to 9% of children under 5 years, 15% to 35% in children 5 to 18 years of age, and 30% to 60% in adults (19 years or older). Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies to the virus using an enzyme-linked immunosorbent assay testing.

Useful For: Serologic detection of recent or past parvovirus B19 infection

Interpretation: Parvovirus B19 IgM Parvovirus B19 IgG Interpretation Negative Negative No antibody to Parvovirus B19 detected. Acute infection cannot be ruled out as antibody levels may be below the limit of detection. If clinically indicated, a second serum should be submitted in 14 to 21 days. Negative Positive Results suggest past infection. Equivocal Positive or negative Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive Positive, negative, or equivocal Results suggest recent infection and should be interpreted in the context of clinical presentation. The presence of IgM class antibodies suggests recent infection. The presence of IgG antibodies only is indicative of past exposure. Both IgG and IgM may be present at or soon after onset of illness and reach peak titers within 30 days. Because IgG antibody may persist for years, diagnosis of acute infection is made by the detection of IgM antibodies.

Reference Values:
IgG: Negative
IgM: Negative

Clinical References: 1. Brown KE, Young NS. Parvovirus B19 in human disease. Ann Rev Med. 1997;48:59-67 2. Reno ML, Cox CR, Powell EA. Parvovirus B19: A Clinical and Diagnostic Review. Clinical Microbiology Newsletter. 2022 Jun 15;44(12):107-14

PARVG
48320

Parvovirus B19 Antibodies, IgG, Serum

Clinical Information: Parvovirus B19 is the causative agent of fifth disease (ie, erythema infectiosum, slapped cheek syndrome), which usually produces a mild illness characterized by an intensive erythematous maculopapular facial rash. Most outbreaks of parvovirus infection are acquired by direct contact with respiratory secretions and primarily occur in the spring. Close contact between individuals is responsible for infection in schools, daycare centers, and hospitals. The virus has also been associated with fetal damage (hydrops fetalis), aplastic crisis, and arthralgia. Infection during pregnancy presents the risk of transmission to the fetus that may cause intrauterine death. The rate of fetal death following maternal infection ranges between 1% and 9%. Parvovirus B19 preferentially replicates in erythroid progenitor cells.(1) Infection with parvovirus B19 occurs early in life, and the virus is transmitted by respiratory secretion and occasionally by blood products. The prevalence of parvovirus B19 IgG antibodies increases with age. The age-specific prevalence of antibodies to parvovirus is 2% to 9% of children under 5 years, 15% to 35% in children 5 to 18 years, and 30% to 60% in adults (19 years or older). Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies to the virus using an enzyme-linked immunosorbent assay testing.

Useful For: Serologic detection of recent or past parvovirus B19 infection using IgG antibodies This test is not useful as a screening procedure for the general population.

Interpretation: Parvovirus B19 IgM Parvovirus B19 IgG Interpretation Negative Negative No antibody to parvovirus B19 detected. Acute infection cannot be ruled out as antibody levels may be below the limit of detection. If clinically indicated, a second serum should be submitted in 14 to 21 days. Negative Positive Results suggest past infection. Equivocal Positive or negative Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive Positive, negative, or equivocal Results suggest recent infection and should be interpreted in the context of clinical presentation. The presence of IgM class antibodies suggests recent infection. The presence of IgG antibodies only is indicative of past exposure. Both IgG and IgM may be present at or soon after onset of illness and reach peak titers within 30 days. Because IgG antibody may persist for years, diagnosis of acute infection is made by the detection of IgM antibodies.

Reference Values:
Only orderable as part of a profile. For more information see PARVS / Parvovirus B19 Antibodies, IgG and IgM, Serum.

Negative

Clinical References: 1. Brown KE, Young NS. Parvovirus B19 in human disease. Ann Rev Med. 1997;48:59-67 2. Reno ML, Cox CR, Powell EA. Parvovirus B19: A clinical and diagnostic review. Clinical Microbiology Newsletter. 2022;44(12):107-114

PARVM
48321

Parvovirus B19 Antibody, IgM, Serum

Clinical Information: Parvovirus B19 is the causative agent of fifth disease (ie, erythema infectiosum, slapped cheek syndrome), which usually produces a mild illness characterized by an intensive erythematous maculopapular facial rash. Most outbreaks of parvovirus infection are acquired by direct contact with respiratory secretions and primarily occur in the spring. Close contact between individuals is responsible for infection in schools, daycare centers, and hospitals. The virus has also been associated with fetal damage (hydrops fetalis), aplastic crisis, and arthralgia. Infection during pregnancy presents the risk of transmission to the fetus that may cause intrauterine death. The rate of fetal death following maternal infection ranges between 1% and 9%. Parvovirus B19 preferentially replicates in erythroid progenitor cells.(1) Infection with parvovirus B19 occurs early in life, and the virus is transmitted by respiratory secretion and occasionally by blood products. The prevalence of parvovirus B19 IgG antibodies increases with age. The age-specific prevalence of antibodies to parvovirus is 2% to 9% of children under 5 years, 15% to 35% in children 5 to 18 years of age, and 30% to 60% in adults (19 years or older). Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies to the virus using an enzyme-linked immunosorbent assay testing.

Useful For: Serologic detection of recent or past parvovirus B19 infection using IgM antibodies This test is not useful as a screening procedure for the general population.

Interpretation: Parvovirus B19 IgM Parvovirus B19 IgG Interpretation Negative Negative No antibody to parvovirus B19 detected. Acute infection cannot be ruled out as antibody levels may be below the limit of detection. If clinically indicated, a second serum should be submitted in 14 to 21 days. Negative Positive Results suggest past infection. Equivocal Positive or negative Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive Positive, negative, or equivocal Results suggest recent infection and should be interpreted in the context of clinical presentation. The presence of IgM class antibodies suggests recent infection. The presence of IgG antibodies only is indicative of past exposure. Both IgG and IgM may be present at or soon after onset of illness and reach peak titers within 30 days. Because IgG antibody may persist for years, diagnosis of acute infection is made by the detection of IgM antibodies.

Reference Values:
Only orderable as part of a profile. For more information see PARVS / Parvovirus B19 Antibodies, IgG and IgM, Serum.

Negative

Clinical References: 1. Brown KE, Young NS. Parvovirus B19 in human disease. Ann Rev Med. 1997;48:59-67 2. Reno ML, Cox CR, Powell EA. Parvovirus B19: A clinical and diagnostic review. Clinical Microbiology Newsletter. 2022;44(12):107-114

PARVN
48322

Parvovirus B19 Antibody, Technical Interpretation

Clinical Information: Parvovirus B19 is the causative agent of fifth disease (ie, erythema infectiosum, slapped cheek syndrome), which usually produces a mild illness characterized by an intensive erythematous maculopapular facial rash. Most outbreaks of parvovirus infection are acquired by direct contact with respiratory secretions and primarily occur in the spring. Close contact between individuals is responsible for infection in schools, daycare centers, and hospitals. The virus has also been associated with fetal damage (hydrops fetalis), aplastic crisis, and arthralgia. Infection during pregnancy presents the risk of transmission to the fetus that may cause intrauterine death. The rate of fetal death following maternal infection ranges between 1% and 9%. Parvovirus B19 preferentially replicates in erythroid progenitor cells.(1) Infection with parvovirus B19 occurs early in life, and the virus is transmitted by respiratory secretion and occasionally by blood products. The prevalence of parvovirus B19 IgG antibodies increases with age. The age-specific prevalence of antibodies to parvovirus is 2% to 9% of children under 5 years, 15% to 35% in children 5 to 18 years of age, and 30% to 60% in adults (19 years or older). Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies to the virus using an enzyme-linked immunosorbent assay testing.

Useful For: Interpretation of serologic testing for recent or past parvovirus B19 infection This test is not useful as a screening procedure for the general population

Interpretation: Parvovirus B19 IgM Parvovirus B19 IgG Interpretation Negative Negative No antibody to parvovirus B19 detected. Acute infection cannot be ruled out as antibody levels may be below the limit of detection. If clinically indicated, a second serum should be submitted in 14 to 21 days. Negative Positive Results suggest past infection. Equivocal Positive or negative Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive Positive, negative, or equivocal Results suggest recent infection and should be interpreted in the context of clinical presentation. The presence of IgM class antibodies suggests recent infection. The presence of IgG antibodies only is indicative of past exposure. Both IgG and IgM may be present at or soon after onset of illness and reach peak titers within 30 days. Because IgG antibody may persist for years, diagnosis of acute infection is made by the detection of IgM antibodies.

Reference Values:
Only orderable as part of a profile. For more information see PARVS / Parvovirus B19 Antibodies, IgG and IgM, Serum.

IgG: Negative
IgM: Negative

Clinical References: 1. Brown KE, Young NS. Parvovirus B19 in human disease. Ann Rev Med. 1997;48:59-67 2. Reno ML, Cox CR, Powell EA. Parvovirus B19: A Clinical and Diagnostic Review. Clinical Microbiology Newsletter. 2022 Jun 15;44(12):107-14.

PARVP
86337

Parvovirus B19, Molecular Detection, PCR, Plasma

Clinical Information:

Useful For: Diagnosing parvovirus B19 infection in plasma specimens

Interpretation: A positive result indicates that parvovirus B19 DNA is present in the clinical sample. However, a positive result does not differentiate between actively replicating virus, transient infection that may be asymptomatic, or the presence of remnant viral nucleic acid. A negative result

suggests the absence of parvovirus B19 infection.

Reference Values:
Negative

Clinical References: 1. Guo J, Wang Y, Zhang M, et al: Human parvovirus B19 infection in hospitalized patients suspected of infection with pathogenic microorganism. Front Cell Infect Microbiol. 2022 Dec 21;12:1083839 2. Heegaard ED, Brown KE: Human parvovirus B19. Clin Microbiol Rev 2002 Jul;15(3):485-505 3. Bultmann BD, Klingel K, Soltar K, et al: Fatal parvovirus B19 associated myocarditis clinically mimicking ischemic heart disease: an endothelial cell-mediated disease. Hum Pathol. 2003 Jan;34(1):92-95 4. Rerolle JP, Helal I, Morelon E: Parvovirus B19 infection after renal transplantation. Nephrologie. 2003;24(6):309-315 5. Chisaka H, Morita E, Yaegashi N: Parvovirus B19 and the pathogenesis of anaemia. Rev Med Virol. 2003 Nov-Dec; 13(6):347-359

PARVO
83151

Parvovirus B19, Molecular Detection, PCR, Varies

Clinical Information:

Useful For: Diagnosing parvovirus B19 infection

Interpretation: A positive result indicates that parvovirus B19 DNA is present in the clinical sample. However, a positive result does not differentiate between actively replicating virus, transient infection that may be asymptomatic, or the presence of remnant viral nucleic acid. A negative result suggests the absence of parvovirus B19 infection.

Reference Values:
Negative

Clinical References: 1. Guo J, Wang Y, Zhang M, et al: Human parvovirus B19 infection in hospitalized patients suspected of infection with pathogenic microorganism. Front Cell Infect Microbiol. 2022 Dec 21;12:1083839 2. Heegaard ED, Brown KE: Human parvovirus B19. Clin Microbiol Rev 2002 Jul;15(3):485-505 3. Bultmann BD, Klingel K, Soltar K, et al: Fatal parvovirus B19 associated myocarditis clinically mimicking ischemic heart disease: an endothelial cell-mediated disease. Hum Pathol. 2003 Jan;34(1):92-95 4. Rerolle JP, Helal I, Morelon E: Parvovirus B19 infection after renal transplantation. Nephrologie. 2003;24(6):309-315 5. Chisaka H, Morita E, Yaegashi N: Parvovirus B19 and the pathogenesis of anaemia. Rev Med Virol. 2003 Nov-Dec; 13(6):347-359

PARVI
70532

Parvovirus Immunostain, Technical Component Only

Clinical Information: Parvovirus infection is implicated as a cause of hydrops fetalis and may result in spontaneous abortions. It has also been implicated in chronic hemolytic anemia. The virus is associated with erythema infectiosum (Fifth disease) in children and acute arthritis in adults.

Useful For: Identification of parvovirus infection

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Loughrey AC, O'Neill HJ, Coyle PV, DeLeys R. Identification and use of a neutralizing epitope of parvovirus B19 for the rapid detection of virus infection. J Med Virol. 1993;39(2):97-100 2. Morey AL, Ferguson DJ, Fleming KA. Combined immunocytochemistry and non-isotopic in situ hybridization for the ultrastructural investigation of human parvovirus B19 infection. Histochem J. 1995;27(1):46-53 3. Morey AL, Ferguson DJ, Fleming KA. Ultrastructural features of fetal erythroid precursors infected with parvovirus B19 in vitro: evidence of cell death by apoptosis. J Pathol. 1993;169(2):213-220 4. Morey AL, O'Neill HJ, Coyle PV, Fleming KA. Immunohistological detection of human parvovirus B19 in formalin-fixed, paraffin-embedded tissues. J Pathol 1992;166(2):105-108 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PFRUT
82355

Passion Fruit, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to passion fruit Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive

6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CONFL
620379

Pathology Consultation

Clinical Information: Mayo Clinic in Jacksonville, FL is staffed by pathologists whose expertise and special interests cover the entirety of pathology-from surgical pathology with all of its respective subspecialty areas, to hematopathology, renal pathology, and dermatopathology. Consultation services are provided for difficult diagnostic problems. Consultation cases may be sent by a referring pathologist and directed to one of the pathologists who is an expert in the given area or directed more broadly to the subspecialty group. Cases are frequently shared and, sometimes, transferred between the pathologists, as deemed appropriate for the type of case or diagnostic problem encountered. Emphasis is placed on prompt and accurate results. Stained slides and paraffin blocks received are reviewed in conjunction with the clinical history provided, laboratory findings, radiographic findings (if applicable), and sending pathologist's report or letter. If additional special stains or studies are needed, the results are included in the final interpretive report. In some cases, electron microscopy and other special procedures are utilized as required. A variety of ancillary studies are available (eg, cytochemistry, immunohistochemistry, immunofluorescence, electron microscopy, mass spectrometry, cytogenetics, and molecular genetics) to aid in establishing a diagnosis. These ancillary studies are often expensive, labor intensive, and most efficiently utilized and interpreted in the context of the morphologic features. The goal is to provide the highest possible level of diagnostic consultative service, while balancing optimal patient care with a cost-conscious approach to solving difficult diagnostic problems.

Useful For: A subspecialty second opinion for a specific pathology question referred by a primary pathologist Note: A consultative opinion is not a full rendering of a primary diagnostic report (eg, multiple parts, margin status, CAP synoptics) Obtaining special studies not available locally This test is not intended to be used to obtain a primary diagnosis.

Interpretation: Results of the consultation are reported in a formal pathology report that includes a description of ancillary test results (if applicable) and an interpretive comment.

Reference Values:
An interpretive report will be provided.

Clinical References:

PATHC
70317

Pathology Consultation

Clinical Information: Mayo Clinic in Rochester, Minnesota is staffed by pathologists whose expertise and special interests cover the entirety of pathology-from surgical pathology with all its respective subspecialty areas, to hematopathology, renal pathology, and dermatopathology. Consultation services are provided for difficult diagnostic problems. Consultation cases may be sent by a referring pathologist and directed to one of the pathologists who is an expert in the given area or directed more broadly to the subspecialty group. Cases are frequently shared and, sometimes, transferred between the pathologists, as deemed appropriate for the type of case or diagnostic problem encountered. Emphasis is placed on prompt and accurate results. Stained slides and paraffin blocks received are reviewed in

conjunction with the clinical history provided, laboratory findings, radiographic findings (if applicable), and sending pathologist's report or letter. If additional special stains or studies are needed, the results are included in the final interpretive report. In some cases, electron microscopy and other special procedures are utilized as required. A variety of ancillary studies are available (eg, cytochemistry, immunohistochemistry, immunofluorescence, electron microscopy, mass spectrometry, cytogenetics, and molecular genetics) to aid in establishing a diagnosis. These ancillary studies are often expensive, labor intensive, and most efficiently utilized and interpreted in the context of the morphologic features. The goal is to provide the highest possible level of diagnostic consultative service, while balancing optimal patient care with a cost-conscious approach to solving difficult diagnostic problems.

Useful For: A subspecialty second opinion for a specific pathology question referred by a primary pathologist Note: A consultative opinion is not a full rendering of a primary diagnostic report (eg, multiple parts, margin status, CAP synoptics) Obtaining special studies not available locally This test is not intended to be used to obtain a primary diagnosis.

Interpretation: Results of the consultation are reported in a formal pathology report that includes a description of ancillary test results (if applicable) and an interpretive comment.

Reference Values:
An interpretive report will be provided.

Clinical References: Renshaw AA, Gould EW. Measuring the value of review of pathology material by a second pathologist. Am J Clin Pathol. 2006;125(5):737-739. doi:10.1309/6A0R-AX9K-CR8V-WCG4

PAX5
70533

PAX-5 Immunostain, Technical Component Only

Clinical Information: PAX-5, also known as B-cell-specific activator protein (BSAP), is a B-cell specific transcription factor expressed during differentiation. Plasma cells (terminally differentiated B cells) are usually negative. PAX-5 is used in the classification of B-cell lymphomas.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Desouki MM, Post GR, Cherry D, Lazarchick J. PAX-5: A Valuable immunohistochemical marker in the differential diagnosis of lymphoid neoplasms. Clin Med Res. 2010;8(2):84-88 2. Feldman AL, Dogan A. Diagnostic uses of PAX5 immunohistochemistry. Adv Anat Pathol. 2007;14(5):323-334 3. Jensen KC, Higgins JPT, Montgomery K, et al. The utility of PAX5 immunohistochemistry in the diagnosis of undifferentiated malignant neoplasms. Mod Pathol. 2007;20:871-877 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PAX2
607795

PAX2 Immunostain, Technical Component Only

Clinical Information:

Useful For: Aiding in the diagnosis of endocervical adenocarcinoma and renal cell carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Rabban J, McAlhany S, Lerwill M, et al. PAX2 Distinguishes Benign Mesonephric and Mullerian Glandular Lesions of the Cervix From Endocervical Adenocarcinoma, Including Minimal Deviation Adenocarcinoma. Am J Surg Pathol. 2010;34(2):137-146 2. Ozcan A, Roza G, Ro J, et al. PAX2 and PAX8 Expression in Primary and Metastatic Renal Tumors: A Comprehensive Comparison. Arch Pathol Lab Med. 2012;136(12):1541-1551 3. Knoepp S, Kunju L, Roh M. Utility of PAX8 and PAX2 immunohistochemistry in the identification of renal cell carcinoma in diagnostic cytology. Diagn Cytopathol. 2012;40(8):667-672 4. Shukla A, Thomas D, Roh M. PAX8 and PAX2 expression in endocervical adenocarcinoma in situ and high-grade squamous dysplasia. Int J Gynecol Pathol. 2013;32(1):116-1121 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PAX8
70534

PAX8 Immunostain, Technical Component Only

Clinical Information: PAX8 is a member of the paired box gene (PAX) family of transcription factors involved in kidney cell and thyroid development. PAX8 has been shown to be expressed in a high percentage of renal neoplasms, including both malignant renal cell carcinomas and benign renal tumors (oncocytomas). PAX8 has also been reported to be expressed in ovarian carcinomas.

Useful For: Aids in the identification of renal cell carcinomas, as well as papillary thyroid carcinomas and tumors of Mullerian origin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

PDGF
58102

PDGFB (22q13), Dermatofibrosarcoma Protuberans/Giant Cell Fibroblastoma, FISH, Tissue

Clinical Information: Dermatofibrosarcoma protuberans (DFSP) is a superficial, low-grade sarcoma genetically characterized by the unbalanced chromosomal translocation t(17;22)(q21;q13), usually in the form of a supernumerary ring chromosome. The product of this chromosomal translocation is the chimeric gene COL1A1-PDGFB. Rearrangements of this gene have been detected in approximately 90% of DFSP and its related infantile form, giant cell fibroblastoma, but not in other tumors.

Useful For: Confirming the diagnosis of dermatofibrosarcoma protuberans (DFSP)/giant cell fibroblastoma (GCF) and excluding other spindle neoplasms that closely simulate the DFSP histology, including dermatofibroma (benign fibrous histiocytoma), neurofibroma, spindle cell lipoma, and a variety

of other benign and malignant spindle cell neoplasms

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for the PDGFB FISH probe. A positive result is consistent with rearrangement/amplification of the PDGFB gene locus on 22q13 and supports the diagnosis of dermatofibrosarcoma protuberans (DFSP) or giant cell fibroblastoma (GCF). A negative result is consistent with no rearrangement/amplification of the PDGFB gene locus on 22q13. However, this result does not exclude the diagnosis of DFSP or GCF. The degree of PDGFB copy gain/amplification/rearrangement varies in individual tumors and among different cells in the same tumor. It is not currently known if patients with different levels of rearrangement/amplification have the same prognosis and response to therapy.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Abbott JJ, Erickson-Johnson M, Wang X, et al: Gains of COL1A1-PDGFB genomic copies occur in fibrosarcomatous transformation of dermatofibrosarcoma protuberans. Mod Pathol 2006 Nov;19(11):1512-1518 2. Labropoulos SV, Fletcher JA, Oliveira AM, et al: Sustained complete remission of metastatic dermatofibrosarcoma protuberans with imatinib mesylate. Anticancer Drugs 2005 April;16(4):461-466 3. Macarenco RS, Zamolyi R, Franco MF, et al: Genomic gains of COL1A1-PDGFB occur in the evolution of giant cell fibroblastoma into dermatofibrosarcoma protuberans. Genes Chromosomes Cancer 2008 Mar;47(3):260-265

FBEP
57935

Pea Black-Eyed/Cow Pea (Vigna sinensis) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

FPGNG
57654

Pea Green IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

FPEAC
57666

Peach IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific

IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

PECH
82816

Peach, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to peach Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FPNTG
57537

Peanut IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

FPNG4
57571

Peanut IgG4

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

PEANT
64756

Peanut, IgE with Reflex to Peanut Components, IgE, Serum

Clinical Information: Peanut allergy is one of the most common food allergies in the United States, with an estimated prevalence of approximately 1% to 2%.(1) The clinical symptoms of peanut allergy may range from relatively mild, such as rhinorrhea, pruritus, or nausea, to a systemic and potentially life-threatening anaphylactic reaction. The diagnosis of peanut allergy is dependent upon the presence of compatible clinical symptoms in the context of peanut exposure, with support from identification of potential peanut-specific IgE allergen antibodies, either by skin testing or in vitro serology testing. In vitro testing has generally focused on assessing for the presence of total peanut IgE antibodies. These antibodies are identified by immunoassay in which the capture allergen is an extract prepared from natural peanut raw material. Most studies have demonstrated a correlation between total peanut IgE allergen antibodies and an increased likelihood of a clinical allergic response. Once an elevated antibody response to total peanut IgE extract is established, assessment for the presence of specific IgE antibodies to the most common peanut allergenic components will be performed. During peanut component allergen testing the presence of IgE antibodies specific for potentially allergenic individual proteins, namely Ara h 1, Ara h 2, Ara h 3, Ara h 6, Ara h 8, Ara h 9, and profilin protein Bet v2, are assessed. The determination of the relative amount of IgE antibody to specific peanut components can aid in assessment of the potential strength and type of allergenic response (see Table). Ara h 1, 2, 3, and 6 are seed storage proteins and are the most relevant for evaluation of suspected peanut allergy.(2,3) The presence of antibodies to Ara h 2, in particular, exhibits strong association with potential systemic reactions. Ara h 1, 2, and 3-specific IgE antibodies tend to be associated with more severe allergic reactions. Ara h6 shares substantial, but not complete, cross-reactivity with Ara h2, and

often exhibits similarity in terms of the degree and type of allergenicity. Immunoglobulin E antibodies against Ara h 8 are generally associated with milder peanut allergies and may be seen in the context of birch pollen sensitization. Ara h 8 is a homologue of the birch pollen allergen Bet v1.(4) Ara h 9 is a member of the lipid transfer protein (LTP) family. LTP is ubiquitous throughout the plant kingdom and is also extremely homologous. IgE antibodies specific for Ara h 9 may be associated with allergic reactions upon peanut ingestion, although published data on this is not conclusive.(5) In addition, because of the significant sequence homology, cross-reactivity of IgE antibodies may be observed between Ara h 9 and LTP in commonly consumed plants, such as peaches, apples, and plums. Finally, IgE antibodies to the profilin Bet v2, while associated with birch pollen sensitivity, also represent a minor peanut allergen marker as it is cross-reactive with the peanut profilin, Ara h5. As profilin proteins are present in many other foods, sensitivity to profilin Bet v2 may be associated in broad allergen cross-reactivity among foods, including mango, peach, apple, hazelnut, celery, carrot, paprika, anise, fennel, coriander, cumin, tomato, and potato. The presence of antibodies to profilin Bet v2 is typically associated with milder allergic reactions and oral allergy syndrome. Table. Specific Peanut Allergens Allergen Most common reaction type Heat and digestion stability Selected potential cross-reactivity with other allergens Ara h1 (storage peanut protein) Systemic Stable Some potential allergenic cross reactivity with plant vicilin, including those found in soy and pea Ara h2 (storage peanut protein) Systemic Strongly stable Some potential allergenic cross reactivity with almond and brazil nut allergens Ara h6 Ara h3 (storage peanut protein) Systemic Stable Some potential allergenic cross reactivity with hazelnut and soybean allergens Ara h6 (storage peanut protein) Systemic Strongly stable Ara h2 Ara h8 (PR-10 protein, Bet v 1-homologous allergen) Associated with local reactions such as oral allergy syndrome (OAS) Labile to heat and digestion Associated with allergy to birch and birch related tree pollen Ara h9 (lipid transfer protein) Associated with both systemic reactions and local reactions such as OAS Stable Associated with allergy to peach and peach related fruits Profilin Bet v2 Associated with more minor local reactions such as OAS Labile to heat and digestion Associated with allergy to a broad variety of pollen and plant products from trees, nuts, grasses, and weeds

Useful For: Evaluating patients with suspected peanut allergy Evaluating patients with possible peanut cross-reactivity

Interpretation: When detectable total peanut IgE antibody is present (> or =0.10 IgE kUa/L), additional specific component IgE antibody testing will be performed. If at least one potential specific allergenic peanut component IgE is detectable (> or =0.10 IgE kUa/L), an interpretative report will be provided. When the sample is negative for total peanut IgE antibody (<0.10 IgE kUa/L), further testing for specific peanut component IgE antibodies will not be performed. Negative IgE results for total peanut antibody may indicate a lack of sensitization to potential peanut allergenic components.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline / Equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Sicherer SH, Wood RA: Advances in diagnosing peanut allergy. J Allergy Clin Immunol Pract. 2013 Jan;1(1):1-13. doi: 10.1016/j.jaip.2012.10.004 2. Eller E, Bindslev-Jensen C: Clinical value of component-resolved diagnostics in peanut-allergic patients. Allergy. 2013 Feb;68(2):190-194. doi: 10.1111/all.12075 3. Hong X, Caruso D, Kumar R, et al: IgE, but not IgG4, antibodies to Ara h 2 distinguish peanut allergy from asymptomatic peanut sensitization. Allergy. 2012 Dec;67(12):1538-1546. doi: 10.1111/all.12047 4. Asarnoj A, Nilsson C, Lidholm J, et al: Peanut component Ara h 8 sensitization and tolerance to peanut. J Allergy Clin Immunol. 2012 Aug;130(2):468-472. doi: 10.1016/j.jaci.2012.05.019 5. Klemans RJ, van Os-Medendorp H, Blankestijn M, Bruijzeel-Koomen CA, Knol EF, Knulst AC: Diagnostic accuracy of specific IgE to components in diagnosing peanut allergy: a systematic review. Clin Exp Allergy. 2015 Apr;45(4):720-730. doi: 10.1111/cea.12412 6. Koid AE, Chapman MD, Hamilton RG, et al: Ara h 6 complements Ara h 2 as an important marker for IgE reactivity to peanut. J Agric Food Chem. 2014 Jan 8;62(1):206-213. doi:10.1021/jf4022509 7. Bublin M, Breiteneder H: Cross-reactivity of peanut allergens. Curr Allergy Asthma Rep. 2014 Apr;14(4):426. doi: 10.1007/s11882-014-0426-8 8. Chan ES, Greenhawt MJ, Fleischer DM, Caubet JC: Managing cross-reactivity in those with peanut allergy. J Allergy Clin Immunol Pract. 2019 Feb;7(2):381-386. doi: 10.1016/j.jaip.2018.11.012 9. Simberloff T, Parambi R, Bartnikas LM, el al: Implementation of a standardized clinical assessment and management plan (SCAMP) for food challenges. J Allergy Clin Immunol Pract. 2017 Mar-Apr;5(2):335-344. doi:10.1016/j.jaip.2016.05.021

PEAN
82888

Peanut, IgE, Serum

Clinical Information: Peanut allergy is one of the most common food allergies in the United States, with an estimated prevalence of approximately 1% to 2%.(1) The clinical symptoms of peanut allergy may range from relatively mild, such as rhinorrhea, pruritus, or nausea, to a systemic and potentially life-threatening anaphylactic reaction. The diagnosis of peanut allergy is based upon the presence of compatible clinical symptoms in the context of peanut exposure, with support from identification of potential peanut-specific IgE allergen antibodies, either by skin testing or in vitro serology testing. In vitro serology testing has generally focused on assessing for the presence of total peanut IgE antibodies. These antibodies are identified by immunoassay in which the capture allergen is an extract prepared from natural peanut raw material. Most studies have demonstrated a correlation between the amount of total peanut IgE allergen antibody present and an increased likelihood of a clinical allergic response. Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. Once an elevated antibody response to total peanut IgE extract is established, assessment for the presence of specific IgE antibodies to the most common individual peanut allergenic components may be considered.

Useful For: Establishing a diagnosis of an allergy to peanut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Sicherer SH, Wood RA: Advances in diagnosing peanut allergy. J Allergy Clin Immunol Pract. 2013 Jan;1(1):1-13. doi: 10.1016/j.jaip.2012.10.004 2. Eller E, Bindslev-Jensen C: Clinical value of component-resolved diagnostics in peanut-allergic patients. Allergy. 2013 Feb;68(2):190-194. doi: 10.1111/all.12075 3. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56 4. Klemans RJ, van Os-Medendorp H, Blankestijn M, Bruijzeel-Koomen CA, Knol EF, Knulst AC: Diagnostic accuracy of specific IgE to components in diagnosing peanut allergy: a systematic review. Clin Exp Allergy. 2015 Apr;45(4):720-730. doi: 10.1111/cea.12412

FPEAR
57683

Pear IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

PEAR
82807

Pear, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by

respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pear Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FPCFG
57688

Pecan Food IgG

Interpretation:

Reference Values:

Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

PCANH
62600

Pecan Hickory, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pecan hickory Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PEC
82880

Pecan-Food, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pecan-food Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PAS38
83346

Pediatric Allergy Screen 3 to 8 Years, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an

allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pediatric allergy screen Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070

PAS3
83345

Pediatric Allergy Screen

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years of age due to food sensitivity (milk, egg, soy, and wheat proteins)

followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to egg whites, milk, wheat, soybeans, and house dust mites Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG. Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070

PAS8
83347

Pediatric Allergy Screen >8 Years, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years of age due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pediatric allergy screen Defining the allergen

responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, ed. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070

PCDES
605129

Pediatric Autoimmune Encephalopathy/CNS Disorder Evaluation, Serum

Clinical Information: Autoimmune encephalitis and myelitis is increasingly recognized as a cause of central nervous system disease in children and adolescents. N-methyl-D-aspartate receptor antibody (NMDA-R) encephalitis and myelin oligodendrocyte glycoprotein (MOG) autoimmunity are most common, though other entities, including aquaporin-4 autoimmunity, contactin-associated protein-like 2 (CASPR2) autoimmunity, autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy, and paraneoplastic encephalomyelopathies, may also occur in children.

Useful For: Evaluating children with autoimmune central nervous system disorders using serum specimens

Interpretation: This profile is consistent with an autoimmune central nervous system disorder.

Reference Values:

Test ID	Reporting name	Methodology*	Reference value
PCSI	Peds Autoimmune CNS Interp, S	Medical interpretation	Interpretive report
AMPCS	AMPA-R Ab CBA, S	CBA	Negative
ANN1S	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
CS2CS	CASPR2-IgG CBA, S	CBA	Negative
DPPCS	DPPX Ab CBA, S	CBA	Negative
GABCS	GABA-B-R Ab CBA, S	CBA	Negative
GD65S	GAD65 Ab Assay, S	RIA	< or =0.02 nmol/L Reference values apply to all ages.
GFAIS	GFAP IFA, S	IFA	Negative
LG1CS	LGI1-IgG CBA, S	CBA	Negative
GL1IS	mGluR1 Ab IFA, S	IFA	Negative
NCDIS	Neurochondrin IFA, S	IFA	Negative
MOGFS	MOG FACS, S	FACS	Negative
NMDCS	NMDA-R Ab CBA, S	CBA	Negative
NMOFS	NMO/AQP4 FACS, S	FACS	Negative
PCATR	Purkinje Cell Cytoplasmic Ab Type Tr	IFA	Negative
Reflex Information: Test ID	Reporting name	Methodology	Reference value
AMPIS	AMPA-R Ab IF Titer Assay, S	IFA	
AN1BS	ANNA-1 Immunoblot, S	IB	Negative
AN1TS	ANNA-1 Titer, S	IFA	
AN2BS	ANNA-2 Immunoblot, S	IB	Negative
DPPTS	DPPX Ab IFA Titer, S	IFA	
GABIS	GABA-B-R Ab IF Titer Assay, S	IFA	
GFACS	GFAP CBA, S	CBA	Negative
GFATS	GFAP IFA Titer, S	IFA	
GL1CS	mGluR1 Ab CBA, S	CBA	Negative
GL1TS	mGluR1 Ab IFA Titer, S	IFA	
MOGTS	MOG FACS Titer, S	FACS	
NCDCS	Neurochondrin CBA, S	CBA	Negative
NCDTS	Neurochondrin IFA Titer, S	IFA	
NMDIS	NMDA-R Ab IF Titer Assay, S	IFA	

NMOTS	NMO/AQP4 FACS Titer, S	FACS	
PCTTS	PCA-Tr Titer, S	IFA	
PCTBS	PCA-Tr Immunoblot, S	IB	Negative

Clinical References: 1. Dubey D, Pittock SJ, Krecke KN, et al. Clinical, radiologic, and prognostic features of myelitis associated with myelin oligodendrocyte glycoprotein autoantibody. JAMA Neurol. 2019;76(3):301-309. doi:10.1001/jamaneurol.2018.4053 2. McKeon A, Lennon VA, Lotze T, et al. CNS aquaporin-4 autoimmunity in children. Neurology. 2008;71(2):93-100 3. Dubey D, Hinson SR, Jolliffe EA, et al. Autoimmune GFAP astrocytopathy: Prospective evaluation of 90 patients in 1 year. J Neuroimmunol. 2018;321:157-163. doi:10.1016/j.jneuroim.2018.04.016 4. Philipps G, Alisanski SB, Pranzatelli M, Clardy SL, Lennon VA, McKeon A. Purkinje cell cytoplasmic antibody type 1 (anti-Yo) autoimmunity in a child with Down syndrome. JAMA Neurol. 2014;71(3):347-349 5. Lopez-Chiriboga AS, Klein C, Zekeridou A, et al. LGI1 and CASPR2 neurological autoimmunity in children. Ann Neurol. 2018;84(3):473-480. doi:10.1002/ana.25310 6. Lopez-Chiriboga AS, Majed M, Fryer J, et al. Association of MOG-IgG serostatus with relapse after acute disseminated encephalomyelitis and proposed diagnostic criteria for MOG-IgG-associated disorders. JAMA Neurol. 2018;75(11):1355-1363. doi:10.1001/jamaneurol.2018.1814 7. Clardy SL, Lennon VA, Dalmau J, Childhood onset of stiff-man syndrome. JAMA Neurol. 2013;70(12):1531-1536. doi:10.1001/jamaneurol.2013.4442 8. Banwell B, Tenembaum S, Lennon VA, et al. Neuromyelitis optica-IgG in childhood inflammatory demyelinating CNS disorders. Neurology. 2008;70(5):344-352. doi:10.1212/01.wnl.0000284600.80782.d5

PCDEC
605130

Pediatric Autoimmune Encephalopathy/CNS Disorder Evaluation, Spinal Fluid

Clinical Information: Autoimmune encephalitis and myelitis is increasingly recognized as a cause of central nervous system disease in children and adolescents. N-methyl-D-aspartate receptor antibody (NMDA-R) encephalitis and myelin oligodendrocyte glycoprotein (MOG) autoimmunity are most common, although other entities, including aquaporin-4 autoimmunity, contactin-associated protein-like 2 (CASPR2) autoimmunity, autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy, and paraneoplastic encephalomyelopathies, may also occur in children.

Useful For: Evaluating children with autoimmune central nervous system disorders using spinal fluid specimens

Interpretation: This profile is consistent with an autoimmune central nervous system disorder.

Reference Values:

Test ID	Reporting name	Methodology	Reference value
PCCI	Peds Autoimmune CNS Interp, CSF	Medical interpretation	Interpretive report
AMPCC	AMPA-R Ab CBA, CSF	CBA	Negative
ANN1C	Anti-Neuronal Nuclear Ab, Type 1	IFA	Negative
CS2CC	CASPR2-IgG CBA, CSF	CBA	Negative
DPPCC	DPPX Ab CBA, CSF	CBA	Negative

GABCC	GABA-B-R Ab CBA, CSF	CBA	Negative
GD65C	GAD65 Ab Assay, CSF	RIA	< or =0.02 nmol/L Reference values apply to all ages.
GFAIC	GFAP IFA, CSF	IFA	Negative
GL1IC	mGluR1 Ab IFA, CSF	IFA	Negative
LG1CC	LGI1-IgG CBA, CSF	CBA	Negative
NCDIC	Neurochondrin IFA, CSF	IFA	Negative
NMDCC	NMDA-R Ab CBA, CSF	CBA	Negative
NMOFC	NMO/AQP4 FACS, CSF	FACS	Negative
PCTRC	Purkinje Cell Cytoplasmc Ab Type Tr	IFA	Negative
Reflex Information: Test ID	Reporting name	Methodology	Reference value
AMPIC	AMPA-R Ab IF Titer Assay, CSF	IFA	
AN1BC	ANNA-1 Immunoblot, CSF	IB	Negative
AN1TC	ANNA-1 Titer, CSF	IFA	
AN2BC	ANNA-2 Immunoblot, CSF	IB	Negative
DPPTC	DPPX Ab IFA Titer, CSF	IFA	
GABIC	GABA-B-R Ab IF Titer Assay, CSF	IFA	
GFACC	GFAP CBA, CSF	CBA	Negative
GFATC	GFAP IFA Titer, CSF	IFA	
GL1CC	mGluR1 Ab CBA, CSF	CBA	Negative
GL1TC	mGluR1 Ab IFA Titer, CSF	IFA	
NCDCC	Neurochondrin CBA, CSF	CBA	Negative
NCDTC	Neurochondrin IFA Titer, CSF	IFA	
NMDIC	NMDA-R Ab IF Titer Assay, CSF	IFA	
NMOTC	NMO/AQP4 FACS Titer, CSF	FACS	
PCTTC	PCA-Tr Titer, CSF	IFA	
PCTBC	PCA-Tr Immunoblot, CSF	IB	Negative

Clinical References: 1. Dubey D, Pittock SJ, Krecke KN, et al. Clinical, radiologic, and prognostic features of myelitis associated with myelin oligodendrocyte glycoprotein autoantibody. JAMA Neurol. 2019;76(3):301-309 doi:10.1001/jamaneurol.2018.4053 2. McKeon A, Lennon VA, Lotze T, et al. CNS aquaporin-4 autoimmunity in children. Neurology. 2008;71(2):93-100 3. Dubey D, Hinson SR, Jolliffe EA, et al. Autoimmune GFAP astrocytopathy: Prospective evaluation of 90 patients in 1 year. J Neuroimmunol. 2018;321:157-163 4. Philipps G, Alisanski SB, Pranzatelli M, et al. Purkinje cell cytoplasmic antibody type 1 (anti-Yo) autoimmunity in a child with Down syndrome. JAMA Neurol. 2014;71(3):347-349 5. Lopez-Chiriboga AS, Klein C, Zekeridou A, et al. LGI1 and CASPR2 neurological autoimmunity in children. Ann Neurol. 2018;84(3):473-480 6. Lopez-Chiriboga AS, Majed M, Fryer J, et al. Association of MOG-IgG serostatus with relapse after acute disseminated encephalomyelitis and proposed diagnostic criteria for MOG-IgG-associated disorders. JAMA Neurol. 2018;75(11):1355-1363 7. Clardy SL, Lennon VA, Dalmau J. Childhood onset of stiff-man syndrome. JAMA Neurol. 2013;70(12):1531-1536 8. Banwell B, Tenembaum S, Lennon VA, et al. Neuromyelitis optica-IgG in childhood inflammatory demyelinating CNS disorders. Neurology. 2008;70(5):344-352

PBPO
82660

Penicillin G, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to penicillin G Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive

4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PENIV
82656

Penicillin V, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to penicillin V Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive

6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PENL
82913

Penicillium chrysogenum, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Penicillium chrysogenum Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PENTS
8239

Pentobarbital, Serum

Clinical Information: Pentobarbital is a short-acting barbiturate with anticonvulsant and sedative-hypnotic properties. Uses include sedation induction, relief of preoperative anxiety, control of status epilepticus or seizures resulting from meningitis, tetanus, alcohol withdrawal, poisons, chorea, or eclampsia, and induction of coma in the management of cerebral ischemia and increased intracranial pressure that may follow stroke or head trauma.(1,2) Pentobarbital is administered orally, parenterally, and rectally. The duration of hypnotic effect is about 1 to 4 hours. The drug distributes throughout the body with about 35% to 45% of a dose bound to plasma proteins in the blood. Metabolism takes place in the liver via oxidation to the inactive metabolite, hydroxypentobarbital. Elimination is biphasic; half-life is about 4 hours in the first phase, and 35 to 50 hours in the second phase. Excretion occurs through the urine, mainly as glucuronide conjugates of metabolites, with only about 1% excreted as unchanged drug.(1,2) Tolerance to the hypnotic effects of pentobarbital occurs after about 2 weeks of continuous dosing.

Useful For: Monitoring of pentobarbital therapy treatment

Interpretation: Pentobarbital concentrations above 10 mcg/mL have been associated with toxicity.

Reference Values:
Therapeutic range
Hypnotic: 1-5 mcg/mL
Therapeutic coma: 20-50 mcg/mL
Reducing intracranial pressure: 30-40 mcg/mL
This degree of sedation requires artificial respiratory support.
Toxic concentration: >10 mcg/mL

Clinical References: 1. NEMBUTAL Sodium Solution (pentobarbital sodium injection). Package insert: Ovation Pharmaceuticals Inc; October 2007 2. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:454-454.e484 3. Baselt RC. Disposition of toxic drugs and chemical in man. 12th ed. Biomedical Publications; 2020 4. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453 5. Mihic SJ, Mayfield J. Hypnotics and sedatives. In: Brunton LL, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 14th ed. McGraw-Hill Education; 2023

FPBPG
57657

Pepper Bell/Paprika IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should

only be ordered by physicians who recognize the limitations of the test.

FPBLG
57645

Pepper Black IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

FPCYE
57538

Pepper Cayenne (Capsicum frutescens) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

FPEPI
75916

Pepsinogen I (PG I)

Reference Values:
24-214 ng/mL

PERAM
609438

Perampanel, Serum

Clinical Information: Perampanel (Fycompa) is approved for adjunctive therapy to treat primary generalized tonic-clonic seizures in patients aged 12 years and older as well as the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 4 years and older.

Useful For: Monitoring serum concentration of perampanel, in specific clinical conditions (ie, severe kidney impairment, mild to moderate hepatic impairment, and end-stage kidney disease) Assessing compliance Assessing potential toxicity

Interpretation: The serum concentration should be interpreted in the context of the patient's clinical response and may provide useful information in patients showing poor response or adverse effects, particularly when perampanel is coadministered with other anticonvulsant drugs. Most individuals display optimal response to perampanel with serum levels of 180 to 980 ng/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Toxic levels have not been well established. Therapeutic ranges are based on specimen collected at trough (ie, immediately before the next dose).

Reference Values:
180-980 ng/mL

Clinical References: 1. Reimers A, Berg JA, Burns ML, Brodtkorb E, Johannessen SI, Johannessen Landmark C. Reference ranges for antiepileptic drugs revisited: a practical approach to establish national guidelines. Drug Des Devel Ther. 2018;12:271-280. doi:10.2147/DDDT.S154388 2. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62. doi:10.1055/s-0043-116492 3. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

SAT
2503

Percent Saturation

Clinical Information:

Useful For: Calculation of percent saturation

Interpretation: Percent saturation often exceeds 45% in hereditary hemochromatosis and 90% in advanced iron overload states.(2) Percent saturation less than 16% is generally used to screen for iron deficiency, but a threshold of 20% is used in the presence of inflammation.(3)

Reference Values:
Only orderable as part of profile. For more information see SFEC / Iron and Total Iron-Binding Capacity, Serum

14-50%

Clinical References: 1. Swinkels DW. Iron metabolism. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier. 2023:chap 40 2. Kowdley KV, Brown KE, Ahn J, Sundaram V. ACG Clinical Guideline: Hereditary Hemochromatosis [published correction appears in Am J Gastroenterol. 2019 Dec;114(12):1927. doi:10.14309/ajg.0000000000000469]. Am J Gastroenterol. 2019;114(8):1202-1218. doi:10.14309/ajg.0000000000000315 3. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet. 2016;387(10021):907-916. doi:10.1016/S0140-6736(15)60865-0

FOPE
57938

Perch Ocean

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >=50 Very Strong Positive

Reference Values:
<0.35 kU/L

SMPB
37406

Peripheral Blood Smear Review

Clinical Information: Under normal conditions, the morphology of each red blood cell is fairly consistent in corresponding age groups. The morphology and proportion of each blood cell type may

change in various hematologic diseases.

Useful For: Confirmation of red blood cell membrane morphology

Interpretation: Description of red blood cell morphology will be provided, if applicable.

Reference Values:
Only orderable as part of a profile. For more information see RBCME / Red Blood Cell Membrane Evaluation, Blood.

Not applicable

Clinical References: 1. Kjeldsberg CR, eds. Practical Diagnosis of Hematologic Disorders. 5th ed. American Society of Clinical Pathologists; 2010 2. Pozdnyakova O, Connell NT, Battinelli EM, Connors JM, Fell G, Kim AS. Clinical significance of CBC and WBC morphology in the diagnosis and clinical course of COVID-19 infection. Am J Clin Pathol.. 2021 Feb 11;155(3):364-375. doi: 10.1093/ajcp/aqaa231Look in special smear test code

PNBX 70598 Peripheral Nerve Pathology Consultation

Clinical Information: Neuropathy is a common neurological complaint and a frequent source of morbidity in many patient populations. Direct investigation of small fiber involvement has been limited as most classical techniques (eg, electromyography, nerve conduction studies, and nerve biopsy) focus on large diameter nerve fibers and may be normal in patients with small fiber neuropathies. Nerve biopsies provide information about nerve fibers and the interstitium of the nerve. Neuropathic abnormalities include decreased density of myelinated fibers, segmental demyelination, and axonal degeneration. Some possible interstitial abnormalities that affect nerves include necrotizing vasculitis and amyloidosis. This consultation is for fixed tissue, slides, or blocks.

Useful For: Evaluating diseases of the nerve and disorders that affect nerve function

Interpretation: The clinical and neurological history is reviewed with the interpretation of the biopsy. The histologic slides, special stains, and history, along with the physician's report are correlated by a neuromuscular pathologist. An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Tracy JA, Dyck PJ, Klein CJ, Engelstad JK, Meyer JE, Dyck PJB. Onion-bulb patterns predict acquired or inherited demyelinating polyneuropathy. Muscle Nerve. 2019;59(6):665-670 2. Xu M, Pinto M, Sun C, et al. Expanded teased nerve fibre pathological conditions in disease association. J Neurol Neurosurg Psychiatry. 2019;90(2):138-140 3. Dyck PJB, Spinner RJ, Amrami KK, Klein CJ, Engelstad JK, Dyck PJ. MRI-targeted fascicular nerve biopsies of proximal nerves: historic reports and illustrative case reports. In: Dyck PJ, Dyck PJB, Engelstad JK, et al, eds. Companion to Peripheral Neuropathy: Illustrated Cases and New Developments. Elsevier; 2010:3-14 4. Dyck PJ, Dyck PJB, Engelstad J. Pathologic alterations of nerves. In: Dyck PJ, Thomas PK, eds. Peripheral Neuropathy, Vol 1. 4th ed. Elsevier; 2005:733-829

DMNES 621103 Peripheral Nervous System Demyelinating Neuropathy,

Autoimmune Evaluation, Serum

Clinical Information: Immune-mediated neuropathies refer to a group of disorders that share overlapping sensory, motor, and autonomic clinical, laboratory, and electrodiagnostic features. Testing for autoantibodies associated with immune-mediated neuropathies should be considered after a detailed history and physical examination is completed. In most situations, nerve conduction studies and electromyography are crucial in distinguishing between primary axonal, primary demyelinating, or mixed axonal and demyelinating neuropathies. This enables a more focused testing approach for disease-relevant autoantibodies. This evaluation focuses on persons with immune-mediated demyelinating neuropathies. The antibody tests included in this evaluation aim to support the diagnosis of an immune-mediated demyelinating neuropathy as well as aid in distinguishing between the more common forms of immune-mediated demyelinating neuropathies that are associated with sensitive and specific antibody biomarkers. Autoantibodies directed against myelin-associated glycoprotein (MAG) are associated with sensory motor demyelinating peripheral neuropathy. A distal acquired demyelinating symmetric (DADS) neuropathy phenotype is the most commonly associated presentation. This may mimic distal forms of chronic inflammatory demyelinating polyneuropathy (CIDP). Patients typically have a slowly progressive symmetric sensory ataxia with or without distal weakness and an IgM monoclonal gammopathy of undetermined significance. Nerve conduction studies typically demonstrate a characteristic progressive sensory-predominant mixed axonal and demyelinating neuropathy with reduced distal conduction velocities that are greater distally. In general, patients with a DADS neuropathy show limited treatment responses to intravenous immunoglobulin (IVIg), and more aggressive immunotherapy may be needed. A subset of patients with suspected CIDP have been identified with autoantibodies targeting nodal-paranodal proteins. These patients share common immunopathological mechanisms of disease, clinical features, and treatment responses that are distinct from classic CIDP. A common target of these autoantibodies is the neurofascin-155 (NF155)-contactin-1 (CNTN1) adhesion complex, which is critical in maintaining the paranodal myelin-axon junction. NF155 is expressed at the paranodal loops of Schwann cells where it interacts with CNTN1 expressed on adjacent axons. This interaction stabilizes and allows the proper organization of the paranodal axoglial junction. Antibody-mediated disruption of this interaction in animal models recapitulates the pathophysiology observed in humans. Neurofascin-155 IgG antibodies are present in approximately 5% to 10% of patients with CIDP-like presentations and, more rarely, in those with more acute forms of demyelinating polyradiculoneuropathy. NF155 IgG positive cases are more likely to present with distal weakness, gait disturbance, tremor, and dysarthria as compared to classic CIDP. Most patients who are seropositive for NF155 IgG have been reported to be refractory to IVIg therapy and often require second-line treatment that includes B-cell depleting therapies, such as rituximab. The detection of NF155 IgG4 is a highly specific finding and has not been reported in other disease mimics, such as hereditary neuropathies, distal acquired demyelinating symmetric neuropathy, and motor neuron disease. Contactin-1 IgG antibodies are present in approximately 2% of patients with CIDP-like presentations. CNTN1 IgG-positive cases are more likely to present with neuropathic pain, sensory ataxia, and subacute progressive demyelinating polyradiculoneuropathy or polyradiculopathy. The majority of seropositive patients have been reported to be refractory to treatment with IVIg. However, some of these patients respond well to B-cell depleting therapies, such as rituximab. Up to half of CNTN1 IgG-positive patients with CIDP or CIDP-like presentations have been reported to develop membranous nephropathy; thus, screening for proteinuria may be warranted. Autoantibodies targeting ganglioside GQ1b are associated with a group of disorders that includes Miller Fisher syndrome (MFS), Bickerstaff brainstem encephalitis (BBE), and classic Guillain-Barre syndrome (GBS) with ophthalmoplegia. Collectively these are referred to as GQ1b IgG-related syndromes, which reflects the diverse clinical presentations associated with these autoantibodies. The prevalence of GQ1b IgG in MFS and BBE is high and has been reported to be greater than 80% in well-defined clinical cohorts. GQ1b IgG may occur in patients with GBS but generally with a lower prevalence. Autoantibodies targeting ganglioside GD1b antibodies frequently occur in sensory ataxic conditions such as chronic, ataxic, neuropathy, ophthalmoplegia, IgM gammopathy, cold agglutinins, and disialosyl antibodies (CANOMAD), acute sensory ataxic neuropathy (ASAN), and chronic ataxic neuropathy with disialosyl antibodies (CANDA). Autoantibodies targeting ganglioside GM1 more commonly occur in patients

with multifocal motor neuropathy (MMN), multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy, and motor-predominant Guillain-Barre syndrome.

Useful For: Evaluating patients with a suspected immune-mediated demyelinating peripheral neuropathy

Interpretation: The presence of specific autoantibodies or combinations of antibodies in this panel provides supportive evidence of an immune-mediated demyelinating peripheral neuropathy. However, these results must be interpretated in the appropriate clinical context. A negative result does not exclude the possibility of an immune-mediated demyelinating peripheral neuropathy.

Reference Values:

Contactin-1 IgG CBA: Negative
GQ1b-IgG ELISA: Negative
IgG Disialo. GD1b: Negative
IgM Disialo. GD1b: Negative
IgG Monos. GM1: Negative
IgM Monos. GM1: Negative
MAG IgM: <1500 Buhlmann titer unit
Neurofascin-155 IgG4: Negative

Reflex Information:
IgG Disialo GD1b Titer: <1:2000
IgM Disialo GD1b Titer: <1:2000
IgG Monos GD1b Titer: <1:2000
IgM Monos GD1b Titer: <1:4000

Clinical References: 1. Asati A, Kachurina O, Kachurin A. Simultaneous measurements of auto-immune and infectious disease specific antibodies using a high throughput multiplexing tool. PLoS One. 2012;7(8):e42681 2. Beecher G, Shelly S, Dyck PJB, et al. Pure motor onset and IgM-gammopathy occurrence in multifocal acquired demyelinating sensory and motor neuropathy. 2021;97(14):e1392-e1403 3. Dubey D, Honorat J, Shelly S, et al. Contactin-1 autoimmunity: Serologic, neurologic, and pathologic correlates. Neurol Neuroimmunol Neuroinflamm. 2020;7(4):e771 4. Klein CJ. Autoimmune-mediated peripheral neuropathies and autoimmune pain. Handb Clin Neurol. 2016;133:417-446 5. Klein CJ. Charcot-Marie-Tooth disease and other hereditary neuropathies [published correction appears in Continuum (Minneap Minn). 2021;27(1):289 6. Le Cann M, Bouhour F, Viala K, et al. CANOMAD: a neurological monoclonal gammopathy of clinical significance that benefits from B-cell-targeted therapies. Blood. 2020;136(21):2428-2436 7. Le Quintrec M, Teisseyre M, Bec N, et al. Contactin-1 is a novel target antigen in membranous nephropathy associated with chronic inflammatory demyelinating polyneuropathy. Kidney Int. 2021;100(6):1240-1249 8. Liberatore G, Giannotta C, Sajeev BP, et al. Sensitivity and specificity of a commercial ELISA test for anti-MAG antibodies in patients with neuropathy. J Neuroimmunol. 2020;345:577288 9. Martinez-Thompson JM, Snyder MR, Ettore M, et al. Composite ganglioside autoantibodies and immune treatment response in MMN and MADSAM. Muscle Nerve. 2018;57(6):1000-1005 10. Querol L, Nogales-Gadea G, Rojas-Garcia R, et al. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. Neurology. 2014;82(10):879-886 11. Shahrizaila N, Yuki N. Bickerstaff brainstem encephalitis and Fisher syndrome: anti-GQ1b antibody syndrome. J Neurol Neurosurg Psychiatry. 2013;84(5):576-583 12. Shelly S, Klein CJ, Dyck PJB, et al. Neurofascin-155 Immunoglobulin Subtypes: Clinicopathologic Associations and Neurologic Outcomes. Neurology. 2021;97(24):e2392-e2403 13. Shelly S, Dubey D, Mills JR, Klein CJ. Paraneoplastic neuropathies and peripheral nerve hyperexcitability disorders. In: Giometto B, Pittock S, eds. Paraneoplastic Neurologic Disorders. Elsevier; 2024:chap 15 Handbook of Clinical Neurology, Vol 200 14. Svahn J, Petiot P, Antoine JC, et al. Anti-MAG antibodies in 202 patients: clinicopathological and therapeutic features. J Neurol Neurosurg Psychiatry. 2018;89(5):499-505 15. Yuki N, Uncini A. Acute and chronic ataxic neuropathies with disialosyl antibodies: a continuous clinical spectrum and a common

pathophysiological mechanism. Muscle Nerve. 2014;49(5):629-635

PINTP
71114

Peripheral Smear Interpretation, Whole Blood

Clinical Information: Under normal conditions, the morphology and proportion of each blood cell type is fairly consistent in corresponding age groups. The morphology and proportion of each blood cell type may change in various hematologic diseases. Differential leukocyte count/special smear evaluation is helpful in revealing the changes in morphology or proportion of each cell type in the peripheral blood.

ACASM
83632

Pernicious Anemia Cascade, Serum

Clinical Information: Vitamin B12 deficiency can be caused by many factors, one of which is pernicious anemia, a condition resulting in deficient production of intrinsic factor in the parietal cells of the stomach. Intrinsic factor is a protein that is needed to assist in the absorption of vitamin B12 into the small intestine. Vitamin B12 is converted into adenosylcobalamin, which converts L-methylmalonic acid to succinyl coenzyme A; hence, a decrease in vitamin B12 absorption in the intestine can cause an excess of methylmalonic acid within the body. Vitamin B12 deficiency may present with any combination of the following: macrocytic anemia, glossitis (painful inflammation of the tongue), peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. Many patients present with neurologic symptoms without macrocytic anemia. A group of tests is often required to establish the correct diagnosis as determination of vitamin B12 in serum does not detect all cases of vitamin B12 deficiency. Mayo Clinic's Department of Laboratory Medicine and Pathology offers a diagnostic algorithm to expedite the identification of patients with vitamin B12 deficiency. This algorithm accounts for the following facts: -The most sensitive test for vitamin B12 deficiency at the cellular level is the assay for methylmalonic acid (MMA). -Nearly half of the cases of pernicious anemia can be unambiguously identified if the serum test for intrinsic factor blocking antibody is positive (this is simpler and less expensive than MMA). -Serum gastrin is usually markedly increased in pernicious anemia (as a result of gastric atrophy), and this test can be used as a substitute for the more complicated and more expensive Schilling test of intestinal absorption of vitamin B12. The algorithm is similar to that published by Green,(1) except that the serum gastrin assay is performed in place of the Schilling test. Experience with both Mayo Clinic and Mayo Clinic Laboratories' cases has corroborated that this is a cost-effective alternative to the Schilling test. In our experience, greater than 90% of laboratory test costs can be saved by using the algorithm rather than ordering all the services for a patient suspected of having B12 deficiency. Furthermore, the substitution of the serum gastrin assay for the Schilling test offers 3 advantages: 1. It is an in vitro test that does not require administration of radioisotopes to patients 2. It can be performed on mailed-in specimens 3. It is much less expensive Only those tests that are appropriate, as defined by the algorithm, will be performed.

Useful For: Diagnosis of pernicious anemia Diagnosis of vitamin B12 deficiency-associated neuropathy

Interpretation: Vitamin B12 >400 ng/L Results do not suggest B12 deficiency-no further testing. Vitamin B12 150 to 400 ng/L Borderline vitamin B12 level-methylmalonic acid (MMA) is performed. If MMA is >0.40 nmol/mL, then intrinsic factor blocking antibody (IFBA) is performed. Vitamin B12 <150 ng/L Vitamin B12 deficiency-IFBA is performed. If IFBA is negative or indeterminate, then gastrin is performed. MMA < or =0.40 nmol/mL This value implies that there is no vitamin B12 deficiency at the cellular level. IFBA positive Consistent with pernicious anemia, Graves disease, or Hashimoto thyroiditis. Gastrin >200 pg/mL Result consistent with pernicious anemia. Gastrin <200 pg/mL Result does not suggest pernicious anemia. For more information see Vitamin B12 Deficiency Evaluation.

Reference Values:
180-914 ng/L

Clinical References: 1. Green R, Kinsella LJ. Current concepts in the diagnosis of cobalamin deficiency. Neurology. 1995;45(8):1435-1440 2. Lahner E, Annibale. Pernicious anemia: new insights from a gastroenterological point of view. World J Gastroenterol. 2009;15(41):5121-5128 3. Bizzaro N, Antico A. Diagnosis and classification of pernicious anemia. Autoimmun Rev. 2014;13(4-5):565-568 4. Toh BH. Pathophysiology and laboratory diagnosis of pernicious anemia. Immunol Res. 2017;65(1):326-330

PDGP
608013

Peroxisomal Disorder Gene Panel, Varies

Clinical Information:

Useful For: Follow up of abnormal biochemical result, usually very long-chain fatty acid test consistent with peroxisomal disorder Establishing a molecular diagnosis for patients with peroxisomal disorders Identifying variants within genes known to be associated with peroxisomal disorders, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Waterham, HR, Ebberink MS. Genetics and molecular basis of human peroxisome biogenesis disorders. Biochim Biophys Acta. 2012;1822(9):1430-1441 3. Wanders RJ. Metabolic and molecular basis of peroxisomal disorders: a review. Am J Med Genet A. 2004;126A(4):355-375 4. Wanders RJ, Waterham HR: Peroxisomal disorders: the single peroxisomal enzyme deficiencies. Biochim Biophys Acta. 2006;1763(12):1707-1720 5. Fidaleo M. Peroxisomes and peroxisomal disorders: the main facts. Exp Toxicol Pathol. 2010;62(6):615-625

PNZN
9789

Perphenazine, Serum or Plasma

Reference Values:
Reference Range: 5.0 - 30.0 ng/mL

Low-dose therapeutic range for Perphenazine: 0.5 - 2.5 ng/mL

PERS
82353

Persimmon, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an

allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to Persimmon, IgE Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

STK1Z
614588

Peutz-Jeghers Syndrome, STK11, Full Gene Analysis, Varies

Clinical Information: Germline variants in the STK11 gene are associated with Peutz-Jeghers syndrome (PJS), an autosomal dominant hereditary cancer syndrome.(1-4) PJS is characterized by many manifestations beginning in childhood, including gastrointestinal hamartomatous polyps, pigmentation changes (called melanocytic macules) around the mouth, eyes, buccal mucosa, perianal area, hands, and feet, and an increased lifetime risk for developing a variety of cancers.(1-4) The highest cancer risks for PJS are in breast, colorectal, gastric, pancreas, lung, gonads, cervix, and uterus.(1-4) Approximately

10% to 20% of individuals with PJS have no family history and are thought to have genetic variants that occurred de novo.(1,5) The National Comprehensive Cancer Network and the American College of Gastroenterology provide recommendations regarding the medical management of children and adults with PJS.(5,6)

Useful For: Evaluating patients with a personal or family history suggestive of Peutz-Jeghers syndrome (PJS) Establishing a diagnosis of PJS allowing for targeted cancer surveillance based on associated risks Identifying variants within genes known to be associated with increased risk for PJS allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. McGarrity TJ, Amos CI, Baker MJ: Peutz-Jeghers syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2001. Updated September 2, 2021. Accessed Septemberr 9, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1266/ 2. Beggs AD, Latchford AR, Vasen HF, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut. 2010;59(7):975-986 3. Hearle N, Schumacher V, Menko FH, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006;12(10):3209-3215 4. Gupta S, Provenzale D, Llor X, et al. NCCN guidelines insights: genetic/familial high-risk assessment: colorectal, version 2.2019. J Natl Compr Canc Netw. 2019;17(9):1032-1041 5. Hernan I, Roig I, Martin B, Gamundi MJ, Martinez-Gimeno M, Carballo M. De novo germline mutation in the serine-threonine kinase STK11/LKB1 gene associated with Peutz-Jeghers syndrome. Clin Genet. 200466(1):58-62 6. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223-262 7. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

UPH24 606521 pH, 24 Hour, Urine

Clinical Information: Urine pH is a measure of the acidity/alkalinity of urine and, by itself, usually provides little useful information. Under normal conditions its value is influenced by the type of diet. Some diets (eg, diets rich in meat) have more acid content than others (eg, vegetarian diets). Changes in urine pH may reflect systemic acid-base disorders. For example, the normal response during metabolic acidosis is a lowering of the urine pH to less than 5. If the pH is greater than 5, then a defect in urine acidification should be considered. A urine pH of greater than 8 is suggestive of infection by a urea-splitting organism such as Proteus mirabilis. Therapeutic interventions to either alkalinize or acidify the urine are necessary for some diseases. For example, some crystals have a propensity to form in alkaline urine, while others form in relative acidic urine, and changing the pH may reduce stone formation.

Useful For: Assessment of patients with metabolic acidosis, crystalluria, as well as monitoring the effectiveness of alkalinization or acidification of urine for certain medical conditions (eg, treatment of uric acid nephrolithiasis) using a 24-hour collection period

Interpretation: Dependent on clinical condition. A pH greater than 8 suggests the presence of urinary

tract infection with a urea-splitting organism.

Reference Values:
4.5-8.0

Clinical References: 1. Menezes CJ, Worcester EM, Coe FL, Asplin J, Bergsland KJ, Ko B: Mechanisms for falling urine pH with age in stone formers. Am J Physiol Renal Physiol. 2019 Jul 1;317(7):F65-F72 2. Ilyas R, Cho K, Young JG: What is the best method to evaluate urine pH? A trial of three urinary pH measurement methods in a stone clinic. J Endourol. 2015 Jan;29(1):70-74 3. Davidsohn I, Henry JB: Todd-Sanford Clinical Diagnosis by Laboratory Methods. 15th ed. Elsevier; 1974; 43-44 4. Free AH, Free HBS: Urodynamics, concepts relating to urinalysis. Ames Co; 1974:57-61 5. Kaplan LA, Pesce AJ: Clinical Chemistry: Theory, Analysis, Correlation. 3rd ed. Mosby-Year Book Inc; 1996:823

UPHB
606522

pH, Body Fluid

Clinical Information: The pH value is a measure of hydrogen ion concentration. Increased metabolic activity and production of acidic byproducts (eg, lactic acid) due to infection are known to decrease pH. A variety of disease processes can alter pH values; therefore, low pH has reduced specificity. Gastric content typically has a low pH, and measurement of pH has been used to help identify gastric fluid. Determining the pH value of a body fluid may help characterize the nature of the fluid.

Useful For: Indicating the presence of infections or fistulas Verifying the effectiveness of treatment to reduce stomach pH Diagnosing disease states characterized by abnormal stomach acidity This test is not appropriate for measurement of pleural fluid pH, as that measurement should be made using a blood gas analyzer locally due to sample stability and transport requirements.

Interpretation: Normal gastric fluid has a pH below 3.0; any higher pH is abnormal. Low peritoneal fluid pH (<7.35) may be observed in spontaneous bacterial peritonitis.(1)

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Wong CL, Holroyd-Leduc J, Thorpe KE, Straus SE. Does this patient have bacterial peritonitis or portal hypertension? How do I perform a paracentesis and analyze the results? JAMA. 2008;299(10):1166-1178 2. Menezes CJ, Worcester EM, Coe FL, Asplin J, Bergsland KJ, Ko B. Mechanisms for falling urine pH with age in stone formers. Am J Physiol Renal Physiol. 2019;317:F65-F72 3. Ilyas R, Cho K, Young JG. What is the best method to evaluate urine pH? A trial of three urinary pH measurement methods in a stone clinic. J Endourol. 2015:29:70-74 4. Davidson I, Henry JB, eds. Todd-Sanford Clinical Diagnosis by Laboratory Methods; 15th ed. Elsevier; 1974:43-44 5. Free AH, Free HBS. Urodynamics, concepts relating to urinalysis. Ames Co; 1974:57-61 6. Kaplan, LA, Pesce AJ, eds: Clinical Chemistry Theory, Analysis, Correlation. 3rd ed. Mosby-Year Book Inc; 1996:823

FPHFL
57309

pH, Fecal

Reference Values:
5.0 - 8.5

PHU_
606510

pH, Random, Urine

Clinical Information: Urine pH is a measure of the acidity/alkalinity of urine and, by itself, usually provides little useful information. Under normal conditions its value is influenced by the type of diet (some diets: eg, diets rich in meat-having more acid content than others, eg, vegetarian diets). Assessment of urine pH may be useful in the evaluation of systemic acid-base disorder. For example, the normal response during metabolic acidosis is a lowering of the urine pH to less than 5. If it is greater than 5, then a defect in urine acidification should be considered. Often a urine pH above 8 is suggestive of infection of a urea splitting organism such as Proteus mirabilis. Monitoring of urine pH may also be helpful during therapeutic interventions to either alkalinize the urine (such as for treatment of uric acid nephrolithiasis) or acidify the urine. Finally, when assessing crystalluria, noting the urine pH may be helpful since some crystals have a propensity to form in alkaline urine while others form in relative acidic urine.

Useful For: Assessment of patients with metabolic acidosis Assessment of crystalluria Monitoring the effectiveness of alkalinization or acidification of urine for certain medical conditions (eg, treatment of uric acid nephrolithiasis)

Interpretation: Dependent on clinical condition.

Reference Values:
4.5 to 8.0

Clinical References: 1. Menezes CJ, Worcester EM, Coe FL, Asplin J, Bergsland KJ, Ko B: Mechanisms for falling urine pH with age in stone formers. Am J Physiol Renal Physiol. 2019 Jul 1;317(7):F65-F72. doi: 10.1152/ajprenal.00066.2019 2. Ilyas R, Cho K, Young JG: What is the best method to evaluate urine pH? A trial of three urinary pH measurement methods in a stone clinic. J Endourol. 2015 Jan;29(1):70-4. doi: 10.1089/end.2014.0317 3. Davidsohn I, Henry JB: Todd-Sanford Clinical Diagnosis by Laboratory Methods; 15th ed. Elsevier; 1974:43-44 4. Free AH, Free HBS: Urodynamics, concepts relating to urinalysis. Ames Co; 1974;57-61 5. Kaplan LA, Pesce AJ: Clinical Chemistry: Theory, Analysis, Correlation. 3rd ed. Mosby-Year Book Inc; 1996:823

FPHAS
57580

Phadiatop (Allergy Screen)

Interpretation: The Phadia Phadiatop test is an allergy screening test with excellent sensitivity and specificity for inhalant allergy. It uses an ImmunoCAP with a balanced mixture of representative allergens, including grasses, trees, weeds, cat, dog, mites and molds. A positive result indicates that the patient is allergic to one or more of these allergens; a negative indicates the patient is not allergic to inhalant allergens. Note that the test does not assess a patient's sensitivity to food, drug, chemical or certain unusual or rare allergens.

Reference Values:
Negative

PHCGD
621575

Phagocytic Disorders and Chronic Granulomatous Disease Gene Panel, Varies

Clinical Information: Inborn errors of immunity that affect the function of phagocytes (neutrophils, monocytes, macrophages, and eosinophils) predispose patients to specific infections as a result of impaired killing of bacteria and fungi. Chronic granulomatous disease (CGD) due to impaired production of reactive oxygen intermediates is characterized by infections (eg, Staphylococcus aureus, Burkholderia

cepacia complex, Serratia marcescens, Nocardia, and Aspergillus sp.) that involve the skin, lungs, lymph nodes, liver, and bones, although any organ or tissue can be affected. Patients may also experience immune dysregulation, resulting in granuloma formation, colitis, and other inflammatory disorders. While most affected individuals are diagnosed prior to age 5 years, patients may present into late adulthood. Tests that measure neutrophil superoxide production by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, usually the dihydrorhodamine (DHR) test, may be used in establishing a diagnosis. X-linked CGD, the most common form, is caused by disease-causing variants in CYBB. In some cases, a contiguous gene deletion may result in CGD along with McLeod neuroacanthocytosis syndrome. In cases of a large contiguous gene deletion, patients may also inherit RPGR-related retinitis pigmentosa, Duchenne muscular dystrophy, and ornithine transcarbamylase deficiency. A chromosomal microarray may be indicated if a contiguous gene deletion is suspected. In addition to the X-linked form, CGD may also be inherited in an autosomal recessive pattern, due to biallelic disease-causing variants in the other genes that encode the remainder of the subunits of phagocyte NADPH, including CYBA, NCF1, NCF2, and NCF4. Similarly to CGD, complete glucose 6-phosphate dehydrogenase (G6PD) deficiency can result in an increased susceptibility to infection due to impaired neutrophil respiratory burst. G6PD deficiency is also inherited in an X-linked pattern due to disease-causing variants in G6PD. Chronic nonspherocytic hemolytic anemia occurs in severe deficiency, while acute hemolytic episodes (typically triggered by some medications, ingestion of fava beans, viral or bacterial infections, etc) are observed in less severe G6PD deficiency. Neutrophils contain azurophilic (or primary) granules, specific (or secondary) granules, and tertiary granules that contain antimicrobial substances. Azurophilic granules contain myeloperoxidase, bactericidal/permeability-increasing protein, defensins, neutrophil elastase, and cathepsin G. Specific granules contain lactoferrin, lysozyme, NADPH oxidase, alkaline phosphatase, collagenase, histaminase, and cathelicidin. Tertiary granules contain cathepsin, gelatinase, and collagenase. Papillon-Lefevre syndrome (PALS) is an autosomal recessive disorder due to disease-causing variants in CTSC (lysosomal cysteine protease cathepsin C, also known as dipeptidyl peptidase I [DPPI]). DPPI is necessary for posttranslational modification of the serine proteases in the neutrophil azurophilic granules, activation of granzymes A and B of cytotoxic lymphocytes, and activation of mast cell chymases. PALS typically presents with severe periodontal disease and keratosis palmoplantaris, along with mild immunodeficiency. In specific granule deficiency (SGD), neutrophils lack expression of secondary and tertiary granule proteins, have an atypical bilobed nuclear morphology, and demonstrate defects in chemotaxis and bactericidal activity. SGD is due to disease-causing variants in CEBPE, which is a myeloid-specific transcription factor, or SMARCD2, which interacts with the CCAAT-enhancer-binding protein epsilon transcription factor. Leukocyte adhesion deficiencies (LAD) are characterized by recurrent bacterial infections due to reduced ability of neutrophils to adhere to various substances and migrate to sites of infection, as well as defective phagocytic and respiratory burst response to bacteria and yeast. Patients often are first noticed due to omphalitis, but later gingivitis/periodontitis, pneumonia, peritonitis, and deep abscesses may develop. LAD can be caused by disease-causing variants in ITGB2, which encodes for the CD18 antigen (LAD1); and SLC35C1, which encodes for a guanosine diphosphate fucose transporter (LAD2) or FERMT3 (LAD3). Although the neutrophil functional studies are similar between LAD1 and LAD2, the clinical course in LAD2 is milder, though patients may also present with other features (ie, developmental delay, intellectual disability, and short stature) and show the rare Bombay (hh) blood type due to abnormal fucose metabolism. LAD3 presents similarly to LAD1, but platelets are also affected resulting in clotting defects. Granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulates the formation of colonies of neutrophils and macrophages from bone marrow precursors but is also required for proper neutrophil function. Recessive inheritance of disease-causing variants in CSF2RA and CSF2RB, which encode for the alpha and beta chains of the GM-CSF receptor, disrupts GM-CSF signaling and results in defects in neutrophil adhesion, phagocytosis, superoxide formation, and microbial killing. Clinically, this manifests as pulmonary alveolar proteinosis and increased susceptibility to infections (pulmonary and extrapulmonary).

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history of chronic granulomatous disease, Papillon-Lefevre syndrome, specific granule deficiency,

leukocyte adhesion deficiency, or other phagocytic disorder Establishing a diagnosis of chronic granulomatous disease or other phagocytic disorder, allowing for appropriate management and surveillance for disease features based on the gene or variant involved Identifying variants within genes known to be associated with chronic granulomatous disease and other phagocytic disorders, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

PCPMX 62740 Phencyclidine (PCP) Confirmation, Chain of Custody, Meconium

Clinical Information: Phencyclidine (PCP) was originally developed as an anesthetic in the 1950s but later was abandoned because of a high frequency of postoperative delirium with hallucinations. It was classed as a dissociative anesthetic because, in the anesthetized state, the patient remains conscious with staring gaze, flat facies, and rigid muscles.(1) PCP binds with high affinity to sites located in the cortex and limbic structures, resulting in blocking of N-methyl-D-aspartate (NMDA)-type glutamate receptors.(1) PCP became a drug of abuse in the 1970s because of its hallucinogenic effects.(1,2) PCP is approximately 65% protein bound and has a volume of distribution of 5.3 to 7.5 L/kg. The drug is metabolized by the liver via oxidative hydroxylation and has a dose-dependent half-life ranging from 7 to 46 hours.(2) Meconium is the first fecal material passed by the neonate. Meconium forms in the first trimester of pregnancy but is seldom excreted before the 34th week. It is composed of approximately 70% water, bile acids, cholesterol, squamous cells, protein and drug metabolites, and no bacteria are normally present. Prebirth excretion of meconium is a sign of fetal distress. Because drugs and metabolites can accumulate in meconium, assessment of meconium for the presence of illicit drugs can be an indicator of maternal drug use during pregnancy. Illicit drug use during pregnancy can have a profound effect on fetal development. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(3) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(4) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(3) Chain of custody is a record of the disposition of a specimen to document each individual who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detection of in utero drug exposure up to 5 months before birth Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

Interpretation: The presence of phencyclidine in meconium is indicative of in utero drug exposure up to 5 months before birth.

Reference Values:

Negative

Positives are reported with a quantitative liquid chromatography tandem mass spectrometry result.
Cutoff concentration: 5 ng/g

Clinical References: 1. O'Brien CP. Drug addiction and drug abuse. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Book Company; 2006 2. Baselt RC. Phencyclidine. In: Baselt RC, ed. Disposition of Toxic Drugs and Chemicals in Man. 10th ed. Biomedical Publications; 2014 3. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989;115(3):474-477 4. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-56; quiz 73-74 5. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 6. Langman LJ, Rushton AM, Thomas D, et al. Drug testing in support of the diagnosis of neonatal abstinence syndrome: The current situation. Clin Biochem. 2023;111:1-10. doi:10.1016/j.clinbiochem.2022.11.002

PCPMC
89069

Phencyclidine (PCP) Confirmation, Meconium

Clinical Information: Phencyclidine (PCP) was originally developed as an anesthetic in the 1950s but later was abandoned because of a high frequency of postoperative delirium with hallucinations. It was classed as a dissociative anesthetic because, in the anesthetized state, the patient remains conscious with staring gaze, flat facies, and rigid muscles.(1) PCP binds with high affinity to sites located in the cortex and limbic structures, resulting in blocking of N-methyl-D-aspartate (NMDA)-type glutamate receptors.(1) PCP became a drug of abuse in the 1970s because of its hallucinogenic effects.(1,2) PCP is approximately 65% protein bound and has a volume of distribution of 5.3 to 7.5 L/kg. The drug is metabolized by the liver via oxidative hydroxylation and has a dose-dependent half-life ranging from 7 to 46 hours.(2) Meconium is the first fecal material passed by the neonate. Meconium forms in the first trimester of pregnancy but is seldom excreted before the 34th week. It is composed of approximately 70% water, bile acids, cholesterol, squamous cells, protein and drug metabolites, and no bacteria are normally present. Prebirth excretion of meconium is a sign of fetal distress. Because drugs and metabolites can accumulate in meconium, assessment of meconium for the presence of illicit drugs can be an indicator of maternal drug use during pregnancy. Illicit drug use during pregnancy can have a profound effect on fetal development. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(3) The first evidence of meconium in the fetal intestine appears at approximately the tenth to twelfth week of gestation, and slowly moves into the colon by the sixteenth week of gestation.(4) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(3)

Useful For: Detection of in utero to phencyclidine (PCP) exposure up to 5 months before birth

Interpretation: The presence of phencyclidine (PCP) in meconium is indicative of in utero drug exposure up to 5 months before birth.

Reference Values:

Negative

Positives are reported with a quantitative liquid chromatography tandem mass spectrometry result.
Cutoff concentration: 5 ng/g

Clinical References: 1. O'Brien CP. Drug addiction and drug abuse. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Book Company; 2006 2. Baselt RC. Phencyclidine. In: Baselt RC, ed. Disposition of Toxic Drugs and Chemicals in Man. 10th ed. Biomedical Publications; 2014 3. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. J Pediatr. 1989;115(3):474-477 4. Ahanya SN, Lakshmanan J, Morgan BL, Ross MG. Meconium passage in utero mechanisms, consequences, and management. Obstet Gynecol Surv. 2005;60(1):45-56; quiz 73-74 5. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 6. Langman LJ, Rushton AM, Thomas D, et al. Drug testing in support of the diagnosis of neonatal abstinence syndrome: The current situation. Clin Biochem. 2023;111:1-10. doi:10.1016/j.clinbiochem.2022.11.002

PCPUG
9788

Phencyclidine (PCP), Confirmation, serum

Reference Values:
Toxic: Greater than 100 ng/mL
Serious Toxicities likely: Greater than 300 ng/mL

PCPX
62739

Phencyclidine Confirmation, Chain of Custody, Random, Urine

Clinical Information: Phencyclidine (PCP) is a drug of abuse. This compound affects diverse neural pathways and interacts with cholinergic, adrenergic, gamma-aminobutyric acid-secreting, serotoninergic, opiate neuronal receptors, and gamma receptors. It has analgesic, anesthetic, and stimulatory effects, yielding bizarre behavior, ranging from depression through catatonia, euphoria, violent rage, and hallucinations. Most fatalities result from its hypertensive effect. Diagnosis of PCP usage depends on drug screening. PCP is excreted in the urine. Chain of custody is a record of the disposition of a specimen to document the personnel who collected, handled, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Useful For Detection of drug abuse involving phencyclidine (street names: angel dust, hog, or angel hair) in urine specimens handled through the chain-of-custody process Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Useful For: Detection of drug abuse involving phencyclidine (street names: angel dust, hog, or angel hair) in urine specimens handled through the chain-of-custody process Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of phencyclidine (PCP) in urine is a strong indicator that the patient has used PCP.

Reference Values:
Negative

Positive result is reported with a quantitative result.

Cutoff concentrations:

Immunoassay screen:
25 ng/mL

Gas chromatography mass spectrometry:
Phencyclidine: 10 ng/mL

Clinical References: 1. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020. 2. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

PCPU
80371

Phencyclidine Confirmation, Random, Urine

Clinical Information: Phencyclidine (PCP) is a drug of abuse. This compound affects diverse neural pathways and interacts with cholinergic, adrenergic, gamma-aminobutyric acid secreting, serotoninergic, opiate neuronal receptors, and gamma receptors. It has analgesic, anesthetic, and stimulatory effects, yielding bizarre behavior, ranging from depression through catatonia, euphoria, violent rage, and hallucinations. Most fatalities result from its hypertensive effect. Diagnosis of PCP usage depends on drug screening. PCP is excreted in the urine.

Useful For: Detection of drug abuse involving phencyclidine (street names: angel dust, hog, or angel hair)

Interpretation: The presence of phencyclidine (PCP) in urine is a strong indicator that the patient has used PCP.

Reference Values:
Negative (Positive result is reported with a quantitative result.)

Cutoff concentrations by gas chromatography mass spectrometry:
Phencyclidine: 10 ng/mL

Clinical References: 1. Schuster DI, Arnold FJ, Murphy RB. Purification, pharmacological characterization and photoaffinity labeling of sigma receptors from rat and bovine brain. Brain Res. 1995;670(1):14-28 2. Bayorh MA, Zokowska-Grojec A, Palkovits M, Kopin IJ. Effect of phencyclidine (PCP) on blood pressure and catecholamine levels in discrete brain nuclei. Brain Res. 1984;321(2):315-318 3. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 11th ed. Biomedical Publications; 2017

FCDUA
75785

Phencyclidine, Umbilical Cord Tissue

Reference Values:
Reporting limit determined each analysis.

Units: ng/g

Only orderable as part of a profile-see FCDSU.

PBR
37049

Phenobarbital, Serum

Clinical Information: Phenobarbital is a general central nervous system (CNS) suppressant that has proven effective in the control of generalized and partial seizures. It is frequently coadministered with phenytoin for control of complex seizure disorders and with valproic acid for complex parietal seizures. Phenobarbital is administered in doses of 60 to 300 mg/day in adults or 3 to 6 mg/kg/day in children. Phenobarbital is slowly but completely absorbed, with bioavailability in the range of 100%. It is approximately 50% protein bound with a volume of distribution of 0.5 L/kg. Phenobarbital has a long half-life of 96 hours, with no known active metabolites. Sedation is common at therapeutic concentrations for the first 2 to 3 weeks of therapy, but this side effect disappears with time. Toxicity due to phenobarbital overdose is characterized by CNS sedation and reduced respiratory function. Mild symptoms characterized by ataxia, nystagmus, fatigue, or attention loss, occur at blood concentrations above 40.0 mcg/mL. Symptoms become severe at concentrations of 60.0 mcg/mL and higher. Toxicity becomes life-threatening at concentrations over 100.0 mcg/mL. Death usually occurs due to respiratory arrest when pulmonary support is not supplied manually. There are no known drug interactions that significantly affect the pharmacokinetics of phenobarbital; conversely, phenobarbital affects the pharmacokinetics of other drugs significantly because it induces the synthesis of enzymes associated with the hepatic cytochrome P450 metabolic pathway. Acute intermittent porphyria attacks may be induced by phenobarbital stimulation of hepatic cytochrome P450.

Useful For: Monitoring for appropriate therapeutic concentration of phenobarbital Assessing compliance or toxicity

Interpretation: Clinical response to the drug correlates strongly with blood concentration. Dosage adjustments are made after 2 weeks of therapy to achieve steady-state blood levels in the range of 20.0 to 40.0 mcg/mL for adults; 15.0 to 30.0 mcg/mL for infants and children. Patients chronically administered phenobarbital usually do not experience sedation unless the blood concentration is above 40.0 mcg/mL.

Reference Values:
Therapeutic: 10.0-40.0 mcg/mL
Critical value: > or =60.0 mcg/mL

Clinical References: Foero O, Kastrup KW, Nielsen EL, et al: Successful prophylaxis of febrile convulsions with phenobarbital. Epilepsia 1972;13:279-285

FPGT
91757

Phenosense Combination HIV Drug Resistance Assay

Useful For: Determines viral phenotype and genotype resistance to three classes of commonly prescribed antiretroviral drugs: nucleoside reverse transcriptase inhibitors (NRTI), nonnucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI). Viral replication capacity is also included.

Reference Values:
A final report will be attached in MayoAccess.

FPFUZ
91755

Phenosense Entry HIV Drug Resistance Assay

Useful For: Determines phenotypic susceptibility to enfuvirtide (Fuzeon) and assesses likely effectiveness before enfuvirtide is added to a patient's regimen or before changing a regimen that includes enfuvirtide.

Reference Values:
A final report will be attached in MayoAccess.

FPHIV
91756

Phenosense HIV Drug Resistance Replication Capacity

Useful For: Determines viral phenotype resistance to three classes of commonly prescribed antiretroviral drugs: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI). Viral replication capacity is also included.

Reference Values:
A final report will be attached in MayoAccess.

PKUBS
65593

Phenylalanine and Tyrosine, Blood Spot

Clinical Information: Phenylketonuria (PKU) is the most frequent inherited disorder of amino acid metabolism (occurring in about 1:10,000-1:15,000 births) and was the first successfully treated inborn error of metabolism. It is inherited in an autosomal recessive manner and is caused by a defect in the enzyme phenylalanine hydroxylase (PAH), which converts the essential amino acid phenylalanine to tyrosine. Deficiency of PAH results in decreased levels of tyrosine and an accumulation of phenylalanine in blood and tissues. Untreated, PKU leads to severe brain damage with intellectual impairment, behavior abnormalities, seizures, and spasticity. The level of enzyme activity differentiates classic PKU (PAH activity <1%) from other milder forms; however, all are characterized by increased levels of phenylalanine (hyperphenylalaninemia). Treatment includes the early introduction of a diet low in phenylalanine. Some patients may also benefit from adjuvant tetrahydrobiopterin (BH4) supplementation (a cofactor for PAH), or enzyme substitution therapy. BH4 is a cofactor of not only PAH but also of the tyrosine and tryptophan hydroxylases. Approximately 2% of patients with hyperphenylalaninemia have a deficiency of BH4, which causes a secondary deficit of the neurotransmitters dopamine and serotonin. There are 4 autosomal-recessive disorders associated with BH4 deficiency plus hyperphenylalaninemia: guanosine triphosphate cyclohydrolase deficiency, 6-pyruvoyl tetrahydropterin synthase deficiency, dihydropteridine reductase deficiency, and pterin-4 alpha carbinolamine dehydratase (PCD) deficiency. This group of disorders, except for PCD, is characterized by progressive dystonia, truncal hypotonia, extremity hypertonia, seizures, and intellectual disability though milder presentations exist. PCD has no symptoms other than transient alterations in tone. Treatment may include administration of BH4, L-dopa (and carbidopa) 5-hydroxytryptophan supplements, and a low phenylalanine diet. Tyrosine is a nonessential amino acid that is derived from dietary sources, the hydroxylation of phenylalanine, or protein breakdown. Primary (PKU) and secondary (defects of BH4 metabolism) hyperphenylalaninemia can cause abnormally low levels of tyrosine. Measurement of the phenylalanine:tyrosine ratio is helpful in monitoring appropriate dietary intake.

Useful For: Monitoring effectiveness of therapy in patients with hyperphenylalaninemia This test is not sufficient for follow-up for abnormal newborn screening results or for establishing a diagnosis of a specific cause of hyperphenylalaninemia

Interpretation: The quantitative results of phenylalanine and tyrosine with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical information. A phenylalanine:tyrosine ratio higher than 3 is considered abnormal.

Reference Values:

PHENYLALANINE
27-107 nmol/mL

TYROSINE
<4 weeks: 40-280 nmol/mL
> or =4 weeks: 25-150 nmol/mL

Clinical References: 1. Mitchell GA, Grompe M, Lambert M, Tanguay RM. Hypertyrosinemia. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed December 26 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225082825 2. Donlon J, Sarkissian C, Levy H, Scriver CR: Hyperphenylalaninemia: Phenylalanine hydroxylase deficiency. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed December 26, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225081923 3. Regier DS, Greene CL. Phenylalanine hydroxylase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated January 5, 2017. Accessed December 26, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1504/

PKU
8380

Phenylalanine and Tyrosine, Plasma

Clinical Information: Phenylketonuria (PKU) is the most frequent inherited disorder of amino acid metabolism (about 1:10,000-1:15,000) and was the first successfully treated inborn error of metabolism. It is inherited in an autosomal recessive manner and is caused by a defect in the enzyme phenylalanine hydroxylase (PAH), which converts the essential amino acid phenylalanine to tyrosine. Deficiency of PAH results in decreased levels of tyrosine and an accumulation of phenylalanine in blood and tissues. If left untreated, PKU leads to severe brain damage with intellectual impairment, behavior abnormalities, seizures, and spasticity. The level of enzyme activity differentiates classic PKU (PAH activity <1%) from other milder forms; however, all are characterized by increased levels of phenylalanine (hyperphenylalaninemia). Treatment includes the early introduction of a diet low in phenylalanine. Tetrahydrobiopterin (BH4) is a cofactor of PAH as well as tyrosine and tryptophan hydroxylase. Approximately 2% of patients with hyperphenylalaninemia have a deficiency of BH4, which causes a secondary deficit of the neurotransmitters, dopamine and serotonin. There are 4 autosomal recessive disorders associated with BH4 deficiency plus hyperphenylalaninemia: guanosine triphosphate cyclohydrolase deficiency; 6-pyruvoyl tetrahydropterin synthase deficiency; dihydropteridine reductase deficiency; and pterin-4 alpha carbinolamine dehydratase (PCD) deficiency. This group of disorders, with the exception of PCD, is characterized by progressive dystonia, truncal hypotonia, extremity hypertonia, seizures, and intellectual disability though milder presentations exist. PCD has no symptoms other than transient alterations in tone. Treatment may include administration of BH4, L-dopa (and carbidopa) 5-hydroxytryptophan supplements, and a low phenylalanine diet. Tyrosine is a nonessential amino acid, which is derived from dietary sources, the hydroxylation of phenylalanine, or protein breakdown. Primary PKU and secondary (defects of BH4 metabolism) hyperphenylalaninemia can cause abnormally low levels of tyrosine. Measurement of the phenylalanine:tyrosine ratio is helpful in monitoring appropriate dietary intake.

Useful For: Monitoring effectiveness of dietary therapy in patients with hyperphenylalaninemia

Interpretation: The quantitative results of phenylalanine and tyrosine with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical interpretation. A phenylalanine:tyrosine ratio higher than 3 is considered abnormal.

Reference Values:
PHENYLALANINE
Premature: 98-213 nmol/mL
0-31 days: 38-137 nmol/mL
1-24 months: 31-75 nmol/mL
2-18 years: 26-91 nmol/mL
> or =19 years: 35-85 nmol/mL

Conversion Formulas:
Result in mg/dL x 60.5=result in nmol/mL
Result in nmol/mL x 0.0165=result in mg/dL

TYROSINE
Premature: 147-420 nmol/mL
0-31 days: 55-147 nmol/mL
1-24 months: 22-108 nmol/mL
2-18 years: 24-115 nmol/mL
> or =19 years: 34-112 nmol/mL

Conversion Formulas:
Result in mg/dL x 55.2=result in nmol/mL
Result in nmol/mL x 0.0181=result in mg/dL

Clinical References: 1. Mitchell GA, Grompe M, Lambert M, Tanguay RM. Hypertyrosinemia. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed October 2, 2024. Available at https://ommbid.mhmedical.com/content.aspx? bookid=2709&sectionid=225082825 2. Donlon J, Sarkissian C, Levy H, Scriver CR. Hyperphenylalaninemia: Phenylalanine hydroxylase deficiency. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed October 2, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225081923 3. Burgard P, Luo X, Hoffmann GF. Phenylketonuria. In: Sarafoglou K, Hoffman GF, Roth KS, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. McGraw-Hill Medical Division; 2009:163-168 4. Blau N, Thony B. Hyperphenylalanemias: Disorders of tetrahydrobiopterin metabolism. In: Sarafoglou K, Hoffmann GF, Roth KS, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. McGraw-Hill Medical Division; 2009:169-175

PKUSC
610508

Phenylalanine and Tyrosine, Self-Collect, Blood Spot

Clinical Information: Phenylketonuria (PKU) is the most frequent inherited disorder of amino acid metabolism (occurring in about 1:10,000-1:15,000 births) and was the first successfully treated inborn error of metabolism. It is inherited in an autosomal recessive manner and is caused by a defect in the enzyme phenylalanine hydroxylase (PAH), which converts the essential amino acid phenylalanine to tyrosine. Deficiency of PAH results in decreased levels of tyrosine and an accumulation of phenylalanine in blood and tissues. Untreated PKU leads to severe brain damage with intellectual impairment, behavior abnormalities, seizures, and spasticity. The level of enzyme activity differentiates classic PKU (PAH activity <1%) from other milder forms; however, all are characterized by increased levels of phenylalanine (hyperphenylalaninemia). Treatment includes the early introduction of a diet low in phenylalanine. Some patients may also benefit from adjuvant tetrahydrobiopterin (BH4) supplementation (a cofactor for PAH) or enzyme substitution therapy. BH4 is a cofactor of not only PAH but also of the tyrosine and tryptophan hydroxylases. Approximately 2% of patients with hyperphenylalaninemia have a deficiency of BH4, which causes a secondary deficit of the neurotransmitters dopamine and serotonin. There are 4 autosomal-recessive disorders associated with

BH4 deficiency plus hyperphenylalaninemia; guanosine triphosphate cyclohydrolase deficiency, 6-pyruvoyl tetrahydropterin synthase deficiency, dihydropteridine reductase deficiency, and pterin-4 alpha carbinolamine dehydratase (PCD) deficiency. This group of disorders, except for PCD, is characterized by progressive dystonia, truncal hypotonia, extremity hypertonia, seizures, and intellectual disability though milder presentations exist. PCD has no symptoms other than transient alterations in tone. Treatment may include administration of BH4, L-dopa (and carbidopa) 5-hydroxytryptophan supplements, and a low phenylalanine diet. Tyrosine is a nonessential amino acid that is derived from dietary sources, the hydroxylation of phenylalanine, or protein breakdown. Primary (PKU) and secondary (defects of BH4 metabolism) hyperphenylalaninemia can cause abnormally low levels of tyrosine. Measurement of the phenylalanine:tyrosine ratio is helpful in monitoring appropriate dietary intake.

Useful For: Monitoring effectiveness of therapy in patients with hyperphenylalaninemia in a patient-collected specimen This test is not sufficient for follow-up for abnormal newborn screening results or for establishing a diagnosis of a specific cause of hyperphenylalaninemia.

Interpretation: The quantitative results of phenylalanine and tyrosine with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical information. A phenylalanine:tyrosine ratio higher than 3 is considered abnormal.

Reference Values:
PHENYLALANINE:
27-107 nmol/mL

TYROSINE
<4 weeks: 40-280 nmol/mL
> or =4 weeks: 25-150 nmol/mL

Clinical References: 1. Mitchell GA, Grompe M, Lambert M, Tanguay RM. Hypertyrosinemia. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed December 26, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225082825 2. Donlon J, Sarkissian C, Levy H, Scriver CR, Hyperphenylalaninemia. Phenylalanine hydroxylase deficiency. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed December 26, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225081923 3. Regier DS, Greene CL. Phenylalanine hydroxylase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated January 5, 2017. Accessed December 26, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1504/

PHEGP
608032

Phenylalanine Disorders Gene Panel, Varies

Clinical Information: Hyperphenylalaninemia is a heterogeneous disorder of phenylalanine catabolism caused by a deficiency of any one of 6 enzymes involved in the conversion of phenylalanine to tyrosine. Phenylketonuria (PKU) is the most frequent inherited disorder of amino acid metabolism (about 1:10,000-1:15,000) and was the first successfully treated inborn error of metabolism and included in newborn screening programs worldwide. It is inherited in an autosomal recessive manner and is caused by a defect in the enzyme phenylalanine hydroxylase (PAH), which converts the essential amino acid phenylalanine to tyrosine. Deficiency of PAH results in decreased levels of tyrosine and an accumulation of phenylalanine in blood and tissues. Untreated, PKU leads to severe brain damage with intellectual impairment, behavior abnormalities, seizures, and spasticity. The level of enzyme activity differentiates classic PKU (PAH activity <1%) from other milder forms; however, all are characterized by increased

levels of phenylalanine (hyperphenylalaninemia). Treatment includes the early introduction of a diet low in phenylalanine. Approximately 2% of patients with hyperphenylalaninemia have a deficiency of tetrahydrobiopterin (BH4), which causes a secondary deficit of the neurotransmitters, dopamine and serotonin. There are 4 autosomal recessive disorders associated with BH4 deficiency plus hyperphenylalaninemia; guanosine triphosphate cyclohydrolase deficiency (GCH1), 6-pyruvoyl tetrahydropterin synthase deficiency (PTS), dihydropteridine reductase deficiency (QDPR), and pterin-4 alpha carbinolamine dehydratase (PCD) deficiency (PCBD1). This group of disorders, with the exception of PCD, is characterized by progressive dystonia, truncal hypotonia, extremity hypertonia, seizures, and intellectual disability though milder presentations exist. PCD has no symptoms other than transient alterations in tone. Treatment may include administration of BH4, L-dopa (and carbidopa) 5-hydroxytryptophan supplements, and a low phenylalanine diet. Recently, variants in DNAJC12, which encodes a heat-shock protein that interacts with the phenylalanine, tyrosine, and tryptophan hydroxylases to help catalyze the conversion of the substrates to their respective products, has been shown to cause hyperphenylalaninemia, progressive neurodegeneration, and dystonia. Treatment may include early administration of BH4 and/or neurotransmitter precursors. Related additional disorders of neurotransmitter metabolism include: -Aromatic l-amino acid decarboxylase (AADC) deficiency, caused by variants in DDC, is an autosomal recessive inborn error in neurotransmitter metabolism that leads to combined serotonin and catecholamine deficiency. -Patients with dopa-responsive dystonia due to variants in SPR causing sepiapterin reductase deficiency have progressive psychomotor retardation and dystonia. -Variants in tyrosine hydroxylase (TH) prevent the conversion of L-tyrosine to L-dopa resulting in Segawa syndrome. -Variants in SLC18A2, a vesicular transporter of dopamine, cause infantile parkinsonism-dystonia-2 (PKDYS2)

Useful For: Follow up for abnormal biochemical results suggestive of a phenylalanine disorder Establishing a molecular diagnosis for patients with phenylalanine disorders Identifying variants within genes known to be associated with phenylalanine disorders, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Burgard P, Luo X, Levy HL, Hoffmann GF: Phenylketonuria. In: Sarafoglou K, Hoffmann GF, Roth KS, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. 2nd ed. McGraw-Hill Education; 2017:251-258 3. Blau N, Thony B: Hyperphenylalanemias: Disorders of tetrahydrobiopterin metabolism. In: Sarafoglou K, Hoffmann GF, Roth KS, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. 2nd ed. McGraw-Hill Education; 2017:259-266 4. Anikster Y, Haack TB, Vilboux T, et al. Biallelic mutations in DNAJC12 cause hyperphenylalaninemia, dystonia, and intellectual disability. Am J Hum Genet. 2017;100(2):257-266. doi:10.1016/j.ajhg.2017.01.002 5. OMIM. Johns Hopkins University; Updated March 7, 2024. Accessed March 8, 2024. Available at https://omim.org/

PNYF 37052 Phenytoin, Free, Serum

Clinical Information: Phenytoin is the drug of choice to treat and prevent tonic-clonic and

psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Phenytoin is highly protein-bound (90%), mostly to albumin. Ten percent of the phenytoin circulates in the free, unbound form. Free phenytoin is the active form of the drug, available to cross biologic membranes and bind to receptors. Increased free phenytoin produces an enhanced pharmacologic effect. At the same time, the free fraction is more available to the liver to be metabolized, so it is cleared more quickly. Concurrent use of phenytoin and valproic acid (another frequently used antiepileptic) may result in altered valproic acid levels and/or altered phenytoin levels. Due to the complex situation involving displacement of protein-bound phenytoin and inhibition of phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be monitored for both phenytoin toxicity and therapeutic efficacy. Free phenytoin levels should be measured to provide the most accurate assessment of phenytoin activity early in therapy. At steady-state, free phenytoin and free valproic acid concentrations should be normalized. In renal failure, the opportunity for the free phenytoin fraction to be cleared is significantly reduced. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. Accordingly, the free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity is typified by tremor, hyperreflexia, lethargy, and coma.

Useful For: Monitoring for appropriate therapeutic concentration of free phenytoin: free phenytoin level is the best indicator of adequate therapy in renal failure Assessing compliance and toxicity

Interpretation: Dose should be adjusted to achieve steady-state blood concentration of free phenytoin between 1.0 and 2.0 mcg/mL. The range for percent free phenytoin is 8% to 14%. Severe toxicity occurs when the free phenytoin concentration is > or =2.5 mcg/mL. However, response and side effects will be individual.

Reference Values:
Therapeutic: 1.0-2.0 mcg/mL Critical value: > or =2.5 mcg/mL

Clinical References: Richens A: Clinical pharmacokinetics of phenytoin. Clin Pharmacokinet 1979;4:153-169

PNTFT
37051

Phenytoin, Total and Free, Serum

Clinical Information: Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Initial therapy with phenytoin is started at doses of 100 to 300 mg/day for adults or 4 mg/kg/day for children. Because absorption is variable and the drug exhibits zero-order (nonlinear) kinetics, dose must be adjusted within 5 days using blood concentration to guide therapy. Oral bioavailability ranges from 80% to 95% and is diet-dependent. Phenytoin exhibits zero-order pharmacokinetics; the rate of clearance of the drug is dependent upon the concentration of drug present. Therefore, phenytoin does not have a classical half-life like other drugs, since it varies with blood concentration. At a blood concentration of 15 mcg/mL, approximately half the drug in the patient's body will be eliminated in 20 hours. As the blood concentration drops, the rate at which phenytoin is excreted increases. Phenytoin has a volume of distribution of 0.65 L/kg, and is highly protein bound (90%), mostly to albumin. Phenytoin pharmacokinetics are significantly affected by a number of other drugs. Phenytoin and phenobarbital are frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels. Uremia has a similar effect on phenytoin protein

binding. In uremia, by-products of normal metabolism accumulate and bind to albumin, displacing phenytoin, which causes an increase in the free (active) fraction. Concurrent use of phenytoin and valproic acid (another frequently used antiepileptic) may result in altered valproic acid levels and/or altered phenytoin levels. Due to the complex situation involving displacement of protein-bound phenytoin and inhibition of phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be monitored for both phenytoin toxicity and therapeutic efficacy. Free phenytoin levels should be measured to provide the most accurate assessmet of phenytoin acivity early in therapy. At steady-state, free phenytoin and free valproic acid concentrations should be normalized. The free phenytoin level is the best indicator of adequate therapy. In renal failure, the opportunity for the free phenytoin fraction to be cleared is significantly reduced. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. Accordingly, the free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity is typified by tremor, hyperreflexia, lethargy, and coma. The outcome of phenytoin toxicity is not as serious as phenobarbital because phenytoin is not a central nervous system sedative.

Useful For: Monitoring for appropriate therapeutic concentration of both free and total phenytoin: free phenytoin level is the best indicator of adequate therapy in renal failure

Interpretation: Dose should be adjusted to achieve steady-state concentrations of total phenytoin between 10.0 and 20.0 mcg/mL, and free phenytoin between 1.0 and 2.0 mcg/mL. The range for percent free phenytoin is 8% to 14%. However, response and side effects will be individual. In patients with renal failure, total phenytoin is likely to be less than the therapeutic range of 10.0 to 20.0 mcg/mL. Severe toxicity occurs when the total blood concentration exceeds 30.0 mcg/mL.

Reference Values:
Phenytoin, Total
Therapeutic: 10.0-20.0 mcg/mL
Critical value: > or =30.0 mcg/mL

Phenytoin, Free
Therapeutic: 1.0-2.0 mcg/mL
Critical value: > or =2.5 mcg/mL

Clinical References: 1. Richens A: Clinical pharmacokinetics of phenytoin. Clin Pharmacokinet 1979;4:153-169 2. Moyer TP: Therapeutic drug monitoring. In Tietz Textbook of Clinical Chemistry. Fourth edition. Edited by CA Burtis, ER Ashwood. Philadelphia, WB Saunders Company, 2005, pp 1237-1285

PNYG
37050

Phenytoin, Total and Phenobarbital Group, Serum

Clinical Information: Phenytoin, Total: Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Initial therapy with phenytoin is started at doses of 100 to 300 mg/day for adults or 4 mg/kg/day for children. Because absorption is variable and the drug exhibits zero-order (nonlinear) kinetics, dose must be adjusted within 5 days using blood concentration to guide therapy. Oral bioavailability ranges from 80% to 95% and is diet-dependent. Phenytoin exhibits zero-order pharmacokinetics; the rate of clearance of the drug is dependent upon the concentration of drug present. Therefore, phenytoin does not have a classical half-life like other drugs, since it varies with blood concentration. At a blood concentration of 15 mcg/mL, approximately half the drug in the

patient's body will be eliminated in 20 hours. As the blood concentration drops, the rate at which phenytoin is excreted increases. Phenytoin has a volume of distribution of 0.65 L/kg, and is highly protein bound (90%), mostly to albumin. Some drug side-effects occur in the therapeutic range; these include gingival hyperplasia, hyperglycemia, and skin rash. Phenytoin pharmacokinetics are significantly affected by a number of other drugs. As noted above, phenytoin and phenobarbital are frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels. Uremia has a similar effect on phenytoin protein binding. In uremia, by-products of normal metabolism accumulate and bind to albumin, displacing phenytoin which causes an increase in the free fraction. Valproic acid, an antiepileptic frequently coadministered with phenytoin, competes for the same binding sites on albumin as phenytoin. Valproic acid displaces phenytoin from albumin, reducing the bound fraction and increasing the free fraction. The overall effect of coadministration of a therapeutic dose of valproic acid is that the total concentration of phenytoin decreases due to increased clearance but the free fraction increases; the free concentration of phenytoin, which is the active form remains virtually the same. Thus, no dosage adjustment is needed when valproic acid is added to maintain the same pharmacologic effect, but the total concentration of phenytoin decreases. In contrast to the valproic acid situation, in renal failure, there is not the same opportunity for the free phenytoin fraction to be cleared. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. The free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity occurs when the blood concentration is >30 mcg/mL and is typified by tremor, hyperreflexia, and lethargy. The outcome of phenytoin toxicity is not as serious as phenobarbital because phenytoin is not a central nervous system sedative. Phenobarbital: Phenobarbital is a general central nervous system (CNS) suppressant that has proven effective in the control of generalized and partial seizures. It is frequently coadministered with phenytoin for control of complex seizure disorders and with valproic acid for complex parietal seizures. Phenobarbital is administered in doses of 60 to 300 mg/day in adults or 3 to 6 mg/kg/day in children. Phenobarbital is slowly but completely absorbed, with bioavailability in the range of 100%. It is approximately 50% protein bound with a volume of distribution of 0.5 L/kg. Phenobarbital has a long half-life of 96 hours, with no known active metabolites. Sedation is common at therapeutic concentrations for the first 2 to 3 weeks of therapy, but this side effect disappears with time. Toxicity due to phenobarbital overdose is characterized by CNS sedation and reduced respiratory function. Mild symptoms characterized by ataxia, nystagmus, fatigue, or attention loss, occur at blood concentrations >40 mcg/mL. Symptoms become severe at concentrations > or =60 mcg/mL. Toxicity becomes life-threatening at concentrations >100 mcg/mL. Death usually occurs due to respiratory arrest when pulmonary support is not supplied manually. There are no known drug interactions that significantly affect the pharmacokinetics of phenobarbital; conversely, phenobarbital affects the pharmacokinetics of other drugs significantly because it induces the synthesis of enzymes associated with the hepatic cytochrome P450 metabolic pathway. Acute intermittent porphyria attacks may be induced by phenobarbital stimulation of hepatic cytochrome P450.

Useful For: Monitoring for appropriate therapeutic concentration of phenytoin and phenobarbital
Assessing compliance or toxicity

Interpretation: The therapeutic ranges for adults taking phenytoin have been established at 10 to 20 mcg/mL for total phenytoin (bound plus unbound). The therapeutic range for phenobarbital is10 to 40 mcg/mL. Within these ranges, most people will respond to the drugs without symptoms of toxicity. However, response and side effects will be individual. Dosage determinations and adjustments must be evaluated on a case-by-case basis. A free (unbound) phenytoin level may also need to be ordered when a person has kidney failure, liver disease, hypoalbuminemia, or is taking other medications like aspirin, naproxen, or ibuprofen, in which situation the percentage of free (active) phenytoin may be increased.

Reference Values:
PHENYTOIN, TOTAL
Therapeutic: 10.0-20.0 mcg/mL
Critical value: > or =30.0 mcg/mL

PHENOBARBITAL
Therapeutic: 10.0-40.0 mcg/mL:
Critical value: > or =60.0 mcg/mL

Clinical References: Phenytoin, Total: 1. Richens A: Clinical pharmacokinetics of phenytoin. Clin Pharmacokinet 1979;4:153-169 2. Moyer TP: Therapeutic drug monitoring. In Tietz Textbook of Clinical Chemistry. Fourth edition. Edited by CA Burtis, ER Ashwood. WB Saunders Company, Philadelphia, 2005, pp 1237-1285 Phenobarbital: Foero O, Kastrup KW, Nielsen EL, et al: Successful prophylaxis of febrile convulsions with phenobarbital. Epilepsia 1972;13:279-285

PNYA
37048

Phenytoin, Total, Serum

Clinical Information: Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Initial therapy with phenytoin is started at doses of 100 to 300 mg/day for adults or 4 mg/kg/day for children. Because absorption is variable and the drug exhibits zero-order (nonlinear) kinetics, dose must be adjusted within 5 days using blood concentration to guide therapy. Oral bioavailability ranges from 80% to 95% and is diet-dependent. Phenytoin exhibits zero-order pharmacokinetics; the rate of clearance of the drug is dependent upon the concentration of drug present. Therefore, phenytoin does not have a classical half-life like other drugs, since it varies with blood concentration. At a blood concentration of 15 mcg/mL, approximately half the drug in the patient's body will be eliminated in 20 hours. As the blood concentration drops, the rate at which phenytoin is excreted increases. Phenytoin has a volume of distribution of 0.65 L/kg, and is highly protein bound (90%), mostly to albumin. Some drug side-effects occur in the therapeutic range; these include gingival hyperplasia, hyperglycemia, and skin rash. Phenytoin pharmacokinetics are significantly affected by a number of other drugs. As noted above, phenytoin and phenobarbital are frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels. Uremia has a similar effect on phenytoin protein binding. In uremia, by-products of normal metabolism accumulate and bind to albumin, displacing phenytoin, which causes an increase in the free (active) fraction. Concurrent use of phenytoin and valproic acid (another frequently used antiepileptic) may result in altered valproic acid levels and/or altered phenytoin levels. Due to the complex situation involving displacement of protein-bound phenytoin and inhibition of phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be monitored for both phenytoin toxicity and therapeutic efficacy. Free phenytoin levels should be measured to provide the most accurate assessment of phenytoin activity early in therapy. At steady-state, free phenytoin and free valproic acid concentrations should be normalized. The free phenytoin level is the best indicator of adequate therapy in renal failure. In renal failure, the opportunity for the free phenytoin fraction to be cleared is significantly reduced. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. Accordingly, the free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity occurs when the blood concentration is above 30 mcg/mL and is typified by tremor, hyperreflexia, and lethargy. The outcome of phenytoin toxicity is not as serious as phenobarbital because phenytoin is not a central nervous system sedative.

Useful For: Monitoring for appropriate therapeutic concentration Assessing compliance or toxicity

Interpretation: Dose should be adjusted to achieve steady-state total phenytoin concentrations between 10.0 and 20.0 mcg/mL. In patients with renal failure, total phenytoin is likely to be less than the therapeutic range of 10.0 to 20.0 mcg/mL. Severe toxicity occurs when the total blood concentration exceeds 30.0 mcg/mL.

Reference Values:
Therapeutic: 10.0-20.0 mcg/mL
Critical value: > or =30.0 mcg/mL

Clinical References: 1. Richens A: Clinical pharmacokinetics of phenytoin. Clin Pharmacokinet 1979;4:153-169 2. Moyer TP: Therapeutic drug monitoring. In Tietz Textbook of Clinical Chemistry. Fourth edition. Edited by CA Burtis, ER Ashwood. WB Saunders Company, Philadelphia, 2005, pp 1237-1285

PHLDF
609577

Philadelphia Chromosome-like Acute Lymphoblastic Leukemia (Ph-like ALL), Diagnostic FISH, Varies

Clinical Information: In the United States, the incidence of acute lymphoblastic leukemia (ALL) is roughly 6000 new cases per year (as of 2019). ALL accounts for approximately 70% of all childhood leukemia cases (ages 0-19 years), making it the most common type of childhood cancer. Approximately 85% of pediatric cases of ALL are of B-cell lineage (B-ALL) and 15% are of T-cell lineage (T-ALL). It has a peak incidence at 2 to 5 years of age. The incidence decreases with increasing age, before increasing again at around 50 years of age. ALL is slightly more common in male patients than female patients. There is an increased incidence of ALL in individuals with Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, X-linked agammaglobulinemia, and severe combined immunodeficiency. The overall cure rate for ALL in children is about 90% and about 45% to 60% of adults have long-term disease-free survival. CRLF2/IGH rearrangements are more commonly observed in patients with Down syndrome or of Hispanic descent. Specific genetic abnormalities are identified in the majority of cases of B-ALL, either by conventional chromosome studies or fluorescence in situ hybridization (FISH) studies. Each of the B-ALL genetic subgroups are important to detect and can be critical prognostic markers. The decision for early transplantation may be made if t(9;22)(q34;q11.2), MLL (KMT2A) translocations, RUNX1 duplication/amplification (iAMP21) or a hypodiploid clone is identified. In contrast, if the ETV6/RUNX1 fusion is detected by FISH or hyperdiploidy is identified by chromosome studies, the patient has a favorable prognosis and transplantation is rarely considered. A newly recognized World Health Organization entity BCR-ABL1-like ALL, also known as Philadelphia chromosome-like acute lymphoblastic leukemia, is increasing in importance due to the poor prognosis seen in pediatric, adolescent, and young adult ALL. Common features of this entity involve rearrangements with tyrosine kinase genes involving the following genes: ABL2, PDGFRB, JAK2, ABL1, CRLF2, and P2RY8. Deletion of IKZF1 often accompanies this entity. Some patients who have failed conventional therapies have demonstrated favorable responses to targeted therapies in clinical trials when rearrangements involving these specific gene regions have been identified. Per National Comprehensive Cancer Network guidelines, a combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients with B-ALL/lymphoblastic lymphoma.

Useful For: Detecting a neoplastic clone associated with Philadelphia chromosome-like acute lymphoblastic leukemia (ALL), particularly when a classic abnormality is not detected with the initial panel An adjunct to conventional chromosome studies in patients with B-cell ALL Evaluating specimens in which standard cytogenetic analysis is unsuccessful

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds

the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Moorman AV, Harrison CJ, Buck GA, et al: Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood. 2007 Apr 15;109(8):3189-3197 2. Moorman AV: The clinical relevance of chromosomal and genetic abnormalities in B-cell precursor acute lymphoblastic leukemia. Blood. Rev. 2012 May;26(3):123-135 3. Roberts KG, Li Y, Payne-Turner D, et al: Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med. 2014 Sept;371(11):1005-1015 4. Mullighan CG: The genomic landscape of acute lymphoblastic leukemia in children and young adults. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):174-180 5. Arber DA, Orazi A, Hasserjian R, et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-2405

PHMA
82736

Phoma betae, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Phoma betae Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PTEN
614126

Phosphatase and Tensin Homolog (PTEN) Immunostain, Technical Component Only

Clinical Information: Immunostaining for phosphatase and tensin homolog (PTEN) is used for the diagnosis of intraductal carcinoma (IDC) of the prostate, where PTEN expression is often lost and can also help distinguish IDC from high grade prostatic intraepithelial neoplasia.

Useful For: Diagnosis of intraductal prostate carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Lotan TL, Gumuskaya B, Rahimi H, et al. Cytoplasmic PTEN protein loss distinguishes intraductal carcinoma of the prostate from high-grade prostatic intraepithelial neoplasia. Mod Pathol. 2013;26(4):587-603 2. Morais CL, Han JS, Gordetsky J, et al. Utility of PTEN and ERG immunostaining for distinguishing high-grade PIN from intraductal carcinoma of the prostate on needle biopsy. Am J Surg Pathol. 2015;39(2):169-178 3. Djordjevic B, Hennessy BT, Li J, et al. Clinical assessment of PTEN loss in endometrial carcinoma: immunohistochemistry outperforms gene sequencing. Mod Pathol. 2012;25(5):699-708 4. Epstein JI, Amin MB, Fine SW, et al. The 2019 Genitourinary Pathology Society (GUPS) White Paper on Contemporary Grading of Prostate Cancer. Arch Pathol Lab Med. 2021;145(4):461-493 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PETH
617480

Phosphatidylethanol Confirmation, Blood

Clinical Information: Phosphatidylethanol (PEth) is a direct biomarker for alcohol (ethanol) intake. In presence of ethanol, phosphatidylcholine is converted to PEth on the red blood cell membrane by the phospholipase D enzyme. PEth homologues (16:0/18:1 [POPEth: 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanol] and 16:0/18:2 [PLPEth: 1-palmitoyl-2-linoleoyl-sn-glycero-3-phosphoethanol]) levels correlate with the amount of alcohol consumed within the previous 2 weeks and may be detected in the blood up to 2 to 4 weeks after excessive alcohol consumption. POPEth and PLPEth comprise approximately 60% of all observed PEth homologues in the blood.(1)

Useful For: Verifying abstinence or use of ethanol, especially in liver transplant candidates/patients

Interpretation: POPEth (1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanol): A result of 20 ng/mL to 200 ng/mL is considered evidence of moderate ethanol consumption, while results over 200 ng/mL indicate heavy ethanol consumption. However, the Center for Substance Abuse Treatment advises caution in interpretation and use of biomarkers alone to assess alcohol use. Results should be interpreted in the context of all available clinical and behavioral information.(2) PLPEth (1-Palmitoyl-2-linoleoyl-sn-glycero-3-phosphoethanol): There are no current clinical reference limits for this phosphatidylethanol (PEth) homologue. PEth 16:0/18:1 (POPEth) Less than 10 ng/mL: Not detected 10-19 ng/mL: Abstinence or light alcohol consumption (<2 drinks per day for several days a week) 20-200 ng/mL: Moderate alcohol consumption (up to 4 drinks per day for several days a week) Greater than 200 ng/mL: Heavy alcohol consumption or chronic alcohol use (at least 4 drinks per day several days a week) PEth 16:0/18:2 (PLPEth): Reference ranges are not well established.

Reference Values:
Negative (<10 ng/mL)

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
PEth 16:0/18:1 (POPEth): 10 ng/mL
PEth 16:0/18:2 (PLPEth): 10 ng/mL

Clinical References: 1. Helander A, Zheng Y. Molecular species of the alcohol biomarker phosphatidyethanol in human blood measured by LC-MS. Clin Chem. 2009:55:(7):1395-1405. doi:10.1373/clinchem.2008.120923 2. Substance Abuse and Mental Health Services Administration (SAMHSA) and National Institute on Alcohol Abuse and Alcoholism. Medication for the Treatment of Alcohol Use Disorder: A Brief Guide. HHS Publication No. (SMA) 15-4907. SAMHSA; 2015 3. Ulwelling W, Smith K. The PEth blood test in the security environment: What it is; why it is important; and interpretative guidelines. J Forensic Sci. 2018;63(6):1634-1640. doi:10.1111/1556-4029.13874 4. Hakim F, Wiart JF, Menard O, Allorge D, Gaulier JM. Dosage sanguin du phosphatidylethanol Phosphatidylethanol blood analysis. Ann Biol Clin (Paris). 2019;77(6):638-644. French. doi:10.1684/abc.2019.1499 5. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

PSPTG
62578

Phosphatidylserine/Prothrombin Antibody, IgG, Serum

Clinical Information: The 2023 American College of Rheumatology/European Alliance of Associations for Rheumatology antiphospholipid syndrome (APS) classification criteria includes an entry criterion of at least one positive antiphospholipid antibody (aPL) test within 3 years of identification of an aPL-associated clinical criterion, followed by additive weighted criteria (score range 1-7 points each) clustered into 6 clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and 2 laboratory domains (lupus anticoagulant functional coagulation assays, and solid-phase enzyme-linked immunosorbent assays for IgG/IgM anticardiolipin and/or IgG/IgM anti-beta 2-glycoprotein I

antibodies) (1)Cardiolipin is an anionic phospholipid that interacts with the protein cofactor beta 2-glycoprotein I. Lupus anticoagulant (LA) is an indirect assessment for the presence of antiphospholipid antibodies, which is evident in the in vitro prolongation of phospholipid-dependent coagulation.(2) Anticardiolipin and anti-beta 2-glycoprotein I antibodies are detected in solid-phases immunoassays using beta 2-glycoprotein I-dependent cardiolipin/or beta 2-glycoprotein I alone as substrate, respectively.(2,3) There is evidence from multiple studies to suggest that patients with APS may develop autoantibodies to other phospholipid/protein complexes, specifically phosphatidylserine/prothrombin (PS/PT).(4-9) Like beta 2-glycoprotein-dependent I cardiolipin, PS/PT is a complex composed of the anionic phospholipid phosphatidylserine and the protein cofactor prothrombin. In a systematic review, Sciascia et al demonstrated that the presence of anti-PS/PT IgG antibodies is an independent risk factor for arterial and/or venous thrombotic events, with odds ratio (OR) of 5.11 (95% CI: 4.2-6.3).(4) A multicenter study showed that IgG anti-PS/PT were more prevalent in APS patients (51%) than in those without (9%), OR 10.8, 95% CI (4.0-29.3), p <0.0001.(5) Furthermore, a number of studies have shown clinical and laboratory evidence that PS/PT antibodies may be a useful second-line test for the evaluation of patients at-risk or suspected with suspected APS, particularly for those individuals with evidence of thrombosis or abnormal LA testing.(6,7) While anti-PS/PT antibodies were highly prevalent and correlated with other anti-PL antibodies, IgG anti-PS/PT conferred a high risk for thrombosis (8,9) but not for pure hematologic involvement.(9) These antibodies may also be seen in patients with other autoimmune diseases such as systemic lupus erythematosus.(5,8) In individuals who test positive for antiphospholipid antibodies without clinical features of APS (carriers), the cumulative incidence rate of thrombotic events has also been reported to be significantly higher for anti-PS/PT IgG positive than anti-PS/PT IgM positive subjects.(10)

Useful For: Detecting IgG antibodies against phosphatidylserine/prothrombin complex in patients with strong suspicion of antiphospholipid syndrome (APS) who are negative for the APS criteria laboratory tests (lupus anticoagulant, IgG and IgM anticardiolipin/beta 2-glycoprotein I and anti-beta 2-glycoprotein I antibodies) May be useful for the evaluation of patients with prior positive lupus anticoagulant results who are on direct oral anticoagulant therapy May be useful as a risk marker for thrombosis in antiphospholipid antibody carriers

Interpretation: A positive and persistent result for anti-phosphatidylserine/prothrombin complex IgG antibodies may be suggestive of a diagnosis of antiphospholipid syndrome (APS) in patients with evidence of arterial, venous, or specific pregnancy-related morbidities. These antibodies may also exist prior to the occurrence APS clinical manifestations as well as in patients with other systemic autoimmune diseases such systemic lupus erythematosus. Anti-phosphatidylserine/prothrombin complex IgG antibodies have relatively higher correlations with positive results for lupus anticoagulant than the IgM isotype as well as significant risk for APS-associated thrombotic events compared to the IgM isotype in antiphospholipid antibody carriers. A negative result does not exclude a diagnosis of APS, as other phospholipid and/or protein antibodies are also associated with this disorder.

Reference Values:
<18 years: Not established
> or =18 years:
Negative < or =30.0 U
Borderline 30.1-40.0 U
Positive > or =40.1 U

Clinical References: 1. Barbhaiya M, Zuily S, Naden R, et al. The 2023 ACR/EULAR antiphospholipid syndrome classification criteria. Arthritis Rheumatol. 2023;75(10):1687-1702. doi:10.1002/art.42624 2. Pengo V, Bison E, Denas G, Jose SP, Zoppellaro G, Banzato A. Laboratory diagnostics of antiphospholipid syndrome. Semin Thromb Hemost. 2018;44(5):439-444. doi:10.1055/s-0037-1601331 3. Tebo AE. Laboratory evaluation of antiphospholipid syndrome: An update on autoantibody testing. Clin Lab Med. 2019;39(4):553-565. doi:10.1016/j.cll.2019.07.004 4. Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA, Bertolaccini ML. Anti-prothrombin (aPT)

and anti-phosphatidylserine/prothrombin (aPS/PT) antibodies and the risk of thrombosis in the antiphospholipid syndrome. A systematic review. Thromb Haemost. 2014;111(2):354-364. doi:10.1160/TH13-06-0509 5. Amengual O, Forastiero R, Sugiura-Ogasawara M, et al. Evaluation of phosphatidylserine-dependent antiprothrombin antibody testing for the diagnosis of antiphospholipid syndrome: results of an international multicentre study. Lupus. 2017;26(3):266-276. doi:10.1177/0961203316660203 6. Heikal NM, Jaskowski TD, Malmberg E, Lakos G, Branch DW, Tebo AE. Laboratory evaluation of anti-phospholipid syndrome: A preliminary prospective study of phosphatidylserine/prothrombin antibodies in an at-risk patient cohort. Clin Exp Immunol. 2015;180(2):218-226. doi:10.1111/cei.12573 7. Nakamura H, Oku K, Amengual O, et al. First-line, non-criterial antiphospholipid antibody testing for the diagnosis of antiphospholipid syndrome in clinical practice: A combination of anti-beta 2 -glycoprotein I domain I and anti-phosphatidylserine/prothrombin complex antibodies tests. Arthritis Care Res (Hoboken). 2018;70(4):627-634 8. Radin M, Foddai SG, Cecchi I, et al. Antiphosphatidylserine/prothrombin antibodies: An update on their association with clinical manifestations of antiphospholipid syndrome. Thromb Haemost. 2020;120(4):592-598. doi:10.1055/s-0040-1705115 9. Nunez-Alvarez CA, Hernandez-Molina G, Bermudez-Bermejo P, et al. Prevalence and associations of anti-phosphatidylserine/prothrombin antibodies with clinical phenotypes in patients with primary antiphospholipid syndrome: aPS/PT antibodies in primary antiphospholipid syndrome. Thromb Res. 2019;174:141-147. doi:10.1016/j.thromres.2018.12.023 10. Tonello M, Mattia E, Favaro M, et al. IgG phosphatidylserine/prothrombin antibodies as a risk factor of thrombosis in antiphospholipid antibody carriers. Thromb Res. 2019;177:157-160. doi:10.1016/j.thromres.2019.03.006

PT217
621635

Phospho-Tau 217, Plasma

Clinical Information: The two main neuropathologic features observed in the brain of patients with Alzheimer disease (AD) are the presence of plaques composed of beta-amyloid (Abeta) peptides and intracellular neurofibrillary tangles containing hyperphosphorylated Tau (p-Tau) proteins. To date, positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarkers are the most widely used biomarkers in clinical practice for detection of Abeta and tau pathologies. There are several PET tracers that can detect the load of Abeta fibrils in the brain (amyloid-PET). Studies have demonstrated high concordance between the in vivo uptake of these amyloid-PET tracers and the density of Abeta plaques as determined post-mortem. In CSF, Abeta42 concentrations and especially the ratios of Abeta42/Abeta40 and p-Tau181/Abeta42 concentrations correlate strongly with amyloid-PET status and AD neuropathology. Several CSF Abeta and p-Tau assays on high-performing, fully automated platforms are currently used in clinical practice. However, there is a need for accurate AD blood-based biomarkers that are easily accessible and minimally invasive. Different p-Tau isoforms that are increased in the presence of amyloid pathology are detectable in plasma, including pTau181, pTau217, and pTau231. Head-to-head comparisons of assays for p-Tau181, p-Tau217, and p-Tau231 using plasma from patients with mild cognitive impairment indicate that increases in plasma p-Tau217 were superior at detecting AD pathology and predicting future development of AD dementia. Both p-Tau181 and p-Tau217 were associated with both Abeta plaques and tau tangles, with p-Tau217 showing stronger correlations with both pathologies. In addition, plasma concentrations of p-Tau217, but not p-Tau181 and p-Tau231, have been shown to increase over time in people with abnormal brain Abeta deposition correlating with brain atrophy and cognitive decline.

Useful For: Evaluation of individuals, aged 50 years and older, presenting with cognitive impairment who are being assessed for Alzheimer disease and other causes of cognitive decline This test is not intended as a screening test for Alzheimer disease in asymptomatic individuals.

Interpretation: Negative: A normal (negative) phosphorylated Tau217 (p-Tau217) result is consistent with a negative (normal) amyloid-positron emission tomography (PET) scan result. This result indicates a reduced likelihood that an individual has neuropathological changes associated with Alzheimer disease. Intermediate: An intermediate p-Tau217 result cannot accurately differentiate

between the presence or absence of neuropathological changes associated with Alzheimer disease. Further testing, such as amyloid-positron emission tomography (PET) or cerebrospinal fluid Abeta42 and tau biomarkers, is needed to determine the likelihood of neuropathological changes associated with Alzheimer disease being present. Positive: An elevated (positive) p-Tau217 result is consistent with a positive (abnormal) amyloid-positron emission tomography (PET) scan result. This result is consistent with the presence of neuropathological changes associated with Alzheimer disease. In the proper clinical context this test is supportive of Alzheimer disease being related to current clinical symptoms. This test has not been demonstrated to provide information on the risk of an asymptomatic individual developing symptoms related to Alzheimer disease in the future. Clinical performance of this test was established in a study of 427 individuals aged 50 years and older with mild cognitive impairment or early dementia with a 64% prevalence of amyloid pathology defined by an amyloid-PET and a Centiloid scale value of 25 or more. For detection of an abnormal amyloid-PET, pTau217 test sensitivity at the lower cutpoint (< or =0.185 pg/mL) was 92% and the specificity at the upper cutpoint (> or =0.325 pg/mL) was 96%. The diagnostic performance of this test has not been established in asymptomatic individuals.

Reference Values:

Negative: < or =0.185 pg/mL
Intermediate: 0.186-0.324 pg/mL
Positive: > or =0.325 pg/mL

Clinical References: 1. Arranz J, Zhu N, Rubio-Guerra S, et al. Diagnostic performance of plasma pTau 217, pTau 181, Ab 1-42 and Ab 1-40 in the LUMIPULSE automated platform for the detection of Alzheimer disease. Preprint. Res Sq. 2023;rs.3.rs-3725688. doi:10.21203/rs.3.rs-3725688/v1 2. Brum WS, Cullen NC, Janelidze S, et al. A two-step workflow based on plasma p-tau217 to screen for amyloid b positivity with further confirmatory testing only in uncertain cases. Nat Aging. 2023;3(9):1079-1090. doi:10.1038/s43587-023-00471-5 3. Mattsson-Carlgren N, Collij LE, Stomrud E, et al. Plasma biomarker strategy for selecting patients with Alzheimer disease for antiamyloid immunotherapies JAMA Neurol. 2024;81(1):69-78. doi:10.1001/jamaneurol.2023.4596 4. Janelidze S, Berron D, Smith R, et al. Associations of plasma phospho-tau217 levels with tau positron emission tomography in early Alzheimer disease. JAMA Neurol. 2021;78(2):149-156. doi:10.1001/jamaneurol.2020.4201 5. Blennow K, Galasko D, Perneczky R, et al. The potential clinical value of plasma biomarkers in Alzheimer's disease. Alzheimers Dement. 2023;19(12):5805-5816. doi:10.1002/alz.13455 6. Ashton NJ, Puig-Pijoan A, Mila-Aloma M, et al. Plasma and CSF biomarkers in a memory clinic: Head-to-head comparison of phosphorylated tau immunoassays. Alzheimers Dement. 2023;19(5):1913-1924. doi:10.1002/alz.12841 7. Mielke MM, Dage JL, Frank RD, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. Nat Med. 2022;28(7):1398-1405. doi:10.1038/s41591-022-01822-2 8. Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA. 2020;324(8):772-781. doi:10.1001/jama.2020.12134 9. Gonzalez-Ortiz F, Kac PR, Brum WS, Zetterberg H, Blennow K, Karikari TK. Plasma phospho-tau in Alzheimer's disease: towards diagnostic and therapeutic trial applications. Mol Neurodegener. 2023;18(1):18. doi:10.1186/s13024-023-00605-8 10. Barthelemy NR, Horie K, Sato C, Bateman RJ. Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease. J Exp Med. 2020;217(11):e20200861. doi:10.1084/jem.20200861 11. Jack CR, Wiste HJ, Algeciras-Schimnich A, et al. Predicting amyloid PET and tau PET stages with plasma biomarkers. Brain. 2023;146(5):2029-2044. doi:10.1093/brain/awad042 12. Karikari TK, Ashton NJ, Brinkmalm G, et al. Blood phospho-tau in Alzheimer disease: analysis, interpretation, and clinical utility. Nat Rev Neurol. 2022;18(7):400-418. doi:10.1038/s41582-022-00665-2

PDETS
620070

Phosphodiesterase 10A (PDE10A) IgG, Tissue Immunofluorescence Titer, Serum

Clinical Information: Phosphodiesterase 10A (PDE10A) is a marker of paraneoplastic neurological

autoimmunity in patients presenting with movement disorders, encephalopathy and often cancer.

Useful For: Reporting an end titer result from phosphodiesterase 10A (PDE10A) in serum specimens Evaluation of autoimmune/paraneoplastic neurological syndromes among patients presenting with movement disorders and encephalopathy

Interpretation: A positive result is consistent with phosphodiesterase 10A (PDE10A) autoimmunity that manifests with autoimmune movement disorders or encephalitis. A paraneoplastic cause should be considered.

Reference Values:
Only orderable as a reflex. For more information see:
ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum

<1:240

Clinical References: Zekeridou A, Kryzer T, Guo Y, et al. Phosphodiesterase 10A IgG: a novel biomarker of paraneoplastic neurologic autoimmunity. Neurology. 2019; 93(8):e815-e822. doi:10.1212/WNL.0000000000007971

PDETC 620069 Phosphodiesterase 10A (PDE10A) IgG, Tissue Immunofluorescence Titer, Spinal Fluid

Clinical Information: Phosphodiesterase 10A (PDE10A) is a marker of paraneoplastic neurological autoimmunity in patients presenting with movement disorders, encephalopathy and often cancer.

Useful For: Reporting an end titer result from phosphodiesterase 10A (PDE10A) in spinal fluid specimens Evaluation of autoimmune/paraneoplastic neurological syndromes among patients presenting with movement disorders and encephalopathy

Interpretation: A positive result is consistent with phosphodiesterase 10A (PDE10A) autoimmunity that manifests with autoimmune movement disorders or encephalitis. A paraneoplastic cause should be considered.

Reference Values:
Only orderable as a reflex. For more information see:
DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

<1:2

Clinical References: Zekeridou A, Kryzer T, Guo Y, et al. Phosphodiesterase 10A IgG: a novel biomarker of paraneoplastic neurologic autoimmunity. Neurology. 2019; 93(8):e815-e822. doi:10.1212/WNL.0000000000007971

PDEIS
620068

Phosphodiesterase 10A (PDE10A) IgG, Tissue Immunofluorescence, Serum

Clinical Information: Phosphodiesterase 10A (PDE10A) is a marker of paraneoplastic neurological autoimmunity in patients presenting with movement disorders, encephalopathy, and often, cancer.

Useful For: Detecting phosphodiesterase 10A (PDE10A)-IgG in serum specimens Evaluation of autoimmune/paraneoplastic neurological syndromes among patients presenting with movement disorders and encephalopathy

Interpretation: A positive result is consistent with phosphodiesterase 10A (PDE10A) autoimmunity that manifests with autoimmune movement disorders or encephalitis. A paraneoplastic cause should be considered.

Reference Values:
Only orderable as part of a profile. For more information see:
ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum

Negative

Clinical References: Zekeridou A, Kryzer T, Guo Y, et al. Phosphodiesterase 10A IgG: A novel biomarker of paraneoplastic neurologic autoimmunity. Neurology. 2019;93(8):e815-e822. doi:10.1212/WNL.0000000000007971

PDEIC
620067

Phosphodiesterase 10A (PDE10A) IgG, Tissue Immunofluorescence, Spinal Fluid

Clinical Information: Phosphodiesterase 10A (PDE10A) is a marker of paraneoplastic neurological autoimmunity in patients presenting with movement disorders, encephalopathy, and often, cancer.

Useful For: Detecting phosphodiesterase 10A (PDE10A)-IgG in cerebrospinal fluid specimens Evaluation of autoimmune/paraneoplastic neurological syndromes among patients presenting with movement disorders and encephalopathy

Interpretation: A positive result is consistent with phosphodiesterase 10A (PDE10A) autoimmunity that manifests with autoimmune movement disorders or encephalitis. A paraneoplastic cause should be considered.

Reference Values:
Only orderable as part of a profile. For more information see:
DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

Negative

Clinical References: Zekeridou A, Kryzer T, Guo Y, et al. Phosphodiesterase 10A IgG: a novel biomarker of paraneoplastic neurologic autoimmunity. Neurology. 2019;93(8):e815-e822. doi:10.1212/WNL.0000000000007971

PFK1
607456

Phosphofructokinase Enzyme Activity, Blood

Clinical Information: Phosphofructokinase (PFK) is the third enzyme in glycolysis. It converts fructose-6-phosphate to fructose 1,6-diphosphate. PFK deficiency, also called glycogen storage disease, type VII or Tarui disease (OMIM 232800), is a rare hereditary autosomal recessive disorder that is typically noticed in childhood. Different clinical subtypes (classical, late-onset, infantile and hemolytic) have been described. Manifestations can vary, including exercise intolerance, exertional myopathy, nausea, stiffness, and myoglobinuria. Although not classically described, a second-wind effect is noticed by some patients.(1) A subset of individuals have compensated (high normal hemoglobin values) or mild hemolytic anemia, episodic jaundice, hyperuricemia, or gout-like symptoms. No distinctive morphologic abnormalities are seen on the peripheral blood smear. Red blood cell PFK activity is typically partially decreased (30%-50% mean normal) and muscle biopsy PFK activity is markedly decreased.

Useful For: Evaluation of individuals with Coombs-negative nonspherocytic hemolytic anemia Evaluation of individuals with exercise intolerance or myopathy Genetic studies in families with phosphofructokinase deficiency

Interpretation: Clinically significant disorders due to phosphofructokinase deficiency are associated with red blood cell activity levels less than 50% of mean normal. Unaffected heterozygotes have been reported with levels of 63% of normal. Therefore, genetic correlation will often be important in ambiguous cases.

Reference Values:
> or =12 months of age: 5.8-10.9 U/g Hb
Reference values have not been established for patients younger than 12 months.

Clinical References: 1. Sherman JB, Raben N, Nicastri C, et al. Common mutations in the phosphofructokinase-M gene in Ashkenazi Jewish patients with glycogenesis VII--and their population frequency. Am J Hum Genet. 1994;55(2):305-313 2. Tarui S, Okuno G, Ikura Y, Tanaka T, Suda M, Nishikawa M. Phosphofructokinase deficiency in a skeletal muscle. A new type of glycogenosis. Biochem Biophys Res Commun. 1965;19:517-23. doi:10.1016/0006-291x(65)90156-7 3. Musumeci O, Bruno C, Mongini T, et al. Clinical features and new molecular findings in muscle phosphofructokinase deficiency (GSD type VII). Neuromuscul Disord. 2012;22(4):325-330 4. Nakajima H, Raben N, Hamaguchi T, Yamasaki T. Phosphofructokinase deficiency; past, present and future. Curr Mol Med. 2002;2(2):197-212. doi:10.2174/1566524024605734 5. Auranen M, Palmio J, Ylikallio E, et al: PFKM gene defect and glycogen storage disease GSDVII with misleading enzyme histochemistry. Neurol Genet. 2015;1(1):e7. doi:10.1212/NXG.0000000000000007 6. Raben N, Sherman JB. Mutations in muscle phosphofructokinase gene. Hum Mutat. 1995;6(1):1-6. doi:10.1002/humu.1380060102 7. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia-pathophysiology, clinical aspects and laboratory diagnosis. Int J Lab Hematol. 2014;36:388-397. doi:10.1111/ijlh.12223

PFKC
608422

Phosphofructokinase Enzyme Activity, Blood

Clinical Information: Phosphofructokinase (PFK) is the third enzyme in glycolysis. It converts fructose 6-phosphate to fructose 1,6-diphosphate. PFK deficiency, also called glycogen storage disease,

type VII or Tarui disease (OMIM 232800), is a rare hereditary autosomal recessive disorder that is typically noticed in childhood. Different clinical subtypes, classical, late-onset, infantile, and hemolytic, have been described. Manifestations can vary and include exercise intolerance, exertional myopathy, nausea, stiffness, and myoglobinuria. Although not classically described, a second-wind effect is noticed by some patients.(1) A subset of individuals has compensated (high normal hemoglobin values) or mild hemolytic anemia, episodic jaundice, hyperuricemia, or gout-like symptoms. No distinctive morphologic abnormalities are seen on the peripheral blood smear. Red blood cell PFK activity is typically partially decreased (30%-50% mean normal) and muscle biopsy PFK activity is markedly decreased.

Useful For: Evaluation of individuals with Coombs-negative nonspherocytic hemolytic anemia Evaluation of individuals with exercise intolerance or myopathy Genetic studies in families with phosphofructokinase deficiency

Interpretation: Clinically significant disorders due to phosphofructokinase (PFK) deficiency are associated with red blood cell activity levels less than 50% of mean normal. Unaffected heterozygous individuals have been reported with levels of 63% of normal. Therefore, genetic correlation will often be important in ambiguous cases.

Reference Values:
Only available as part of a profile. For more information see:
-HAEV1 / Hemolytic Anemia Evaluation, Blood
-EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation, Blood

> or =12 months of age: 5.8-10.9 U/g Hb
Reference values have not been established for patients who are younger than 12 months.

Clinical References: 1. Sherman JB, Raben N, Nicastri C, et al. Common mutations in the phosphofructokinase-M gene in Ashkenazi Jewish patients with glycogenesis VII--and their population frequency. Am J Hum Genet. 1994;55(2):305-313 2. Tarui S, Okuno G, Ikura Y, Tanaka T, Suda M, Nishikawa M. Phosphofructokinase deficiency in a skeletal muscle. A new type of glycogenosis. Biochem Biophys Res Commun. 1965;19:517-523 3. Musumeci O, Bruno C, Mongini T, et al. Clinical features and new molecular findings in muscle phosphofructokinase deficiency (GSD type VII). Neuromuscul Disord. 2012;22(4):325-330 4. Nakajima H, Raben N, Hamaguchi T, Yamasaki T. Phosphofructokinase deficiency; past, present and future. Curr Mol Med. 2002;2(2):197-212 5. Auranen M, Palmio J, Ylikallio E, et al. PFKM gene defect and glycogen storage disease GSDVII with misleading enzyme histochemistry. Neurol Genet. 2015;1(1) 6. Raben N, Sherman JB. Mutations in muscle phosphofructokinase gene. Hum Mutat. 1995;6(1):1-6 7. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia-pathophysiology, clinical aspects and laboratory diagnosis. Int J Lab Hematol. 2014;36(3):388-397

PGKC
608423

Phosphoglycerate Kinase Enzyme Activity, Blood

Clinical Information: Phosphoglycerate kinase (PGK) is an enzyme that converts 1,3-diphosphoglycerate to 3-phosphoglyceric acid) in one of the adenosine triphosphate (ATP) generating steps in glycolysis. PGK deficiency (OMIM 300653) is an X-linked disorder with a variable clinical phenotype. Manifestations include hemolytic anemia, myopathy/rhabdomyolysis, or neurologic impairment. Patients can have 1 or 2 systems affected but rarely have all 3. Clinical severity may not correlate with enzyme activity and female heterozygotes may possibly be mildly affected.

Useful For: Evaluation of individuals with Coombs-negative nonspherocytic hemolytic anemia, especially if X-linked inheritance pattern. Evaluation of individuals with myopathic or neurologic symptoms

Interpretation: In phosphoglycerate kinase deficiency, red blood cell activity levels have been reported ranging from 1% to 49% of mean normal; however, affected patients more typically have values less than 20% of normal mean.(1)

Reference Values:
Only available as part of a profile. For more information see:
-HAEV1 / Hemolytic Anemia Evaluation
-EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation

> or =12 months: 142-232 U/g Hb
Reference values have not been established for patients who are younger than 12 months.

Clinical References: 1. Chiarelli LR, Morera SM, Bianchi P, et al. Molecular insights on pathogenic effects of mutations causing phosphoglycerate kinase deficiency. PLoS One. 2012;7(2):e32065. doi:10.1371/journal.pone.0032065 2. Valentine WN, Hsieh HS, Paglia DE, et al: Hereditary hemolytic anemia associated with phosphoglycerate kinase deficiency in erythrocytes and leukocytes: a probable X-chromosome-linked syndrome. New Eng J Med. 1969;280(10):528-534 3. Beutler E: PGK deficiency. Br J Haematol. 2007;136(1):3-11 4. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia-pathophysiology, clinical aspects and laboratory diagnosis. Int J Lab Hematol. 2014;36:388-397

PGK1
607457

Phosphoglycerate Kinase Enzyme Activity, Blood

Clinical Information: Phosphoglycerate kinase (PGK) is an enzyme that converts 1,3-diphosphoglycerate to 3-phosphoglyceric acid in one of the adenosine triphosphate generating steps in glycolysis. PGK deficiency (OMIM # 300653) is an X-linked disorder with a variable clinical phenotype. Manifestations include hemolytic anemia, myopathy/rhabdomyolysis, or neurologic impairment. Patients can have 1 or 2 systems affected but rarely have all 3. Clinical severity may not correlate with enzyme activity, and female heterozygous individuals may be mildly affected.

Useful For: Evaluation of individuals with Coombs-negative nonspherocytic hemolytic anemia, especially if X-linked inheritance pattern Evaluation of individuals with myopathic or neurologic symptoms

Interpretation: In phosphoglycerate kinase deficiency, red blood cell activity levels have been reported ranging from 1% to 49% of mean normal; however, affected patients more typically have values below 20% of normal mean.(1)

Reference Values:
> or =12 months: 142-232 U/g Hb
Reference values have not been established for patients younger than 12 months.

Clinical References: 1. Chiarelli LR, Morera SM, Bianchi P, et al. Molecular insights on pathogenic effects of mutations causing phosphoglycerate kinase deficiency. PLoS One. 2012;7(2):e32065 2. Valentine WN, Hsieh HS, Paglia DE, et al. Hereditary hemolytic anemia associated with phosphoglycerate kinase deficiency in erythrocytes and leukocytes. A probable X-chromosome-linked syndrome. N Engl J Med. 1969;280(10):528-534 3. Beutler E. PGK deficiency. Br J Haematol. 2007;136(1):3-11 4. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia-pathophysiology, clinical aspects, and laboratory diagnosis. Int J Lab Hematol. 2014;36(3):388-397

PLAIF
70592

Phospholipase A2 Receptor (PLA2R), Renal Biopsy

Clinical Information: Membranous nephropathy is the most common cause of nephrotic syndrome in White adults. Eighty-five percent of membranous nephropathy cases are primary or idiopathic, and the other 15% are secondary. Phospholipase A2 receptor (PLA2R) is an antigen located on podocytes. The majority of cases of primary membranous nephropathy have circulating autoantibodies against PLA2R.

Useful For: Distinguishing primary membranous nephropathy from secondary membranous nephropathy

Interpretation: This test, when not accompanied by a pathology consultation request, will be reported as either positive or negative.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Larsen CP, Messias NC, Silva FG, Messias E, Walker PD. Determination of primary versus secondary membranous glomerulopathy utilizing phospholipase A2 receptor staining in renal biopsies. Mod Pathol. 2013;26(5):709-715 2. Svobodova B, Honsova E, Ronco P, Tesar V, Debiec H. Kidney biopsy is a sensitive tool for retrospective diagnosis of PLA2R-related membranous nephropathy. Nephrol Dial Transplant. 2013;28(7):1839-1844 3. Cossey LN, Walker PD, Larsen CP. Phospholipase A2 receptor staining in pediatric idiopathic membranous glomerulopathy. Pediatr Nephrol. 2013;28(12):2307-2311 4. Larsen CP, Walker PD. Phospholipase A2 receptor (PLA2R) staining is useful in the determination of de novo versus recurrent membranous glomerulopathy. Transplantation. 2013;95(10):1259-1262 5. Tomas NM, Beck LH Jr, Meyer-Schwesinger C, et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med. 2014;371(24):2277-2287

EURO
606475

Phospholipase A2 Receptor, Enzyme Linked Immunosorbent Assay, Serum

Clinical Information: Membranous nephropathy (MN) is a rare disease in which immune complexes deposit at the glomerular basement membrane, causing damage to the filtration barrier, resulting in proteinuria. Recent studies have shown that in approximately 70% of patients with primary MN (pMN), the immune complexes consist of autoantibodies against the podocyte protein M-type phospholipase A2 receptor (PLA2R).(1) There is also evidence that levels of anti-PLA2R autoantibodies correlate well with disease activity and progression.(2) The presence of anti-PLA2R antibodies could also potentially be used to differentiate pMN from other causes of nephrotic syndrome if a biopsy is not possible. Among patients with chronic kidney disease awaiting kidney transplantation, higher levels of anti-PLA2R could predict those more likely to recur after transplantation.(2)

Useful For: Distinguishing primary from secondary membranous nephropathy

Interpretation: Therapy outcome can be monitored by measuring the anti-phospholipase A2 receptor antibody titer. A titer increase, decrease, or disappearance generally precedes a change in clinical status. Thus, the determination of the antibody titer has a high predictive value with respect to clinical remission, relapse, or risk assessment after kidney transplantation.

Reference Values:
Only orderable as part of a profile. For more information see PMND1 / Primary Membranous Nephropathy Diagnostic Cascade, Serum.

<14 RU/mL: Negative
14 to 19 RU/mL: Borderline
> or =20 RU/mL: Positive

Clinical References: 1. Beck LH Jr, Bonegio RGB, Lambeau G, et al: M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009 Jul 2;361(1):11-21 2. Schlumberger W, Hornig N, Lange S, et al: Differential diagnosis of membranous nephropathy with autoantibodies to phospholipase A2 receptor 1. Autoimmun Rev. 2014 Feb;13(2)108-113

PLA2I 607367 Phospholipase A2 Receptor, Immunofluorescence, Serum

Clinical Information: Membranous nephropathy (MN) is a rare disease in which immune complexes deposit at the glomerular basement membrane, causing damage to the filtration barrier, resulting in proteinuria. Recent studies have shown that in approximately 70% of patients with primary MN (pMN), the immune complexes consist of autoantibodies against the podocyte protein M-type phospholipase A2 receptor (PLA2R).(1) There is also evidence that levels of anti-PLA2R autoantibodies correlate well with disease activity and progression.(2) The presence of anti-PLA2R antibodies could also potentially be used to differentiate pMN from other causes of nephrotic syndrome if a biopsy is not possible. Among patients with chronic kidney disease (CKD) awaiting kidney transplantation, higher levels of anti-PLA2R could predict those more likely to recur after transplantation.(2) Mayo Clinic Laboratory data suggest that there is a high concordance between the enzyme-linked immunosorbent assay and indirect immunofluorescence assay (IFA) PLA2R results, although the IFA may be more sensitive in monitoring patients with membranous nephropathy with very low antibody titers.

Useful For: Distinguishing primary from secondary membranous nephropathy in patients with low levels of anti-phospholipase A2 receptor (PLA2R) antibodies Screening for anti-PLA2R antibodies Monitoring patients with membranous nephropathy at very low antibody titers

Interpretation: According to the manufacturer's package insert, the EUROIMMUN Anti-PLA2R indirect immunofluorescence assay was positive in 77.1% of patients with biopsy proven primary membranous nephropathy (pMN). This corresponds well with published literature that approximately 70% of patients with pMN will have anti-phospholipase A2 receptor antibodies.

Reference Values:
Negative

Clinical References: 1. Beck L, Bonegio R, Lambeau G, et al: M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;361:11-21 2. Schlumberger W, Hornig N, Lange S, et al: Differential diagnosis of membranous nephropathy with autoantibodies to phospholipase A2 receptor 1. Autoimmun Rev. 2014 Feb;13(2):108-113

PLA2M 607366 Phospholipase A2 Receptor, Monitoring, Enzyme-Linked Immunosorbent Assay, Serum

Clinical Information: Membranous nephropathy (MN) is a rare disease in which immune complexes deposit at the glomerular basement membrane, causing damage to the filtration barrier, resulting in proteinuria. Recent studies have shown that in approximately 70% of patients with primary MN (pMN), the immune complexes consist of autoantibodies against the podocyte protein M-type

phospholipase A2 receptor (PLA2R).(1) There is also evidence that levels of anti-PLA2R autoantibodies correlate well with disease activity and progression.(2) The presence of anti-PLA2R antibodies could also potentially be used to differentiate pMN from other causes of nephrotic syndrome if a biopsy is not possible. Among patients with chronic kidney disease awaiting kidney transplantation, higher levels of anti-PLA2R could predict those more likely to recur after transplantation.(2) Mayo Clinic Laboratories data suggests high concordance between the enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence assay PLA2R results; however, the ELISA assay alone may be preferred for monitoring patients with membranous nephropathy over time for trends in anti-PLA2R antibody levels.

Useful For: Distinguishing primary from secondary membranous nephropathy Monitoring patients with membranous nephropathy, over time, for trends in anti-phospholipase A2 receptor antibody levels

Interpretation: Therapy outcome can be monitored by measuring the anti-phospholipase A2 receptor antibody titer. A titer increase, decrease, or disappearance generally precedes a change in clinical status. Thus, the determination of the antibody titer has a high predictive value with respect to clinical remission, relapse, or risk assessment after kidney transplantation.

Reference Values:
<14 RU/mL: Negative
14 to 19 RU/mL: Borderline
> or =20 RU/mL: Positive

Clinical References: 1. Beck Lh Jr, Bonegio RGB, Lambeau G, et al: M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009 Jul 2;361(1):11-21 2. Schlumberger W, Hornig N, Lange S, et al: Differential diagnosis of membranous nephropathy with autoantibodies to phospholipase A2 receptor 1. Autoimmun Rev. 2014 Feb;13(2)108-113

ACLIP
86179

Phospholipid (Cardiolipin) Antibodies, IgA, Serum

Clinical Information: Antiphospholipid syndrome (APS) has traditionally been described as a systemic autoimmune disease characterized by thrombosis and/or specific pregnancy-related morbidities associated with persistent documentation of "criterial" antiphospholipid antibody (aPL) tests.(1,2) Based on the 2006 revised Sapporo consensus classification, the "criterial" aPL antibody tests include lupus anticoagulant (LAC) and IgG/IgM antibodies to the cardiolipin and beta2-glyocoprotein I (anti-B2 GPI) with all tests carrying equal diagnostic significance for disease.(1) In 2023, the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) published new classification criteria for APS that includes an entry criterion of at least one positive aPL antibody test within 3 years of identification of an aPL-associated clinical criterion, followed by additive weighted criteria (score range 1-7 points each) clustered into 6 clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and 2 laboratory domains (LAC functional coagulation assays, and solid-phase enzyme-linked immunosorbent assays for IgG/IgM aCL and/or IgG/IgM anti-B2 GPI).(3) Of note, aPL antibodies also occur in patients with autoimmune diseases with significant prevalence in systemic lupus erythematosus (SLE) as well as other clinical manifestations (eg, heart valve disease, livedo reticularis, thrombocytopenia, nephropathy and neurological) often associated with APS.(1-3) Thus, in addition to the 2023 APS classification criteria, the 2012 derivation and validation of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE recommends testing for the criteria aPL antibody tests as well as aCL IgA and anti-B2GPI IgA.(4) Unlike LAC, which is evaluated using functional assays, diverse solid-phase immunoassays, such as enzyme-linked immunosorbent assay, multiplex bead assay, chemiluminescent immunoassay, and fluorescence enzyme immunoassay are used in the clinical laboratories for the detection and measurement of aCL and anti-B2GPI IgA, IgG, and IgM antibodies.(5,6) For aCL IgG and IgM determinations, the APS classification guidance recommends

antibody cutoff values greater than 40 IgG phospholipid (GPL) or IgM phospholipid (MPL) units (units traceable to the Harris standards for aCL antibody assays) or more than the 99th percentile for the testing laboratory's population for positivity. It also advocates for the use of values greater than the 99th percentile for the laboratory's population in the establishment of reference intervals for anti-B2GPI IgG and IgM antibody tests.(1) The use of cutoff values greater than 40 GPL or MPL units to define positivity is not be applicable to all aCL antibody immunoassays, as the threshold used to distinguish moderate-to-high positive from low positive results are test dependent.(6-8) In addition, the cutoff used at the 99th percentile of a laboratory's testing population may not be consistent with kits from the same manufacturer or 40 GPL units, in the case of aCL antibodies.(2,6-8) The 2023 ACR/EULAR classification criteria for APS are meant for clinical studies and may not be appropriate for routine patient evaluation and management. Therefore, in clinical practice, if suspicion for disease is high but criteria aPL antibody tests are inconclusive or negative, deviation from the APS classification criteria may be justified. This may include testing for noncriteria aPL antibody tests such the aCL IgA and anti-B2GPI IgA recommended in 2012 SLICC guidance for SLE or evaluation of other noncriteria aPL antibody tests.(4-6,9,10) However, there is no formal guidance for the measurement and interpretation of aCL and anti-B2GPI IgA antibodies in patients with APS or SLE. Some clinical relevance between APS-related clinical symptoms and the presence of aCL/anti-B2GPI IgA have been reported, however, the added value is minimal.(10,11) Isolated aPL IgA is rare, and these antibodies are usually found in association with IgG and/or IgM.

Useful For: May be of diagnostic significance for patients at risk for antiphospholipid syndrome or systemic lupus erythematosus who test negative for criterial antiphospholipid antibodies

Interpretation: The presence of anticardiolipin (aCL) IgA antibodies (greater than 15 IgA phospholipid units [APL]) may be associated with a diagnosis of antiphospholipid syndrome (APS) and/or systemic lupus erythematosus (SLE). In the absence "criteria" aPL antibodies for APS and diagnostic tests for SLE, isolated aCL IgA must be interpreted with a high degree of caution. Documentation of persistence aCL IgA as is the case for criteria aCL IgG and IgM antibodies would be consistent with best clinical practice. Detection of anticardiolipin antibodies using the method is not affected by anticoagulant treatment.

Reference Values:
APL refers to IgA phospholipid units. One APL unit is 1 microgram of IgA antibody.

Negative: <15.0 APL
Weakly positive: 15.0-39.9 APL
Positive: 40.0-79.9 APL
Strongly positive: > or =80.0 APL

Reference values apply to all ages.

Clinical References:

CLPMG
82976

Phospholipid (Cardiolipin) Antibodies, IgG and IgM, Serum

Clinical Information: Antiphospholipid syndrome (APS) has traditionally been described as a systemic autoimmune disease characterized by thrombosis and/or specific pregnancy-related morbidities associated with persistent documentation of "criterial" antiphospholipid antibody (aPL) tests.(1,2) Based on the 2006 revised Sapporo consensus classification, the "criterial" aPL antibody tests include lupus anticoagulant (LAC) and IgG/IgM antibodies to the cardiolipin (aCL) and beta2-glyocoprotein I (anti-B2GPI) with all tests carrying equal diagnostic significance for disease.(1) In 2023, the American College of Rheumatology (ACR)/European League Against Rheumatism

(EULAR) published new classification criteria for APS that includes an entry criterion of at least one positive aPL antibody test within 3 years of identification of an aPL-associated clinical criterion, followed by additive weighted criteria (score range 1-7 points each) clustered into 6 clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and 2 laboratory domains (LAC functional coagulation assays and solid-phase enzyme-linked immunosorbent assays (ELISA) for IgG/IgM aCL and/or IgG/IgM anti-B2GPI).(3) Unlike LAC, which is evaluated using functional assays, diverse solid-phase immunoassays such as ELISA, multiplex bead assay, chemiluminescent immunoassay, and fluorescence enzyme immunoassay are used in the clinical laboratories for the detection and measurement of aCL and anti-B2GPI IgA, IgG, and IgM antibodies.(4,5) For aCL IgG and IgM determinations, the APS classification guidance recommends antibody cutoff values greater than 40 IgG phospholipid (GPL) or IgM phospholipid (MPL) units (units traceable to the Harris standards for aCL antibody assays) or more than the 99th percentile for the testing laboratory's population for positivity. It also advocates for the use of values greater than the 99th percentile for the laboratory's population in the establishment of reference intervals for anti-B2GPI IgG and IgM antibody tests.(1) The use of cutoff values greater than 40 GPL or MPL units to define positivity is not be applicable to all aCL antibody immunoassays, as the threshold used to distinguish moderate-to-high positive from low positive results are test dependent.(5-7) In addition, the cutoff used at the 99th percentile of a laboratory's testing population may not be consistent with kits from the same manufacturer or 40 GPL units, in the case of aCL antibodies.(2,5-7) Early observations that aCL antibody determinations made in the presence of B2GPI were more specific for APS led to the recommendation of B2GPI-dependent cardiolipin ELISA for APS evaluation.(1,8) Cardiolipin is a negatively charged phospholipid capable of binding diverse proteins, of which B2GP1 is one of the best characterized in APS. B2GP1 is a 326-amino acid protein that contains five repetitive structures or "sushi domains," termed domain 1 through 5, for a combined molecular weight of 54 kDa for the protein.(8). Anti-B2GP1 antibodies associated with thromboembolic events target domain 1 of the molecule and are responsible for LAC (functional, phospholipid-dependent prolongation of the clotting time) and aCL antibody positivity.(2) Compared to LAC and anti-B2GPI IgG antibodies, aCL IgG antibodies are less specific but sensitive for the diagnosis of APS. Of the aCL IgG and IgM, the IgG and not IgM confers higher diagnostic relevance and risk for definite APS.(3,6,7) Thrombosis and obstetric complications are common clinical events in the general population and are not unique to APS; therefore, the presence of aPL antibodies is an absolute requirement for the diagnosis of definite APS.(1,2,6) Furthermore, aPL antibodies are heterogeneous with overlapping tendencies; the lack of aPL test harmonization or standardization requires the use of all three tests for optimal APS diagnosis.(1,3) The aPL antibodies were traditionally determined using classic ELISA, with more diverse methods recently developed and adapted for clinical testing. Recognizing the analytical and diagnostic challenges associated with aPL antibody testing, initiatives to support assay harmonization and utilization, including the development of calibrators, test development, and validation efforts as well as preanalytical, analytical, and postanalytical measures have been published.(2,4,5,7) Based on these and other published studies, the interpretation and relevance of aPL antibody tests are dependent on factors such as the type of aPL (LAC, aCL or anti-B2GPI), the source of cardiolipin and/or B2GPI, aPL antibody class (IgG, IgM, or IgA) and level as well as whether antibody positivity is single, double, or triple.(1-7) The 2023 ACR/EULAR classification criteria for APS are meant for clinical studies and may not be appropriate for routine patient evaluation and management. Therefore, in clinical practice, if suspicion for disease is high but criteria aPL antibody tests are inconclusive or negative, deviation from the APS diagnostic criteria may be justified. This may include testing for noncriteria aPL antibody tests such the aCL IgA, anti-beta2GPI IgA and anti-phosphatidylserine/prothrombin complex IgG and IgM antibodies.(2,5,9,10) However, there is no formal guidance for the measurement and interpretation of these noncriteria aPL antibodies in patients with APS or systemic lupus erythematosus.

Useful For: The following clinical situations: -Unexplained arterial or venous thrombosis -A history of pregnancy morbidity defined as 1 or more unexplained deaths of a morphologically normal fetus beyond the 10th week of gestation, 1 or more premature births before 34 weeks of gestation caused by severe preeclampsia or placental insufficiency, or 3 or more unexplained, consecutive spontaneous abortions before the 10th week of gestation with no identifiable maternal hormonal or anatomic, or maternal or

paternal chromosomal causes -Presence of a systemic autoimmune rheumatic disease especially systemic lupus erythematosus -Presence of an unexplained cutaneous manifestations varying from livedo reticularis to cutaneous necrosis such as leg ulcers -Unexplained thrombocytopenia -Possible nonbacterial, thrombotic endocarditis

Interpretation: Moderate-to-strong positive results for anticardiolipin (aCL) IgG or IgM antibodies (> or =40 IgG phospholipid [GPL] or IgM phospholipid [MPL] units) in association with specific clinical manifestations may be diagnostic for antiphospholipid syndrome (APS). Low levels of aCL IgG or IgM antibodies, especially in the absence of other criteria phospholipid (aPL) antibodies should be interpreted with a high degree of suspicion. Compared to aCL IgG, low and isolated levels aCL IgM antibodies have a very low risk for APS and should be interpreted with a high degree of suspicion. Documentation of persistent aCL IgG and IgM antibodies is a requirement for the diagnosis of definite APS. Antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of beta-2 glycoprotein 1 antibodies using the enzyme-linked immunosorbent method or other solid-phase immunoassays is not affected by anticoagulant treatment.

Reference Values:

MPL refers to IgM phospholipid units. One MPL unit is 1 microgram of IgM antibody.
GPL refers to IgG phospholipid units. One GPL unit is 1 microgram of IgG antibody.

Negative: <15.0 MPL or GPL
Weakly positive: 15.0-39.9 MPL or GPL
Positive: 40.0-79.9 MPL or GPL
Strongly positive: > or =80.0 MPL or GPL

Reference values apply to all ages.

Clinical References:

GCLIP
80993

Phospholipid (Cardiolipin) Antibodies, IgG, Serum

Clinical Information: Antiphospholipid syndrome (APS) has traditionally been described as a systemic autoimmune disease characterized by thrombosis and/or specific pregnancy-related morbidities associated with persistent documentation of "criterial" antiphospholipid antibody (aPL) tests.(1,2) Based on the 2006 revised Sapporo consensus classification, the "criterial" aPL antibody tests include lupus anticoagulant (LAC) and IgG/IgM antibodies to the cardiolipin and beta2-glyocoprotein I (anti-B2GPI) with all tests carrying equal diagnostic significance for disease.(1) In 2023, the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) published new classification criteria for APS that includes an entry criterion of at least one positive aPL antibody test within 3 years of identification of an aPL-associated clinical criterion, followed by additive weighted criteria (score range 1-7 points each) clustered into 6 clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and 2 laboratory domains (LAC functional coagulation assays, and solid-phase enzyme-linked immunosorbent assays (ELISA) for IgG/IgM aCL and/or IgG/IgM anti-beta 2GPI).(3) Unlike LAC, which is evaluated using functional assays, diverse solid-phase immunoassays (SPA) such as ELISA, multiplex bead assay, chemiluminescent immunoassay, and fluorescence enzyme immunoassay are used in the clinical laboratories for the detection and measurement of aCL and anti-B2GPI IgA, IgG, and IgM antibodies.(4,5) For aCL IgG and IgM determinations, the APS classification guidance recommends antibody cutoff values greater than 40 IgG phospholipid (GPL) or IgM phospholipid (MPL) units (units traceable to the Harris standards for aCL antibody assays) or more than the 99th percentile for the testing laboratory's population for positivity. It also advocates for the use of values

greater than the 99th percentile for the laboratory's population in the establishment of reference intervals for anti-B2GPI IgG and IgM antibody tests.(1) The use of cutoff values greater than 40 GPL or MPL units to define positivity is not be applicable to all aCL antibody immunoassays, as the threshold used to distinguish moderate-to-high positive from low positive results are test dependent.(5-7) In addition, the cutoff used at the 99th percentile of a laboratory's testing population may not be consistent with kits from the same manufacturer or 40 GPL units, in the case of aCL antibodies.(2,5-7) Early observations that aCL antibody determinations made in the presence of B2GPI were more specific for APS led to the recommendation of B2GPI-dependent cardiolipin ELISA for APS evaluation.(1,8) Cardiolipin is a negatively charged phospholipid (PL) capable of binding diverse proteins, of which B2GP1 is one of the best characterized in APS. B2GP1 is a 326-amino acid protein that contains five repetitive structures or "sushi domains," termed domain 1 through 5, for a combined molecular weight of 54 kDa for the protein.(8). Anti-B2GP1 antibodies associated with thromboembolic events target domain 1 of the molecule and are responsible for LAC (functional, phospholipid-dependent prolongation of the clotting time) and aCL antibody positivity.(2) Compared to LAC and anti-B2GPI IgG antibodies, aCL IgG antibodies are less specific but sensitive for the diagnosis of APS. Of the aCL IgG and IgM, the IgG and not IgM confers higher diagnostic relevance and risk for definite APS.(1-3,6) Thrombosis and obstetric complications are common clinical events in the general population and are not unique to APS; therefore, the presence of aPL antibodies is an absolute requirement for the diagnosis of definite APS.(1,2,6) Furthermore, aPL antibodies are heterogeneous with overlapping tendencies; the lack of aPL test harmonization or standardization requires the use of all three tests for optimal APS diagnosis.(1,3) The aPL antibodies were traditionally determined using classic ELISA, with more diverse methods recently developed and adapted for clinical testing. Recognizing the analytical and diagnostic challenges associated with aPL antibody testing, initiatives to support assay harmonization and utilization, including the development of calibrators, test development, and validation efforts as well as preanalytical, analytical, and postanalytical measures have been published. (2,4,5,7) Based on these and other published studies, the interpretation and relevance of aPL antibody tests are dependent on factors such as the type of aPL (LAC, aCL or anti-B2GPI), the source of cardiolipin and/or B2GPI, aPL antibody class (IgG, IgM, or IgA) and level as well as whether antibody positivity is single, double, or triple.(1-7) The 2023 ACR/EULAR classification criteria for APS are meant for clinical studies and may not be appropriate for routine patient evaluation and management. Therefore, in clinical practice, if suspicion for disease is high but criteria aPL antibody tests are inconclusive or negative, deviation from the APS diagnostic criteria may be justified. This may include testing for noncriteria aPL antibody tests such the aCL IgA, anti-beta2 GPI IgA and anti-phosphatidylserine/prothrombin complex IgG and IgM antibodies.(2,5,9,10) However, there is no formal guidance for the measurement and interpretation of these noncriteria aPL antibodies in patients with APS and/or SLE.

Useful For: The following clinical situations, when used in conjunction with other criterial antiphospholipid antibody tests: -Unexplained arterial or venous thrombosis -A history of pregnancy morbidity defined as 1 or more unexplained deaths of a morphologically normal fetus beyond the 10th week of gestation, 1 or more premature births before 34 weeks of gestation caused by severe preeclampsia or placental insufficiency, or 3 or more unexplained, consecutive spontaneous abortions before the 10th week of gestation with no identifiable maternal hormonal or anatomic, or maternal or paternal chromosomal causes -Presence of a systemic autoimmune rheumatic disease especially systemic lupus erythematosus -Presence of an unexplained cutaneous manifestations varying from livedo reticularis to cutaneous necrosis such as leg ulcers -Unexplained thrombocytopenia -Possible nonbacterial, thrombotic endocarditis

Interpretation: Moderate-to-strong positive results for anticardiolipin (aCL) IgG antibodies (> or =40 IgG phospholipid units) in association with specific clinical manifestations may be diagnostic for antiphospholipid syndrome (APS). Low levels of aCL IgG antibodies, especially in the absence of other criteria antiphospholipid antibodies should be interpreted with a high degree of suspicion. Documentation of persistent aCL IgG antibodies is a requirement for the diagnosis of definite APS. Antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of aCL antibodies using the enzyme-linked immunosorbent assay method or other solid-

phase immunoassays is not affected by anticoagulant treatment.

Reference Values:
GPL refers to IgG phospholipid units. One GPL unit is 1 microgram of IgG antibody.

Negative: <15.0 GPL)
Weakly positive: 15.0-39.9 GPL
Positive: 40.0-79.9 GPL
Strongly positive: > or =80.0 GPL

Reference values apply to all ages.

Clinical References:

MCLIP 81900 Phospholipid (Cardiolipin) Antibodies, IgM, Serum

Clinical Information: Antiphospholipid syndrome (APS) has traditionally been described as a systemic autoimmune disease characterized by thrombosis and/or specific pregnancy-related morbidities associated with persistent documentation of "criterial" antiphospholipid antibody (aPL) tests.(1,2) Based on the 2006 revised Sapporo consensus classification, the "criterial" aPL antibody tests include lupus anticoagulant (LAC) and IgG/IgM antibodies to the cardiolipin (aCL) and beta2-glyocoprotein I (anti-B2GPI) with all tests carrying equal diagnostic significance for disease.(1) In 2023, the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) published new classification criteria for APS that includes an entry criterion of at least one positive aPL antibody test within 3 years of identification of an aPL-associated clinical criterion, followed by additive weighted criteria (score range 1-7 points each) clustered into 6 clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and 2 laboratory domains (LAC functional coagulation assays, and solid-phase enzyme-linked immunosorbent assays (ELISA) for IgG/IgM aCL and/or IgG/IgM anti-B2GPI).(3) Unlike LAC, which is evaluated using functional assays, diverse solid-phase immunoassays (SPA) such as ELISA, multiplex bead assay, chemiluminescent immunoassay, and fluorescence enzyme immunoassay are used in the clinical laboratories for the detection and measurement of aCL and anti-B2GPI IgA, IgG, and IgM antibodies.(4,5) For aCL IgG and IgM determinations, the APS classification guidance recommends antibody cut-off values greater than 40 IgG phospholipid (GPL) or IgM phospholipid (MPL) units (units traceable to the Harris standards for aCL antibody assays) or more than the 99th percentile for the testing laboratory's population for positivity. It also advocates for the use of values greater than the 99th percentile for the laboratory's population in the establishment of reference intervals for anti-B2GPI IgG and IgM antibody tests.(1) The use of cutoff values greater than 40 GPL or MPL units to define positivity is not be applicable to all aCL antibody immunoassays, as the threshold used to distinguish moderate-to-high positive from low positive results are test dependent.(5-7) In addition, the cutoff used at the 99th percentile of a laboratory's testing population may not be consistent with kits from the same manufacturer or 40 GPL units, in the case of aCL antibodies.(2,5-7) Early observations that aCL antibody determinations made in the presence of B2GPI were more specific for APS led to the recommendation of B2GPI-dependent cardiolipin ELISA for APS evaluation.(1,8) Cardiolipin is a negatively charged phospholipid (PL) capable of binding diverse proteins, of which B2GP1 is one of the best characterized in APS. B2GP1 is a 326-amino acid protein that contains five repetitive structures or "sushi domains," termed domain 1 through 5, for a combined molecular weight of 54 kDa for the protein.(8) Anti-B2GP1 antibodies associated with thromboembolic events target domain 1 of the molecule and are responsible for LAC (functional, phospholipid-dependent prolongation of the clotting time) and aCL antibody positivity.(2) Compared to LAC and anti-B2GPI IgG antibodies, aCL IgG antibodies are less specific but sensitive for the diagnosis of APS. Of the aCL IgG and IgM, the IgG and not IgM confers higher diagnostic relevance and risk for definite APS.(1,3,6,7) Thrombosis and obstetric complications are common clinical events in the general

population and are not unique to APS; therefore, the presence of aPL antibodies is an absolute requirement for the diagnosis of definite APS.(1,2,6) Furthermore, aPL antibodies are heterogeneous with overlapping tendencies; the lack of aPL test harmonization or standardization requires the use of all three tests for optimal APS diagnosis.(1,3) The aPL antibodies were traditionally determined using classic ELISA, with more diverse methods recently developed and adapted for clinical testing. Recognizing the analytical and diagnostic challenges associated with aPL antibody testing, initiatives to support assay harmonization and utilization, including the development of calibrators, test development, and validation efforts as well as preanalytical, analytical, and postanalytical measures have been published. (2,4,5,7) Based on these and other published studies, the interpretation and relevance of aPL antibody tests are dependent on factors such as the type of aPL (LAC, aCL or anti-B2GPI), the source of cardiolipin and/or B2GPI, aPL antibody class (IgG, IgM, or IgA) and level as well as whether antibody positivity is single, double, or triple.(1,7) The 2023 ACR/EULAR classification criteria for APS are meant for clinical studies and may not be appropriate for routine patient evaluation and management. Therefore, in clinical practice, if suspicion for disease is high but criteria aPL antibody tests are inconclusive or negative, deviation from the APS diagnostic criteria may be justified. This may include testing for noncriteria aPL antibody tests such the aCL IgA, anti-B2GPI IgA and anti-phosphatidylserine/prothrombin complex IgG and IgM antibodies.(2,5,9,10) However, there is no formal guidance for the measurement and interpretation of these noncriteria aPL antibodies in patients with APS or SLE.

Useful For: The following clinical situations, when used in conjunction with other criterial antiphospholipid antibody tests: -Unexplained arterial or venous thrombosis -A history of pregnancy morbidity defined as 1 or more unexplained deaths of a morphologically normal fetus beyond the 10th week of gestation, 1 or more premature births before 34 weeks of gestation caused by severe preeclampsia or placental insufficiency, or 3 or more unexplained, consecutive spontaneous abortions before the 10th week of gestation with no identifiable maternal hormonal or anatomic, or maternal or paternal chromosomal causes -Presence of a systemic autoimmune rheumatic disease, especially systemic lupus erythematosus -Unexplained thrombocytopenia -Presence of an unexplained cutaneous manifestations varying from livedo reticularis to cutaneous necrosis, such as leg ulcers -Possible nonbacterial, thrombotic endocarditis

Interpretation: Moderate-to-strong positive results for anticardiolipin (aCL) IgM antibodies (> or =40 IgM phospholipid [MPL] units) are a diagnostic criterion for antiphospholipid syndrome (APS). Compared to aCL IgG, isolated and low levels aCL IgM antibodies have a very low risk for APS and should be interpreted with a high degree of suspicion. Documentation of persistent aCL IgM antibodies is a requirement for the diagnosis of definite APS. Antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of anticardiolipin antibodies using the enzyme-linked immunosorbent assay or other solid-phase immunoassays is not affected by anticoagulant treatment.

Reference Values:
MPL refers to IgM phospholipid units. One MPL unit is 1 microgram of IgM antibody.

Negative: <15.0 MPL)
Weakly positive: 15.0-39.9 MPL
Positive: 40.0-79.9 MPL
Strongly positive:> or =80.0 MPL

Reference values apply to all ages.

Clinical References:

PMMIL 89656 Phosphomannomutase and Phosphomannose Isomerase,

Leukocytes

Clinical Information:

Useful For: Diagnosing congenital disorders of glycosylation Ia (phosphomannomutase-2 deficiency: PMM2-CDG) and Ib (phosphomannose isomerase deficiency: MPI-CDG) as measured in leukocytes Follow-up testing for patients with an abnormal type I CDG transferrin isoform profile This test is not useful for carrier testing.

Interpretation: Normal results are not consistent with either phosphomannomutase-2 deficiency (PMM2-CDG) or phosphomannose isomerase deficiency (MPI-CDG). Markedly reduced activity of phosphomannomutase is consistent with a diagnosis of PMM2-CDG. Markedly reduced activity of phosphomannose isomerase is consistent with a diagnosis of MPI-CDG. Mild to moderately reduced enzyme activities will be interpreted in the context of clinical and other laboratory test information submitted with the specimen.

Reference Values:

PHOSPHOMANNOMUTASE
Normal >350 nmol/h/mg protein

PHOSPHOMANNOSE ISOMERASE
Normal >1,300 nmol/h/mg protein

Clinical References: 1. Grunewald S, Schollen E, Van Schaftingen E, Jaeken J, Matthijs G. High residual activity of PMM2 in patients' fibroblasts: possible pitfall in the diagnosis of CDG-Ia (phosphomannomutase deficiency). Am J Hum Genet. 2001;68(2):347-354 2. Pirard M, Matthijs G, Heykants L, et al. Effect of mutations found in carbohydrate-deficient glycoprotein syndrome type IA on the activity of phosphomannomutase 2. FEBS Lett. 1999;452(3):319-322 3. Lam C, Krasnewich DM. PMM2-CDG. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2005. Updated May 20, 2021. Accessed January 19, 2024. Available at: www.ncbi.nlm.nih.gov/books/NBK1110/ 4. Schiff M, Roda C, Monin ML, et al. Clinical, laboratory and molecular findings and long-term follow-up data in 96 French patients with PMM2-CDG (phosphomannomutase 2-congenital disorder of glycosylation) and review of the literature. J Med Genet. 2017;54(12):843-851 5. Girard M, Douillard C, Debray D, et al. Long term outcome of MPI-CDG patients on D-mannose therapy. J Inherit Metab Dis. 2020;43(6):1360-1369 6. Jaeken J, Matthijs G, Carchon H, Van Schaftingen E. Defects of N-glycan synthesis. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed January 19, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225081470

PHOS
8408

Phosphorus (Inorganic), Serum

Clinical Information: Of the phosphorus contained in the body, 88% is localized in bone in the form of hydroxyapatite. The remainder is utilized during intermediary carbohydrate metabolism and bound to physiologically important substances such as phospholipids, nucleic acids, and adenosine triphosphate (ATP). Phosphorus exists in blood in the form of inorganic phosphate and organically bound phosphoric acid. The small amount of extracellular organic phosphorus is found exclusively in the form of phospholipids. Serum contains approximately 2.5 to 4.5 mg/dL of inorganic phosphate (the fraction measure in routine biochemical assays). Serum phosphate concentrations are dependent on dietary intake and regulation by hormones such as parathyroid hormone (PTH) and 1,25 vitamin D, and systemic acid base status and may vary widely. Hypophosphatemia may have 4 general causes: shift of phosphate from extracellular to intracellular, renal phosphate wasting, loss from the gastrointestinal

tract, and loss from intracellular stores. Hyperphosphatemia is usually secondary to an inability of the kidneys to excrete phosphate and is common in patients with chronic kidney disease stage 4 or greater. Acute hyperphosphatemia can occur as a result of tissue breakdown such as rhabdomyolysis. Other possible contributory factors are increased intake, especially in combination with chronic kidney disease, or a shift of phosphate from tissues into the extracellular fluid.

Useful For: Diagnosis and management of a variety of disorders including bone, parathyroid, and kidney disease

Interpretation: Hypophosphatemia is relatively common in hospitalized patients. Serum concentrations of phosphate between 1.5 and 2.4 mg/dL may be considered moderately decreased and are not usually associated with clinical signs and symptoms. Levels below 1.5 mg/dL may result in muscle weakness, hemolysis of red cells, coma, bone deformity, and impaired growth. The most acute problem associated with rapid elevations of serum phosphate levels is hypocalcemia with tetany, seizures, and hypotension. Soft tissue calcification is also an important long-term effect of high phosphorus levels. Phosphorus levels below 1.0 mg/dL are potentially life-threatening and are considered a critical value in the Mayo Health System.

Reference Values:

Males
1-4 years: 4.3-5.4 mg/dL
5-13 years: 3.7-5.4 mg/dL
14-15 years: 3.5-5.3 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL
Reference values have not been established for patients that are less than 12 months of age.

Females
1-7 years: 4.3-5.4 mg/dL
8-13 years: 4.0-5.2 mg/dL
14-15 years: 3.5-4.9 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL
Reference values have not been established for patients that are less than 12 months of age.

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1280-1283 2. Agarwal R, Knochel JP: Hypophosphatemia and hyperphosphatemia. In: Brenner BM, ed. The Kidney. 6th ed. WB Saunders Company; 2000:1071-1125 3. Yu GC, Lee DBN: Clinical disorders of phosphorus metabolism. West J Med. 1987 Nov;147(5):569-576 4. Koumakis E, Cormier C, Roux C, Briot K: The causes of hypo- and hyperphosphatemia in humans. Calcif Tissue Int. 2021 Jan;108(1):41-73. doi: 10.1007/s00223-020-00664-9

POU
610832

Phosphorus, 24 Hour, Urine

Clinical Information: Approximately 80% of filtered phosphorus is reabsorbed by renal proximal tubule cells. The regulation of urinary phosphorus excretion is principally dependent on regulation of proximal tubule phosphorus reabsorption. A variety of factors influence renal tubular phosphate reabsorption and consequent urine excretion. Factors that increase urinary phosphorus excretion include high phosphorus diet, parathyroid hormone, extracellular volume expansion, low dietary potassium intake, and proximal tubule defects (eg, Fanconi Syndrome, X-linked hypophosphatemic Rickets, tumor-induced osteomalacia). Factors that decrease, or are associated with decreases in, urinary phosphorus excretion include low dietary phosphorus intake, insulin, high dietary potassium intake, and decreased

intestinal absorption of phosphorus (eg, phosphate-binding antacids, vitamin D deficiency, malabsorption states). A renal leak of phosphate has also been implicated as contributing to kidney stone formation in some patients.

Useful For: Evaluation of hypo- or hyper-phosphatemic states Evaluation of patients with nephrolithiasis

Interpretation: Interpretation of urinary phosphorus excretion is dependent upon the clinical situation, and should be interpreted in conjunction with the serum phosphorus concentration.

Reference Values:
> or =18 years: 226-1,797 mg/24 hours
Reference values have not been established for patients who are less than 18 years of age.

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1280-1283 2. Agarwal R, Knochel JP: Hypophosphatemia and hyperphosphatemia. In: Brenner BM, ed. The Kidney. 6th ed. WB Saunders Company; 2000:1071-1125

POU_F
606757

Phosphorus, Feces

Clinical Information: The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors: -Normal daily dietary intake of electrolytes -Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure -Electrolyte transport into fecal water due to exogenous substances and rare toxins (eg, cholera toxin) Fecal osmolality is normally in equilibrium with vascular osmolality, and sodium is the major effector of this equilibrium. Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or drugs inducing secretions, such as phenolphthalein or bisacodyl. Osmotic diarrhea is caused by ingestion of poorly absorbed ions or sugars.(1) There are multiple potential causes of osmotic diarrhea. Measurement of phosphate and/or magnesium in liquid stool can assist in identifying intentional or inadvertent use of magnesium and/or phosphate-containing laxatives as the cause.(2-4) The other causes of osmotic diarrhea include ingestion of osmotic agents such as sorbitol or polyethylene glycol laxatives, or carbohydrate malabsorption due most commonly to lactose intolerance. Carbohydrate malabsorption can be differentiated from other osmotic causes by a low stool pH (<6).(5,6) Non-osmotic causes of diarrhea include bile acid malabsorption, inflammatory bowel disease, endocrine tumors, and neoplasia.(1) Secretory diarrhea is classified as non-osmotic and is caused by disruption of epithelial electrolyte transport when secretory agents such as anthraquinones, phenolphthalein, bisacodyl, or cholera toxin are present. The fecal fluid usually has elevated electrolytes (primarily sodium and chloride) and a low osmotic gap (<50 mOsm/kg). Infection is a common secretory process; however, it does not typically cause chronic diarrhea (defined as symptoms >4 weeks).

Useful For: Workup of cases of chronic diarrhea Identifying the use of phosphate-containing laxatives contributing to osmotic diarrhea

Interpretation: Phosphorus elevation above 102 mg/dL is suggestive of phosphate-induced diarrhea.(4)

Reference Values:
An interpretive report will be provided

Clinical References: 1. Steffer KJ, Santa Ana CA, Cole JA, Fordtran JS: The practical value of comprehensive stool analysis in detecting the cause of idiopathic chronic diarrhea. Gastroenterol Clin North Am. 2012;41:539-560 2. Ho J, Moyer TP, Phillips SF: Chronic diarrhea: the role of magnesium. Mayo Clin Proc. 1995;70:1091-1092 3. Fine KD, Santa Ana CA, Fordtran JS: Diagnosis of magnesium-induced diarrhea. N Engl J Med. 1991;324:1012-1017 4. Fine KD, Ogunji F, Florio R, Porter J, Ana CS: Investigation and diagnosis of diarrhea caused by sodium phosphate. Dig Dis Sci. 1998;43(12):2708-2714 5. Eherer AJ, Fordtran JS: Fecal osmotic gap and pH in experimental diarrhea of various causes. Gastroenterology. 1992;103:545-551 6. Casprary WF: Diarrhea associated with carbohydrate malabsorption. Clin Gastroenterol. 1986;15:631-655

RPHOC
610829

Phosphorus, Random, Urine

Clinical Information: Approximately 80% of filtered phosphorus is reabsorbed by renal proximal tubule cells. The regulation of urinary phosphorus excretion is principally dependent on regulation of proximal tubule phosphorus reabsorption. A variety of factors influence renal tubular phosphate reabsorption and consequent urine excretion. Factors that increase urinary phosphorus excretion include high phosphorus diet, parathyroid hormone, extracellular volume expansion, low dietary potassium intake, and proximal tubule defects (eg, Fanconi syndrome, X-linked hypophosphatemic rickets, tumor-induced osteomalacia). Factors that decrease, or are associated with decreases in, urinary phosphorus excretion include low dietary phosphorus intake, insulin, high dietary potassium intake, and decreased intestinal absorption of phosphorus (eg, phosphate-binding antacids, vitamin D deficiency, malabsorption states). A renal leak of phosphate has also been implicated as contributing to kidney stone formation in some patients. A timed 24-hour urine collection is the preferred specimen for measuring and interpreting this urinary analyte. Random collections normalized to urinary creatinine may be of some clinical use in patients who cannot collect a 24-hour specimen, typically small children.

Useful For: Evaluation of hypo- or hyperphosphatemic states Evaluation of patients with nephrolithiasis

Interpretation: Interpretation of urinary phosphorous excretion is dependent upon the clinical situation and should be interpreted in conjunction with the serum phosphorous concentration.

Reference Values:
No established reference values
Random urine phosphorus may be interpreted in conjunction with serum phosphorus, using both values to calculate fractional excretion of chloride.

The calculation for fractional excretion (FE) of phosphorus is
FE(P)= ([P(urine) X Creat(serum)]/[P(serum) X Creat(urine)])X100

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1280-1283 2. Matos V, van Melle G, Boulat O et al: Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. J Pediatr. 1997;131:252-257 3. Agarwal R, Knochel JP: Hypophosphatemia and hyperphosphatemia. In: Brenner BM, ed. The Kidney. 6th ed. WB Saunders Company; 2000:1071-1125

STAT3
622778

Phosphorylated STAT3 at Tyrosine 705 (pSTAT3-Y705), Technical Component Only

Clinical Information: Among all STAT (signal transducers and activators of transcription) proteins, STAT3 plays a central role in development and carcinogenesis through its tight regulation on the gene transcription involved in cell proliferation, differentiation, apoptosis, angiogenesis, immune responses, and metastasis. In anaplastic large cell lymphoma, gene expression profiling studies have identified two overarching molecular subtypes based on the presence (type I) or absence (type II) of JAK-STAT3 pathway activation. Immunohistochemistry for phosphorylated STAT3 expression can be used as a surrogate marker for subtyping in cases of anaplastic large cell lymphoma.

Useful For: Subclassification for anaplastic large cell lymphoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Xiong A, Yang Z, Shen Y, Zhou J, Shen Q. Transcription factor STAT3 as a novel molecular target for cancer [prevention. Cancers (Basel). 2014;6(2):926-957 2. Bromberg JF, Wrzeszczynska MH, Devgan G, et al. Stat3 as an oncogene [published correction appears in Cell 1999 Oct 15;99(2):239]. Cell. 1999;98(3):295-303 3. Yu H, Jove R. The STATs of cancer--new molecular targets come of age. Nat Rev Cancer. 2004;4(2):97-105 4. Luchtel R, Dasari S, Oishi N, et al. Molecular profiling reveals immunogenic cues in anaplastic large cell lymphomas with DUSP22 rearrangement. Blood. 2018;132(13):1386-1398 5. Feldman A, Dasari S, Rimsza L, et al. Gene expression profiling reveals two overarching types of anaplastic large cell lymphoma with distinct targetable biology: An L.L.M.P.P. Study. Blood. 2023;142:847-849

PHTDP
71482

Phosphorylated TDP43 Immunostain, Technical Component Only

Clinical Information: TAR DNA-binding protein 43 (TDP-43) has multiple functions in transcriptional repression, translational regulation, and pre-mRNA splicing. In normal cells, TDP-43 is found in the nucleus, whereas in affected cells TDP-43 is phosphorylated and found in intracytoplasmic inclusions and neurites. The phosphoTDP-43-specific antibody will only stain the intracytoplasmic inclusions and neurites, thus highlighting the patterns that are hallmarks for amyotrophic lateral sclerosis and frontotemporal lobular degeneration.

Useful For: Identification of pathological forms of TDP-43 in neurodegenerative diseases

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

PAHD
82786

Phthalic Anhydride, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from

IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to phthalic anhydride Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CVSPC
72163

Physician Interpretation Conventional, Varies

Reference Values:
This is not an orderable test.

TPSPC
72162

Physician Interpretation Screen, Varies

Reference Values:
This test is for billing purposes only.

This is not an orderable test.

TPDPC
72129

Physician Interpretation, Diagnostic, Varies

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

PIGE
82781

Pig Epithelium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pig Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive

4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FPIGF
75555

Pigeon Feathers IgG

Clinical Information: Although there have been many publications concerning the measurement of allergen-specific IgG, the clinical utility of such tests has not been established except in special situations. Thus, the quantitative IgG test should only be ordered by specialists who recognize the limitations of the test. The normal reference ranges reported represent the expected results for individuals who have no unusual exposure and have not been immunized with the indicated allergen. The ranges reported have no disease-associated significance.

Reference Values:
<22.0 mcg/mL

PIGF
82145

Pigeon Feathers, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to pigeon feathers Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FPDD
75548

Pigeon/Dove Droppings Gel Diffusion

Clinical Information:

Interpretation: The gel diffusion method was used to test this patient's serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and immunological sensitization. The clinical significance varies, depending on the history and symptoms.

Reference Values:
Negative

PIK3T
614801

PIK3CA Mutation Analysis, Tumor

Clinical Information: More than 70% of breast cancers are hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER2) negative (HR+/HER2-). Approximately 40% of patients with HR+/HER2- advanced breast cancer have activating mutations in the gene PIK3CA, inducing hyperactivation of the alpha isoform (p110alpha) of phosphatidylinositol 3-kinase, a key upstream component of the PI3K pathway. Mutations in PIK3CA are associated with tumor growth, resistance to endocrine therapy, and a poor overall prognosis. Patients with HR+/HER2- advanced breast cancer identified to have a PIK3CA mutation may be eligible for treatment with targeted kinase inhibitor therapy (eg, alpelisib). This test uses DNA extracted from tumors to evaluate for the presence of 10 clinically actionable PIK3CA mutations: E542K (c.1624G>A) E542K (c.1633G>A) E545D (c.1635G>T) E545G (c.1634A>G) E545A (c.1634A>C) H1047Y (c.3139C>T) C420R (c.1285C>T) Q546E (c.1636C>G) H1047L (c.3140A>T) H1047R (c.3140A>G)

Useful For: Identification of hormone receptor positive and human epidermal growth factor receptor 2 negative (HR+/HER2-) advanced breast cancer tumors that may be eligible for treatment with targeted

kinase inhibitor therapy (eg, alpelisib).

Interpretation: The interpretation of molecular biomarker results includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Bachman K, Argani P, Samuels Y, et al: The PIK3CA gene is mutated with high frequency in human breast cancers. Cancer Biol Ther. 2004 Aug;3(8):772-775 2. Andre F, Ciruelos EM, Rubovszky G, et al: Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med. 2019 May 16;380(20):1929-1940 3. Andre F, Ciruelos EM, Juric D, et al: Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. Ann Oncol. 2021 Feb;32(2):208-217

PINE
82381

Pine Nut, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to pine nut Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal

2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FPINP
75410

Pine Ponderosa IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

FPIAP
57670

Pineapple IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

PNAP
82815

Pineapple, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pineapple Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PINW
9204

Pinworm Exam, Perianal

Clinical Information: Enterobius vermicularis, also known as pinworm, is a common intestinal nematode with a worldwide distribution. In the United States, pinworm infection is the most common helminth infection of humans and is most frequently found in young school-age children. Transmission is by the fecal-oral route. Individuals become infected when inadvertently ingesting pinworm eggs from the environment (eg, contaminated objects and surfaces). The eggs then hatch in the small intestine and the adults reside in the lumen of the cecum. Gravid adult females migrate to the perianal area during the night and deposit large numbers of eggs in the perianal area, using a glue-like substance to promote adherence anal skin folds. Most infections are asymptomatic. When present, the most common symptom is nocturnal pruritus ani (nightly anal itching) from the host inflammatory reaction to the eggs and associated adhesion. With itching, the eggs contaminate the fingers of the host and then spread into the environment to infect others. Autoinoculation is also common. Heavy infections may be associated with irritability, difficulty sleeping, abdominal pain, nausea, and vomiting. Ectopic migration of the adult female worm may also lead to vulvovaginitis, salpingo-oophoritis, peritonitis, and, possibly, appendicitis. Pinworm infection is best diagnosed through identification of eggs, and occasionally adults, obtained from the perianal skin folds. This is classically accomplished via collection with clear adhesive cellophane tape.

The pinworm paddle (eg, SWUBE device) facilitates this collection and provides a safer and more reliable means of collection and examination. To collect eggs with the pinworm paddle, the adhesive side of the paddle is pressed firmly and repeatedly to the perianal region and then returned to its plastic tube for safe transportation to the laboratory. The specimen should be collected first thing in the morning, before the patient bathes or defecates. When the paddle arrives in the laboratory, it is placed on a glass slide and examined using a light microscope for eggs and adult worms. Care must be taken when collecting and examining the specimen, as pinworm eggs are infectious within 4 to 6 hours of being laid. Repeat testing may be recommended to increase the sensitivity of detection in cases of light infection. Several agents are effective in treating pinworm infection (pyrantel pamoate, mebendazole), and good personal hygiene will prevent transmission of the eggs.

Useful For: Detection of the eggs of Enterobius vermicularis on the skin of the perianal folds

Interpretation: Positive results are provided indicating the presence of eggs of Enterobius vermicularis.

Reference Values:
Negative (reported as positive or negative)

Clinical References: 1. Global Health, Division of Parasitic Diseases: Parasites-Enterobiasis (also known as Pinworm Infection). Centers for Disease Control and Prevention; Updated June 5, 2023. Accessed January 19, 2024. Available at www.cdc.gov/parasites/pinworm/index.html 2. Mayo Clinic: Pinworm infection. Mayo Clinic; Updated June 4, 2022. Accessed January 19, 2024. Available at www.mayoclinic.org/diseases-conditions/pinworm/symptoms-causes/syc-20376382

PIPU
81248

Pipecolic Acid, Random, Urine

Clinical Information: Pipecolic acid (PA) is an intermediate of lysine metabolism and is oxidized in the peroxisomes by the enzyme L-pipecolate oxidase. In peroxisome biogenesis disorders (eg, Zellweger syndrome), the activity of this enzyme is lost, resulting in an increase in pipecolic acid levels. In contrast, in peroxisomal disorders involving single enzyme deficiencies such as D-bifunctional protein deficiency, PA is not elevated; therefore, PA analysis is useful for differentiating between these 2 groups of disorders. Increased pipecolic acid levels may also be seen in alpha-aminoadipic semialdehyde dehydrogenase deficiency (pyridoxine dependent epilepsy), hyperlysinemia types 1 and 2, and defects in proline metabolism. Theoretically, a defect in L-pipecolate oxidase can exist, and several cases of hyperpipecolic acidemia have been reported, but a specific enzyme deficiency has not been described in any of the patients.

Useful For: Differentiating between disorders of peroxisomal biogenesis (eg, Zellweger syndrome) and disorders with loss of a single peroxisomal function Detecting abnormal elevations of pipecolic acid in urine

Interpretation: Elevated pipecolic acid levels are seen in disorders of peroxisomal biogenesis; normal levels are seen in disorders with loss of a single peroxisomal function. Abnormal levels of pipecolic acid should be interpreted together with the results of other biochemical markers of peroxisomal disorders, such as serum C22-C26 very long-chain fatty acids, phytanic acid, pristanic acid (POX / Fatty Acid Profile, Peroxisomal [C22-C26], Serum); red blood cell plasmalogens (PGRBC / Plasmalogens, Blood); and bile acid intermediates (BAIPD / Bile Acids for Peroxisomal Disorders, Serum).

Reference Values:
< or =31 days: < or =223.8 nmol/mg creatinine

32 days-5 months: < or =123.1 nmol/mg creatinine
6 months-11 months: < or =45.0 nmol/mg creatinine
> or =1 year: < or =5.7 nmol/mg creatinine

Clinical References: 1. Gartner J, Rosewich H, Thoms S. The peroxisome biogenesis disorders. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Medical; 2019. Accessed November 02, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=22554226 2. Wanders RJA, Barth PG, Heymans HAS. Single peroxisomal enzyme deficiencies. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Medical; 2019. Accessed November 02, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225542524 3. Peduto A, Baumgartner MR, Verhoeven NM, et al. Hyperpipecolic acidaemia: a diagnostic tool for peroxisomal disorders. Mol Genet Metab. 2004;82:224-230 4. Braverman N, Raymond G, Rizzo WB, et al. Peroxisome biogenesis disorders in the Zellweger spectrum: An overview of current diagnosis, clinical manifestations, and treatment guidelines. Mol Genet Metab. 2016;117(3):313-321

PIPA
81326

Pipecolic Acid, Serum

Clinical Information: Pipecolic acid (PA) is an intermediate of lysine metabolism and is oxidized in the peroxisomes by the enzyme L-pipecolate oxidase. In peroxisome biogenesis disorders (eg, Zellweger syndrome), the activity of this enzyme is lost, resulting in an increase in pipecolic acid levels. In contrast, in peroxisomal disorders involving single enzyme deficiencies such as D-bifunctional protein deficiency, PA is not elevated; therefore, PA analysis is useful for differentiating between these 2 groups of disorders. Increased pipecolic acid levels may also be seen in alpha-aminoadipic semialdehyde dehydrogenase deficiency (pyridoxine-dependent epilepsy), hyperlysinemia types 1 and 2, and defects in proline metabolism. Theoretically, a defect in L-pipecolate oxidase can exist, and several cases of hyperpipecolic acidemia have been reported, but a specific enzyme deficiency has not been described in any of the patients.

Useful For: Differentiating between disorders of peroxisomal biogenesis (eg, Zellweger syndrome) and disorders with loss of a single peroxisomal function Detecting abnormal elevations of pipecolic acid in serum

Interpretation: Elevated pipecolic acid levels are seen in disorders of peroxisomal biogenesis; normal levels are seen in disorders with loss of a single peroxisomal function. Abnormal levels of pipecolic acid should be interpreted together with the results of other biochemical markers of peroxisomal disorders, such as plasma C22-C26 very long-chain fatty acids, phytanic acid, and pristanic acid (POX / Fatty Acid Profile, Peroxisomal [C22-C26], Serum); red blood cell plasmalogens (PGRBC / Plasmalogens, Blood); and bile acid intermediates (BAIPD / Bile Acids for Peroxisomal Disorders, Serum).

Reference Values:
<6 months: < or =6.0 nmol/mL
6 months-<1 year: < or =5.9 nmol/mL
1-17 years: < or =4.3 nmol/mL
> or =18 years: < or =7.4 nmol/mL

Clinical References: 1. Gartner J, Rosewich H, Thoms S. The peroxisome biogenesis disorders. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Medical; 2019. Accessed November 02, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=22554226 2. Wanders RJA, Barth PG, Heymans HAS. Single peroxisomal enzyme deficiencies. In: Valle D, Antonarakis S, Ballabio A,

Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Medical; 2019. Accessed November 02, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225542524 3. Peduto A, Baumgartner MR, Verhoeven NM, et al. Hyperpipecolic acidaemia: a diagnostic tool for peroxisomal disorders. Mol Genet Metab. 2004;82(3):224-230 4. Braverman N, Raymond G, Rizzo WB, et al. Peroxisome biogenesis disorders in the Zellweger spectrum: An overview of current diagnosis, clinical manifestations, and treatment guidelines. Mol Genet Metab. 2016;117(3):313-321

PISTA
82808

Pistachio, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pistachio Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PIT1
72124

PIT-1 Immunostain, Technical Component Only

Clinical Information: Pit-1, also known as POU1F1, is a transcription factor involved in the development of the anterior pituitary and is useful in the classification of pituitary adenomas. Expression of Pit-1 is observed in somatotropic hormone-producing tumors (prolactin, growth hormone, or thyroid-stimulating hormone).

Useful For: Classification of pituitary adenomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Reference Values:
NA

Clinical References: 1. Friend KE, Chiou YK, Laws ER, et al. Pit-1 messenger ribonucleic acid is differentially expressed in human pituitary adenomas. J Clin Endocrinol Metab. 1993;77(5):1281-1286 2. Asa SL, Puy LA, Lew AM, et al. Cell type-specific expression of the pituitary transcription activator pit-1 in the human pituitary and pituitary adenomas. J Clin Endocrinol Metab. 1993;77(5):1275-1280 3. Mete O, Asa S. Clinicopathological Correlations in Pituitary Adenomas. Brain Pathol. 2012;22:443-453 4. Mete O, Asa S. Therapeutic implications of accurate classification of pituitary adenomas. Semin Diagn Pathol. 2013;30(3):158-164 5. McDonald WC, Banerji N, McDonald KN, et al. Steroidogenic Factor 1, Pit-1, and Adrenocorticotropic Hormone: A Rational Starting Place for the Immunohistochemical Characterization of Pituitary Adenoma. Arch Pathol Lab Med. 2017;141(1):104-112 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PKLRZ
610058

PKLR Full Gene Analysis, Varies

Clinical Information: The glycolytic pathway is used by all tissues for energy production through the formation of adenosine triphosphate (ATP). It is particularly important in red blood cells, which are dependent upon this pathway for energy due to their lack of mitochondria. The PKLR gene encodes for pyruvate kinase (PK), the rate-limiting glycolytic enzyme that catalyzes the transphosphorylation from phosphoenolpyruvate to adenosine diphosphate, creating pyruvate and ATP. Pyruvate kinase deficiency is a relatively common cause of hereditary nonspherocytic hemolytic anemia,(1) with an estimated prevalence of 1:20,000 among people of European descent. The severity of hemolysis varies from fully compensated forms to life-threatening neonatal anemia requiring transfusions.(2) Over 200 different variants have been reported in the PKLR gene. Most are single nucleotide substitutions, although rarer large deletions have also been identified. PK deficiency is inherited in an autosomal recessive manner, and genetic results should be correlated with enzyme levels performed as remote from transfusion when possible. PK deficiency can be difficult to interpret based on enzyme level alone and may be only mildly decreased or normal in those with the most severe symptoms or after splenectomy due to reticulocytosis.(2) Comparison to other erythrocyte enzyme levels is usually very helpful in this regard. Heterozygous carriers of PKLR variants have intermediate enzyme levels and are not expected to be

symptomatic.

Useful For: Aiding in the diagnosis of pyruvate kinase (PK) deficiency Ascertaining a causative variant in the PKLR gene of patients with low or relatively low levels of erythrocytic PK enzymatic activity Ascertaining carrier status of family members of individuals diagnosed with PK deficiency for genetic counseling purposes

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. van Wijk R, Huizinga E, van Wesel AC, et al. Fifteen novel mutations in PKLR associated with pyruvate (PK) deficiency: structural implications of amino acid substitutions in PK. Hum Mutat. 2009;30(3):446-453 2. Zanella A, Fermo E, Bianchi P, et al. Pyruvate kinase deficiency: the genotype-phenotype association. Blood Rev. 2007;21(4):217-231 3. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 4. OMIM: 609712 Pyruvate Kinase, Liver and Red Blood Cell; PKLR. Johns Hopkins University; 2005. Updated November 2022. Accessed January 6, 2023. Available at www.omim.org/entry/609712 5. Baronciani L, Beutler E. Molecular study of pyruvate deficient patients with hereditary nonspherocytic hemolytic anemia. J Clin Invest. 1995;95(4):1702-1709 6. Bianchi P, Zanella A. Hematologically important mutations: red cell pyruvate kinase (Third update). Blood Cells Mol Dis. 2000;26(3):47-53 7. Costa C, Albuisson J, Le TH, et al. Severe hemolytic anemia in a Vietnamese family, associated with novel mutations in the gene encoding for pyruvate kinase. Haematologica. 2005;90(1):25-30 8. So CC, Tang M, Li CH, et al. First reported case of prenatal diagnosis for pyruvate kinase deficiency in a Chinese family. Hematology. 2011;16(6):377-379 9. van Wijk R, van Solinge WW, Nerlov C, et al. Disruption of a novel regulatory element in the erythroid-specific promoter of the human PKLR gene causes severe pyruvate kinase deficiency. Blood. 2003;101(4):1596-1062

PLAP
70539

Placental Alkaline Phosphatase (PLAP) Immunostain, Technical Component Only

Clinical Information: Placental alkaline phosphatase (PLAP) is expressed in cytotrophoblasts, syncytiotrophoblasts, and intermediate trophoblast cells. PLAP has been shown to be positive in various tumors, particularly germ-cell tumors and adenocarcinomas. PLAP expression has been described in tumors of Mullerian derivation, pulmonary and colonic carcinomas, and renal cell carcinomas.

Useful For: Aids in the identification of germ cell tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

PLAI
82837

Plaice, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to plaice Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PBLI
9302

Plasma Cell Assessment, Blood

Clinical Information: Plasma cell proliferative disorders are a group of hematologic neoplasms, all of which are derived from clonal plasma cells. These disorders exhibit a wide range of biologic activity ranging from monoclonal gammopathy of uncertain significance, a usually indolent disorder with a low rate of disease progression, to multiple myeloma, a disease that most often is aggressive with poor long-term survival. Detecting plasma cell immunoglobulin light chain restriction (ie, the presence of either predominately kappa or predominately lambda light chains) is an important element in assessing plasma cell clonality and, hence, establishing the diagnosis. Furthermore, a greater degree of peripheral blood involvement by these disorders is associated with more aggressive disease types and, therefore, is an adverse prognostic indicator. Flow cytometric immunophenotyping (FCIP) is a recognized method for detecting plasma cell immunoglobulin light chain restriction. However, short comings of the traditionally performed technique include relative insensitivity and consistent underestimation of the number of clonal plasma cells present. Both short comings are likely attributable to limitations of the instruments and antibodies used, as well as the presence of intraclonal phenotypic heterogeneity, which creates difficulties in accurately detecting and enumerating all clonal plasma cells. For this reason, the FCIP plasma cell clonality assessment previously performed in our laboratory was supplemented with a slide-based immunofluorescence technique. However, recent advances in flow cytometry have led to the development of more powerful instruments and antibody reagents that allow for the use of greater antibody combinations and increased resolution of the data. With these tools, the ability of FCIP to detect and enumerate plasma cell clones has been greatly enhanced, allowing us to discontinue the supplemental, labor-intensive, slide-based plasma cell evaluation in peripheral blood specimens.

Useful For: Detecting peripheral blood involvement by plasma cell proliferative disorders
Establishing the diagnosis of and determining prognosis for plasma cell proliferative disorders

Interpretation: In normal peripheral blood specimens, no clonal plasma cells are present (polytypic or too few to detect). Plasma cells are CD38 and CD138 positive. Normal (polyclonal, nonneoplastic) plasma cells are typically CD19-positive, whereas neoplastic (clonal) plasma cells typically are CD19-negative. CD19 expression is especially helpful in distinguishing clonal from nonclonal plasma cells when few analyzable cells are present. CD45 may be expressed by both normal and neoplastic plasma cells. In some plasma cell proliferative disorders, there are both CD45-positive and CD45-negative subsets within the clonal cell population. The evaluation of these antigens aids in the identification of abnormal plasma cells; however, they will not be reported independently.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Chakraborty R, Muchtar E, Kumar SK, et al. Risk stratification in myeloma by detection of circulating plasma cells prior to autologous stem cell transplantation in the novel agent era. Blood Cancer J. 2016;6(12):e512. doi:10.1038/ bcj.2016.117 2. Chakraborty R, Muchtar E, Kumar SK, et al. Serial measurements of circulating plasma cells before and after induction therapy have an independent prognostic impact in patients with multiple myeloma undergoing upfront autologous transplantation. Haematologica. 2017;102(8):1439-1445 3. Evans LA, Jevremovic D, Nandakumar B, et al. Utilizing multiparametric flow cytometry in the diagnosis of patients with primary plasma cell leukemia. Am J Hematol. 2020;95(6):637-642. doi:10.1002/ajh.25773 4. Gonsalves WI, Jevremovic D, Nandakumar B, et al. Enhancing the R-ISS classification of newly diagnosed multiple myeloma by quantifying circulating clonal plasma cells. Am J Hematol. 2020;95(3):310-315. doi:10.1002/ajh.25709 5. Ravi P, Kumar SK, Roeker L, et al. Revised diagnostic criteria for plasma cell leukemia: results of a Mayo Clinic study with comparison of outcomes to multiple myeloma. Blood Cancer J. 2018;8(12):116

PCPRO 61654 Plasma Cell DNA Content and Proliferation, Bone Marrow

Clinical Information: Plasma cell proliferative disorders are a group of plasma cell derived clonal hematologic neoplasms that exhibit a wide range of biologic activity ranging from monoclonal gammopathy of uncertain significance (MGUS), a usually indolent disorder with a low rate of disease progression, to multiple myeloma (MM), a disease that is often aggressive with poor long-term survival. Detecting plasma cell clonality through demonstrating immunoglobulin (Ig) light chain restriction (ie, the presence of either predominately kappa or predominately lambda light chains), supplemented by the plasma cell immunophenotype and DNA index, is an important element in establishing the diagnosis. It is important to correctly classify patients with plasma cell proliferative disorders as the various disease entities are treated differently. A number of factors are used for this classification including the proportions of clonal bone marrow plasma cells, the DNA index of the clonal plasma cells, and their proliferative activity. The plasma cell DNA index and proliferation assessment by flow cytometry are rapid and reliable. This information can be used to distinguish patients with overt active MM from less aggressive diseases such as MGUS and smoldering MM. Furthermore, in combination with other laboratory data, the results of these studies can be used as a measure of disease aggressiveness in newly diagnosed MM and to determine therapeutic efficacy and detect disease relapse in treated MM patients. The following algorithms are available: -Amyloidosis: Laboratory Approach to Diagnosis -Multiple Myeloma: Laboratory Screening

Useful For: Establishing a diagnosis of a plasma cell proliferative disorder Providing prognostic information for newly diagnosed multiple myeloma and other plasma cell proliferative disorders Assessing response to therapy and detecting disease relapse and progression in treated plasma cell proliferative disorder patients Determining plasma cell DNA content and proliferation

Interpretation: Plasma Cell Clonality: Plasma cell populations with a kappa to lambda ratio of either greater than 3.9 or less than 0.5 will be considered either kappa or lambda immunoglobulin light chain restricted (monotypic), respectively. As, in rare instances, immunoglobulin light chain restricted plasma cell populations may be polyclonal at the genetic level, the term monotypic rather than monoclonal plasma cells will be used. In addition to immunoglobulin light chain expression, other data collected will be used to supplement the detection of abnormal plasma cell populations. In plasma cells, CD19 expression is associated with the presence of benign, polytypic cell populations. Therefore, CD19 expression will be used as a secondary element in detecting clonal plasma cells. While loss of plasma cell CD45 expression is associated with neoplasia, CD45 is expressed by both normal and neoplastic plasma cells. Absence of plasma cell CD45 expression will be used as an aid in detecting abnormal plasma cells. In some plasma cell proliferative disorders there are both CD45-positive and CD45-negative subsets within the clonal cell population, therefore inclusion of antibodies to this antigen allows for more sensitive detection of both subtypes. In addition, as DNA content will be simultaneously assessed, the detection of plasma cell aneuploidy will also serve as a tool for identifying abnormal plasma cell populations. These additional immunophenotypic tools for identifying abnormal plasma cells will increase the sensitivity of the method beyond examining light chain expression; particularly in biclonal plasma cell proliferative disorders in which there are both kappa and lambda immunoglobulin light chain expressing subsets. Plasma Cell Proliferation: The proportion of plasma cells in S-phase will be determined by measuring the proportion of cells with DNA content between the G0/G1 and G2/M peaks. In some instances, plasma cell proliferation will not be able to be determined by this method, including when there are fewer than 300 abnormal plasma cell events and when there are multiple aneuploid plasma cell populations. In newly diagnosed multiple myeloma, a plasma cell S-phase of greater than 2.0%, is associated with a more aggressive disease course; this value is published standard for identifying plasma cell neoplasms with a high proliferative rate, it will be noted in the report if the estimated S-phase exceeds this value. DNA Index: Processed cells are stained with DAPI (4',6-diamidino-2-phenylindole) to determine the DNA index of the abnormal plasma cells. This will be determined by dividing the measured DNA content of the G0/G1 abnormal plasma cells by the DNA content of the normal G0/G1 plasma cells present. For this determination, normal plasma cells are the optimal control cell population due to similarities in nuclear and overall cell size. Plasma cells with a G0/G1 DNA content index of less than 0.95 will be considered hypodiploid (worst prognosis); those with a G0/G1 DNA content index of greater than 1.05 will be considered hyperdiploid (favorable prognosis). Plasma cells with a DNA index of 1.9 to

2.1 will be considered tetraploid (non-favorable prognosis) if a confirmatory G2/M population with a DNA index of 4 is identified. As noted above, since normal plasma cells are neither hyper- nor hypodiploid, DNA index will be used as a supplemental tool in detecting clonal plasma cells. Percent Polyclonal Plasma Cells in Total Plasma Cells: It has been shown that higher percent polyclonal plasma cells in total plasma cells can mean longer progression-free survival, higher response rates, and lower frequency of high-risk cytogenetics abnormalities. Studies have also shown a higher incidence of polytypic plasma cells in monoclonal gammopathy of uncertain significance and smoldering myeloma in comparison to multiple myeloma.

Reference Values:

Plasma Cell Clonality:
Normal bone marrow
No monotypic clonal plasma cells detected

DNA Index:
Normal polytypic plasma cells
DNA index (G0/G1 cells): Diploid 0.95-1.05

Clinical References: 1. Aljama MA, Sidiqi MH, Lakshman A, et al. Plasma cell proliferative index is an independent predictor of progression in smoldering multiple myeloma. Blood Adv. 2018;2(22):3149-3154 2. Mellors PW, Binder M, Ketterling RP, et al. Metaphase cytogenetics and plasma cell proliferation index for risk stratification in newly diagnosed multiple myeloma. Blood Adv. 2020;4(10):2236-2244 3.Palva B, Vidriales MB, Mateo G, et al. The persistence of immunophenotypically normal residual bone marrow plasma cells at diagnosis identifies a good prognostic subgroup of symptomatic multiple myeloma patients. Blood. 2009;114(20):4369-4372 4. Sidana S, Jevremovic D, Ketterling RP, et al. Rapid assessment of hyperdiploidy in plasma cell disorders using a novel multi-parametric flow cytometry method. Am J Hematol. 2019;94(4):424-430 5. Ghosh T, Gonsalves WI, Jevremovic D, et al. The prognostic significance of polyclonal bone marrow plasma cells in patients with relapsing multiple myeloma. Am J Hematol. 2017;92(9):E507-E512 6. Gonsalves WI, Buadi FK, Ailawadhi S, et al. Bone marrow transplant. Utilization of hematopoietic stem cell transplantation for the treatment of multiple myeloma: a mayo stratification of myeloma and risk-adapted therapy (msmart) consensus statement. 2019;54(3):353-367

CSPMM
618626

Plasma Cell Myeloma Pre-Analysis Cell Sorting, Bone Marrow

Clinical Information: Testing allows for further risk categorization of multiple myeloma (MM) through identifying additional abnormalities of prognostic and, potentially, therapeutic value. Application of targeted next-generation sequencing-based analysis is a useful adjunct to the standard evaluation of MM patients at diagnosis and relapse.

Useful For: Pre-analysis cell sorting for the MayoComplete Plasma Cell Myeloma panel

Interpretation: Correlation with clinical, histopathologic, and additional laboratory findings is required for final interpretation of these results. The final interpretation of results for clinical management of the patient is the responsibility of the managing physician.

Reference Values:

Only orderable as a reflex. For more information see NGPCM / MayoComplete Plasma Cell Myeloma, Next-Generation Sequencing, Varies.

Not applicable

Clinical References: 1. Walker BA, Boyle EM, Wardell CP, et al. Mutational spectrum, copy number changes, and outcome: results of a sequencing study of patients with newly diagnosed myeloma. J Clin Oncol. 2015;33(33):3911-3920 2. Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. Nat Rev Cancer. 2012;12(5):335-348 3. Kortuem KM, Braggio E, Bruins L, et al. Panel sequencing for clinically oriented variant screening and copy number detection in 142 untreated multiple myeloma patients. Blood Cancer J. 2016;6(2):e397 4. Kortuem KM, Mai EK, Hanafiah NH, et al. Targeted sequencing of refractory myeloma reveals a high incidence of mutations in CRBN and Ras pathway genes. Blood. 2016;128(9):1226-1233

PLASF 35293 Plasma Cell Proliferative Disorder, FISH, Tissue

Clinical Information: A plasmacytoma is a localized proliferation of plasma cells that are cytologically and immunophenotypically identical to the plasma cell clones seen in myeloma. There are 2 primary types of plasmacytomas, solitary plasmacytoma of bone (SPB) and extramedullary plasmacytoma (EP). SPBs are a localized bone tumor comprised of plasma cells and account for about 5% of all plasma cell neoplasms. Common sites for SPBs are the vertebrae, ribs, skull, pelvis, femur, clavicle, and scapula. Patients often present with pathological fracture or bone pain near the lesion. Treatment is typically radiation therapy; at 10 years, 35% of patients appear to be cured, 55% develop myeloma, and 10% have local recurrence. EPs are tumors of plasma cells that form in areas away from the bone and account for 3% to 5% of all plasma cell neoplasms. Approximately 80% of EPs occur in the upper respiratory tract. Less common locations include the gastrointestinal tract, bladder, testis, central nervous system, and skin. Treatment consists of radiation therapy. Regional recurrence develops in about 25% of patients, but development of myeloma is less frequent, occurring in only about 15% of patients. Genetics of both types of plasmacytomas, while not extensively studied, appear to be the same as plasma cell myeloma. Paraffin plasma cell fluorescence in situ hybridization evaluation of bone marrow clot specimens is also important when a fresh bone marrow specimen is not available or is unsuccessful in the initial/diagnostic evaluation to document the genetic abnormalities associated with a patient's plasma cell clone.

Useful For: Supporting the diagnosis of plasmacytoma or myeloma when coordinated with a surgical pathology consultation

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for a given probe set. A positive result supports the diagnosis of a plasmacytoma or myeloma. A negative result does not exclude the diagnosis of a plasmacytoma or myeloma.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Campo E, Harris NL, Jaffe ES, Pileri SA, Thiele J, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press; 2017 2. Nolan KD, Mone MC, Nelson EW. Plasma cell neoplasms: review of disease progression and report of a new variant. Surg Oncol. 2005 Aug;14(2):85-90 3. Dingli D, Kyle RA, Rajkumar SV, et al. Immunoglobulin free light chains and solitary plasmacytoma of bone. Blood. 2006;108(6):1979-1983

PCPDS 606079 Plasma Cell Proliferative Disorder, High Risk with Reflex Probes, Diagnostic FISH Evaluation, Bone Marrow

Clinical Information: Multiple myeloma is a hematologic neoplasm that generally originates in the bone marrow and develops from malignant plasma cells. There are 4 main categories of plasma cell

proliferative disorders: monoclonal gammopathy of undetermined significance (MGUS), monoclonal immunoglobulin deposition diseases (amyloidosis), plasmacytoma, and multiple myeloma. MGUS, which occurs in 3% to 4% of individuals over age 50 years, represents the identification of an asymptomatic monoclonal protein, yet approximately 1% per year will progress to multiple myeloma. Amyloidosis represents a rare group of deposition disorders including primary amyloidosis vs. light chain and heavy chain disease. Plasmacytomas represent isolated collections of bone or extramedullary plasma cells with a risk for development of multiple myeloma. Generalized bone pain, anemia, limb numbness or weakness, symptoms of hypercalcemia, and recurrent infections are all symptoms that may indicate multiple myeloma. As myeloma progresses, the malignant plasma cells interfere with normal blood product formation in the bone marrow resulting in anemia and leukopenia. Myeloma also causes an overstimulation of osteoclasts, causing excessive breakdown of bone tissue without the normal corresponding bone formation. These bone lesions are seen in approximately 66% of myeloma patients. In advanced disease, bone loss may reach a degree where the patient suffers fractures easily. Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options.

Useful For: Aiding in the diagnosis of new cases of multiple myeloma or other plasma cell proliferative disorders using bone marrow specimens Identifying prognostic markers based on the abnormalities found This test should not be used to track the progression of disease.

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow SH, Campo E, Harris NL, et al, eds: WHO Classification of Tumour of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours, Vol 2 2. Kumar SK, Rajkumar SV. The multiple myelomas-current concepts in cytogenetic classification and therapy. Nat Rev Clin Oncol. 2018l;15(7):409-421. doi:10.1038/s41571-018-0018-y 3. Rajkumar SV, Landgren O, Mateos MV: Smoldering multiple myeloma. Blood. 2015;125(20):3069-3075. doi:10.1182/blood-2014-09-568899 4. Muchtar E, Dispenzieri A, Kumar SK, et al. Interphase fluorescence in situ hybridization in untreated AL amyloidosis has an independent prognostic impact by abnormality type and treatment category. Leukemia. 2017;31(7);1562-1569. doi:10.1038/leu.2016.369 5. Lakshman A, Paul S, Rajkumar SV, et al. Prognostic significance of interphase FISH in monoclonal gammopathy of undetermined significance. Leukemia. 2018;32(8);1811-1815. doi:10.1038/s41375-018-0030-3 6. Bochtler T, Hegenbart U, Kunz C, et al. Prognostic impact of cytogenetic aberrations in AL amyloidosis patients after high-dose melphalan: a long-term follow-up study. Blood. 2016 28;128(4):594-602. doi:10.1182/blood-2015-10-676361 7. Treatment guidelines: multiple myeloma. mSMART 3.0. Accessed February 20, 2024. Available at www.msmart.org/mm-treatment-guidelines

CSPCF 607625 Plasma Cell Proliferative Disorder, Pre-Analysis Cell Sorting, Bone Marrow

Clinical Information: Multiple myeloma is a hematologic neoplasm that generally originates in the bone marrow and develops from malignant plasma cells. There are four main categories of plasma cell proliferative disorders: monoclonal gammopathy of undetermined significance (MGUS), monoclonal

immunoglobulin deposition diseases (amyloidosis), plasmacytoma, and multiple myeloma. MGUS, which occurs in 3% to 4% of individuals over age 50 years, represents the identification of an asymptomatic monoclonal protein, yet approximately 1% per year will progress to multiple myeloma. Amyloidosis represents a rare group of deposition disorders including primary amyloidosis vs. light chain and heavy chain disease. Plasmacytomas represent isolated collections of bone or extramedullary plasma cells with a risk for development of multiple myeloma. Generalized bone pain, anemia, limb numbness or weakness, symptoms of hypercalcemia, and recurrent infections are all symptoms that may indicate multiple myeloma. As myeloma progresses, the malignant plasma cells interfere with normal blood product formation in the bone marrow resulting in anemia and leukopenia. Myeloma also causes an overstimulation of osteoclasts, causing excessive breakdown of bone tissue without the normal corresponding bone formation. These bone lesions are seen in approximately 66% of myeloma patients. In advanced disease, bone loss may reach a degree where the patient suffers fractures easily. Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options.

Useful For: Aiding in the diagnosis of new cases of multiple myeloma or other plasma cell proliferative disorders Sorting plasma cells for fluorescence in situ hybridization analysis

Interpretation: Correlation with clinical, histopathologic and additional laboratory findings is required for final interpretation of these results. The final interpretation of results for clinical management of the patient is the responsibility of the managing physician.

Reference Values:
Only orderable as a reflex. See PCPDS / Plasma Cell Proliferative Disorder, High Risk with Reflex Probes, Diagnostic FISH Evaluation, Bone Marrow

An interpretive report will be provided.

Clinical References: 1 Swerdlow S, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017 2. Kumar SK, Rajkumar SV. The multiple myelomas-current concepts in cytogenetic classification and therapy. Nat Rev Clin Oncol. 2018;15(7):409-421. doi: 10.1038/s41571-018-0018-y 3. Rajkumar SV, Landgren O, Mateos MV. Smoldering multiple myeloma. Blood. 2015 May 14;125(20):3069-3075. doi:10.1182/blood-2014-09-568899 4. Muchtar E, Dispenzieri A, Kumar S et al. Interphase fluorescence in situ hybridization in untreated AL amyloidosis has an independent prognostic impact by abnormality type and treatment category. Leukemia. 2017;31(7);1562-1569. doi: 10.1038/leu.2016.369 5. Lakshman A, Paul S, Rajkumar SV et al. Prognostic significance of interphase FISH in monoclonal gammopathy of undetermined significance. Leukemia. 2018;32(8);1811-1815. doi: 10.1038/s41375-018-0030-3 6. Bochtler T, Hegenbart U, Kunz C, et al. Prognostic impact of cytogenetic aberrations in AL amyloidosis patients after high-dose melphalan: a long-term follow-up study. Blood. 2016;128(4):594-602. doi:10.1182/blood-2015-10-7 7. Treatment guidelines: multiple myeloma. mSMART 3.0. Accessed October 27, 2023. Available at www.msmart.org/mm-treatment-guidelines

PLHBB
9096

Plasma Free Hemoglobin, Plasma

Clinical Information: Hemoglobin is contained within erythrocytes and significant amounts of "free hemoglobin" (outside the red blood cell [RBC]) are not normally present in plasma. This free hemoglobin is also called plasma hemoglobin. Normal blood draw procedures cause a limited degree of unavoidable disruption and therefore a small amount of free hemoglobin may normally be present. When detectable,

the total plasma hemoglobin and a subcomponent, oxyhemoglobin, are both reported. Significant amounts of free hemoglobin occur in plasma following disruption of the RBC for any reason. This might result from a transfusion reaction or mechanical fragmentation of RBCs due to instrumentation, surgical procedures, or mechanical devices. Patients requiring support from extracorporeal membrane oxygenation or centrifugal ventricular assist devices are commonly monitored for trends in plasma free hemoglobin levels to assess for increasing hemolysis. Sharp spikes in plasma hemoglobin levels can indicate pump disruption. However, plasma hemoglobin can be artifactually increased due to a traumatic blood draw or prolonged exposure to post-draw RBCs. Additionally, bilirubin interferes substantially with the ability to calculate total plasma hemoglobin levels and results may be spurious and unreliable. This is a difficulty frequently encountered in serially tested patients. When this occurs, the oxyhemoglobin level tends to show less interference and will be the only analyte reported in the presence of increased bilirubin (>5 mg/dL). When using trending data, total plasma hemoglobin and oxyhemoglobin levels are not interchangeable and should be compared within their subgroups only.

Useful For: Determining whether hemolysis is occurring such as from: -Transfusion reaction -Mechanical fragmentation of red blood cells -Relative comparison to baseline levels in extracorporeal membrane oxygenation and centrifugal ventricular assist device patients to assess pump disruption

Interpretation: An elevation in plasma hemoglobin above the reference range indicates likely intravascular hemolysis due to one of the causes listed in the Useful For section.

Reference Values:

TOTAL PLASMA HEMOGLOBIN
> or =12 months: 0.0-15.2 mg/dL
Reference values have not been established for patients who are younger than 12 months of age.

OXYHEMOGLOBIN
> or =12 months: 0.0-12.4 mg/dL
Reference values have not been established for patients who are younger than 12 months of age.

Clinical References: 1. Lubnow M, Philipp A, Foltan M, et al. Technical complications during veno-venous extracorporeal membrane oxygenation and their relevance predicting a system-exchange-retrospective analysis of 265 cases. PloS One. 2014;9(12):e112316 2. Hayes D Jr, McConnell PI, Preston TJ, Nicol KK. Hyperbilirubinemia complicating plasma-free hemoglobin and antifactor Xa level monitoring on venovenous extracorporeal membrane oxygenation. World J Pediatr Congenit Heart Surg. 2014;5(2):345-347

PGRBC
609675

Plasmalogens, Blood

Clinical Information: Peroxisomes are organelles that carry out essential metabolic functions, including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle, and disorders of peroxisome function with single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Biochemical abnormalities in peroxisomal biogenesis disorders can include accumulations of VLCFA, phytanic acid, pristanic acid, pipecolic acid, bile acids, and reduced plasmalogens. The differential diagnosis of these disorders is based on recognition of clinical phenotypes combined with a series of biochemical tests to assess peroxisomal function and structure. These include measurements and ratios of VLCFA, phytanic acid, and its metabolite pristanic acid (POX / Fatty Acid Profile, Peroxisomal [C22-C26], Serum; or POXP / Fatty Acid Profile, Peroxisomal [C22-C26], Plasma), pipecolic acid (PIPA / Pipecolic Acid, Serum; or PIPU / Pipecolic Acid, Random, Urine), bile acids (BAIPD / Bile Acids for Peroxisomal Disorders, Serum), and plasmalogens. Peroxisomal biogenesis

disorders (PBD) include Zellweger syndrome spectrum disorders, which are clinically diverse and range in severity from neonatal lethal (Zellweger syndrome) to more variable clinical courses in neonatal adrenoleukodystrophy and infantile Refsum disease. Affected children typically have hypotonia, poor feeding, distinctive facial features, seizures, and liver dysfunction. Other features can include retinal dystrophy, hearing loss, developmental delays, and bleeding episodes. Rhizomelic chondrodysplasia punctata (RCDP) is a malformation disorder characterized by rhizomelic shortening, chondrodysplasia punctata, cataracts, intellectual disability, and seizures; however, it can have a milder phenotype with only cataracts and chondrodysplasia punctata. Currently, there are 5 clinical types of rhizomelic chondrodysplasia punctata: RCDP 1, 2, 3, 4 (also known as FAR1 deficiency) and 5. RCDP 1 is the classical form that presents in infancy with skeletal manifestations, including rhizomelic shortening, cataracts, and severe to profound postnatal growth deficiency. Infants with RCDP 1 have developmental delay, and later, intellectually disability. The majority of children with RCDP 1 do not survive beyond the first decade of life. RCDP 1 is an autosomal recessive disorder caused by disease-causing variants in the PEX7 gene. RCDP 2 and 3 have clinical phenotypes similar to RCDP 1 and may be distinguished by plasmalogen deficiency. RCDP 2 and 3 are autosomal recessive conditions caused by disease-causing variants in GNPAT and AGPS genes, respectively. Individuals with RCDP 5 have a milder phenotype when compared to classic RCDP 1, with most individuals able to achieve self-feeding, independent ambulation, and development of limited language skills. RCDP5 results in less pronounced reduction in plasmalogens compared to RCDP 1. This newly recognized subtype of RCDP is an autosomal recessive disorder caused by disease-causing variants in the PEX5 gene. The typical biochemical profile for RCDP shows reduced plasmalogens, elevated phytanic acid, and normal VLCFA. Confirmatory testing via molecular analysis for all types of RCDP is available (PDGP / Peroxisomal Disorder Gene Panel, Varies). Fatty acyl-CoA reductase 1 (FAR1) deficiency, also known as RCDP type 4, is an autosomal recessive peroxisomal disorder caused by disease-causing variants in the FAR1 gene that result in early-onset epilepsy, microcephaly, cataracts, postnatal growth deficiency, and intellectual disability. Unlike RCDP, however, infants with FAR1 deficiency have no skeletal abnormalities. The biochemical profile for FAR1 deficiency includes reduced plasmalogens, normal to elevated phytanic acid, and normal VLCFA.

Useful For: Diagnosing patients with possible peroxisomal disorders, such as peroxisomal biogenesis disorders (Zellweger syndrome spectrum) and rhizomelic chondrodysplasia punctata (RCDP), including fatty acyl-CoA reductase 1 (FAR1) deficiency Evaluating patients with abnormal newborn screen results for X-linked adrenoleukodystrophy who appear to have a different type of peroxisomal disorder, such as a Zellweger syndrome spectrum disorder. Aiding in the assessment of peroxisomal function

Interpretation: Reports include concentrations of C16:0, C18:0 and C18:1 plasmalogens and the ratio of the C16:0 and C18:0 plasmalogens to the respective fatty acid. When no significant abnormalities are detected, a simple descriptive interpretation is provided. A profile of reduced plasmalogens and abnormal very long-chain fatty acids (VLCFA), as well as possible abnormalities in pipecolic acid and bile acids, can be consistent with a diagnosis of a peroxisomal biogenesis disorder (Zellweger syndrome spectrum). A profile of reduced plasmalogens, elevated phytanic acid, and normal VLCFA is consistent with a diagnosis of rhizomelic chondrodysplasia punctata, such as RCDP type 1 or 2, FAR1 deficiency (RCDP type 4), or other types of RCDP. Positive test results could be due to a genetic or nongenetic condition. Additional confirmatory testing would be required to differentiate between these causes.

Reference Values:

Hexadecanal-Dimethylacetal, C16:0 DMA:
> or =6.00 mcg/mL

Octadecanal-Dimethylacetal, C18:0 DMA:
> or =9.00 mcg/mL

9Z-Octadecenal-DiMethylacetal C18:1 DMA:
> or =2.00 mcg/mL

C16:0 DMA/C16:0:
> or =0.018

C18:0 DMA/C18:0:
> or =0.040

Clinical References: 1. Braverman NE, Moser AB, Steinberg SJ, Fallatah WF, Duker A, Bober M. Rhizomelic chondrodysplasia punctata type 1. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2001. Updated January 30, 2020. Accessed May 25, 2023. Available at: www.ncbi.nlm.nih.gov/books/NBK1270/ 2. Buchert R, Tawamie H, Smith C, et al. A peroxisomal disorder of severe intellectual disability, epilepsy, and cataracts due to fatty acyl-CoA reductase 1 deficiency. Am J Hum Genet. 2014;95(5):602-610 3. Baroy T, Koster J, Stromme P, et al: A novel type of rhizomelic chondrodysplasia punctata, RCDP5, is caused by a loss of the PEX5 long isoform. Hum Mol Genet. 2015;24(20):5845-5854 4. Braverman NE, Moser AB. Functions of plasmalogen lipids in health and disease. Biochim Biophys Acta. 2012;1822(9):1442-1452

PGDBS
609664

Plasmalogens, Blood Spot

Clinical Information: Peroxisomes are organelles that carry out essential metabolic functions, including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle, and disorders of peroxisome function with single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Biochemical abnormalities in peroxisomal biogenesis disorders can include accumulations of VLCFA, phytanic acid, pristanic acid, pipecolic acid, bile acids, and reduced plasmalogens. The differential diagnosis of these disorders is based on recognition of clinical phenotypes combined with a series of biochemical tests to assess peroxisomal function and structure. These include measurements and ratios of VLCFA, phytanic acid, and its metabolite pristanic acid (POX / Fatty Acid Profile, Peroxisomal [C22-C26], Serum or POXP / Fatty Acid Profile, Peroxisomal [C22-C26], Plasma), pipecolic acid (PIPA / Pipecolic Acid, Serum or PIPU / Pipecolic Acid, Random, Urine), bile acids (BAIPD / Bile Acids for Peroxisomal Disorders, Serum), and plasmalogens. Peroxisomal biogenesis disorders include Zellweger syndrome spectrum disorders, which are clinically diverse and range in severity from neonatal lethal (Zellweger syndrome) to more variable clinical courses in neonatal adrenoleukodystrophy and infantile Refsum disease. Affected children typically have hypotonia, poor feeding, distinctive facial features, seizures, and liver dysfunction. Other features can include retinal dystrophy, hearing loss, developmental delays, and bleeding episodes. Rhizomelic chondrodysplasia punctata (RCDP) is a malformation disorder characterized by rhizomelic shortening, chondrodysplasia punctata, cataracts, intellectual disability, and seizures, although it can have a milder phenotype with only cataracts and chondrodysplasia punctata. Currently, there are 5 clinical types of rhizomelic chondrodysplasia punctata: RCDP 1, 2, 3, 4 (also known as FAR1 deficiency) and 5. RCDP 1 is the classical form that presents in infancy with skeletal manifestations including rhizomelic shortening, cataracts, and severe to profound postnatal growth deficiency. Infants with RCDP 1 have developmental delay, and later, intellectually disability. The majority of children with RCDP 1 do not survive beyond the first decade of life. RCDP 1 is an autosomal recessive disorder caused by disease-causing variants in the PEX7 gene. RCDP 2 and 3 have clinical phenotypes similar to RCDP 1 and may be distinguished by plasmalogen deficiency. RCDP 2 and 3 are autosomal recessive conditions caused by disease-causing variants in GNPAT and AGPS genes, respectively. Individuals with RCDP 5 have a milder phenotype when compared to classic RCDP 1, with most individuals able to achieve self-feeding, independent ambulation, and development of limited language skills. RCDP5 results in less pronounced reduction in plasmalogens compared to RCDP 1. This newly recognized subtype of RCDP is an autosomal recessive disorder caused by disease-causing variants in the PEX5 gene. The typical biochemical profile for RCDP shows reduced plasmalogens, elevated phytanic acid, and normal VLCFA. Confirmatory testing via molecular analysis for all types of RCDP is available (PDGP / Peroxisomal Disorder Gene Panel,

Varies). Fatty acyl-CoA reductase 1 (FAR1) deficiency, also known as RCDP type 4, is an autosomal recessive peroxisomal disorder caused by disease-causing variants in the FAR1 gene that result in early-onset epilepsy, microcephaly, cataracts, postnatal growth deficiency, and intellectual disability. Unlike RCDP, however, infants with FAR1 deficiency have no skeletal abnormalities. The biochemical profile for FAR1 deficiency includes reduced plasmalogens, normal to elevated phytanic acid, and normal VLCFA.

Useful For: Diagnosing patients with possible peroxisomal disorders, such as peroxisomal biogenesis disorders (Zellweger syndrome spectrum) and rhizomelic chondrodysplasia punctata (RCDP), including fatty acyl-CoA reductase 1 (FAR1) deficiency Evaluating patients with abnormal newborn screen results for X-linked adrenoleukodystrophy who appear to have a different type of peroxisomal disorder, such as a Zellweger syndrome spectrum disorder Aiding in the assessment of peroxisomal function

Interpretation: Reports include concentrations of C16:0, C18:0 and C18:1 plasmalogens and the ratio of the C16:0 and C18:0 plasmalogens to the respective fatty acid. When no significant abnormalities are detected, a simple descriptive interpretation is provided. A profile of reduced plasmalogens and abnormal very long-chain fatty acids (VLCFA), as well as possible abnormalities in pipecolic acid and bile acids, can be consistent with a diagnosis of a peroxisomal biogenesis disorder (Zellweger syndrome spectrum). A profile of reduced plasmalogens, elevated phytanic acid, and normal VLCFA is consistent with a diagnosis of rhizomelic chondrodysplasia punctata, such as RCDP type 1 or 2, FAR1 deficiency (RCDP type 4), or other types of RCDP. Positive test results could be due to a genetic or nongenetic condition. Additional confirmatory testing would be required to differentiate between these causes.

Reference Values:

Hexadecanal-Dimethylacetal, C16:0 DMA
> or =7.00 mcg/mL

Octadecanal-Dimethylacetal, C18:0 DMA
> or =12.00 mcg/mL

9Z-Octadecenal-Dimethylacetal C18:1DMA
> or =2.00 mcg/mL

C16:0 DMA/C16:0
> or =0.012

C18:0 DMA/C18:0
> or =0.050

Clinical References: 1. Braverman NE, Moser AB, Steinberg SJ, Fallatah WF, Duker A, Bober M. Rhizomelic chondrodysplasia punctata type 1. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2001. Updated January 30, 2020. Accessed May 25, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1270/ 2. Buchert R, Tawamie H, Smith C, et al. A peroxisomal disorder of severe intellectual disability, epilepsy, and cataracts due to fatty acyl-CoA reductase 1 deficiency. Am J Hum Genet. 2014;95(5):602-610 3. Baroy T, Koster J, Stromme P, et al. A novel type of rhizomelic chondrodysplasia punctata, RCDP5, is caused by a loss of the PEX5 long isoform. Hum Mol Genet. 2015;24(20):5845-5854 4. Braverman NE, Moser AB. Functions of plasmalogen lipids in health and disease. Biochim Biophys Acta. 2012;1822(9):1442-1452

PAI1
86083

Plasminogen Activator Inhibitor Antigen, Plasma

Clinical Information: Plasminogen activator inhibitor type 1 (PAI-1) antigen is a single-chain

glycoprotein (molecular weight 43 kDa) produced by endothelial cells and hepatocytes. It is also present in alpha granules of platelets. PAI-1 is a serine protein inhibitor that is secreted in response to inflammatory reactions. Platelet alpha granules contain large amounts of PAI-1, which is released during vascular injury and assists in fibrin clot stability. PAI-1 is synthesized in the active form but has marked functional instability and a functional half-life of about 2 hours in vivo. Circulating PAI-1 is bound to vitronectin, which protects the inhibitor from inactivation and may assist in targeting the inhibitor to sites of vascular injury. At least 4 different conformations of PAI-1 have been described: 1. The active form that reacts with plasminogen activator 2. A latent form that is nonreactive 3. A substrate form that can be cleaved by plasminogen activators but is non-inhibitory 4. The inert form of PAI-1 generated by the cleavage of the reactive site PAI-1 is the main inhibitor of tissue-type plasminogen activator and urokinase plasminogen activator and, as such, plays an important role in the regulation of fibrinolysis. Elevated levels of PAI-1 result in deficient plasminogen activation and are associated with a predisposition to thrombosis, including veno-occlusive disease (VOD) after bone marrow transplantation (BMT). Primary injury to the hepatic sinusoidal endothelium and hepatocytes induced by high dose chemoradiotherapy is believed to be the key event in the pathogenesis of VOD. The clinical diagnosis of VOD is complex because the clinical signs and symptoms can occur due to other processes that can complicate the posttransplant period, such as sepsis, graft-versus-host disease (GVHD), cyclosporine toxicity, other medications, hemolysis, or parenteral nutrition. Liver biopsy, although safer since the widespread introduction of transjugular procedures, remains hazardous in this thrombocytopenic population. A sensitive and specific assay would be invaluable in guiding management and avoiding potentially hazardous invasive diagnostic procedures. Along these lines several investigators have studied various markers of hypercoagulability for possible pathogenic and predictive relevance. Aside from serum bilirubin level, no laboratory marker has been standardized as a diagnostic marker of VOD, and the severity of VOD remains retrospectively defined. Lee et al analyzed 115 patients after allogenic BMT in an attempt to identify diagnostic and severity markers of VOD. Of the 115 patients, 50 developed VOD.(1) Multiple logistic regression models were constructed that included recognized relevant clinical and hemostatic variables. Of the hemostatic variables, only PAI-1 antigen was identified as an independent marker for the occurrence of VOD. This confirmed the findings of a previous, smaller study that PAI-1 is a powerful diagnostic marker of VOD during the early period post-BMT and can distinguish VOD from other causes of hyperbilirubinemia post-BMT, such as GVHD and drug toxicity. Furthermore, PAI-1 antigen and bilirubin were independent variables for predicting severe VOD. Familial thrombosis has been associated with inherited elevation of plasma PAI-1 activity. Increased levels of PAI-1 have also been reported in many conditions including malignancy, liver disease, the postoperative period, septic shock, the second and third trimesters of pregnancy, obesity, and coronary heart disease. Low plasma levels of the active form of PAI-1 have been associated with abnormal, clinically significant bleeding. Complete deficiency of PAI-1, either congenital or acquired, is associated with bleeding manifestations that include hemarthroses, hematomas, menorrhagia, easy bruising, and postoperative hemorrhage.

Useful For: Identification of heredity elevation or deficiency of plasminogen activator inhibitor type 1 Determination of risk for veno-occlusive disease associated with bone marrow transplantation Differential diagnosis of impaired fibrinolysis Prognostic marker of occurrence or recurrence of thrombosis

Interpretation: Increased levels of plasminogen activator inhibitor type 1 (PAI-1) are associated with a predisposition to thrombosis. Decreased or absent levels of detectable functional PAI-1 will result in a life-long bleeding diathesis.

Reference Values:
3.0-72.0 ng/mL

Clinical References: 1. Lee JH, Lee KH, Lee JH, et al. Plasminogen activator inhibitor-1 is an independent diagnostic marker as well as severity predictor of hepatic veno-occlusive disease after allogeneic bone marrow transplantation in adults conditioned with busulphan and cyclophosphamide. Br

J Haematol. 2002;118(4):1087-1094 2. Stiko A, Hervio L, Loskutoff DJ. Plasminogen activator inhibitors. In: Colman RW, Hirsh J, Marder VJ, et al, eds. Hemostasis and Thrombosis. Lippincott; 2001:355-365 3. Vaughn DE, Declerck PJ. Regulation of fibrinolysis. In: Loscalzo J, Schager A, eds. Thrombosis and Hemorrhage. Lippincott; 2003:389-396 4. Goodnight SH Jr, Hathaway WE. Fibrinolytic defects and thrombosis. In: Disorders of Hemostasis and Thrombosis: A Clinical Guide. McGraw-Hill Book Company; 2001:389-396 5. Kruithof EK, Gudinchet A, Bachman F. Plasminogen activator inhibitor-1 and plasminogen activator inhibitor-2 in various disease states. Thromb Haemostasis. 1988;59(1):7-12 6. Salat C, Holler E, Kolb HJ, et al. Plasminogen activator inhibitor-1 confirms the diagnosis of hepatic veno-occlusive disease in patients with hyperbilirubinemia after bone marrow transplantation. Blood. 1997;89(6):2184-2188 7. Fay WP, Shapiro AD, Shih JL, Schleef RR, Ginsburg D. Brief report: complete deficiency of plasminogen-activator inhibitor type 1 due to a frame-shift mutation. N Engl J Med. 1992;327(24):1729-1733 8. Heiman M, Gupta S, Khan SS, et al. Complete plasminogen activator inhibitor 1 deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]; 2017. Updated February 23, 2023. Accessed February 21, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK447152/

FPAIG
75142

Plasminogen Activator Inhibitor-1, 4G/5G Genotyping (PAI-1 Polymorphism)

Clinical Information: The PAI-1 4G allele is an inherited characteristic. If the polymorphism is present in a heterozygous or homozygous fashion, we recommend that the patient and their family consider genetic counseling to obtain additional information on inheritance and to identify other family members at risk. If a patient possesses two or more congenital or acquired risk factors, the risk of disease may rise to more than the sum of the risk ratios for the individual risk factors. For instance, a combination of the 4G/4G genotype and the insulin resistance syndrome may confer an increase in cardiovascular disease risk over that conferred by the presence of an isolated PAI-1 4G/4G polymorphism.

Clinical References: Barcellona D. Thromb Haemost. 2003;90:1061.;Dossenbach-Glaninger. Clin Chem. 2003;49:1081.; Kohler et al. NEJM. 200;342:1792.; Margaglione M et al. Arterioscl Thromb and Vasc Bio. 1998;18:152.

PSGN
9079

Plasminogen Activity, Plasma

Clinical Information: During the formation of a hemostatic (fibrin) plug, biochemical mechanisms are initiated to limit the extent of the hemostatic process at the site of injury and maintain vascular patency. This process of fibrinolysis is defined as the plasmin-mediated degradation of fibrin. Plasmin limits the extent of the hemostatic process at the site of vessel injury. Plasmin is generated from its precursor, plasminogen, by plasminogen activators (ie, tissue plasminogen-activator: tPa; urokinase-type plasminogen activator: uPa). Plasminogen is a single-chain glycoprotein that is synthesized in the liver and has a biologic half-life of approximately 2 days.(1) Deficiency of plasminogen may be inherited or acquired. Persons with congenital plasminogen deficiency are at an increased risk for development of an ocular condition called ligneous conjunctivitis. Congenital deficiency of plasminogen is autosomally transmitted and rare in the general population, with a prevalence of approximately 0.4%.(2) Based on the results of functional and immunologic (antigenic) assays, 2 types of plasminogen deficiency have been identified: -Quantitative deficiency (type I)-defined by a corresponding decrease in both plasminogen activity and antigen level -Functional deficiency (type II)-caused by a normally synthesized but dysfunctional plasminogen This plasminogen activity assay will identify both types of deficiency. Acquired causes of plasminogen deficiency include consumption such as with thrombolytic therapy (urokinase, tPa) or disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF), or decreased synthesis (liver disease).(1)

Useful For: Evaluating patients with ligneous conjunctivitis (strong association with homozygous plasminogen deficiency) Evaluating fibrinolysis, in combination with other components of the fibrinolytic system (fibrinogen, tissue plasminogen-activator-inhibitor, and d-dimers)

Interpretation: Plasminogen activity below 75% may represent a congenital deficiency state, if acquired deficiency can be excluded. Hereditary abnormalities of plasminogen (deficiency or dysfunction) are very uncommon. Acquired causes of plasminogen deficiency are much more common and may be the result of consumption due to thrombolytic therapy or intravascular coagulation and fibrinolysis or decreased synthesis (ie, liver disease). Plasminogen levels are low at birth (approximately 50% of adult normal level) and reach adult levels at 6 months of age.

Reference Values:
75-140%

Clinical References: 1. Bachman F. Plasminogen-plasmin enzyme system. In: Coman RW, Hirsh J, Marder VJ, et al, eds. Homeostasis and Thrombosis. Lippencott; 2001:275-320 2. Mehta R, Shapiro AD. Plasminogen deficiency. Haemophilia. 2008;14(6):1261-1268 3. Andrews M. The hemostatic system in the infant. In: Nathan DG, Oski FA, eds. Hematology of Infancy and Childhood. Vol 1. 4th ed. WB Saunders Company; 1993:115-153 4. Chandler W. Diagnosis of fibrinolytic disorder. In: Kottke-Marchant Wiley K, ed. Laboratory Hematology Practice. Blackwell Publishing; 2012:460-467 5. Favaloro EJ and Lippi G. eds. Hemostasis and Thrombosis: Methods and Protocols. 1st ed. Humana Press; 2017

MALCT
610710

Plasmodium Percent Parasitemia Reflex, Varies

Clinical Information: Malaria is a potentially life-threatening disease caused by Plasmodium species. Diagnosis is traditionally performed by microscopic examination of Giemsa-stained thick and thin blood films. However, polymerase chain reaction (PCR) testing can also be used for sensitive and specific detection. When positive, PCR results should be followed by calculation of percent parasitemia from blood film examination. The degree of parasitemia is used to predict prognosis as well as monitor response to treatment for patients with malaria.

Useful For: Calculating percent parasitemia, which can be used to predict prognosis and monitor response to treatment for patients with malaria

Interpretation: The percentage of parasitemia represents the percentage of infected red blood cells. This is calculated from representative microscopic fields on the thin blood film. Plasmodium gametocytes are not included in the calculation since they are not infectious to humans and are not killed by most antimalarial drugs.

Reference Values:
Only orderable as a reflex. For more information see LMALP / Malaria PCR with Parasitemia Reflex, Varies.

A percent parasitemia is provided following a positive result for LMALP / Malaria PCR with Parasitemia Reflex, Varies.

Clinical References: 1. Centers for Disease Prevention and Control (CDC). Malaria. CDC. Updated August 19, 2022. Accessed November 17, 2022. Available at www.cdc.gov/malaria/ 2. Swan H, Sloan L, Muyombwe A, et al. Evaluation of a real-time polymerase chain reaction assay for the diagnosis of malaria in patients from Thailand. Am J Trop Med Hyg. 2005;73(5):850-854 3. World Health Organization (WHO). Malaria. WHO. Updated July 26, 2022. Accessed November 17, 2022.

Available at www.who.int/news-room/fact-sheets/detail/malaria

PLABN 35794 Platelet Antibody Screen, Serum

Clinical Information: Platelet antibodies may be allo- or autoantibodies and may be directed to a wide range of antigenic "targets" carried on platelet cytoplasmic membranes. Serum platelet antibody test is optimized to identify the presence of platelet alloantibodies in the patient. Platelet alloantibodies are involved in several clinical situations such as: -Immune mediated refractoriness to platelet transfusions usually due to antibodies to class I human leukocyte antigens and sometimes to antibodies specific to platelet antigens. -Neonatal alloimmune thrombocytopenia -Posttransfusion purpura, which are usually associated with platelet-specific antibodies

Useful For: Detecting alloantibodies to epitopes on platelet glycoproteins IIb/IIIa, Ib/Ix, Ia/IIa, IV and class I human leukocyte antigens to evaluate cases of immune mediated refractoriness to platelet transfusions, posttransfusion purpura, or neonatal alloimmune thrombocytopenia

Interpretation: This assay screens patient sera for platelet-reactive antibodies via enzyme-linked immunosorbent assay.

Reference Values:
Not applicable

Clinical References: 1. Kiefel V, Santoso S, Weisheit M, Mueller-Eckhardt C. Monoclonal antibody-specific immobilization of platelet antigens (MAIPA): A new tool for the identification of platelet-reactive antibodies. Blood. 1987;70(6):1722-1726 2. Moore SB, De Goey SR. Serum platelet antibody testing: evaluation of solid-phase enzyme immunoassay and comparison with indirect immunofluorescence. Am J Clin Pathol. 1998;109(2):190-195 3. Warkentin TE, Smith JW. The alloimmune thrombocytopenic syndromes. Transfus Med Rev. 1997;11(4):296-307 4. Metcalfe P, Watkins NA, Ouwehand WH, et al. Nomenclature of human platelet antigens. Vox Sang. 2003;85(3):240-245 5. Liebman HA. Immune thrombocytopenia (ITP): an historical perspective. Hematology Am Soc Hematol Educ Program. 2008;205 6. Kjeldsen-Kragh J, Killie MK, Tomter G, et al. A screening and intervention program aimed to reduce mortality and serious morbidity associated with severe neonatal alloimmune thrombocytopenia. Blood. 2007;110(3):833-839 7. Hoffbrand AV, Steensma D. Post transfusion purpura. In: Hoffbrand's Essential Haematology. 8th ed. Blackwell Publishing; 2019 8. Juskewitch JE, Norgan AP, De Goey SR, et al. How do I manage the platelet transfusion-refractory patient? Transfusion. 2017;57(12):2828-2835. doi:10.1111/trf.14316 9. Crighton GL, Scarborough R, McQuilten ZK, et al. Australian NAIT registry steering committee: Contemporary management of neonatal alloimmune thrombocytopenia: good outcomes in the intravenous immunoglobulin era: results from the Australian neonatal alloimmune thrombocytopenia registry. J Matern Fetal Neonatal Med. 2017;30(20):2488-2494. doi:10.1080/14767058.2016.1253064

GNPLT 619285 Platelet Disorders, Comprehensive Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Platelets have essential roles in primary hemostasis. Patients with either hereditary or acquired platelet disorders usually have bleeding diathesis, which can potentially be life-threatening and may also have issues with the development and/or functioning of major organs.(2) Inherited platelet disorders can be syndromic (ie, associated with current or future development of other organ system defects) or non-syndromic (ie, isolated to thrombocytopenia with no other organ system defects). A reliable laboratory diagnosis of a platelet disorder can significantly impact patients' and,

potentially, their family members' clinical management and outcome. Identification of an alteration that is known or suspected to cause disease aids in confirmation of the diagnosis and potentially provides prognostic information especially in the syndromic inherited platelet disorders. This panel evaluates 70 genes associated with a variety of hereditary platelet disorders, including reduced adenosine diphosphate (ADP)-induced platelet aggregation; Baraitser-Winter syndrome 1 with macrothrombocytopenia; Scott syndrome; Hermansky-Pudlak syndrome; platelet abnormalities with eosinophilia and immune-mediated inflammatory disease; Takenouchi-Kosaki syndrome with thrombocytopenia; leukocyte integrin adhesion deficiency type III; Paris-Trousseau-Jacobsen syndrome; GATA2 deficiency; Bernard-Soulier syndrome; platelet-type von Willebrand disease; bleeding diathesis due to glycoprotein VI deficiency; Glanzmann thrombasthenia; Chediak-Higashi syndrome; congenital amegakaryocytic thrombocytopenia; May-Hegglin disorder/anomaly; Sebastian syndrome; MYH9-related disorders; autism with platelet dense granule defect; gray platelet syndrome; autosomal dominant tubular aggregate myopathy-2; ADP receptor defect; deficiency of phospholipase A2 group IV A; Quebec platelet disorder; aspirin-like defect; thrombocytopenia-absent radius syndrome; familial platelet disorder with predisposition to acute myeloid leukemia; Stormorken syndrome; York platelet syndrome; familial hemophagocytic lymphohistiocytosis type 5; thromboxane A2 receptor defect; Ghosal syndrome; ARC (arthrogryposis, renal dysfunction, and cholestasis) syndromes 1 and 2; Wiskott-Aldrich syndrome; a variety of platelet-type bleeding disorders; and hereditary/congenital thrombocytopenias, such as various macrothrombocytopenias. These congenital thrombocytopenias include sitosterolemia with macrothrombocytopenia; macrothrombocytopenia and sensorineural hearing loss; thrombocytopenia and susceptibility to cancer; X-linked thrombocytopenia with dyserythropoiesis; myopathy associated with thrombocytopenia; amegakaryocytic thrombocytopenia with radioulnar synostoses 1 and 2; thrombocytopenia and erythrokeraderma; thrombocytopenia anemia and myelofibrosis; and thrombocytopenia progressing to trilineage bone marrow failure. The risk for developing bleeding or other phenotypic features associated with these disorders and syndromes varies. Several of the genes on this panel have established bleeding, thrombocytopenia, and other hematologic or nonhematologic disease associations. Several of the genes on this panel also have expert group guidelines.(1,3-5) It is recommended that genetic testing be offered to all patients suspected of having a heritable platelet disorder since some patients may have normal platelet laboratory testing results.(1,6)

Useful For: Evaluating hereditary platelet disorders in patients with a personal or family history suggestive of a hereditary platelet disorder Diagnosing hereditary platelet disorders for patients in whom phenotypic testing is nondiagnostic, but there is a strong clinical suspicion of the hereditary platelet disorder Confirming a hereditary platelet disorder diagnosis with the identification of a known or suspected disease-causing alteration in one or more of 70 genes associated with a variety of hereditary platelet disorders Determining the disease-causing alterations within one or more of these 70 genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of a platelet disorder Identifying the causative alteration for genetic counseling purposes Prognosis and risk assessment based on the genotype-phenotype correlations Providing a prognosis in syndromic hereditary platelet disorders Carrier testing for close family members of an individual with a hereditary platelet disorder diagnosis This test is not intended for prenatal diagnosis.

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Gomez K, Anderson J, Baker P, et al: Clinical and laboratory diagnosis of heritable platelet disorders in adults and children: a British Society for Haematology Guideline. Brit J Haematol. 2021 Oct;195(1):46-72 2. Nurden AT, Freson K, Selifsohn U: Inherited platelet disorders.

Haemophilia. 2012 July;18(s4):154-160 3. International Society on Thrombosis and Haemostasis: Bleeding Thrombotic and Platelet Disorder TIER1 genes. ISTH; 2018. Updated July 2022. Accessed October 6, 2022. Available at: www.isth.org/page/GinTh_GeneLists 4. Megy K, Downes K, Simeoni I, et al: Curated disease-causing genes for bleeding, thrombotic, and platelet disorders: Communication from the SSC of the ISTH. J Thromb Haemost. 2019 Aug;17(8):1253-1260 5. Bolton-Maggs PHB, Chalmers EA, Collins PW, et al: A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. Brit J Haematol. 2006 Dec;135(5):603-633 6. Watson SP, Lowe GC, Lordkipanidze M, Morgan NV, GAPP consortiuml: Genotyping and phenotyping of platelet function disorders. J Thromb Haemost. 2013 June;11 Suppl 1:351-363 7. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

GNPFD
619355

Platelet Function Defect Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Platelets have essential roles in primary hemostasis. Patients with either hereditary or acquired platelet disorders usually have bleeding diathesis, which can potentially be life-threatening. They may also have issues with the development and/or functioning of major organs.(2) Inherited platelet disorders can be syndromic (ie, associated with current or future development of other organ system defects) or non-syndromic (ie, isolated to thrombocytopenia with no other organ system defects). A reliable laboratory diagnosis of a platelet disorder can significantly impact patients' and, potentially, their family members' clinical management and outcome. Identification of an alteration that is known or suspected to cause disease aids in confirmation of the diagnosis and potentially provides prognostic information especially in syndromic inherited platelet disorders. This panel evaluates 17 genes associated with a variety of hereditary platelet function defect disorders, including Scott syndrome; leukocyte integrin adhesion deficiency type III; Bernard-Soulier syndrome; mild macrothrombocytopenia; platelet-type von Willebrand disease; bleeding diathesis due to glycoprotein VI deficiency; Glanzmann thrombasthenia; platelet-type bleeding disorder 16; thrombosis/bleeding; adenosine diphosphate receptor defect; deficiency of phospholipase A2 group IV A; aspirin-like defect; platelet-type bleeding disorder 12; platelet-type bleeding disorder 18; thrombocytopenia 6; thromboxane A2 receptor defect; and Ghosal syndrome. The risk for developing bleeding or other phenotypic features associated with these disorders and syndromes varies. Several of the genes on this panel have established bleeding, thrombocytopenia, or other hematologic or non-hematologic disease associations. Several of the genes on this panel also have expert group guidelines.(1,3-5) It is recommended that genetic testing be offered to all patients suspected of having a heritable platelet disorder since some patients may have normal platelet laboratory testing results.(1,6)

Useful For: Diagnosing hereditary platelet function defect disorders for patients who have a distinct platelet function defect pattern, such as Bernard-Soulier syndrome, revealed by laboratory phenotypic testing Confirming a hereditary platelet function defect disorder diagnosis with the identification of a known or suspected disease-causing alteration in one or more of 17 genes associated with a variety of hereditary platelet function defect disorders Determining the disease-causing alterations within one or more of these 17 genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of a platelet function defect disorder Identifying the causative alteration for genetic counseling purposes Prognosis and risk assessment based on the genotype-phenotype correlations Providing a prognosis in syndromic hereditary platelet function defect disorders Carrier testing for close family members of an individual with a hereditary platelet function defect disorder diagnosis This test is not intended for prenatal diagnosis.

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or

possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Gomez K, Anderson J, Baker P, et al: Clinical and laboratory diagnosis of heritable platelet disorders in adults and children: a British Society for Haematology Guideline. Brit J Haematol. 2021 Oct;195(1):46-72 2. Nurden AT, Freson K, Selifsohn U: Inherited platelet disorders. Haemophilia. 2012 July;18(s4):154-160 3. International Society on Thrombosis and Haemostasis: Bleeding Thrombotic and Platelet Disorder TIER1 genes. ISTH; 2018. Updated July 2022. Accessed October 6, 2022. Available at: www.isth.org/page/GinTh_GeneLists 4. Megy K, Downes K, Simeoni I, et al: Curated disease-causing genes for bleeding, thrombotic, and platelet disorders: Communication from the SSC of the ISTH. J Thromb Haemost. 2019 Aug;17(8):1253-1260 5. Bolton-Maggs PHB, Chalmers EA, Collins PW, et al: A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. Brit J Haematol. 2006 Dec;135(5):603-633 6. Watson SP, Lowe GC, Lordkipanidze M, Morgan NV, GAPP consortium: Genotyping and phenotyping of platelet function disorders. J Thromb Haemost. 2013 June;11(Suppl 1):351-63 7. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

PNP
8866

Platelet Neutralization Procedure, Plasma

Clinical Information: Prolonged clotting times may be due to a variety of factors including the presence of clotting factor deficiencies, factor inhibitors, and lupus anticoagulants (antiphospholipid antibodies). When a prolonged activated partial thromboplastin time (APTT) demonstrates inhibition on mixing with normal plasma indicative of presence of an inhibitor, the platelet neutralization procedure (PNP) is useful in determining if this inhibition is due to presence of a lupus anticoagulant (LAC). The PNP involves the addition of washed, freeze-thawed platelets or buffer to the patient's plasma. An APTT is done on both mixtures and the clotting times are compared. Additional phospholipid supplied by the PNP reagent can absorb LAC, thereby diagnostically shortening the APTT. For performance and interpretation of the PNP, the baseline APTT should be significantly prolonged (preferably at least 3 to 5 seconds above the upper limit of the reference range), and APTT inhibition must be demonstrated or suggested by a mixing study with normal plasma (ie, 1:1 mix fails to shorten into the normal range).

Useful For: Aiding in the confirmation or exclusion of the presence of a lupus anticoagulant (LAC) inhibitor when used in conjunction with other appropriate coagulation tests. Aids in differentiating deficiencies or inhibitors of specific coagulation factors (eg, factor VIII inhibitor) from LAC inhibitors

Interpretation: Interpretation of the results of the platelet neutralization procedure (PNP) test is complex and needs to be performed in the context of results of mixing study of the prolonged activated partial thromboplastin time (APTT), the APTT PNP and the buffer control APTT, as well as results of other coagulation tests (eg, prothrombin time and thrombin time as well as available clinical information). Plasma containing lupus anticoagulant (LAC) will demonstrate shortening of the PNP Platelets APTT by 2 or more seconds when compared to the baseline PNP Saline APTT.

Reference Values:
Only orderable as a reflex. For more information see:
ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
AATHR / Thrombophilia Profile, Plasma and Whole Blood

APROL / Prolonged Clot Time Profile, Plasma
ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

An interpretive report will be provided.

Clinical References: 1. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. Thromb Haemost. 1995;74(5):1185-1190 2. Brandt JT, Barna LK, Triplett DA. Laboratory identification of lupus anticoagulants: results of the second international workshop for identification of lupus anticoagulants. Thromb Haemost. 1995;74(6):1597-1603 3. Gastineau DA, Kazmier FJ, Nichols WL, Bowie EJ. Lupus anticoagulant: an analysis of the clinical and laboratory features of 219 cases. Am J Hematol. 1985;19(3):265-275 4. Cardel LK, Fisher PK, Heit JA, et al. Detection of lupus anticoagulants and anticardiolipin antibodies: prevalence of positive test in 665 patients. Thromb Haemost. 1993;69:1221 5. Kottke-Marchant K, Davis BH. Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012 6. Clinical and Laboratory Standards Institute (CLSI). Laboratory Testing for the Lupus Anticoagulant; Approved Guideline. CLSI document H60-A. CLSI; 2014

GNSPD
619327

Platelet Storage Pool Deficiency Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Platelets have essential roles in primary hemostasis. Patients with either hereditary or acquired platelet disorders usually have bleeding diathesis, which can potentially be life-threatening. They may also have issues with the development and/or functioning of major organs.(2) Inherited platelet disorders can be syndromic (ie, associated with current or future development of other organ system defects) or nonsyndromic (ie, isolated to thrombocytopenia with no other organ system defects). A reliable laboratory diagnosis of a platelet disorder can significantly impact patients' and, potentially, their family members' clinical management and outcome. Identification of an alteration that is known or suspected to cause disease aids in confirmation of the diagnosis and potentially provides prognostic information, especially in syndromic inherited platelet disorders. This panel evaluates 24 genes associated with a variety of hereditary platelet storage pool deficiencies, including reduced adenosine diphosphate (ADP)-induced platelet aggregation; Hermansky-Pudlak syndrome; Paris-Trousseau-Jacobsen syndrome; platelet-type bleeding disorder 17; Chediak-Higashi syndrome; autism with platelet dense granule defect; gray platelet syndrome; autosomal dominant tubular aggregate myopathy-2; Quebec platelet disorder; Stormorken syndrome; York platelet syndrome; familial hemophagocytic lymphohistiocytosis type 5; ARC syndromes (arthrogryposis, renal dysfunction, and cholestasis) 1 and 2; and Wiskott-Aldrich syndrome. The risk for developing bleeding or other phenotypic features associated with these disorders and syndromes varies. Several of the genes on this panel have established bleeding, thrombocytopenia, or other hematologic or nonhematologic disease associations. Several of the genes on this panel also have expert group guidelines.(1,3-5) It is recommended that genetic testing be offered to all patients suspected of having a heritable platelet disorder since some patients may have normal platelet laboratory testing results.(1,6)

Useful For: Evaluating hereditary platelet storage pool deficiencies in patients with a personal or family history suggestive of a hereditary platelet storage pool deficiency Diagnosing hereditary platelet storage pool deficiencies for patients in whom phenotypic testing is nondiagnostic, but there is a strong clinical suspicion of the hereditary platelet storage pool deficiency Confirming a hereditary platelet storage pool deficiency diagnosis with the identification of a known or suspected disease-causing alteration in one or more of 24 genes associated with a variety of hereditary platelet storage pool deficiencies Determining the disease-causing alterations within one or more of these 24 genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of a platelet storage pool deficiency Identifying the causative alteration for genetic counseling purposes Prognosis and risk

assessment based on the genotype-phenotype correlations Providing a prognosis in syndromic hereditary platelet storage pool deficiencies Carrier testing for close family members of an individual with a hereditary platelet storage pool deficiency diagnosis This test is not intended for prenatal diagnosis

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Gomez K, Anderson J, Baker P, et al: Clinical and laboratory diagnosis of heritable platelet disorders in adults and children: a British Society for Haematology Guideline. Brit J Haematol. 2021 Oct;195(1):46-72 2. Nurden AT, Freson K, Selifsohn U: Inherited platelet disorders. Haemophilia. 2012 July;18 Suppl 4:154-160 3. International Society on Thrombosis and Haemostasis: Bleeding Thrombotic and Platelet Disorder TIER1 genes. ISTH; 2018. Updated July 2022. Accessed October 6, 2022. Available at: www.isth.org/page/GinTh_GeneLists 4. Megy K, Downes K, Simeoni I, et al: Curated disease-causing genes for bleeding, thrombotic, and platelet disorders: Communication from the SSC of the ISTH. J Thromb Haemost. 2019 Aug;17(8):1253-1260 5. Bolton-Maggs PHB, Chalmers EA, Collins PW, et al: A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. Brit J Haematol. 2006 Dec;135(5):603-633 6. Watson SP, Lowe GC, Lordkipanidze M, Morgan NV, GAPP consortium: Genotyping and phenotyping of platelet function disorders. J Thromb Haemost. 2013 June;11 Suppl 1:351-363 7. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

PLAFL
64278

Platelet Surface Glycoprotein by Flow Cytometry, Blood

Clinical Information: Platelets have essential roles in primary hemostasis. Exposed collagen at a vascular damage site can activate platelets via collagen receptor GPVI and GPIa and bind shear-stretched multimeric VWF proteins, which subsequently interact with the platelet surface receptor, GPIb-V-IX. Upon full activation, platelets can aggregate by binding to fibrinogen through activated GPIIb-GPIIIa receptors. Deficiency of platelet surface glycoproteins can cause bleeding diathesis. Platelet flow cytometric analysis is the preferred method to assess hereditary platelet disorders due to quantitative surface glycoprotein (GP) deficiencies. GP expression levels can be measured by using fluorescent-conjugated GP-specific antibodies and their fluorescent intensities can be compared to normal ranges of various glycoproteins. CD Number Glycoprotein Name Integrin Name CD41 GPIIb Alpha 2b CD42a GPIX NA CD42b GPIb-alpha NA CD49b GPIa Alpha 2 CD61 GPIIIa Beta 3 NA GPVI NA

Useful For: Identification of markedly decreased CD41 (GPIIb) and CD61 (GPIIIa) expression levels, which are diagnostic for Glanzmann thrombasthenia Identification of markedly decreased CD42a (GPIX) and CD42b (GPIb-alpha) expression levels, which are diagnostic for Bernard-Soulier syndrome Identification of decreased GPVI expression, which suggests collagen receptor deficiency Identification of decreased CD49b (GPIa), which suggests collagen receptor deficiency

Interpretation:

Reference Values:
GPIIb CD41: > or =70.0% (Normal Range-Median)

GPIIIa CD61: > or =70.0% (Normal Range-Median)
GPIX CD42a: > or =70.0% (Normal Range-Median)
GPIb-alpha CD42b: > or =70.0% (Normal Range-Median)
GPIa CD49b: > or =60.0% (Normal Range-Median)

Clinical References: 1. Miller, JL. Glycoprotein analysis for the diagnostic evaluation of platelet disorders. Semin Thromb Hemost. 2009;35(2):224-232 2. Kannan M, Ahmad F, Yadav BK, et al. Carrier detection in Glanzmann thrombasthenia: comparison of flow cytometry and Western blot with respect to DNA mutation. Am J Clin Pathol. 2008;130(1):93-98 3. Savoia A, Pastore A, De Rocco D, et al: Clinical and genetic aspects of Bernard-Soulier syndrome: searching for genotype/phenotype correlations. Haematologica. 2011;96(3):417-423 4. Nurden AT, Freson K, Selifsohn U. Inherited platelet disorders. Haemophilia. 2012;18(4):154-160 5. Spurgeon BEJ, Naseem KM. Platelet Flow Cytometry: Instrument Setup, Controls, and Panel Performance. Cytometry B Clin Cytom. 2020;98(1):19-27 6. Frelinger AL, 3rd, Rivera J, Connor DE, et al. Consensus recommendations on flow cytometry for the assessment of inherited and acquired disorders of platelet number and function: Communication from the ISTH SSC Subcommittee on Platelet Physiology. J Thromb Haemost. 2021;19(12):3193-3202

PTEM
75652

Platelet, Transmission Electron Microscopic Study, Whole Blood

Reference Values:
Reporting limit determined each analysis.

Normally: Less than 1 mcg/L.
Total serum platinum concentrations following administration of platinum-based chemotherapeutics vary based on route of administration, duration of treatment and other pharmacokinetic variables.
Peak concentrations in excess of 2000 mcg/L are common.

PLUM
82809

Plum, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to plum Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be

responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PMLR
84114

PML::RARA Quantitative, PCR, Varies

Clinical Information: Acute promyelocytic leukemia (APL) accounts for 5% to 10% of acute myeloid leukemia and, generally, has a good prognosis with current treatment protocols. APL cells contain a fusion gene comprised of the downstream sequences of the retinoic acid receptor alpha gene (RARA) fused to the promoter region and upstream sequences of one of several genes, the most common (>80%) being the promyelocytic leukemia gene (PML). The fusion gene is designated PML::RARA and may be seen in a karyotype as t(15;17)(q22;q12). Messenger RNA produced from the fusion gene can be detected using a polymerase chain reaction (PCR)-based assay and indicates the presence of neoplastic cells. The PCR-based assay has greater sensitivity than standard methods such as morphology review, karyotyping, or fluorescence in situ hybridization. Recent studies have indicated that sensitive monitoring is important because the majority of patients who remain PCR positive, or become PCR positive again following treatment, will relapse and will likely benefit from early intervention for residual/recurrent disease. This quantitative assay allows PML::RARA levels to be monitored rather than simply detecting the presence or absence of disease.

Useful For: Diagnosis of acute promyelocytic leukemia (APL) Detection of residual or recurrent APL Monitoring the level of PML::RARA (promyelocytic leukemia/retinoic acid receptor alpha) in APL patients

Interpretation: The assay is reported in the form of a normalized ratio of PML::RARA (promyelocytic leukemia/retinoic acid receptor alpha) fusion transcript to the control gene ABL1 expressed as a percentage, which is an estimate of the level of PML::RARA RNA present in the specimen, expressed in relation to the level of RNA from an internal control gene (ABL1). The normalized ratio has no units but is directly related to the level of PML::RARA detected (ie, larger numbers indicate higher levels of PML::RARA and smaller numbers indicate lower levels). A relative expression value minimizes variability in the RNA levels measured in separate specimens tested at

different times. Although a quantitative polymerase chain reaction assay is performed, the precision of the assay is such that results must be considered semiquantitative, and it is recommended that only log changes be considered significant. Critical results, such as a change in the status of positivity, should be repeated on a separate specimen to verify the result.

Reference Values:
An interpretive report will be provided.

If positive, a value representing a ratio of PML::RARA fusion transcript to the control gene ABL1 expressed as a percentage will be reported.

Clinical References: 1. Grimwade D, Lo Coco F. Acute promyelocytic leukemia: a model for the role of molecular diagnosis and residual disease monitoring in directing treatment approach in acute myeloid leukemia. Leukemia. 2002;16(10):1959-1973 2. Adams J, Nassiri M. Acute promyelocytic leukemia: A review and discussion of variant translocations. Arch Pathol Lab Med. 2015;139(10):1308-1313 3. Kayser S, Schlenk RF, Platzbecker U. Management of patients with acute promyelocytic leukemia. Leukemia. 2018;32(6):1277-1294 4. Ablain J, de The H. Revisiting the differentiation paradigm in acute promyelocytic leukemia. Blood. 2011;117(22):5795-5802

PMPDD
66569

PMP22 Gene, Large Deletion/Duplication Analysis, Varies

Clinical Information: This test is appropriate as a first-tier test for individuals with clinical features suggestive of Charcot-Marie-Tooth type 1A (CMT1A) and/or hereditary neuropathy with liability to pressure palsies (HNPP). Charcot-Marie-Tooth type 1A is a dominantly inherited disease characterized by progressive distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity starting early in life. Duplications of the PMP22 gene are associated with CMT1A and are thought to account for 45%-50% of all CMT and up to 80% of demyelinating CMT. Deletions of PMP22 are associated with HNPP, a dominantly inherited disease resulting in peripheral neuronal demyelination. HNPP is characterized clinically by recurrent focal motor and sensory neuropathy in a single nerve that can manifest as numbness, muscular weakness, and atrophy. Deletions of PMP22 are thought to account for up 80% of HNPP.

Useful For: Diagnosis of Charcot-Marie-Tooth type 1A or hereditary neuropathy with liability to pressure palsies

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. van Paassen BW, van der Kooi AJ, van Spaendonck-Zwarts KY, Verhamme C, Baas F, de Visser M. PMP22 related neuropathies: Charcot-Marie-Tooth disease type 1A and Hereditary Neuropathy with liability to Pressure Palsies. Orphanet J Rare Dis. 2014;9:38 3. Li J, Parker B, Martyn C, Natarajan C, Guo J. The PMP22 gene and its related diseases. Mol Neurobiol. 2013;47(2):673-698 4. Bird TD. Charcot-Marie-Tooth Hereditary Neuropathy Overview. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated August 1, 2024. Accessed

January 16, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1358/ 5. Chen L, Zhang H, Li C, Yang N, Wang J, Liang J. Literature review of clinical analysis of hereditary neuropathy with liability to pressure palsies. J Neurol. 2024;272(1):41. doi:10.1007/s00415-024-12839-7 6. Chrestian N. Hereditary Neuropathy with Liability to Pressure Palsies. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated August 27, 2020. Accessed January 16, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1392/ 7. Martinez Thompson JM, Klein CJ. Thirty Years Later, Case Closed: A Case of PMP22 Triplication From Anticipation. Mayo Clin Proc. 2016;91(5):687-688. doi:10.1016/j.mayocp.2015.12.019 8. Pisciotta C, Bertini A, Tramacere I, et al. Clinical spectrum and frequency of Charcot-Marie-Tooth disease in Italy: Data from the National CMT Registry. Eur J Neurol. 2023;30(8):2461-2470. doi:10.1111/ene.15860 9. Weterman MA, van Ruissen F, de Wissel M, et al. Copy number variation upstream of PMP22 in Charcot-Marie-Tooth disease. Eur J Hum Genet. 2010;18(4):421-428. doi:10.1038/ejhg.2009.186 10. Zhang F, Seeman P, Liu P, et al. Mechanisms for nonrecurrent genomic rearrangements associated with CMT1A or HNPP: rare CNVs as a cause for missing heritability. Am J Hum Genet. 2010;86(6):892-903. doi:10.1016/j.ajhg.2010.05.001

PMS2
70540

PMS2 Immunostain, Technical Component Only

Clinical Information: Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline variants in the mismatch repair genes: MLH1, MSH2, MSH6, and PMS2. Hereditary nonpolyposis colorectal cancer is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 variants (approximately 50%-80%) is generally higher than the risks associated with variants in the other HNPCC-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include sebaceous neoplasms, gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, variants within the PMS2 gene confer the lowest risk for any of the tumors within the HNPCC spectrum. Several clinical variants of HNPCC have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair variants (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous or compound heterozygous mismatch repair alterations, characterized by the presence of biallelic deleterious alterations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals with a personal or family history of cancer suggestive of HNPCC. Testing tumors from individuals at risk for HNPCC for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair phenotype within the tumor but does not suggest in which gene the abnormality rests. Tumors from individuals affected by HNPCC usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined). The MSI-H phenotype can also be seen in individuals whose tumors have somatic MLH1 promoter hypermethylation. Tumors from individuals that show the MSS/MSI-L phenotype (MSI at <30% of microsatellites examined), are not likely to have HNPCC or somatic hypermethylation of MLH1. Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of HNPCC-related cancers. If defective DNA mismatch repair is identified within the tumor, variant analysis of the associated gene can be performed to identify the causative germline variant and allow for predictive testing of at-risk

individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline alterations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analysis, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that this HNPCC screen is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome and identifies patients who might benefit from subsequent genetic testing.

Useful For: Identifying patients at high risk for having hereditary nonpolyposis colorectal cancer, also known as Lynch syndrome, in an immunopanel including PMS2 and other mismatch repair markers
Evaluation of tumor tissue to identify patients at risk for having hereditary endometrial carcinoma in an immunopanel including PMS2 and other mismatch repair markers

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Burgart LJ. Testing for defective DNA mismatch repair in colorectal carcinoma: a practical guide. Arch Pathol Lab Med. 2005;129(11):1385-1389 2. Klarskov L, Ladelund S, Holck S, et al. Interobserver variability in the evaluation of mismatch repair protein immunostaining. Hum Pathol. 2010;41(10):1387-1396 3. Lanza G, Gafa R, Maestri I, Santini A, Matteuzzi M, Cavazzini L. Immunohistochemical pattern of MLH1/MSH2 expression is related to clinical and pathological features in colorectal adenocarcinomas with microsatellite instability. Mod Pathol. 2002;15(7):741-749 4. Modica I, Soslow RA, Black D, Tornos C, Kauff N, Shia J. Utility of immunohistochemistry in predicting microsatellite instability in endometrial carcinoma. Am J Surg Pathol. 2007;31(5):744-751 5. Mojtahed A, Schrijver I, Ford JM, Longacre TA, Pai RK. A two-antibody mismatch repair protein immunohistochemistry screening approach for colorectal carcinomas, skin sebaceous tumors, and gynecologic tract carcinomas. Mod Pathol. 2011;24(7):1004-1014 6. Rigau V, Sebbagh N, Olschwang S, et al. Microsatellite instability in colorectal carcinoma. The comparison of immunohistochemistry and molecular biology suggests a role for hMSH6 [correction of hMLH6] immunostaining. Arch Pathol Lab Med. 2003;127(6):694-700 7. Shia J. Immunohistochemistry versus microsatellite instability testing for screening colorectal cancer patients at risk for hereditary nonpolyposis colorectal cancer syndrome. Part I. The utility of immunohistochemistry. J Mol Diagn. 2008;10(4):293-300 8. Salem ME, Bodor JN, Puccini A, et al. Relationship between MLH1, PMS2, MSH2 and MSH6 gene-specific alterations and tumor mutational burden in 1057 microsatellite instability-high solid tumors. Int J Cancer. 2020;147(10):2948-2956. doi:10.1002/ijc.33115 9. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FPNAP
57589

Pneumococcal Antibody Panel (12 Serotype)

Reference Values:

Pneumococcal Antibody Panel	Reference Range
Pneumo Ab Type 1	>1.3 ug/mL
Pneumo Ab Type 3	>1.3 ug/mL

Pneumo Ab Type 4	>1.3 ug/mL
Pneumo Ab Type 8	>1.3 ug/mL
Pneumo Ab Type 9 (9N)	>1.3 ug/mL
Pneumo Ab Type 12 (12F)	>1.3 ug/mL
Pneumo Ab Type 14	>1.3 ug/mL
Pneumo Ab Type 19 (19F)	>1.3 ug/mL
Pneumo Ab Type 23 (23F)	>1.3 uh/mL
Pneumo Ab Type 26 (6B)	>1.3 ug/mL
Pneumo Ab Type 51 (7F)	>1.3 ug/mL
Pneumo Ab Type 56 (18C)	>1.3 ug/mL

PNRP
81698

Pneumocystis jiroveci, Molecular Detection, PCR, Varies

Clinical Information: Pneumocystis pneumonia is an important cause of opportunistic infection in patients who are immunocompromised, particularly those with HIV. The causative agent, Pneumocystis jiroveci, cannot be cultured in vitro, and, therefore, laboratory detection has historically relied upon microscopic identification directly from patient specimens using fluorescent stains or antibodies. Stains often lack sensitivity and require expertise on the part of the reader to differentiate Pneumocystis jiroveci from staining artifacts and other fungi. This real-time polymerase chain reaction assay provides a sensitive and specific detection of Pneumocystis from bronchoalveolar lavage fluid and other respiratory specimens.

Useful For: Preferred test for detection of Pneumocystis

Interpretation: A positive result indicates the presence of Pneumocystis DNA. A negative result indicates the absence of detectable Pneumocystis DNA.

Reference Values:
Not applicable

Clinical References: 1. Senecal J, Smyth E, Del Corpo O, et al: Non-invasive diagnosis of Pneumocystis jirovecii pneumonia: a systematic review and meta-analysis. Clin Microbiol Infect. 2022 Jan;28(1):23-30. doi: 10.1016/j.cmi.2021.08.017 2. Apostolopoulou A, Fishman JA: The pathogenesis and diagnosis of Pneumocystis jiroveci pneumonia. J Fungi (Basel). 2022 Nov 5;8(11):1167. doi: 10.3390/jof8111167 3. Fishman JA. Pneumocystis jiroveci. Semin Respir Crit Care Med. 2020 Feb;41(1):141-157. doi: 10.1055/s-0039-3399559

D240
70416

Podoplanin (D2-D40) Immunostain, Technical Component Only

POLET
619676

POLE Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information: This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for mutations involving the POLE gene known to be associated with a variety of tumor types, including endometrial, ovarian, lung, and colorectal cancers, and diffuse glioma. POLE (exonuclease domain) alterations are typically associated with ultramutated tumors with a high tumor mutation burden and may occur as a part of constitutional replication repair deficiency syndrome.

Useful For: Identifying specific mutations within the POLE gene to assist in tumor diagnosis/classification

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. Cancer Genome Atlas Network: Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487(7407):330-337 4. Church DN, Briggs SE, Palles C,et al: DNA polymerase e and d exonuclease domain mutations in endometrial cancer. Hum Mol Genet. 2013;22(14):2820-8 5. Hoang LN, McConechy MK, Kobel M, et al. Polymerase Epsilon Exonuclease Domain Mutations in Ovarian Endometrioid Carcinoma. Int J Gynecol Cancer. 2015;25(7):1187-1193 6. Palles C, Cazier JB, Howarth KM,et al: Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet. 2013;45(2):136-144 7. Rohlin A, Zagoras T, Nilsson Set al. A mutation in POLE predisposing to a multi-tumour phenotype. Int J Oncol. 2014;45(1):77-81 8. Jumaah AS, Salim MM, Al-Haddad HS, et al: The frequency of POLE-mutation in endometrial carcinoma and prognostic implications: a systemic review and meta-analysis. J Pathol Transl Med. 2020;54(6):471-479 9. Wu Q, Zhang N, Xie X: The clinicopathological characteristics of POLE-mutated/ultramutated endometrial carcinoma and prognostic value of POLE status: a meta-analysis based on 49 articles incorporating 12,120 patients. BMC Cancer. 2022;22(1):1157 10. Leon-Castillo A, Britton H, McConechy MK, et al: Interpretation of somatic POLE mutations in endometrial carcinoma. J Pathol. 2020;250(3):323-335

FPOLO 75165 Poliovirus (Types 1, 3) Antibodies, Neutralization

Clinical Information: This sensitive procedure is recommended for vaccine response testing and type-specific serodiagnosis of recent poliovirus infection. It can also serve as an aid for diagnosing immune deficiency disorders.

Reference Values:
Polio 1 Titer: <1:8
Polio 3 Titer: <1:8

The presence of neutralizing serum antibodies (titers 1:8 up to >1:128) against polioviruses implies lifelong immunity. Some persons without detectable titers (<1:8) may also be immune as demonstrated by elicitation of a secondary-type serum antibody response upon rechallenge with live polio vaccine.

FPOLE 57942 Pollock White (Pollachius virens) IgE

Interpretation:

Reference Values:
<0.35 kU/L

PVJAK 65116 Polycythemia Vera, JAK2 V617F with Reflex to JAK2 Exon 12-15, Sequencing for Erythrocytosis, Varies

Clinical Information: The Janus kinase 2 (JAK2) gene codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. The JAK2 V617F mutation is located in exon 14 and present in 50% to 60% of primary myelofibrosis and essential thrombocythemia and in 95% to 98% of polycythemia vera (PV). In the rest of the PV cases, over 50 different mutations have been reported within exons 12 through 15 of JAK2, and essentially all non-V617F JAK2 mutations have been identified in PV. These mutations include point alterations and small insertions or deletions. Several of the exon 12 mutations have been shown to have biologic effects similar to those caused by the V617F mutation such that it is currently assumed other nonpolymorphic mutations have similar clinical effects. However, some mutations may not be well characterized and require further clinical and research evaluation.

Useful For: Aiding in the distinction between the myeloproliferative neoplasm polycythemia vera and other secondary erythrocytosis

Interpretation: The results will be reported as 1 of the 3 following states: -Positive for JAK2 V617F mutation -Positive for JAK2 mutation (other than V617F) -Negative for JAK2 mutations If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence are reported. A positive mutation status is highly suggestive of a myeloid neoplasm and may support a diagnosis of polycythemia vera in the appropriate clinical setting. Correlation with clinicopathologic findings and other laboratory results is necessary in all cases. A negative mutation status makes a diagnosis of polycythemia vera highly unlikely, although it does not completely exclude this possibility, other myeloproliferative neoplasms, or other neoplasms.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. 2005;365(9464):1054-1061. doi:10.1016/S0140-6736(05)71142-9 2. James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive signaling causes polycythaemia vera. Nature. 2005;434(7037):1144-1148. doi:10.1038/nature03546 3. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med. 2005;352(17):1779-1790. doi:10.1056/NEJMoa051113 4. Steensma DP, Dewald GW, Lasho TL, et al. The JAK2 V617F activating tyrosine kinase mutation is an infrequent event in both "atypical" myeloproliferative disorders and the myelodysplastic syndrome. Blood. 2005;106(4):1207-1209. doi:10.1182/blood-2005-03-1183 5. Ma W, Kantarjian H, Zhang X, et al. Mutation profile of JAK2 transcripts in patients with chronic myeloid neoplasias. J Mol Diagn. 2009;11(1):49-53 6. Kilpivaara O, Levine RL. JAK2 and MPL mutations in myeloproliferative neoplasms: discovery and science. Leukemia. 2008;22(10):1813-1817. doi:10.1038/leu.2008.229 7. Kravolics R: Genetic complexity of myeloproliferative neoplasms. Leukemia. 2008;22(10):1841-1848. doi:10.1038/leu.2008.233 8. Defour JP, Chachoua I, Pecquet C, Constantinescu SN. Oncogenic activation of MPL/thrombopoietin receptor by 17 mutations at W515: implications for myeloproliferative neoplasms. Leukemia. 2016;30(5):1214-1216. doi:10.1038/leu.2015.271 9. Tefferi A. The classic myeloproliferative neoplasms: Chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia, and primary myelofibrosis. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019, Accessed January 5, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225078035&bookid=2709

TALDO
61843

Polyols, Quantitative, Urine

Clinical Information:

Useful For: Diagnosing deficiencies of transaldolase, transketolase, sedoheptulose, or ribose-5-phosphate isomerase

Interpretation: An interpretive report will be provided. All profiles are reviewed by the laboratory director and interpretation is based on pattern recognition. A detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo Clinic or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

ERYTHRITOL
< or =11 months: <220 mmol/mol creatinine
1-3 years: <267 mmol/mol creatinine
4-17 years: <171 mmol/mol creatinine
>or =18 years: <99 mmol/mol creatinine

ARABINITOL
< or =11 months: <140 mmol/mol creatinine
1-3 years: <149 mmol/mol creatinine
4-17 years: <97 mmol/mol creatinine
>or =18 years: <51 mmol/mol creatinine

RIBITOL
< or =11 months: <31 mmol/mol creatinine
1-3 years: <31 mmol/mol creatinine
4-17 years: <17 mmol/mol creatinine
>or =18 years: <11 mmol/mol creatinine

SEDOHEPTULOSE
< or =11 months: <76 mmol/mol creatinine
1-3 years: <27 mmol/mol creatinine
4-17 years: <28 mmol/mol creatinine
>or =18 years: <22 mmol/mol creatinine

Clinical References: 1. Wamelink MM, Ramos RJ, van den Elzen AP, et al. First two unrelated cases of isolated sedoheptulokinase deficiency: A benign disorder?. J Inherit Metab Dis. 2015;38(5):889-894. doi:10.1007/s10545-014-9809- 2. OMIM: 617044. Short Stature, Developmental Delay, and Congenital Heart Defects; SDDHD. Johns Hopkins University; 2016. Last updated April 07, 2021, Accessed September 27, 2024. Available at www.omim.org/entry/617044 3. OMIM: 617213. Sedoheptulokinase Deficiency; SHPKD. Johns Hopkins University; 2016. Accessed September 27, 2024. Available at www.omim.org/entry/617213 4. Eyaid W, Al Harbi T, Anazi S, et al. Transaldolase deficiency: report of 12 new cases and further delineation of the phenotype. J Inherit Metab Dis. 2013;36(6):997-1004 5. Huck JH, Verhoeven NM, Struys EA, et al. Ribose-5-phosphate isomerase deficiency: new inborn error in the pentose phosphate pathway associated with a slowly progressive leukoencephalopathy. Am J Hum Genet. 2004;74(4):745-751 6. Stincone A, Prigione A, Cramer T, et al. The return of metabolism: biochemistry and physiology of the pentose phosphate pathway. Biol Rev Camb Philos Soc. 2015;90(3):927-963. doi:10.1111/brv.12140 7. Wamelink MC, Valayannopoulos V, Jakobs C. Ribose-5-phosphate isomerase deficiency and transaldolase deficiency. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed September 27, 2024. Available at

FPOM 57918 Pomegranate (Punica granatum) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

PD2T 65296 Pompe Disease Second-Tier Newborn Screening, Blood Spot

Clinical Information: Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to variants in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and eventually, organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and eventually, death. Patients with Pompe disease, especially those with infantile, childhood, and juvenile onset, can have elevated serum enzymes (such as creatine kinase) secondary to cellular dysfunction. The clinical phenotype of Pompe disease lies on a spectrum, with differing clinical phenotypes dependent on age of onset and residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life, when left untreated. Juvenile and adult-onset forms, as the names suggest, are characterized by later onset and longer survival. All disease variants are eventually associated with progressive muscle weakness and respiratory insufficiency. Cardiomyopathy is associated almost exclusively with the infantile form. Treatment with enzyme replacement therapy is available, making early diagnosis of Pompe disease desirable, as early initiation of treatment may improve prognosis. Newborn screening can identify patients with all forms of Pompe disease, even before onset of symptoms. Newborn screening may also identify unaffected patients with GAA pseudodeficiency alleles and carriers. The ratio calculated using the creatine:creatinine ratio as the numerator and the activity of GAA as the denominator can differentiate true cases of infantile and late-onset Pompe disease from false-positive cases, such as carriers and pseudodeficiency of GAA enzyme. When applied to the newborn screening setting, this second-tier testing can provide results in a timely fashion and provide guidance in the decision to submit samples for additional confirmatory testing by molecular genetic analysis (GAAZ / Pompe Disease, Full Gene Analysis, Varies).

Useful For: Second-tier testing of newborns with an abnormal primary screening result for Pompe disease (decreased acid alpha-glucosidase enzyme activity) Follow-up testing for evaluation of an abnormal newborn screening result for Pompe disease

Interpretation: The quantitative measurements of informative metabolites and related ratios are evaluated using the Collaborative Laboratory Integrated Reports (CLIR) system. The report is in text form only, indicating if the applicable ratio is normal or abnormal and whether the CLIR postanalytical tool is informative for Pompe disease. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic Laboratories. Recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis) are provided in the interpretative report.

Reference Values:

An interpretive report will be provided.

Clinical References: 1. ACMG Newborn Screening ACT Sheets. Accessed August 30, 2023. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508 2. Pascual JM, Roe CR. Systemic metabolic abnormalities in adult-onset acid maltase deficiency: beyond muscle glycogen accumulation. JAMA Neurol. 2013;70(6):756-763 3. Tortorelli S, Eckerman JS, Orsini JJ, et al. Moonlighting newborn screening markers: The incidental discovery of a second-tier test for Pompe disease. Genet Med. 2018;20(8):840-846. doi:10.1038/gim.2017.190 4. Minter Baerg MM, Stoway SD, Hart J, et al. Precision newborn screening for lysosomal disorders. Genet Med. 2018;20(8):847-854. doi:10.1038/gim.2017.194 5. Ames EG, Fisher R, Kleyn M, Ahmad A. Current practices for U.S. newborn screening of Pompe disease and MPSI. Int J Neonatal Screen. 2020;6(3):72. doi:10.3390/ijns6030072

PDBS
602280

Pompe Disease, Blood Spot

Clinical Information: Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to variants in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and eventually, organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and eventually, death. Patients with Pompe disease, especially those with infantile, childhood, and juvenile onset, can have elevated serum enzymes (such as creatine kinase) secondary to cellular dysfunction. Delayed diagnosis of symptomatic patients with later onset Pompe disease is not unusual due to nonspecific and overlapping presentation (such as proximal muscle weakness and respiratory insufficiency) with more common neuromuscular diseases. The clinical phenotype of Pompe disease lies on a spectrum, with differing clinical phenotypes dependent on age of onset and residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life, when left untreated. Juvenile and adult-onset forms, as the names suggest, are characterized by later onset and longer survival. All disease variants are eventually associated with progressive muscle weakness and respiratory insufficiency. Cardiomyopathy is associated almost exclusively with the infantile form. Treatment with enzyme replacement therapy is available, making prompt diagnosis of Pompe disease desirable, as early initiation of treatment may improve prognosis. The ratio calculated using the creatine:creatinine ratio as the numerator and the activity of GAA as the denominator can differentiate true cases of infantile and late-onset Pompe disease from false-positive cases, such as carriers and pseudodeficiency of GAA enzyme. This determination can be performed in a timely fashion and provide guidance in the decision to submit samples for additional confirmatory testing by molecular genetic analysis (GAAZ / Pompe Disease, Full Gene Analysis, Varies).

GAAZ
35430

Pompe Disease, Full Gene Analysis, Varies

Clinical Information: Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive condition caused by deficiency of acid alpha-glucosidase. Enzyme insufficiency results in symptoms such as muscle weakness, cardiomyopathy, and respiratory problems. Pathogenic alterations in the GAA gene (which encodes acid alpha-glucosidase) are associated with Pompe disease. The diagnosis of this heterogeneous condition relies on both clinical and laboratory evaluation. Clinically, the condition is categorized into infantile and late-onset forms based on age of onset, organ involvement, and rate of progression. The infantile form (or classic Pompe disease) is the most severe form and is characterized by early onset and rapid progression of cardiac, liver, and muscle problems resulting in death within the first year. The infantile variant form has a similar age of onset but a milder clinical presentation. On the less severe end of the spectrum is the late-onset form with childhood, juvenile, or adult onset. The rate of progression and severity of symptoms is quite variable, particularly in the late-onset forms. The incidence varies by clinical type and ethnic population; the combined incidence is approximately 1 in 40,000 individuals. The calculated ratio of creatine (Cre) and creatinine (Crn) to acid-

alpha glucosidase (GAA) activity is useful for individuals with a suspected diagnosis of Pompe disease; for patients older than 6 weeks, order PDBS / Pompe Disease, Blood Spot; for patients 6 weeks and younger, order PD2T / Pompe Disease Second-Tier Newborn Screening, Blood Spot. Alternatively, enzyme studies can be ordered on blood via GAAW / Acid Alpha-Glucosidase, Leukocytes. When clinical manifestations and results of that analysis are supportive of a diagnosis of Pompe disease, variant analysis of the GAA gene is warranted. Additionally, measurement of the urine glucotetrasaccharide biomarker can aid in diagnosis and ongoing therapeutic monitoring (HEX4 / Glucotetrasaccharides, Random, Urine) Over 250 different variants have been identified in this gene including point alterations and large deletions. GAA full gene sequencing provided by this test will detect 2 variants in approximately 83% to 93% of individuals with confirmed GAA enzyme deficiency. Identification of genetic variants provides confirmation of the diagnosis and allows for subsequent testing of at risk family members.

Useful For: Confirmation of diagnosis of Pompe disease (as a follow-up to biochemical analyses)

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 2. Kishnani PS, Steiner RD, Bali D, et al: Pompe disease diagnosis and management guideline. Genet Med. 2006 May;8(5):267-288 3. Van der Ploeg AT, Reuser AJJ: Pompe's disease. Lancet. 2008;372(9646):1342-1353 4. Kroos M, Pomponio RJ, van Vliet L, et al: Update of the Pompe disease mutation database with 107 sequence variants and a format for severity rating. Hum Mut. 2008;29(6):E13-26 5. Reuser AJJ, Hirschhorn R, Kroos MA: Pompe disease: Glycogen storage disease type II, acid a-glucosidase (acid maltase) deficiency. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed June 30, 2020. Available at: https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225890450

FPOPW 57557 Poplar White (Populus alba) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

POPSD 82632 Poppy Seed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to

allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to poppy seed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FPORG
57627

Pork IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

FPRK4
57564

Pork IgG4

Interpretation: The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests.

PORK
82700

Pork, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to pork Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive

3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PBALP
64661

Porphobilinogen and Aminolevulinic Acid, Plasma

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and the excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, of the 5 hepatic porphyrias, 4 typically present with acute neurological manifestations and are designated the acute porphyrias. Clinically, however, these attacks can be prolonged and chronic. Three primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP but may be present in HCP and VP. Plasma porphobilinogen (PBG) and aminolevulinic acid (ALA) are elevated during the acute phase of these neurologic porphyrias. Urine and fecal porphyrin analysis should be performed to confirm the diagnosis and to distinguish among AIP, HCP, and VP. A biochemical diagnosis of AIP can be confirmed by measurement of PBG deaminase activity (PBGD_ / Porphobilinogen Deaminase, Whole Blood). VP and HCP can be confirmed by measurement of fecal porphyrins (FQPPS / Porphyrins, Feces). Once the biochemical diagnosis of an acute porphyria is established, molecular genetic testing is available (APGP / Acute Porphyria Gene Panel, Varies), which allows for diagnosis of at-risk family members. The very rare (<10 cases described) autosomal recessive ALA dehydratase deficiency porphyria (ADP) is also a primary acute porphyria causing neurovisceral symptoms with variable age of onset. Biochemically, ADP is characterized by an isolated significant elevation of ALA. More commonly, however, isolated elevations of ALA are due to secondary inhibition of ALA dehydratase with acute lead intoxication, which results in the highest degree of aminolevulinic aciduria. Less significant elevations are seen in chronic lead intoxication, tyrosinemia type I, alcoholism, and pregnancy. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. For more information, see the following or call 800-533-1710 to discuss testing strategies: -The Heme Biosynthetic Pathway -Porphyria (Acute) Testing Algorithm -Porphyria (Cutaneous) Testing Algorithm

Useful For: An equivalent option to urine for first-line test for evaluation of a suspected acute porphyria Monitoring patients undergoing treatment for an acute intermittent porphyria or other acute porphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional

questions.

Reference Values:
Porphobilinogen: < or =0.5 nmol/mL
Aminolevulinic Acid: < or =0.5 nmol/mL

Clinical References: 1.Tortorelli S, White A, Raymond K: Disorders of porphyrin metabolism. In: Dietzen DJ, Bennett MJ, Wong ECC, Haymond S eds. Biochemical and Molecular Basis of Pediatric Disease. 5th ed. Academic Press; 2021:503-528 2. Anderson KE, Lobo R, Salazar D, et al. Biochemical diagnosis of acute hepatic porphyria: Updated expert recommendations for primary care physicians. Am J Med Sci. 2021;362(2):113-121. doi:10.1016/j.amjms.2021.03.004

PBGDW
31894

Porphobilinogen Deaminase, Washed Erythrocytes

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Acute intermittent porphyria (AIP) is caused by diminished erythrocyte activity of porphobilinogen deaminase (PBGD), also known as uroporphyrinogen I synthase or hydroxymethylbilane synthase (HMBS). Onset of AIP typically occurs during puberty or later. Individuals may experience acute episodes of neuropathic symptoms. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. AIP is inherited in an autosomal dominant manner. At-risk family members of patients with a biochemical diagnosis of AIP should undergo appropriate testing. Timely diagnosis is important as acute episodes of AIP can be fatal. Treatment of AIP includes the prevention of symptoms through avoidance of precipitating factors. More than 80% of individuals with a deficiency variant in the HMBS gene remain asymptomatic throughout their lives. The biochemical diagnosis of AIP is made by demonstrating increased urinary excretion of porphobilinogen (PBG) and is most accurate during an acute episode. In addition, the diagnosis of AIP can be confirmed through the measurement of PBGD enzyme activity in erythrocytes, although 5% to 10% of affected individuals exhibit normal erythrocyte PBGD activity. In addition, molecular genetic confirmation (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify gene list ID: IEMCP-WCJKC9) is available on a clinical basis and can be particularly helpful in identifying asymptomatic family members at risk of acute symptoms. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm or call 800-533-1710 to discuss testing strategies.

Useful For: Confirmation of a diagnosis of acute intermittent porphyria using washed erythrocyte specimens

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available.

Reference Values:
Reference ranges have not been established for patients who are younger than 16 years of age.

> or =7.0 nmol/L/sec
6.0-6.9 nmol/L/sec (indeterminate)
<6.0 nmol/L/sec (diminished)

Clinical References: 1. Tortorelli S, Kloke K, Raymond K. Disorders of porphyrin metabolism.

In: Dietzen DJ, Bennett MJ, Wong ECC, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:307-324 2. Nuttall KL, Klee GG. Analytes of hemoglobin metabolism-porphyrins, iron, and bilirubin. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 5th ed. WB Saunders Company; 2001:584-607 3. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed April 19,2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225540906

PBGD_
88925

Porphobilinogen Deaminase, Whole Blood

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Acute intermittent porphyria (AIP) is caused by diminished erythrocyte activity of porphobilinogen deaminase (PBGD), also known as uroporphyrinogen I synthase or hydroxymethylbilane synthase (HMBS). Onset of AIP typically occurs during puberty or later. Individuals may experience acute episodes of neuropathic symptoms. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. AIP is inherited in an autosomal dominant manner. At-risk family members of patients with a biochemical diagnosis of AIP should undergo appropriate testing. Timely diagnosis is important as acute episodes of AIP can be fatal. Treatment of AIP includes the prevention of symptoms through avoidance of precipitating factors. More than 80% of individuals with a deficiency variant in the HMBS gene remain asymptomatic throughout their lives. The biochemical diagnosis of AIP is made by demonstrating increased urinary excretion of porphobilinogen (PBG) and is most accurate during an acute episode. In addition, the diagnosis of AIP can be confirmed through the measurement of PBGD enzyme activity in erythrocytes, although 5% to 10% of affected individuals exhibit normal erythrocyte PBGD activity. In addition, molecular genetic confirmation (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify gene list ID: IEMCP-WCJKC9) is available on a clinical basis and can be particularly helpful in identifying asymptomatic family members at risk of acute symptoms. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm or call 800-533-1710 to discuss testing strategies.

Useful For: Confirmation of a diagnosis of acute intermittent porphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

PBGU
82068

Porphobilinogen, Quantitative, Random, Urine

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP but may be present in HCP and VP. Urinary porphobilinogen (PBG) is elevated during the acute phase of the neurologic porphyrias. Urine and fecal porphyrin analysis should be performed to confirm the diagnosis and to

distinguish between AIP, HCP and VP. A biochemical diagnosis of AIP can be confirmed by measurement of PBG deaminase activity (PBGD_ / Porphobilinogen Deaminase, Whole Blood). VP and HCP can be confirmed by measurement of fecal porphyrins (FQPPS / Porphyrins, Feces). Once the biochemical diagnosis of an acute porphyria is established, molecular genetic testing is available (APGP / Acute Porphyria Gene Panel, Varies), which allows for diagnosis of at-risk family members. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. For more information, see the following or call 800-533-1710 to discuss testing strategies: -The Heme Biosynthetic Pathway -Porphyria (Acute) Testing Algorithm -Porphyria (Cutaneous) Testing Algorithm

PCGP
608023

Porphyria Comprehensive Gene Panel, Varies

Clinical Information:

Useful For: Follow up for abnormal biochemical results suggestive of porphyria Establishing a molecular diagnosis for patients with porphyria Identifying variants within genes known to be associated with porphyria, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Siegesmund M, van Tuyll van Serooskerken AM, Poblete-Gutierrez P, Frank J. The acute hepatic porphyrias: current status and future challenges. Best Pract Res Clin Gastroenterol. 2010;24(5):593-605 3. Tortorelli S, White A, Raymond K. Disorders of porphyrin metabolism. In: Dietzen DJ, Wong ECC, Bennett MJ, Haymond S, eds. Biochemical and Molecular Basis of Pediatric Disease. 5th ed. AACC Press; 2020:chap 15

PEWE
31893

Porphyrins Evaluation, Washed Erythrocytes

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing erythrocyte porphyrin level is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyria (XLDPP). Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors exacerbate symptoms, significantly impacting the severity and course of disease. Erythropoietic protoporphyria is caused by decreased ferrochelatase activity resulting in significantly increased free protoporphyrin levels in erythrocytes, plasma, and feces. X-linked dominant protoporphyria is caused by gain-of-function variants in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin, and

total protoporphyrin levels in plasma and feces. Protoporphyrin fraction is the main component of erythrocyte porphyrins. When total erythrocyte porphyrins are elevated, fractionation and quantitation of zinc-complexed and free protoporphyrin are necessary to differentiate the inherited porphyrias from other causes of elevated porphyrin levels. Other possible causes of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron-deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria, a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria, a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm or call 800-533-1710 to discuss testing strategies. There are 2 test options: -PEE / Porphyrins Evaluation, Whole Blood -PEWE / Porphyrins Evaluation, Washed Erythrocytes. The whole blood option is easiest for clients but requires that the specimen arrive at Mayo Clinic Laboratories within 7 days of collection. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

Useful For: Preferred test for analysis of erythrocyte porphyrins Establishing a biochemical diagnosis of erythropoietic protoporphyria, and X-linked dominant protoporphyria

Interpretation: Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:
PORPHYRINS, TOTAL, RBC
<80 mcg/dL

Clinical References: 1. Badminton MN, Whatley SD, Schmitt C, Aarsand AK. Porphyrins and the porphyrias. In: Rifai N, Chiu RWK, Young I, Burnham CAD, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:419-419.e32 2. Tortorelli S, Kloke K, Raymond K. Disorders of porphyrin metabolism. In: Dietzen DG, Bennett MJ, Wong ECC, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:chap15 3. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill, 2019. Accessed September 6, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225540906&bookid=2709 4. Balwani M, Naik H, Anderson KE, et al. Clinical, biochemical, and genetic characterization of North American patients with erythropoietic protoporphyria and X-linked Protoporphyria. JAMA Dermatol. 2017;153(8):789-796 5. Whatley SD, Ducamp S, Gouya B, et al. C-terminal deletions in the ALAS2 gene lead to gain of function and cause X-linked dominant protoporphyria without anemia or iron overload. Am J Hum Genet. 2008;83(3):408-414

PEE
88886

Porphyrins Evaluation, Whole Blood

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing erythrocyte porphyrin level is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyria (XLDPP). Clinical presentation of EPP and XLDPP is identical, with onset of symptoms typically

occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors can exacerbate symptoms, significantly impacting the severity and course of disease. Erythropoietic protoporphyria is caused by decreased ferrochelatase activity resulting in significantly increased noncomplexed (free) protoporphyrin levels in erythrocytes, plasma, and feces. X-linked dominant protoporphyria is caused by gain-of-function variants in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin, and total protoporphyrin levels in plasma and feces. Protoporphyrin fractionation is the main component of erythrocyte porphyrins. When total erythrocyte porphyrins are elevated, fractionation and quantitation of zinc-complexed and free protoporphyrin is necessary to differentiate the inherited porphyrias from other causes of elevated porphyrin levels. Other possible causes of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron-deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria, a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria, a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm or call 800-533-1710 to discuss testing strategies. There are 2 test options: -PEE / Porphyrins Evaluation, Whole Blood -PEWE / Porphyrins Evaluation, Washed Erythrocytes. The whole blood option is easiest for clients but requires that the specimen arrive at Mayo Clinic Laboratories within 7 days of collection. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

Useful For: Establishing a biochemical diagnosis of erythropoietic protoporphyria and X-linked dominant protoporphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:
PORPHYRINS, TOTAL, RBC
<80 mcg/dL

Clinical References: 1. Tortorelli S, Kloke K, Raymond K. Disorders of porphyrin metabolism. In: Dietzen DG, Bennett MJ, Wong ECC, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:307-324 2. Badminton MN, Whatley SD, Schmitt C, Aarsand AK. Porphyrins and the porphyrias. In: Rifai N, Chiu RWK, Young I, Burnham CAD, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:419-419.e32 3. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill, 2019. Accessed September 6, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225540906&bookid=2709 4. Whatley SD, Ducamp S, Gouya B, et al. C-terminal deletions in the ALAS2 gene lead to gain of function and cause X-linked dominant protoporphyria without anemia or iron overload. Am J Hum Genet. 2008;83(3):408-414 5. Balwani M, Naik H, Anderson KE, et al. Clinical, biochemical, and genetic characterization of North American patients with erythropoietic protoporphyria and X-linked protoporphyria. JAMA Dermatol. 2017;153(8):789-796

FQPPS
81652 **Porphyrins, Feces**

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma, and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. For more information see The Heme Biosynthetic Pathway. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms, which typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. Photosensitivity is not associated with AIP but may be present in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyrias: porphyria cutanea tarda (PCT) and the erythropoietic porphyrias; erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. PCT is the most common form of porphyria and caused by hepatic inhibition of the enzyme uroporphyrinogen decarboxylase (UROD). It is most often sporadic (acquired), but in about 20% of cases, a heterozygous variant in UROD increases the susceptibility to disease. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria (HEP) is a rare autosomal recessive form of porphyria caused by homozygous or compound heterozygous variants in UROD. It typically presents in early childhood with both erythropoietic and cutaneous manifestations and is similar to what is seen in CEP. Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Increased fecal porphyrin excretions are observed most commonly in symptomatic patients with CEP, PCT, HCP, and VP. In quiescent phases, as well as prior to puberty, fecal porphyrin excretion may be within normal limits. Patients with AIP may have elevated fecal porphyrin levels during severe attacks. EPP and XLDPP patients may have elevated protoporphyrin levels, however, these disorders cannot be diagnosed by fecal analysis alone. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm or call 800-533-1710 to discuss testing strategies.

Useful For: Evaluation of patients who present with signs or symptoms suggestive of porphyria cutanea tarda, hereditary coproporphyria, variegate porphyria, congenital erythropoietic porphyria, erythropoietic protoporphyria, or X-linked dominant protoporphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional

questions.

Reference Values:

UroporphyrinI:
<120 mcg/24 h

Uroporphyrin III:
<50 mcg/24 h

Heptacarboxyl porphyrin I:
<40 mcg/24 h

Heptacarboxyl porphyrin III:
<40 mcg/24 hours

Isoheptacarboxyl porphyrins:
<30 mcg/24 h

Hexacarboxnyl porphyrin:
<10 mcg/24 h

Hexacarboxnyl porphyrin III:
<10 mcg/24 h

Isohexacarboxnyl porphyrins :
<10 mcg/24 h

Pentacarboxyl porphyrin I:
<20 mcg/24 hours

Pentacarboxyl porphyrin II:
<20 mcg/24 h

Isopentacarboxyl porphyrins:
<80 mcg/24 hours

Coproporphyrin I:
<500 mcg/24 h

Coproporphyrin III:
<400 mcg/24 h

Isocoproporphyrin:
<200 mcg/24 h

Protoporphyrins:
<1,500 mcg/24 h

Coproporphyrin III/Coproporphyrin I RATIO:
<1.20

See The Heme Biosynthetic Pathway

Clinical References: 1. Tortorelli S, Kloke K, Raymond K: Disorders of porphyrin metabolism.

In: Dietzen DJ, Bennett MJ, Wong EDD, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:307-324 2. Nuttall KL, Klee GG: Analytes of hemoglobin metabolism-porphyrins, iron, and bilirubin. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 5th ed. WB Saunders Company; 2001:584-607 3. Anderson KE, Sassa S, Bishop DF, Desnick RJ: Disorders of heme biosynthesis: X-Linked sideroblastic anemia and the porphyrias. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 6, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225540906&bookid=2709 4. Weiss Y, Chen B, Yasuda M, Nazarenko I, Anderson KE, Desnick RJ. Porphyria cutanea tarda and hepatoerythropoietic porphyria: Identification of 19 novel uroporphyrinogen III decarboxylase mutations. Mol Genet Metab. 2019 Nov;128(3):363-366. doi:10.1016/j.ymgme.2018.11.013

PQNU
8562

Porphyrins, Quantitative, 24 Hour, Urine

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. Photosensitivity is not associated with AIP but may be present in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyrias: porphyria cutanea tarda (PCT) and the erythropoietic porphyrias; erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. PCT is the most common form of porphyria and caused by hepatic inhibition of the enzyme uroporphyrinogen decarboxylase (UROD). It is most often sporadic (acquired), but in about 20% of cases, a heterozygous variant in UROD increases the susceptibility to disease. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria (HEP) is a rare autosomal recessive form of porphyria caused by homozygous or compound heterozygous variants in UROD. It typically presents in early childhood with both erythropoietic and cutaneous manifestations and is similar to what is seen in CEP. Urinary porphyrin determination is helpful in the diagnosis of most porphyrias including CEP, PCT, AIP, HCP, and VP. In addition, measurement of porphobilinogen (PBG) in urine is important in establishing the diagnosis of the acute neurologic porphyrias (AIP, HCP and VP). Neither urine porphyrins nor PBG is helpful in evaluating patients suspected of having EPP or XLDPP. Of note, porphyrinuria may result from exposure to certain drugs and toxins or other medical conditions (ie, hereditary tyrosinemia type I). Heavy metals,

halogenated solvents, various drugs, insecticides, and herbicides can interfere with heme production and cause "intoxication porphyria." Chemically, the intoxication porphyrias are characterized by increased excretion of uroporphyrin and/or coproporphyrin in urine. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm or call 800-533-1710 to discuss testing strategies.

Useful For: Preferred screening test for congenital erythropoietic porphyria and porphyria cutanea tarda and during symptomatic periods for acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria when specimen transport will be longer than 72 hours

Interpretation: Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:
Uroporphyrins (Octacarboxyl):
< or =30 nmol/24 h

Heptacarboxylporphyrins:
< or =9 nmol/24 h

Hexacarboxylporphyrins:
< or =8 nmol/24 h

Pentacarboxyporphyrins:
< or =10 nmol/24 h

Copropprphyrins (Tetracboxyl)
Males: < or =230 nmol/24 h
Females: < or =168 nmol/24 h

Porphobilinogen:
< or =2.2 mcmol/24 h

Clinical References: 1. Tortorelli S, Kloke K, Raymond K. Disorders of porphyrin metabolism. In: Dietzen DJ, Bennett MJ, Wong EDD, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:307-324 2. Nuttall KL, Klee GG. Analytes of hemoglobin metabolism-porphyrins, iron, and bilirubin. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 5th ed. WB Saunders Company; 2001:584-607 3. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-Linked sideroblastic anemia and the porphyrias. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 6, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225540906&bookid=2709 4. Weiss Y, Chen B, Yasuda M, Nazarenko I, Anderson KE, Desnick RJ. Porphyria cutanea tarda and hepatoerythropoietic porphyria: Identification of 19 novel uroporphyrinogen III decarboxylase mutations. Mol Genet Metab. 2019;128(3):363-366. doi:10.1016/j.ymgme.2018.11.013

PQNRU 60597 Porphyrins, Quantitative, Random, Urine

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme

defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. Photosensitivity is not associated with AIP but may be present in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyrias: porphyria cutanea tarda (PCT) and the erythropoietic porphyrias; erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. PCT is the most common form of porphyria and caused by hepatic inhibition of the enzyme uroporphyrinogen decarboxylase (UROD). It is most often sporadic (acquired), but in about 20% of cases, a heterozygous variant in UROD increases the susceptibility to disease. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria (HEP) is a rare autosomal recessive form of porphyria caused by homozygous or compound heterozygous variants in UROD. It typically presents in early childhood with both erythropoietic and cutaneous manifestations and is similar to what is seen in CEP. Urinary porphyrin determination is helpful in the diagnosis of most porphyrias including CEP, PCT, AIP, HCP, and VP. In addition, measurement of porphobilinogen (PBG) in urine is important in establishing the diagnosis of the acute neurologic porphyrias (AIP, HCP and VP). Neither urine porphyrins nor PBG is helpful in evaluating patients suspected of having EPP or XLDPP. Of note, porphyrinuria may result from exposure to certain drugs and toxins or other medical conditions (ie, hereditary tyrosinemia type I). Heavy metals, halogenated solvents, various drugs, insecticides, and herbicides can interfere with heme production and cause "intoxication porphyria." Chemically, the intoxication porphyrias are characterized by increased excretion of, uroporphyrin and/or coproporphyrin in urine. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm or call 800-533-1710 to discuss testing strategies.

Useful For: Preferred test to begin assessment for congenital erythropoietic porphyria and porphyria cutanea tarda and during symptomatic periods for acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria when specimen transport will not exceed 72 hours

Interpretation: Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:
Uroporphyrins, Octacarboxyl:
< or =30 nmol/L

Heptacarboxylporphyrins:
< or =7 nmol/L

Hexacarboxylporphyrins:
< or =2 nmol/L

Pentacarboxyporphyrins:
< or =5 nmol/L

Copropprphyrin, Tetracboxyl:
< or =110 nmol/L

Porphobilinogen:
< or =1.3 mcmol/L

Clinical References: 1. Tortorelli S, Kloke K, Raymond K. Disorders of porphyrin metabolism. In: Dietzen DJ, Bennett MJ, Wong EDD, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:307-324 2. Nuttall KL, Klee GG. Analytes of hemoglobin metabolism-porphyrins, iron, and bilirubin. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 5th ed. WB Saunders Company; 2001:584-607 3. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-Linked sideroblastic anemia and the porphyrias. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 6, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225540906&bookid=2709 4. Weiss Y, Chen B, Yasuda M, Nazarenko I, Anderson KE, Desnick RJ. Porphyria cutanea tarda and hepatoerythropoietic porphyria: Identification of 19 novel uroporphyrinogen III decarboxylase mutations. Mol Genet Metab. 2019;128(3):363-366. doi:10.1016/j.ymgme.2018.11.013

PTP
8731

Porphyrins, Total, Plasma

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. These enzyme defects cause various porphyrins and their precursors to accumulate in different specimen types. The detection and differentiation of the porphyrias is through evaluation of the patterns of porphyrin accumulation observed in erythrocytes and plasma and of the heme precursors excreted in urine and feces. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias, acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP but may occur in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyria, porphyria cutanea tarda (PCT), and the erythropoietic porphyrias including erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. Congenital erythropoietic porphyria is an erythropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity

with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. Porphyria cutanea tarda is the most common form of porphyria and caused by hepatic inhibition of the enzyme uroporphyrinogen decarboxylase (UROD). It is most often sporadic (acquired), but in about 20% of cases, a heterozygous variant in UROD increases the susceptibility to disease. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions; fluid filled vesicles that rupture easily become crusted and heal slowly, which result from mild trauma to sun-exposed areas. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and alopecia following repeated skin damage. Liver disease is common as evidenced by abnormal liver function tests, and 30% to 40% of patients with PCT develop cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria is a rare autosomal recessive form of porphyria caused by homozygous or compound heterozygous variants in UROD. It typically presents in early childhood with both erythropoietic and cutaneous manifestations and is similar to what is seen in CEP. Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Plasma porphyrins are most appropriate for monitoring treatment of PCT. Although analysis in plasma is not recommended for diagnosis, increases in plasma porphyrin concentrations are observed in the cutaneous porphyrias and may be elevated during acute episodes of AIP, VP, and HCP. In addition, persons in chronic kidney failure who develop bullous dermatosis similar to that associated with PCT may have increased plasma porphyrins. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. The following algorithms are available or call 800-533-1710 to discuss testing strategies: -Porphyria (Acute) Testing Algorithm -Porphyria (Cutaneous) Testing Algorithm

Useful For: Monitoring treatment of patients with porphyria cutanea tarda

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
< or =1.0 mcg/dL

Clinical References: 1. Tortorelli S, Kloke K, Raymond K. Disorders of porphyrin metabolism. In: Dietzen DJ, Bennett MJ, Wong EDD, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:307-324 2. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-Linked sideroblastic anemia and the porphyrias. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 6, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225540906&bookid=2709 3. Weiss Y, Chen B, Yasuda M, Nazarenko I, Anderson KE, Desnick RJ. Porphyria cutanea tarda and hepatoerythropoietic porphyria: Identification of 19 novel uroporphyrinogen III decarboxylase mutations. Mol Genet Metab. 2019;128(3):363-366. doi:10.1016/j.ymgme.2018.11.013 4. Phillips JD. Heme biosynthesis and the porphyrias. Mol Genet Metab. 2019;128(3):164-177. doi:10.1016/j.ymgme.2019.04.008

POSA
89591

Posaconazole, Serum

Clinical Information: Posaconazole interferes with fungal cytochrome P450 (CYP) lanosterol-14 alpha demethylase activity, thereby decreasing synthesis of ergosterol, the principal sterol in fungal cell membrane, and inhibiting fungal cell membrane formation.(1,2) Posaconazole has been approved for prophylaxis of invasive Aspergillus and Candida infections in severely immunocompromised patients (eg, hematopoietic stem cell transplant recipients with graft-versus-host disease [GVHD] or those with prolonged neutropenia secondary to chemotherapy for hematologic malignancies) and treatment of oropharyngeal candidiasis (including patients refractory to itraconazole or fluconazole).(1,3) It also is approved for ocular administration (drug monitoring not required for this use). Posaconazole has a variable absorption. Food and liquid nutritional supplements increase absorption, and fasting states do not provide sufficient absorption to ensure adequate plasma concentrations.(4,5) The drug has a high volume of distribution (Vd=465-1774 L) and is highly protein bound (> or =97%), predominantly to albumin.(1,3) The drug does not undergo significant metabolism; approximately 15% to 17% undergoes non-CYP-mediated metabolism, primarily via hepatic glucuronidation into metabolites.(1) The half-life elimination is approximately 35 hours (range: 20-66 hours); steady state is achieved after about 5 to 7 days. Time to maximum concentration is approximately 3 to 5 hours, but due to the highly variable absorption, trough level monitoring is recommended. Therapeutic drug monitoring should be considered in the following situations: -To document optimal absorption when used for prophylaxis or active treatment of a fungal infection Consider rechecking a level even if initial level was in the goal range if the patient: -Is unable to meet optimal nutritional intake -Is receiving continuous tube feeding -Is receiving a proton pump inhibitor (decreased posaconazole levels in some studies) -Has mucositis, diarrhea, vomiting, GVHD, or other reason that the drug may not be absorbed well

Useful For: Monitoring posaconazole therapy

Interpretation: Levels greater than 700 ng/mL (0.7 mcg/mL) have been suggested for prophylaxis. Levels greater than or equal to 1250 ng/mL (1.25 mcg/mL) were shown to be optimal in a salvage trial for treatment of invasive Aspergillus infections. A toxic range has not been established.

Reference Values:
>700 ng/mL (trough)

Clinical References: 1. Noxafil (posaconazole). Package insert: Schering Corporation; 2006 2. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 10th ed. McGraw-Hill Professional; 2001 3. Physicians' Desk Reference (PDR). 61st ed. Thomson PDR; 2007 4. Courtney R, Wexler D, Radwanski E, Lim J, Laughlin M. Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults. Br J Clin Pharmacol. 2004;57(2):218-222. doi:10.1046/j.1365-2125.2003.01977.x 5. Courtney R, Radwanski E, Lim J, Laughlin M. Pharmacokinetics of posaconazole coadministered with antacid in fasting or nonfasting healthy men. Antimicrob Agents Chemother. 2004;48(3):804-808. doi:10.1128/AAC.48.3.804-808.2004 6. Milone MC, Shaw LM: Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

POSV
9205

Post Vasectomy Check, Semen

Clinical Information: Following a vasectomy, sperm may be found in the semen for 6 weeks to 3 months or longer. Regular ejaculation (every 3-4 days) may eliminate sperm from the reproductive tract more quickly. To check for the absence of sperm, semen should be evaluated for the presence of sperm 3 months postvasectomy and after a minimum of 20 ejaculations. Because the sperm count may be very low, the semen is centrifuged for concentration purposes. A negative result from 1 well-mixed postvasectomy semen specimen generally indicates that the use of contraception is no longer necessary. Occasional cases have been reported where postvasectomy semen analysis shows intermittent presence of rare nonmotile sperm in the semen.(1)

Useful For: Determining absence or presence of sperm postvasectomy

Interpretation: Patients may stop using other methods of contraception when examination of 1 well-mixed postvasectomy semen specimen shows azoospermia or rare nonmotile sperm (RNMS) (< or = 100,000 nonmotile sperm/mL). The risk of pregnancy after vasectomy is approximately 1 in 2000 for men who have postvasectomy azoospermia or postvasectomy semen analysis (PVSA) showing RNMS.(1) If >100,000 nonmotile sperm/mL persist beyond 6 months after vasectomy, then trends of serial PVSAs and clinical judgment should be used to decide whether the vasectomy is a failure and whether repeat vasectomy should be considered.(1) Vasectomy should be considered a failure if any motile sperm are seen on PVSA at 6 months after vasectomy, in which case repeat vasectomy should be considered.

Reference Values:
Zero sperm seen

Clinical References: 1. Sharlip ID, Belker AM, Honig S et al; American Urological Association: Vasectomy: AUA guideline. J Urol. 2012 Dec;188(6 Suppl):2482-2491. doi: 10.1016/j.juro.2012.09.080 2. WHO laboratory manual for the examination and processing of human semen. 5th ed. WHO Press; 2010 3. WHO laboratory manual for the examination and processing of human semen. 6th ed. World Health Organization; 2021

PMAOG
620568

Postmortem Aortopathy Gene Panel, Tissue

Clinical Information: Sudden cardiac death (SCD) is estimated to occur at an incidence of between 50 to 100 per 100,000 individuals in North America and Europe each year, claiming between 250,000 and 450,000 lives in the United States annually. In younger individuals (15-35 years of age), the incidence of SCD is between 1 to 2 per 100,000 young individuals. Sudden cardiac death, particularly in young individuals, may suggest an inherited form of heart disease. In some cases of sudden death, autopsy may identify a structural abnormality, such as aortic aneurysm or dissection. Postmortem diagnosis of a hereditary form of aortic aneurysm/dissection may assist in confirmation of the cause of death, as well as risk assessment in living family members. Inherited forms of aortic disease, or aortopathies, may be associated with isolated thoracic aortic aneurysms and dissections or conditions with multi-system involvement. This gene panel includes genes for multiple conditions that may have aortopathy as a feature, including Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, arterial tortuosity syndrome, and heritable thoracic aortic disease (also known as familial thoracic aortic aneurysm/dissection: FTAAD). Other heritable conditions with overlapping clinical presentations are also covered by this panel. Confirming a genetic diagnosis in the setting of aortopathy may aid in differentiating the genetic etiology of complex or ambiguous clinical presentations, treatment decisions, and genetic counseling. Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue that occurs in approximately 1 to 2 per 10,000 individuals. It is characterized by the presence of skeletal, ocular, and cardiovascular manifestations and is caused by variants in the FBN1 gene. Skeletal findings may include tall stature, chest wall deformity, scoliosis, and joint hypermobility. Lens dislocation (ectopia lentis) is the cardinal ocular feature with mitral valve prolapse and aortic root dilatation/dissection the main cardiovascular features.(1) Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with significant overlap with Marfan syndrome but may include involvement of other organ systems and is primarily caused by variants in TGFBR1 and TGFBR2.(2,3) Features of LDS that are not typical of MFS include craniofacial and neurodevelopmental abnormalities and arterial tortuosity with increased risk for aneurysm and dissection throughout the arterial tree. Variants in the SMAD3 gene have been reported in families with an LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis. Variants in the TGFB3 gene have also been reported in families with an LDS-like phenotype, although these individuals tended to not have arterial tortuosity. FTAAD is a genetic condition primarily involving dilatation and dissection of the thoracic aorta but may also include aneurysm and dissection of other arteries. This condition has a highly variable

age of onset and presentation and may involve additional features, such as congenital heart defects and other features of connective tissue disease or smooth muscle abnormalities depending on the causative gene. The gene most commonly involved in FTAAD is ACTA2.(4,5) Vascular Ehlers-Danlos syndrome (also known as vEDS or EDS IV) is an autosomal dominant connective tissue disease caused by variants in the COL3A1 gene. vEDS may present with characteristic facial features, thin, translucent skin, easy bruising, and arterial, intestinal, and uterine fragility. Arterial rupture may be preceded by aneurysm or dissection or may occur spontaneously.(6) Classic Ehlers-Danlos syndrome types I and II (also known as cEDS) are caused by variants in the COL5A1 and COL5A2 genes and may develop aortic root dilation and, more rarely, spontaneous vessel rupture. Vascular fragility has also been demonstrated in a rare form of cEDS (known as COL1A1-cEDS, classic-like EDS syndrome with propensity to arterial rupture, or vascular-like EDS) due to variants in the COL1A1 gene.(7) Other genes included on this panel cause conditions with clinical overlap with those above. Examples include genes associated with rare, autosomal recessive forms of Ehlers-Danlos syndrome, the FLNA gene associated with periventricular nodular heterotopia, the FBN2 gene associated with congenital contractural arachnodactyly, the SLC2A10 gene associated with autosomal recessive arterial tortuosity syndrome, and the NOTCH1 gene associated with aortic valve disease and severe valve calcification. Currently, expert consensus indicates NOTCH1 variants may be predictive of thoracic aortic enlargement without evidence of progression to aortic dissection.(8-12)

Useful For: Providing a comprehensive postmortem genetic evaluation in the setting of a sudden death attributed to thoracic aortic dissection or with a personal or family history suggestive of Marfan syndrome, Loeys-Dietz syndrome, thoracic aortic aneurysm and dissections, vascular Ehlers-Danlos syndrome, or a related condition Identifying a disease-causing variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(13) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010;47(7):476-485 2. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med. 2006;355(8):788-798 3. Loeys BL, Chen J, Neptune ER, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet. 2005;37(3):275-281 4. Milewicz DM, Regalado E. Heritable thoracic aortic disease overview. In: Adam MP, Mirzaa, GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated May 4, 2023. Accessed August 30, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1120/ 5. Guo DC, Pannu H, Tran-Fadulu V, et al. Mutations in smooth muscle a-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. Nat Genet. 2007;39(12):1488-1493 6. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, The vascular type. N Engl J Med. 2000;342(10):673-680 7. Malfait F, Wenstrup R, Paepe AD. Classic Ehlers-Danlos syndrome. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1993-2023. Updated July 26, 2018. Accessed August 30, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1244/ 8. Chen MH, Walsh CA. FLNA deficiency. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated September 30, 2021. Accessed August 30, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1213/ 9. Callewaert B. Congenital contractural arachnodactyly. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2001. Updated July 14, 2022. Accessed August 30, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1386/ 10. Sacharow SJ, Picker JD, Levy HL.

Homocystinuria caused by cystathionine beta-synthase deficiency. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated May 18, 2017. Accessed August 30, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1524/ 11. Coucke PJ, Willaert A, Wessels MW, et al. Mutations in the facilitative glucose transporter GLUT10 alter angiogenesis and cause arterial tortuosity syndrome. Nat Genet. 2006;38(4):452-457 12. Clinical Genome Resource: Gene-Disease Validity Classification Summary for NOTCH1-familial thoracic aortic aneurysm and aortic dissection. ClinGen; 2023. Accessed August 30, 2023. Available at https://search.clinicalgenome.org/kb/gene-validity/CGGCIEX:assertion_8269 13. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-424 14. Fishman GI, Chugh SS, DiMarco JP, et al. Sudden cardiac death prediction and prevention: report from the National Heart, Lung and Blood Institute and Heart Rhythm Society Workshop. Circulation. 2010;122(22):2335-2348 15. Semsarian C, Ingles J. Molecular autopsy in victims of inherited arrhythmias. J Arrhythm. 2016;32(5):359-365 16. Stattin EL, Westin IM, Cederquist K, et al. Genetic screening in sudden cardiac death in the young can save future lives. Int J Legal Med. 2016;130(1):59-66

PMARG
620582

Postmortem Arrhythmia Gene Panel, Tissue

Clinical Information: Sudden cardiac death (SCD) is estimated to occur at an incidence of between 50 to 100 per 100,000 individuals in North America and Europe each year, claiming between 250,000 and 450,000 lives in the United States annually. In younger individuals (15-35 years of age), the incidence of SCD is between 1 to 2 per 100,000 young individuals. The reported incidence of SCD is likely an underestimate since more overt causes of death, such as car accidents and drownings, may result from arrhythmogenic events. In cases of sudden unexplained death where autopsy does not detect a structural basis for sudden death, a hereditary arrhythmia may be suspected. Cardiac arrhythmias are a group of conditions characterized by abnormal heart rhythms. Arrhythmias can be caused by either genetic (inherited) factors or nongenetic (acquired) causes, such as medications and infection. Hereditary forms of cardiac arrhythmias for which this panel assesses include, but are not limited to, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and familial atrial fibrillation.(1) This gene panel also assesses genes associated with rarer, syndromic conditions in which cardiac arrhythmia is a major feature, such as Andersen-Tawil syndrome, Carvajal syndrome, Jervell and Lange-Nielsen syndrome, Naxos disease, Timothy syndrome, and Emery-Dreifuss muscular dystrophy.(1-3) Inherited cardiac arrhythmias can follow autosomal dominant, autosomal recessive, X-linked, and digenic patterns of inheritance. Genes associated with mitochondrial inheritance of cardiac arrhythmias are not assessed on this panel. Postmortem diagnosis of a hereditary arrhythmia may assist in confirmation of the cause and manner of death as well as risk assessment in living family members.

Useful For: Providing a comprehensive postmortem genetic evaluation in the setting of a sudden death suspicious for cardiac arrhythmia or with a personal or family history suggestive of a hereditary form of cardiac arrhythmia Identifying a disease-causing variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(4) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Schwartz PJ, Ackerman MJ, Antzelevitch C, et al. Inherited cardiac arrhythmias. Nat Rev Dis Primers. 2020;6(1):58. doi:10.1038/s41572-020-0188-7 2. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011;8(8):1308-1339. doi:10.1016/j.hrthm.2011.05.020 3. Bonne G, Leturcq F, Ben Yaou R. Emery-Dreifuss muscular dystrophy. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated August 15, 2019. Accessed August 30, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1436/ 4. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-424. 5. Fishman GI, Chugh SS, DiMarco JP, et al. Sudden cardiac death prediction and prevention: report from the National Heart, Lung and Blood Institute and Heart Rhythm Society Workshop. Circulation. 2010;122(22):2335-2348 6. Semsarian C, Ingles J. Molecular autopsy in victims of inherited arrhythmias. J Arrhythm. 2016;32(5):359-365 7. Stattin EL, Westin IM, Cederquist K, et al. Genetic screening in sudden cardiac death in the young can save future lives. Int J Legal Med. 2016;130(1):59-66

PMCAG 620596 Postmortem Cardiomyopathy and Arrhythmia Gene Panel, Tissue

Clinical Information: Sudden cardiac death (SCD) is estimated to occur at an incidence of between 50 to 100 per 100,000 individuals in North America and Europe each year, claiming between 250,000 and 450,000 lives in the United States annually. In younger individuals (15-35 years of age), the incidence of SCD is between 1 to 2 per 100,000 young individuals. Sudden cardiac death, particularly in young individuals, may suggest an inherited form of heart disease. In some cases of SCD, autopsy may identify a structural abnormality, such as a form of cardiomyopathy. In cases with no identified structural abnormality, a hereditary arrhythmia may be suspected. Postmortem diagnosis of a hereditary arrhythmia or cardiomyopathy may assist in confirmation of the cause and manner of death, as well as risk assessment in living family members. Cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by either inherited, genetic factors or nongenetic (acquired) causes, such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC or AC), and left ventricular noncompaction (LVNC).(1) Cardiac arrhythmias are a group of conditions characterized by abnormal heart rhythms. Arrhythmias can be caused by either genetic (inherited) factors or nongenetic (acquired) causes, such as medications and infection. Hereditary forms of cardiac arrhythmias assessed for on this panel include, but are not limited to, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and familial atrial fibrillation.(2) This panel also assesses genes associated with rarer, syndromic conditions in which cardiac arrhythmia is a major feature, such as Andersen-Tawil syndrome, Carvajal syndrome, Jervell and Lange-Nielsen syndrome, Naxos disease, Timothy syndrome, and Emery-Dreifuss muscular dystrophy.(2-4) Inherited cardiomyopathies and cardiac arrhythmias can follow autosomal dominant, autosomal recessive, X-linked, and digenic patterns of inheritance. Genes associated with mitochondrial inheritance of cardiomyopathies and cardiac arrhythmias are not assessed on this panel.

Useful For: Providing a comprehensive postmortem genetic evaluation in the setting of a sudden death attributed to cardiomyopathy or suspicious for cardiac arrhythmia or with a personal or family history suggestive of a hereditary form of cardiomyopathy or cardiac arrhythmia Identifying a disease-

causing variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy-a heart failure society of America practice guideline. J Card Fail. 2018;24(5):281-302. doi:10.1016/j.cardfail.2018.03.004 2. Schwartz PJ, Ackerman MJ, Antzelevitch C, et al. Inherited cardiac arrhythmias. Nat Rev Dis Primers. 202016;6(1):58. doi:10.1038/s41572-020-0188-7 3. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011;8(8):1308-1339. doi:10.1016/j.hrthm.2011.05.020 4. Bonne G, Leturcq F, Ben Yaou R: Emery-Dreifuss muscular dystrophy. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated August 15, 2019. Accessed August 29, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1436/ 5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-424 6. Fishman GI, Chugh SS, DiMarco JP, et al: Sudden cardiac death prediction and prevention: report from the National Heart, Lung and Blood Institute and Heart Rhythm Society Workshop. Circulation. 2010;122(22):2335-2348 7. Stattin EL, Westin IM, Cederquist K, et al. Genetic screening in sudden cardiac death in the young can save future lives. Int J Legal Med. 2016;130(1):59-66

PMCMG
620610

Postmortem Cardiomyopathy Gene Panel, Tissue

Clinical Information: Sudden cardiac death (SCD) is estimated to occur at an incidence of between 50 to 100 per 100,000 individuals in North America and Europe each year, claiming between 250,000 and 450,000 lives in the United States annually. In younger individuals (15-35 years of age), the incidence of SCD is between 1 to 2 per 100,000 young individuals. Sudden cardiac death, particularly in young individuals, may suggest an inherited form of heart disease. In some cases of sudden cardiac death, autopsy may identify a structural abnormality, such as a form of cardiomyopathy. Postmortem diagnosis of a hereditary cardiomyopathy may assist in confirmation of the cause and manner of death, as well as risk assessment in living family members. Cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by either inherited, genetic factors or nongenetic (acquired) causes, such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC or AC), and left ventricular noncompaction (LVNC).(1) The hereditary form of HCM is characterized by left ventricular hypertrophy in the absence of other cardiac or systemic causes that may cause hypertrophy of the heart muscle, such as longstanding, uncontrolled hypertension or aortic stenosis. The incidence of HCM in the general population is approximately 1:200 to 1:500, and it is estimated that 30% to 60% of cases can be attributed to a genetic etiology.(2) Hereditary forms of HCM are most often caused by genes encoding proteins of the cardiac sarcomere, the functional contractile unit of the heart muscle. Hereditary forms of DCM are characterized by ventricular dilation with reduced cardiac performance in the absence

of other cardiac or systemic causes that may cause dilation of the heart muscle, such as hypertension and ischemic heart disease. The incidence of DCM in the general population is approximately 1 in 2500, and it is estimated that approximately 50% of cases can be attributed to a genetic etiology.(3) Hereditary forms of DCM are most often caused by genes encoding proteins of the cardiac cytoskeleton and sarcomere. LVNC is characterized by prominent trabeculations of the left ventricle with trabecular recesses extending into the ventricular cavity. The incidence of LVNC in the general population is estimated to be 1 in 5000.(3) It is currently unclear if LVNC represents a genetically distinct form of cardiomyopathy, as many familial cases of LVNC have been linked to the same genes associated with other forms of hereditary cardiomyopathies and many affected individuals also meet diagnostic criteria for DCM or HCM.(3,4) Arrhythmogenic cardiomyopathy (ACM) is characterized by the presence of arrhythmogenic cardiac muscle in the absence of ischemic, hypertensive, or valvular cardiac disease. ARVC, the most well-defined form of ACM, is characterized by the breakdown of the myocardium and replacement of right ventricular muscle tissue with fibrofatty tissue, resulting in an increased risk of arrhythmia and sudden death. In some cases, there may also be left ventricular involvement. The prevalence of ARVC (genetic and acquired) is estimated to be 1 in 2000 to 1 in 5000 in the general population.(5) Hereditary forms of cardiomyopathy may be an isolated finding or may be a feature of an underlying systemic condition. Hereditary forms of cardiomyopathy can follow autosomal dominant, autosomal recessive, X-linked, and digenic patterns of inheritance. Mitochondrial inheritance is also possible, however, genes associated with mitochondrial inheritance of cardiomyopathy are not assessed on this panel.

Useful For: Providing a comprehensive postmortem genetic evaluation in the setting of a sudden death attributed to cardiomyopathy or with a personal or family history suggestive of a hereditary form of cardiomyopathy Identifying a disease-causing variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Hershberger RE, Givertz MM, Ho CY, et al: Genetic evaluation of cardiomyopathy-a heart failure society of America practice guideline. J Card Fail. 2018;24(5):281-302. doi:10.1016/j.cardfail.2018.03.004 2. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: Executive Summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. Circulation. 2020;142(25):e533-e557. doi:10.1161/CIR.0000000000000938 3. Bozkurt B, Colvin M, Cook J, et al. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association [published correction appears in Circulation. 2016 Dec 6;134(23):e652]. Circulation. 2016;134(23):e579-e646. doi:10.1161/CIR.0000000000000455 4. Aung N, Doimo S, Ricci F, et al. Prognostic significance of left ventricular noncompaction: Systematic review and meta-analysis of observational studies. Circ Cardiovasc Imaging. 2020;13(1):e009712. doi:10.1161/CIRCIMAGING.119.009712 5. Corrado D, Link MS, Calkins H: Arrhythmogenic right ventricular cardiomyopathy. N Engl J Med. 2017;376(1):61-72. doi:10.1056/NEJMra1509267 6. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-424. doi:10.1038/gim.2015.30 7. Fishman GI, Chugh SS, DiMarco JP, et al: Sudden cardiac death prediction and prevention: report from the National Heart, Lung and Blood Institute and Heart Rhythm Society Workshop. Circulation. 2010;122(22):2335-2348 8. Stattin EL, Westin IM, Cederquist K, et al: Genetic screening in sudden cardiac death in the young can save future

lives. Int J Legal Med. 2016;130(1):59-66

PCMSP 620638 Postmortem Inherited Congenital Myasthenia Syndrome Gene Panel, Tissue

Clinical Information: Congenital myasthenic syndromes occur as a result of compromised neuromuscular transmission. Clinical manifestations include fatigable weakness involving ocular, bulbar, and limb muscles. The severity and disease course are highly variable, but individuals usually present in infancy or early childhood. The clinical phenotype associated with a neonatal onset can include feeding difficulties, poor suck and cry, choking spells, eyelid ptosis, and muscle weakness. The clinical phenotype associated with a later childhood onset can include abnormal muscle fatigue, delayed motor milestones, ptosis, and extraocular muscle weakness. The combination of the wide variability in symptoms and age of presentation can make congenital myasthenic syndromes hard to diagnosis. Given that congenital myasthenic syndromes are a heterogeneous group of disorders, multigene panels can be an efficient and cost-effective way to establish a molecular diagnosis for individuals. Postmortem diagnosis of a hereditary form of a congenital myasthenic syndrome may assist in confirmation of the cause of death, as well as risk assessment in living family members.(1-2)

Useful For: Identifying variants within genes known to be associated with congenital myasthenic syndrome, allowing for predictive testing of at-risk family members Providing a comprehensive postmortem genetic evaluation in the setting of a congenital myasthenic syndrome Identifying a disease-causing variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Byring RF, Pihko H, Tsujino A, et al. Congenital myasthenic syndrome associated with episodic apnea and sudden infant death. Neuromuscul Disord. 2002;12(6):548-553. doi:10.1016/s0960-8966(01)00336-4 2. Imperatore V, Mencarelli MA, Fallerini C, et al. Potentially Treatable Disorder Diagnosed Post Mortem by Exome Analysis in a Boy with Respiratory Distress. Int J Mol Sci. 2016;17(3):306. Published 2016 Feb 27. doi:10.3390/ijms17030306 3. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 4. Lyadurai SJP. Congenital myasthenic syndromes. Neurol Clin. 2020;38(3):541-552

PMHLH 620624 Postmortem Primary Hemophagocytic Lymphohistiocytosis (HLH) Gene Panel, Tissue

Clinical Information:

Useful For: Providing a comprehensive postmortem genetic evaluation in the setting of a death attributed to primary hemophagocytic lymphohistiocytosis Identifying a disease-causing variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30 2. Gadoury-Levesque V, Dong L, Su R, et al. Frequency and spectrum of disease-causing variants in 1892 patients with suspected genetic HLH disorders. Blood Adv. 2020;4(12):2578-2594. doi:10.1182/bloodadvances.2020001605 3. Canna SW, Marsh RA. Pediatric hemophagocytic lymphohistiocytosis. Blood. 2020;135(16):1332-1343. doi:10.1182/blood.2019000936 4. Ponnatt TS, Lilley CM, Mirza KM. Hemophagocytic lymphohistiocytosis. Arch Pathol Lab Med. 2022;146(4):507-519. doi:10.5858/arpa.2020-0802-RA 5. Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity: 2022 Update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507. doi:10.1007/s10875-022-01289-3

PMSBB
81931

Postmortem Screening, Bile and Blood Spot

Clinical Information: Postmortem screening involves acylcarnitine analysis in blood and bile specimens to evaluate cases of sudden or unexpected death. Acylcarnitine analysis can diagnose disorders of fatty acid oxidation and several organic acidurias, as relevant enzyme deficiencies cause the accumulation of specific acyl-CoAs measured by this assay.(1) Fatty acid oxidation (FAO) plays a major role in energy production during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue, taken up by the liver and muscles, and oxidized to acetyl-CoA. In the liver, acetyl-CoA is the building block for the synthesis of ketone bodies, which enter the blood stream and provide an alternative substrate for production of energy in other tissues when the supply of glucose is insufficient to maintain a normal level of energy. The acyl groups are conjugated with carnitine to form acylcarnitines, which are measured by tandem mass spectrometry. Diagnostic results are usually characterized by a pattern of significantly elevated acylcarnitine species compared to normal and disease controls. In general, more than 20 inborn errors of metabolism can be identified using this method, including FAO disorders and organic acidurias. The major clinical manifestations associated with individual FAO disorders include hypoketotic hypoglycemia, variable degrees of liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden or unexpected death. Organic acidurias also present as acute life-threatening events early in life with metabolic acidosis, increased anion gap, and neurologic distress. Patients with any of these disorders are at risk of developing fatal metabolic decompensations following the acquisition of even common infections. Once diagnosed, these disorders can be treated by avoidance of fasting, special diets, and cofactor and vitamin supplementation. Analysis of acylcarnitines in blood and bile spots represents the first level of evaluation of a complete postmortem investigation of a sudden or unexpected death of an individual. Urine organic acids can also be analyzed from urine spotted on filter paper, see OAUS / Organic Acids Screen, Urine Spot. Additional confirmatory testing is recommended. The diagnosis of an underlying FAO disorder or organic aciduria allows genetic counseling of the family, including the possible option of future prenatal diagnosis, and testing of at-risk family members of any age. Disorders Detectable by Acylcarnitine Analysis* Fatty Acid Oxidation Disorders: -Short-chain acyl-CoA dehydrogenase deficiency -Medium/Short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency -Medium-chain acyl-CoA dehydrogenase deficiency -Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency and trifunctional protein deficiency -Very long-chain acyl-CoA dehydrogenase deficiency -Carnitine palmitoyl transferase type II deficiency -Carnitine-acylcarnitine

translocase deficiency -Electron-Transferring Flavoproteins (ETF) deficiency, ETF-dehydrogenase deficiency (multiple acyl-CoA dehydrogenase deficiency; glutaric acidemia type II) Organic Acid Disorders: -Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia type I) -Propionic acidemia -Methylmalonic acidemia -Isovaleric acidemia -3-Hydroxy-3-methylglutaryl-CoA carboxylase deficiency -3-Methylcrotonyl carboxylase deficiency -Biotinidase deficiency -Multiple carboxylase deficiency -Isobutyryl-CoA dehydrogenase deficiency -2-Methylbutyryl-CoA dehydrogenase deficiency -Beta-ketothiolase deficiency -Malonic aciduria -Ethylmalonic encephalopathy *Additional confirmatory testing is required for most of these conditions because an acylcarnitine profile can be suggestive of more than one condition. For more information see Postmortem Screening Algorithm for Fatty Acid Oxidation Disorders and Organic Acidurias.

Useful For: Postmortem evaluation of individuals at any age who died suddenly or unexpectedly; testing is particularly recommended under the following circumstances (risk factors): -Family history of sudden infant death syndrome or other sudden unexpected deaths at any age -Family history of Reye syndrome -Maternal complications of pregnancy (acute fatty liver pregnancy, HELLP syndrome [hemolysis, elevated liver enzymes, and low platelet count]) -Lethargy, vomiting, fasting in the 48 hours prior to death -Allegation of child abuse (excluding obvious cases of trauma, physical harm) Macroscopic findings at autopsy: -Fatty infiltration of the liver -Dilated or hypertrophic cardiomyopathy -Autopsy evidence of infection that routinely would not represent a life-threatening event

Interpretation: Reports of abnormal acylcarnitine profiles will include an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnoses, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis) as indicated, name and phone number of contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions. Abnormal results are not always sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on an acylcarnitine analysis, independent biochemical (eg, FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture) or molecular genetic analyses are required using additional tissue such as skin fibroblasts from the deceased patient. If not available, molecular genetic analysis of a patient's parents may enable the confirmation of a diagnosis.

Reference Values:
Quantitative results are compared to a constantly updated range which corresponds to the 5 to 95 percentile interval of all postmortem cases analyzed in our laboratory.

Clinical References: 1. Miller MJ, Cusmano-Ozog K, Oglesbee D, Young S. ACMG Laboratory Quality Assurance Committee. Laboratory analysis of acylcarnitines, 2020 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(2):249-258 2. Rinaldo P, Matern D, Bennet BJ. Fatty acid oxidation disorders. Ann Rev Physiol. 2002;64:477-502 3. Rashed MS, Ozand PT, Bennett MJ, et al. Inborn errors of metabolism diagnosed in sudden death cases by acylcarnitine analysis of postmortem bile. Clin Chem. 1995;4(8 Pt 1):1109-1114 4. Pryce JW, Weber MA, Heales S, et al. Tandem mass spectrometry findings at autopsy for detection of metabolic disease in infant deaths: postmortem changes and confounding factors. J Clin Pathol. 2011;64(11):1005-1009. doi:10.1136/jclinpath-2011-200218 5. van Rijt WJ, Koolhaas GD, Bekhof J, et al. Inborn errors of metabolism that cause sudden infant death: A systematic review with implications for population neonatal screening programmes. Neonatology. 2016;109(4):297-302

KUR
614060

Potassium, 24 Hour, Urine

Clinical Information: Potassium (K+) is the major intracellular cation. Functions of potassium include regulation of neuromuscular excitability, heart contractility, intracellular fluid volume, and hydrogen ion concentration. The physiologic function of K+ requires the body to maintain a low

extracellular fluid concentration of the cation; the intracellular concentration is 20 times greater than the extracellular K+ concentration. Only 2% of total body K+ circulates in the plasma. The kidneys provide the most important regulation of K+. The proximal tubules reabsorb almost all the filtered K+. Under the influence of aldosterone, the remaining K+ can then be secreted into the urine in exchange for sodium in both the collecting ducts and the distal tubules. Thus, the distal nephron is the principal determinant of urinary K+ excretion. Decreased excretion of K+ in acute kidney disease and end-stage kidney failure are common causes of prolonged hyperkalemia. Renal losses of K+ may occur during the diuretic (recovery) phase of acute tubular necrosis, during administration of non-potassium sparing diuretic therapy, and during states of excess mineralocorticoid or glucocorticoid.

Useful For: Determining the cause for hyper- or hypokalemia

Interpretation: Hypokalemia reflecting true total body deficits of potassium (K+) can be classified into renal and nonrenal losses based on the daily excretion of K+ in the urine. During hypokalemia, if urine excretion of K+ is below 30 mEq/day, it can be concluded that kidney reabsorption of K+ is appropriate. In this situation, the causes for the hypokalemic state are either decreased K+ intake or extra renal loss of K+ rich fluid. Urine excretion of more than 30 mEq/d in a hypokalemia setting is inappropriate and indicates that the kidneys are the primary source of the lost K+.

Reference Values:
> or =18 years: 16-105 mmol/24 hours

Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1308-1309 2. Toffaletti J: Electrolytes. In: Dufour DR, Rifai N, eds. Professional Practice in Clinical Chemistry: A Review. AACC Press; 1993

RKUR
610696

Potassium, Random, Urine

Clinical Information: Potassium (K+) is the major intracellular cation. Functions of K+ include regulation of neuromuscular excitability, heart contractility, intracellular fluid volume, and hydrogen ion concentration. The physiologic function of K+ requires the body to maintain a low extracellular fluid (ECF) concentration of the cation; the intracellular K+ concentration is 20 times greater than the extracellular concentration. Only 2% of total body K+ circulates in the plasma. The kidneys provide the most important regulation of K+. The proximal tubules reabsorb almost all the filtered K+. Under the influence of aldosterone, the remaining K+ can then be secreted into the urine in exchange for sodium in both the collecting ducts and the distal tubules. Thus, the distal nephron is the principal determinant of urinary K+ excretion. Decreased excretion of K+ in acute kidney disease and end-stage kidney failure are common causes of prolonged hyperkalemia. Renal losses of K+ may occur during the diuretic (recovery) phase of acute tubular necrosis, during administration of non-potassium sparing diuretic therapy, and during states of excess mineralocorticoid or glucocorticoid.

Useful For: Determining the cause for hyper- or hypokalemia using a random urine specimen

Interpretation: Hypokalemia reflecting true total body deficits of potassium (K+) can be classified into renal and nonrenal losses based on the daily excretion of K+ in the urine. During hypokalemia, if urine excretion of K+ is less than 30 mEq/day, it can be concluded that renal reabsorption of K+ is appropriate. In this situation, the causes for the hypokalemic state are either decreased K+ intake or extra renal loss of K+ rich fluid. Urine excretion of more than 30 mEq/day in a hypokalemia setting is inappropriate and indicates that the kidneys are the primary source of the lost K+.

Reference Values:
No established reference values
Random urine potassium may be interpreted in conjunction with serum potassium, using both values to calculate fractional excretion of potassium.

The calculation for fractional excretion (FE) of potassium (K) is
FE(K)= ([K(urine) X Creat(serum)]/[K(serum) X Creat(urine)]) X 100

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1308-1309 2. Toffaletti J: Electrolytes. In: Dufour DR, Rifai N, eds. Professional Practice in Clinical Chemistry: A Review. AACC Press; 1993

KS
602352

Potassium, Serum

Clinical Information: Potassium is the major cation of the intracellular fluid. Disturbance of potassium homeostasis has serious consequences. Decreases in extracellular potassium are characterized by muscle weakness, irritability, and eventual paralysis. Cardiac effects include tachycardia, other cardiac conduction abnormalities that are apparent by electrocardiographic examination, and eventual cardiac arrest. Hypokalemia (low potassium) is common in vomiting, diarrhea, alcoholism, and folic acid deficiency. Additionally, more than 90% of hypertensive patients with aldosteronism have hypokalemia. Abnormally high extracellular potassium levels produce symptoms of mental confusion; weakness, numbness, and tingling of the extremities; weakness of the respiratory muscles; flaccid paralysis of the extremities; slowed heart rate; and eventually peripheral vascular collapse and cardiac arrest. Hyperkalemia may be seen in end-stage renal failure, hemolysis, trauma, Addison disease, metabolic acidosis, acute starvation, dehydration, and with rapid potassium infusion. Potassium should be monitored during treatment of many conditions but especially in diabetic ketoacidosis and any intravenous therapy for fluid replacement.

Useful For: Evaluation of electrolyte balance, cardiac arrhythmia, muscular weakness, hepatic encephalopathy, and renal failure

Interpretation: Potassium levels below 3.0 mmol/L are associated with marked neuromuscular symptoms and are evidence of a critical degree of intracellular depletion. Potassium levels below 2.5 mmol/L are potentially life-threatening. High potassium can be an acute medical emergency, particularly if the potassium increases over a short period of time. At values above 6.0 mmol/L, symptoms are typically apparent. Potassium levels above 6.0 mmol/L are potentially lifethreatening. Levels above 10.0 mmol/L are, in most cases, fatal.

Reference Values:
<1 year: not established
> or =1 year: 3.6-5.2 mmol/L

Clinical References: Tietz Textbook of Clinical Chemistry. Fourth edition. Edited by CA Burtis, ER Ashwood, DE Bruns. WB Saunders Company, Philadelphia, 2006;27:984-987; 2006;46:1754-1757

POU2F
618483

POU2F3 Immunostain, Technical Component Only

Clinical Information: POU2F3 (POU Class 2 Homeobox 3) may be useful in the diagnosis of small cell lung carcinomas that are negative for conventional neuroendocrine markers and TTF-1 (thyroid transcription factor 1). It may also be expressed in squamous cell carcinomas of the thymus.

Useful For:
Diagnosis of a variant of small cell lung carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Baine MK, Hsieh MS, Lai WV, et al. SCLC Subtypes Defined by ASCL1, NEUROD1, POU2F3, and YAP1: A Comprehensive Immunohistochemical and Histopathologic Characterization. J Thorac Oncol. 2020;15(12):1823-1835 2. Gay CM, Stewart CA, Park EM, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell. 2021;39(3):346-360.e7 3. Yamada Y, Simon-Keller K, Belharazem-Vitacolonnna D, et al. A Tuft Cell-Like Signature Is Highly Prevalent in Thymic Squamous Cell Carcinoma and Delineates New Molecular Subsets Among the Major Lung Cancer Histotypes. J Thorac Oncol. 2021;16(6):1003-1016 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FMPG 57931 Poultry and Meat Panel IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

POWV 616098 Powassan Virus, IgM, Enzyme-Linked Immunosorbent Assay, Serum

Clinical Information: Powassan virus (POWV) is an emerging tick-borne virus, harbored by Ixodes species ticks, which are the same ticks that transmit Lyme disease (Borrelia spp.), Babesia spp., and Anaplasma phagocytophilum, among other pathogens. POWV is a member of the Flavivirus genus, which includes other arthropod-borne viruses (arboviruses) such as West Nile virus and St. Louis encephalitis virus. Two lineages of POWV have been identified, sharing approximately 94% amino acid sequence identity, including Lineage 1, which is the prototypical POWV lineage transmitted by Ixodes marxi and Ixodes cookei, and Lineage 2, which includes deer tick virus and is transmitted by Ixodes scapularis. POWV is maintained in the environment in groundhogs, skunks, squirrels, and white footed mice. Unlike other tick-borne pathogens, following tick attachment to a host, POWV can be transmitted in as little as 15 minutes. Following infection, the incubation period can last anywhere from 4 to 14 days, after which approximately 66% of patients will remain asymptomatic. Symptomatic patients may present with a nonspecific influenza-like illness, including high fever, fatigue, malaise, and myalgia. Approximately 30% of symptomatic patients will progress to develop neurologic manifestations, most commonly encephalitis. While some patients may recover, over 50% of individuals will have persistent neurologic sequelae. POWV has been associated with an overall mortality rate of 10%. Although there

is no targeted antiviral therapy and treatment is entirely supportive care, diagnosis is important for a number of reasons, including the ability to discontinue empiric antibiotics and to provide prognostic information for patients and families.

Useful For: Diagnosis of Powassan virus infection. This test should not be used as a screening procedure for the general population. This test should not be used as a "test of cure."

Interpretation: Negative: No antibodies to Powassan virus detected. Negative results may occur in samples collected too soon following infection, prior to the development of a robust immune response, or in immunocompromised patients. Positive: Antibodies to Powassan virus detected. Confirmatory testing through a local public health laboratory and/or the Centers for Disease Control and Prevention is recommended. False positive results may occur in patients with current or prior infection with other flaviviruses (West Nile virus, Zika virus, dengue virus, etc).

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Vector-Borne Diseases (DVBD): Powassan virus disease. CDC; Updated January 10, 2019. Available at www.cdc.gov/ticks/tickbornediseases/powassan.html 2. Kemenesi G, Banyai K: Tick-borne Flaviviruses, with a focus on Powassan virus. Clinical Microbiology Reviews. 2019;32(1):e00106-00117

POWVB
617484

Powassan Virus, RNA, Molecular Detection, PCR, Blood

Clinical Information: Powassan virus (POWV) is an emerging tick-borne virus, harbored by Ixodes species ticks, which are the same ticks that transmit Lyme disease (Borrelia spp.), Babesia spp., and Anaplasma phagocytophilum, among other pathogens. POWV is a member of the Flavivirus genus, which includes other arthropod-borne viruses (arboviruses) such as West Nile virus (WNV) and St. Louis encephalitis virus. Two lineages of POWV have been identified, sharing approximately 94% amino acid sequence identity, including lineage 1, which is the prototypical POWV lineage transmitted by Ixodes marxi and Ixodes cookei, and lineage 2, which includes deer tick virus and is transmitted by Ixodes scapularis. POWV is maintained in the environment in groundhogs, skunks, squirrels, and white footed mice. Unlike other tick-borne pathogens, following tick attachment to a host, POWV can be transmitted in as little as 15 minutes. Following infection, the incubation period can last anywhere from 4 to 14 days, after which approximately 66% of patients will remain asymptomatic. Symptomatic patients may present with a nonspecific influenza-like illness, including high fever, fatigue, malaise, and myalgia. Approximately 30% of symptomatic patients will progress to develop neurologic manifestations, most commonly encephalitis. While some patients may recover, over 50% of individuals will have persistent neurologic sequelae. POWV has been associated with an overall mortality rate of 10%. Although there is no targeted antiviral therapy and treatment is entirely supportive care, diagnosis is important for a number of reasons, including the ability to discontinue empiric antibiotics and to provide prognostic information for patients and families. While limited data exist for POWV real-time reverse transcription polymerase chain reaction (RT-PCR) detection, data from testing for the related flavivirus, WNV, suggests that blood may be a more sensitive source than serum for detecting viral RNA. Similarly, data from WNV and other flaviviruses suggest that viral RNA may be detected in urine for a longer period of time than in blood or serum. POWV RNA may be detected from cerebrospinal fluid in cases of neuroinvasive disease. Powassan infections are often diagnosed based on a patient's symptoms and exposure risk in conjunction with molecular and serologic testing. The use of RT-PCR can provide a rapid laboratory confirmation of POWV RNA early in infection, particularly during the first 7 days of illness when serologic testing is typically negative. After 7 days, POWV RT-PCR is less sensitive and serologic testing is the preferred

diagnostic method. It is common for RT-PCR and serology to be used together for diagnosis of early infection, as they are complementary methods.

Useful For: Rapid testing for Powassan virus RNA (lineage 1 and lineage 2) using whole blood specimens An adjunctive test to serology for detection of early Powassan virus infection (ie, first few days after symptom onset) This assay should not be used for screening asymptomatic individuals and should only be used to test patients with signs and symptoms of Powassan virus disease.

Interpretation: A positive result indicates the presence of Powassan virus RNA and is consistent with early Powassan virus infection.

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases, Division of Vector-Borne Diseases: Powassan Virus. For Healthcare Providers: Diagnostic Testing. CDC; Updated January 26, 2023. Accessed March 28, 2023. Available at www.cdc.gov/powassan/diagnostic-testing.html 2. Piantadosi A, Rubin DB, McQuillen DP, et al. Emerging cases of Powassan virus encephalitis in New England: Clinical presentation, imaging, and review of the literature. Clin Infect Dis. 2016 Mar 15;62(6):707-713. doi: 10.1093/cid/civ1005

POWVU 617487 Powassan Virus, RNA, Molecular Detection, PCR, Random, Urine

Clinical Information: Powassan virus (POWV) is an emerging tick-borne virus, harbored by Ixodes species ticks, which are the same ticks that transmit Lyme disease (Borrelia spp.), Babesia spp., and Anaplasma phagocytophilum, among other pathogens. POWV is a member of the Flavivirus genus, which includes other arthropod-borne viruses (arboviruses) such as West Nile virus (WNV) and St. Louis encephalitis virus. Two lineages of POWV have been identified, sharing approximately 94% amino acid sequence identity, including lineage 1, which is the prototypical POWV lineage transmitted by Ixodes marxi and Ixodes cookei, and lineage 2, which includes deer tick virus and is transmitted by Ixodes scapularis. POWV is maintained in the environment in groundhogs, skunks, squirrels, and white footed mice. Unlike other tick-borne pathogens, following tick attachment to a host, POWV can be transmitted in as little as 15 minutes. Following infection, the incubation period can last anywhere from 4 to 14 days, after which approximately 66% of patients will remain asymptomatic. Symptomatic patients may present with a nonspecific influenza-like illness, including high fever, fatigue, malaise, and myalgia. Approximately 30% of symptomatic patients will progress to develop neurologic manifestations, most commonly encephalitis. While some patients may recover, over 50% of individuals will have persistent neurologic sequelae. POWV has been associated with an overall mortality rate of 10%. Although there is no targeted antiviral therapy and treatment is entirely supportive care, diagnosis is important for a number of reasons, including the ability to discontinue empiric antibiotics and to provide prognostic information for patients and families. While limited data exist for POWV real-time reverse transcription polymerase chain reaction (RT-PCR) detection, data from testing for the related flavivirus, WNV, suggests that blood may be a more sensitive source than serum for detecting viral RNA. Similarly, data from WNV and other flaviviruses suggest that viral RNA may be detected in urine for a longer period of time than in blood or serum. POWV RNA may be detected from cerebrospinal fluid in cases of neuroinvasive disease. Powassan infections are often diagnosed based on a patient's symptoms and exposure risk in conjunction with molecular and serologic testing. The use of RT-PCR can provide a rapid laboratory confirmation of POWV RNA early in infection, particularly during the first 7 days of illness when serologic testing is typically negative. After 7 days, POWV RT-PCR is less sensitive and serologic testing is the preferred diagnostic method. It is

common for RT-PCR and serology to be used together for diagnosis of early infection, as they are complementary methods.

Useful For: Rapid testing for Powassan virus RNA (lineage 1 and lineage 2) using random urine specimens An adjunctive test to serology for detection of early Powassan virus infection (ie, first few days after symptom onset). This assay should not be used for screening asymptomatic individuals and should only be used to test patients with signs and symptoms of Powassan virus disease.

Interpretation: A positive result indicates the presence of Powassan virus RNA and is consistent with early Powassan virus infection.

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases, Division of Vector-Borne Diseases: Powassan virus. For healthcare providers: Diagnostic testing. CDC; Updated January 26, 2023. Accessed March 28, 2023. Available at www.cdc.gov/powassan/diagnostic-testing.html 2. Piantadosi A, Rubin DB, McQuillen DP, et al: Emerging cases of Powassan virus encephalitis in New England: Clinical presentation, imaging, and review of the literature. Clin Infect Dis. 2016 Mar 15;62(6):707-713. doi: 10.1093/cid/civ1005

POWVS
617486

Powassan Virus, RNA, Molecular Detection, PCR, Serum

Clinical Information: Powassan virus (POWV) is an emerging tick-borne virus, harbored by Ixodes species ticks, which are the same ticks that transmit Lyme disease (Borrelia spp.), Babesia spp., and Anaplasma phagocytophilum, among other pathogens. POWV is a member of the Flavivirus genus, which includes other arthropod-borne viruses (arboviruses) such as West Nile virus (WNV) and St. Louis encephalitis virus. Two lineages of POWV have been identified, sharing approximately 94% amino acid sequence identity, including lineage 1, which is the prototypical POWV lineage transmitted by Ixodes marxi and Ixodes cookei, and lineage 2, which includes deer tick virus and is transmitted by Ixodes scapularis. POWV is maintained in the environment in groundhogs, skunks, squirrels, and white footed mice. Unlike other tick-borne pathogens, following tick attachment to a host, POWV can be transmitted in as little as 15 minutes. Following infection, the incubation period can last anywhere from 4 to 14 days, after which approximately 66% of patients will remain asymptomatic. Symptomatic patients may present with a nonspecific influenza-like illness, including high fever, fatigue, malaise, and myalgia. Approximately 30% of symptomatic patients will progress to develop neurologic manifestations, most commonly encephalitis. While some patients may recover, over 50% of individuals will have persistent neurologic sequelae. POWV has been associated with an overall mortality rate of 10%. Although there is no targeted antiviral therapy and treatment is entirely supportive care, diagnosis is important for a number of reasons, including the ability to discontinue empiric antibiotics and to provide prognostic information for patients and families. While limited data exist for POWV real-time reverse transcription polymerase chain reaction (RT-PCR) detection, data from testing for the related flavivirus, WNV, suggests that blood may be a more sensitive source than serum for detecting viral RNA. Similarly, data from WNV and other flaviviruses suggest that viral RNA may be detected in urine for a longer period of time than in blood or serum. POWV RNA may be detected from cerebrospinal fluid in cases of neuroinvasive disease. Powassan infections are often diagnosed based on a patient's symptoms and exposure risk in conjunction with molecular and serologic testing. The use of RT-PCR can provide a rapid laboratory confirmation of POWV RNA early in infection, particularly during the first 7 days of illness when serologic testing is typically negative. After 7 days, POWV RT-PCR is less sensitive and serologic testing is the preferred diagnostic method. It is common for RT-PCR and serology to be used together for diagnosis of early infection, as they are complementary methods.

Useful For: Rapid testing for Powassan virus RNA (lineage 1 and lineage 2) using serum specimens An adjunctive test to serology for detection of early Powassan virus infection (ie, first few days after symptom onset) This assay should not be used for screening asymptomatic individuals and should only be used to test patients with signs and symptoms of Powassan virus disease.

Interpretation: A positive result indicates the presence of Powassan virus RNA and is consistent with early Powassan virus infection.

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases, Division of Vector-Borne Diseases: Powassan Virus. For Healthcare Providers: Diagnostic testing. CDC; Updated January 26, 2023. Accessed March 28, 2023. Available at www.cdc.gov/powassan/diagnostic-testing.html 2. Piantadosi A, Rubin DB, McQuillen DP, et al: Emerging cases of Powassan virus encephalitis in New England: clinical presentation, imaging, and review of the literature. 2016 Clin Infect Dis. 2016 Mar 15;62(6):707-713

POWVC
617485

Powassan Virus, RNA, Molecular Detection, PCR, Spinal Fluid

Clinical Information: Powassan virus (POWV) is an emerging tick-borne virus, harbored by Ixodes species ticks, which are the same ticks that transmit Lyme disease (Borrelia spp.), Babesia spp., and Anaplasma phagocytophilum, among other pathogens. POWV is a member of the Flavivirus genus, which includes other arthropod-borne viruses (arboviruses) such as West Nile virus (WNV) and St. Louis encephalitis virus. Two lineages of POWV have been identified, sharing approximately 94% amino acid sequence identity, including lineage 1, which is the prototypical POWV lineage transmitted by Ixodes marxi and Ixodes cookei, and lineage 2, which includes deer tick virus and is transmitted by Ixodes scapularis. POWV is maintained in the environment in groundhogs, skunks, squirrels, and white footed mice. Unlike other tick-borne pathogens, following tick attachment to a host, POWV can be transmitted in as little as 15 minutes. Following infection, the incubation period can last anywhere from 4 to 14 days, after which approximately 66% of patients will remain asymptomatic. Symptomatic patients may present with a nonspecific influenza-like illness, including high fever, fatigue, malaise, and myalgia. Approximately 30% of symptomatic patients will progress to develop neurologic manifestations, most commonly encephalitis. While some patients may recover, over 50% of individuals will have persistent neurologic sequelae. POWV has been associated with an overall mortality rate of 10%. Although there is no targeted antiviral therapy and treatment is entirely supportive care, diagnosis is important for a number of reasons, including the ability to discontinue empiric antibiotics and to provide prognostic information for patients and families. While limited data exist for POWV real-time reverse transcription polymerase chain reaction (RT-PCR) detection, data from testing for the related flavivirus, WNV, suggests that blood may be a more sensitive source than serum for detecting viral RNA. Similarly, data from WNV and other flaviviruses suggest that viral RNA may be detected in urine for a longer period of time than in blood or serum. POWV RNA may be detected from cerebrospinal fluid in cases of neuroinvasive disease. Powassan infections are often diagnosed based on a patient's symptoms and exposure risk in conjunction with molecular and serologic testing. The use of RT-PCR can provide a rapid laboratory confirmation of POWV RNA early in infection, particularly during the first 7 days of illness when serologic testing is typically negative. After 7 days, POWV RT-PCR is less sensitive and serologic testing is the preferred diagnostic method. It is common for RT-PCR and serology to be used together for diagnosis of early infection, as they are complementary methods.

Useful For: Rapid testing for Powassan virus RNA (lineage 1 and lineage 2) using cerebrospinal fluid specimens An adjunctive test to serology for detection of early Powassan virus infection (ie, first

few days after symptom onset) This assay should not be used for screening asymptomatic individuals and should only be used to test patients with signs and symptoms of Powassan virus disease.

Interpretation: A positive result indicates the presence of Powassan virus RNA and is consistent with early Powassan virus infection.

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases, Division of Vector-Borne Diseases: Powassan Virus. For Healthcare Providers: Diagnostic testing. CDC; Updated January 26, 2023. Accessed March 28, 2023. Available at www.cdc.gov/powassan/diagnostic-testing.html 2. Piantadosi A, Rubin DB, McQuillen DP, et al. Emerging cases of Powassan virus encephalitis in New England: Clinical presentation, imaging, and review of the literature. Clin Infect Dis. 2016 Mar 15;62(6):707-713. doi: 10.1093/cid/civ1005

PWAS
35535

Prader-Willi/Angelman Syndrome, Molecular Analysis, Varies

Clinical Information: Prader-Willi syndrome (PWS) is a congenital disorder characterized by a biphasic clinical course. Neonates with PWS are hypotonic, have a weak cry, and are initially poor feeders that improve over time. In later infancy and childhood, individuals with PWS have global developmental delay, short stature, hypogonadism, small hands and feet, and marked hyperphagia leading to obesity. PWS is thought to be due to loss of function of paternally expressed genes, although specific genes have not yet been definitively implicated in the phenotype of PWS. Etiology of Prader-Willi syndrome: -Chromosome 15 deletion (15q11-13): Approximately 60% to 70% -Maternal uniparental disomy (UPD): 20% to 35% -Imprinting defect: 1% to 5% -Chromosome rearrangement: Rare Paternal deletions of 15q11-13 are more frequently associated with hypopigmentation, characteristic facial features, and skill with jigsaw puzzles, whereas individuals with maternal UPD typically have higher verbal IQ and are more likely to have psychosis and autism spectrum disorder. Angelman syndrome (AS) is a nonprogressive congenital disorder characterized by more significant developmental delay and intellectual disability, ataxia, seizures, jerky arm movements, macrostomia, tongue thrusting, unprovoked laughter, brachycephaly, and virtual absence of speech. AS is due to loss of function of the maternally expressed gene UBE3A. Etiology of Angelman syndrome: -Chromosome 15 deletion (15q11-13): Approximately 70% to 75% -Paternal UPD: Approximately 5% -UBE3A variant: Approximately 10% -Imprinting defect: 2% to 5% -Chromosome rearrangement: Rare -Unknown: Approximately 10% The phenotype of AS patients with maternal deletions is generally more severe than that associated with paternal UPD or imprinting defects, including a higher rate or severity of microcephaly, seizures, and motor difficulties. Patients with AS caused by paternal UPD or imprinting defects generally show better growth and higher developmental and language abilities. Both chromosome 15 deletions and UPD most often occur as de novo events during conception, and thus, recurrence risk to siblings is very low. In rare cases, chromosome 15 deletions and UPD occur as a result of parental translocations or other rare cytogenetic rearrangements. In these cases, the recurrence risk to siblings is increased. The recurrence risk associated with imprinting defects is dependent on whether there is an identifiable variant. UBE3A variants can occur sporadically or be inherited in an autosomal dominant fashion. There is a 50% recurrence risk to siblings in cases of an inherited UBE3A variant. Due to the complex genetic etiology of PWS and AS and the corresponding variability in recurrence risks, careful cytogenetic and molecular testing and family assessment are necessary to provide accurate genetic counseling. Initial studies to rule-out PWS or AS should include chromosomal microarray analysis to identify chromosome abnormalities that may have phenotypic overlap with PWS or AS, and methylation-sensitive multiple ligation-dependent probe amplification (MLPA) to identify deletions, duplications, and methylation defects. In cases where methylation-sensitive MLPA suggests either a deletion or duplication, fluorescence in situ hybridization can be used to confirm type I and type II deletions or characterize the disease mechanism, respectively. In

cases where methylation-sensitive MLPA suggests abnormal methylation in the absence of a deletion or duplication, UPD studies can be used to characterize the disease mechanism. For more information see Prader-Willi and Angelman Syndromes: Laboratory Approach to Diagnosis.

Useful For: Confirmation of diagnosis in patients suspected of having either Prader-Willi syndrome (PWS) or Angelman syndrome (AS) based on clinical assessment or previous laboratory analysis
Prenatal diagnosis in families at risk for PWS or AS

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Buiting K. Prader-Willi syndrome and Angelman syndrome. Am J Med Genet C Semin Med Genet. 2010;154C(3):365-376 2. Williams CA, Beaudet AL, Clayton-Smith J, et al. Angelman syndrome 2005: updated consensus for diagnostic criteria. Am J Med Genet A. 2006;140(5):413-418 3. Driscoll DJ, Miller JL, Cassidy SB. Prader-Willi Syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated November 2, 2023. Accessed November 19, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1330/ 4. Nygren AOH, Ameziane N, Duarte HMB, et al. Methylation-specific MLPA (MS-MLPA): simultaneous detection of CpG methylation and copy number changes of up to 40 sequences. Nucleic Acids Res. 2005;33(14):e128 5. Procter M, Chou LS, Tang W, Jama M, Mao R. Molecular diagnosis of Prader-Willi and Angelman syndromes by methylation-specific melting analysis and methylation-specific multiplex ligation-dependent probe amplification. Clin Chem. 2006;52(7):1276-1283

PRAME
615794

PRAME Immunostain, Technical Component Only

Clinical Information: PRAME (Preferentially expressed Antigen in Melanoma) expression in melanocytic neoplasms is strongly associated with melanoma and may be useful in differentiating benign nevi from malignant melanocytic lesions.

Useful For: Differentiation between melanoma and benign nevi.

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Lezcano C, Jungbluth AA, Nehal KS, et al: PRAME expression in melanocytic tumors. Am J Surg Pathol. 2018 Nov;42(11):1456-1465. doi: 10.1097/PAS.0000000000001134 2. Raghavan SS, Wang JY, Toland A, et al: Diffuse PRAME expression is highly specific for malignant melanoma in the distinction from clear cell sarcoma. J of Cutan Pathol. 2020 Dec;47(12):1226-1228. doi: 10.1111/cup.13812 3. Gradecki SE, Slingluff CL Jr, Gru AA: PRAME expression in 155 cases of metastatic melanoma. J Cutan Pathol. 2021 Apr;48(4):479-485. doi: 10.1111/cup.13876 4. Lezcano C, Jungbluth AA, Busam KJ: Comparison of immunohistochemistry for PRAME with cytogenetic test results in the evaluation of challenging melanocytic tumors. Am J Surg Pathol. 2020 Jul;44(7):893-900. doi: 10.1097/PAS.0000000000001492 5. Lezcano C, Jungbluth AA, Busam KJ: PRAME immunohistochemistry as an ancillary test for the assessment of melanocytic lesions. Surg Pathol Clin. 2021 Jun;14(2):165-175. doi:

10.1016/j.path.2021.01.001

PALB 9005 Prealbumin, Serum

Clinical Information: Prealbumin is synthesized in the liver and acts as a binding protein for thyroxine and retinol-binding protein. The serum concentration of prealbumin reflects the synthesis capacity of the liver and is markedly diminished in malnutrition and other conditions. Due to its short half-life of approximately 2 days, prealbumin can be used for monitoring the nutritional status and efficacy of parenteral nutrition.

Useful For: Assessing nutritional status, especially in monitoring the response to nutritional support in the acutely ill patient

Interpretation: Results below the reference intervals for adults and pediatric patients may suggest protein depletion. Clinical correlation recommended with patient status and other nutritional markers.

Reference Values:
< or =18 years: 12-32 mg/dL
>18 years: 19-38 mg/dL

Clinical References: 1. Haider M, Haider SQ. Assessment of protein-calorie malnutrition. Clin Chem 1984;30(8):1286-1299 2. Grant JP, Custer PB, Thurlow J. Current techniques of nutritional assessment. Surg Clin North Am 1981;61(3):437-463 3. Bernstein LH, Leukhardt-Fairfield CJ, Pleban W, et al. Usefulness of data on albumin and prealbumin concentrations in determining effectiveness of nutritional support. Clin Chem 1989;35(2):271-274 4. Kanakoudi F, Drossou V, Tzimouli V, et al: Serum concentrations of 10 acute-phase proteins in healthy term and pre-term infants from birth to age 6 months. Clin Chem 1995;41(4):605-608 5. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

C2NAD 621651 PrecivityAD, Plasma

Clinical Information:

Useful For: Assisting in the evaluation of adult patients, aged 55 years and older, with signs or symptoms of mild cognitive impairment or dementia who are being assessed for Alzheimer disease and other causes of cognitive decline This is not intended for patients younger than 55 years, or for use as a screening test in patients without signs or symptoms of cognitive impairment, or for serial testing for assessment of longitudinal changes.

Interpretation: The Amyloid Probability Score (APS) represents the estimated likelihood from 0 (low likelihood) to 100 (high likelihood) that the patient is currently positive on amyloid positron emission tomography (PET) imaging (presence of amyloid plaques) based on their amyloid beta (Abeta) 42/40 ratio, age, and established APOE genotype. A low APS result (0-35) is consistent with a negative amyloid PET scan result and, thus, a low likelihood of amyloid plaques. Absence of amyloid plaques is inconsistent with an Alzheimer disease diagnosis and indicates other causes of cognitive symptoms should be investigated. An intermediate APS result (36-57) does not distinguish between the presence or absence of amyloid plaques and indicates further diagnostic evaluation may be needed to assess the underlying causes for the patient's cognitive symptoms. A high APS result (58-100) is consistent with a positive amyloid PET scan result and, thus, a high likelihood of amyloid plaques. Presence of amyloid plaques is consistent with an Alzheimer disease diagnosis in someone who has cognitive decline, but

alone is insufficient for a final diagnosis; clinical presentation and other factors should be considered along with the APS result.

Reference Values:

Amyloid Probability Score (APS): 0-100
Low (0-35): Consistent with absence of amyloid plaques
Intermediate (36-57)
High (58- 100): Consistent with presence of amyloid plaques

Abeta42/40 Ratio
> or =0.095: Consistent with absence of amyloid plaques

ApoE Proteotype
E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, E4/E4
-E3 is the most common allele.
-E4 allele is associated with increased risk of amyloid plaques.
-E2 allele is associated with lower risk of amyloid plaques.

Clinical References: 1. Centers for Disease Control and Prevention. Alzheimer's Disease and Related Dementias. CDC; Updated October 26,2020. Accessed March 25, 2024. Available at www.cdc.gov/aging/aginginfo/alzheimers.htm 2. Bird TD. Alzheimer Disease Overview. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. GeneReviews. University of Washington, Seattle; October 23, 1998. Updated December 20, 2018. Accessed March 13, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1161/ 3. Alzheimer's Association. Mild Cognitive Impairment (MCI). Accessed June 16, 2023. Available at www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/mild-cognitive-impairment. 4. Johnson KA, Minoshima S, Bohnen NI, et al. Update on appropriate use criteria for amyloid PET imaging: dementia experts, mild cognitive impairment, and education. Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging. Alzheimers Dement. 2013;9(4):e106-e109. doi:10.1016/j.jalz.2013.06.001 5. Shaw LM, Arias J, Blennow K, et al. Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease. Alzheimers Dement. 2018;14(11):1505-1521. doi:10.1016/j.jalz.2018.07.220 6. Kirmess KM, Meyer MR, Holubasch MS, et al. The PrecivityAD test: Accurate and reliable LC-MS/MS assays for quantifying plasma amyloid beta 40 and 42 and apolipoprotein E proteotype for the assessment of brain amyloidosis. Clin Chim Acta. 2021;519:267-275. doi:10.1016/j.cca.2021.05.011 7. West T, Kirmess KM, Meyer MR, et al. A blood-based diagnostic test incorporating plasma Abeta42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: findings from a multi cohort validity analysis. Mol Neurodegener. 2021;16(1):30. Published 2021 May 1. doi:10.1186/s13024-021-00451-6 8. Hu Y, Kirmess KM, Meyer MR, et al. Assessment of a plasma amyloid probability score to estimate amyloid positron emission tomography findings among adults with cognitive impairment. JAMA Netw Open. 2022;5(4):e228392. Published 2022 Apr 1. doi:10.1001/jamanetworkopen.2022.8392 9. Cummings J, Aisen P, Apostolova LG, Atri A, Salloway S, Weiner M. Aducanumab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2021;8(4):398-410. doi:10.14283/jpad.2021.41. 10. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948

C2AD2
621652

PrecivityAD2, Plasma

Clinical Information: Alzheimer disease (AD) is defined pathologically by the presence of amyloid plaques and neurofibrillary tangles in the brain. Clinical characteristics include gradual onset of mild cognitive impairment (MCI), behavioral changes such as apathy, withdrawal, or agitation, and disease progression to middle and later stage dementia.(1,2) Currently, no test detects AD with 100% accuracy; definitive diagnosis occurs at brain autopsy. Recent availability of anti-amyloid therapies

increases the importance of detection of AD at an early stage.(3-5) MCI impacts 12 to 18% of people in the United States over age 60 and is often an initial clinical sign of AD.(6) Establishing or excluding an AD diagnosis with a high degree of certainty at first signs of memory decline may optimize medical management. Brain amyloid pathology is detectable by amyloid positron emission tomography (PET) scan, cerebrospinal fluid testing, or liquid chromatography tandem mass spectrometry blood biomarker testing with high sensitivity and specificity in patients with MCI and early dementia.(7-12) In all testing modalities, healthcare providers interpret test results in the context of the patient's clinical findings and other clinical work-up, as the neuropathological changes associated with AD can be seen in other forms of dementia and in unaffected individuals.(7,8,13) The PrecivityAD2 test is an analytically and clinically validated blood test that aids healthcare providers in ruling in or ruling out AD in patients presenting with MCI or dementia. This evaluation simultaneously quantifies specific plasma amyloid beta (Abeta) and tau peptide concentrations to calculate the Abeta42/40 ratio and percent tau phosphorylated at threonine-217 (%p-tau217).(12) The inclusion of plasma analyte ratios has been shown to mitigate the effects of confounding factors such as chronic kidney disease.(14,15) The ratios are combined into a proprietary statistical algorithm to calculate the Amyloid Probability Score 2 (APS2), a numerical value ranging from 0 to100 that determines whether a patient is positive (has high likelihood) or negative (has low likelihood) for the presence of brain amyloid plaques by amyloid PET scan.

Useful For: Assisting in the evaluation of adult patients, aged 55 years and older, with signs or symptoms of mild cognitive impairment or dementia who are being assessed for Alzheimer disease and other causes of cognitive decline This is not intended for patients younger than 55 years, or for use as a screening test in patients without signs or symptoms of cognitive impairment, or for serial testing for assessment of longitudinal changes.

Interpretation: The Amyloid Probability Score 2 (APS2) result is a composite score ranging from 0 to 100 that demonstrates the strongest correlation with brain amyloid pathology compared to the individual biomarkers (amyloid beta [Abeta] 42/40 ratio or percent tau phosphorylated at threonine-217 [%p-tau217]) considered separately. Discordance of the individual biomarkers can occur. Table. Amyloid Probability Score and Interpretation APS2 Interpretation 0-47 Negative Consistent with a negative amyloid positron emission tomography (PET) scan; reflects a low likelihood of brain amyloid plaques and is therefore not consistent with a neuropathological diagnosis of Alzheimer disease (AD). 48-100 Positive Consistent with a positive amyloid PET scan; reflects a high likelihood of brain amyloid plaques, one of the neuropathological findings of AD. The APS2 result should be interpreted in conjunction with other patient information. Clinical correlation is recommended.

Reference Values:

Amyloid Probability Score 2 (APS2) (range of 0-100):
Negative: 0-47
Positive: 48-100

Abeta42/40 Ratio:
> or =0.095 Consistent with absence of amyloid plaques

Percent p-tau217:
<4.2% consistent with absence of brain amyloid plaques

Clinical References: 1. Centers for Disease Control and Prevention. Alzheimer's Disease and Related Dementias. CDC; Updated October 26,2020. Accessed March 25, 2024. Available at www.cdc.gov/aging/aginginfo/alzheimers.htm 2. Bird TD. Alzheimer Disease Overview. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. GeneReviews. University of Washington, Seattle; October 23, 1998. Updated December 20, 2018. Accessed March 13, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1161/ 3. Cummings J, Aisen P, Apostolova LG, Atri A, Salloway S, Weiner M. Aducanumab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2021;8(4):398-410. doi:10.14283/jpad.2021.41 4. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's

disease. N Engl J Med. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948 5. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023;330(6):512-527. doi:10.1001/jama.2023.13239 6. Alzheimer's Association. Mild Cognitive Impairment (MCI). Accessed July 21, 2023. Available at https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/mild-cognitive-impairment 7. Johnson KA, Minoshima S, Bohnen NI, et al. Update on appropriate use criteria for amyloid PET imaging: dementia experts, mild cognitive impairment, and education. Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging. Alzheimers Dement. 2013;9(4):e106-e109. doi:10.1016/j.jalz.2013.06.001 8. Shaw LM, Arias J, Blennow K, et al. Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease. Alzheimers Dement. 2018;14(11):1505-1521. doi:10.1016/j.jalz.2018.07.220 9. Kirmess KM, Meyer MR, Holubasch MS, et al. The PrecivityAD test: Accurate and reliable LC-MS/MS assays for quantifying plasma amyloid beta 40 and 42 and apolipoprotein E proteotype for the assessment of brain amyloidosis. Clin Chim Acta. 2021;519:267-275. doi:10.1016/j.cca.2021.05.011 10. West T, Kirmess KM, Meyer MR, et al. A blood-based diagnostic test incorporating plasma Abeta42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: findings from a multi cohort validity analysis. Mol Neurodegener. 2021;16(1):30. Published 2021 May 1. doi:10.1186/s13024-021-00451-6 11. Hu Y, Kirmess KM, Meyer MR, et al. Assessment of a plasma amyloid probability score to estimate amyloid positron emission tomography findings among adults with cognitive impairment. JAMA Netw Open. 2022;5(4):e228392. Published 2022 Apr 1. doi:10.1001/jamanetworkopen.2022.8392 12. Meyer MR, Kirmess KM, Eastwood S, et al. Clinical validation of the PrecivityAD2 blood test: A mass spectrometry-based test with algorithm combining %p-tau217 and Abeta42/40 ratio to identify presence of brain amyloid. Alzheimers Dement. Published online March 16, 2024. doi:10.1002/alz.13764 13. Jansen WJ, Janssen O, Tijms BM, et al. Prevalence estimates of amyloid abnormality across the Alzheimer disease clinical spectrum [published correction appears in JAMA Neurol. 2022 Mar 1;79(3):313]. JAMA Neurol. 2022;79(3):228-243. doi:10.1001/jamaneurol.2021.5216 14. Janelidze S, Barthelemy NR, He Y, Bateman RJ, Hansson O. Mitigating the associations of kidney dysfunction with blood biomarkers of Alzheimer disease by using phosphorylated tau to total tau ratios [published correction appears in JAMA Neurol. 2023 Aug 1;80(8):873]. JAMA Neurol. 2023;80(5):516-522. doi:10.1001/jamaneurol.2023.0199 15. Pichet Binette A, Janelidze S, Cullen N, et al. Confounding factors of Alzheimer's disease plasma biomarkers and their impact on clinical performance. Alzheimers Dement. 2023;19(4):1403-1414. doi:10.1002/alz.12787

AD2AR
621654

PrecivityAD2, Reflex to Apolipoprotein E, Plasma

Clinical Information: Alzheimer disease (AD) is defined pathologically by the presence of amyloid plaques and neurofibrillary tangles in the brain. Clinical characteristics include gradual onset of Mild cognitive impairment (MCI), behavioral changes such as apathy, withdrawal, or agitation, and disease progression to middle and later stage dementia.(1,2) Currently, no test detects AD with 100% accuracy; definitive diagnosis occurs at brain autopsy. Recent availability of anti-amyloid therapies increases the importance of detection of AD at an early stage.(3-5) MCI impacts 12% to 18% of people in the United States over age 60 and is often an initial clinical sign of AD.(6) Establishing or excluding an AD diagnosis with a high degree of certainty at first signs of memory decline may optimize medical management. Brain amyloid pathology is detectable by amyloid positron emission tomography (PET) scan, cerebrospinal fluid testing, or liquid chromatography tandem mass spectrometry blood biomarker testing with high sensitivity and specificity in patients with MCI and early dementia.(7-12) In all testing modalities, healthcare providers interpret test results in the context of the patient's clinical findings and other clinical work-up, as the neuropathological changes associated with AD can be seen in other forms of dementia and in unaffected individuals.(7,8,13) The PrecivityAD2 test is an analytically and clinically validated blood test that aids healthcare providers in ruling in or ruling out AD in patients presenting with MCI or dementia. This evaluation simultaneously quantifies specific plasma amyloid beta (Abeta) and tau peptide concentrations to calculate the Abeta42/40 ratio and percent tau

phosphorylated at threonine-217 (% p-tau217).(12) The inclusion of plasma analyte ratios has been shown to mitigate the effects of confounding factors such as chronic kidney disease.(14,15) The ratios are combined into a proprietary statistical algorithm to calculate the Amyloid Probability Score 2 (APS2), a numerical value ranging from 0 to 100, that determines whether a patient is positive (has high likelihood) or negative (has low likelihood) for the presence of brain amyloid plaques by amyloid PET scan. For patients with a positive PrecivityAD2 blood test result, apolipoprotein E (ApoE) proteotyping is performed to determine APOE E4 status. ApoE is a component of several classes of lipoprotein particles, including chylomicron remnants, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and high-density lipoprotein (HDL) and is highly expressed in the liver and brain.(16) The protein has seven isoforms (ApoE1-7), the most common of which are ApoE2, ApoE3 and ApoE4. ApoE isoforms are encoded by the APOE gene alleles E1-E7. The E3 allele, most frequent in all populations, has a frequency range of 50% to 90%, whereas E4 and E2 allele frequencies range from 5% to 35% and 1% to 5%, respectively.(17) ApoE isoforms differentially influence the buildup of amyloid beta plaques and tau neurofibrillary tangles in the brain. Determination of APOE proteotype/genotype status may aid in clinical evaluation for AD in symptomatic patients and can inform decision-making for optimal treatment pathways.(18-21) In recent clinical trials for amyloid-reducing therapies, the E4 allele showed an association with the development of amyloid-related imaging abnormalities (ARIA): cerebral edema (ARIA-E), and cerebral microhemorrhages (ARIA-H).(3,4)

Useful For: Assisting in the evaluation of adult patients, aged 55 years and older, with signs or symptoms of mild cognitive impairment or dementia who are being assessed for Alzheimer disease and other causes of cognitive decline Determining APOE E4 status to aid in medical management and treatment decisions when the PrecivityAD2 blood test result is positive This test is not intended for patients younger than 55 years, or for use as a screening test in patients without signs or symptoms of cognitive, or for serial testing for assessment of longitudinal changes.

Interpretation: The Amyloid Probability Score 2 (APS2) result is a composite score ranging from 0 to 100 that demonstrates the strongest correlation with brain amyloid pathology compared to the individual biomarkers (amyloid beta [Abeta] 42/40 ratio or percent tau phosphorylated at threonine-217 [%p-tau217]), considered separately. Discordance of the individual biomarkers can occur. Table 1. Amyloid Probability Score and Interpretation APS2 Interpretation 0-47 Negative Consistent with a negative amyloid positron emission tomography (PET) scan; reflects a low likelihood of brain amyloid plaques and is therefore not consistent with a neuropathological diagnosis of Alzheimer disease (AD). 48-100 Positive Consistent with a positive amyloid PET scan; reflects a high likelihood of brain amyloid plaques, one of the neuropathological findings of AD. For apolipoprotein E (ApoE) testing, there are six possible allele combinations for AD risk interpretation. ApoE proteotyping determines which ApoE protein types are present in the submitted sample. The protein types detected determine the presence of E2, E3, and/or E4 alleles, corresponding to the patient's APOE genotype (see Table 2). Table 2. Proteotype Interpretation Proteotype result Corresponding genotype Interpretation ApoE2/ApoE2 APOE2/APOE2 E2/E2 homozygous individuals have a significantly decreased risk for AD compared to E3/E3 and E4 carriers. ApoE2/ApoE3 APOE2/APOE3 E2/E3 heterozygous individuals have a decreased risk for AD compared to E3/E3, and E4 carriers. ApoE2/ApoE4 APOE2/APOE4 E2/E4 heterozygous individuals have an increased risk for AD compared to E3/E3, E2/ E2, and E2/E3 proteotypes/ genotypes. ApoE3/ApoE3 APOE3/APOE3 E3/E3 homozygous individuals are most common and have decreased risk for AD compared to E4 carriers, and increased risk compared to E2/E2 and E2/ E3 proteotypes/genotypes. ApoE3/ApoE4 APOE3/APOE4 E3/E4 heterozygous individuals have an approximately three-fold increased risk for AD compared to E4 noncarriers. ApoE4/ApoE4 APOE4/APOE4 E4/E4 homozygous individuals have an approximately eight- to twelve-fold increased risk for AD compared to E4 noncarriers.

Reference Values:

Amyloid Probability Score 2 (APS2) (range of 0-100):
Negative: 0-47
Positive: 48-100

Abeta42/40 Ratio:
> or =0.095 Consistent with absence of amyloid plaques

Percent p-tau217:
<4.2% consistent with absence of brain amyloid plaques

ApoE Proteotype
E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, E4/E4
-E3 is the most common allele.
-E4 allele is associated with increased risk of amyloid plaques.
-E2 allele is associated with lower risk of amyloid plaques.

Clinical References: 1. Centers for Disease Control and Prevention. Alzheimer's Disease and Related Dementias. CDC; Updated October 26,2020. Accessed March 25, 2024. Available at www.cdc.gov/aging/aginginfo/alzheimers.htm 2. Bird TD. Alzheimer Disease Overview. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. GeneReviews. University of Washington, Seattle; October 23, 1998. Updated December 20, 2018. Accessed March 13, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1161/ 3. Cummings J, Aisen P, Apostolova LG, Atri A, Salloway S, Weiner M. Aducanumab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2021;8(4):398-410. doi:10.14283/jpad.2021.41 4. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948 5. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023;330(6):512-527. doi:10.1001/jama.2023.13239 6. Alzheimer's Association. Mild Cognitive Impairment (MCI). Accessed July 21, 2023. Available at https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/mild-cognitive-impairment 7. Johnson KA, Minoshima S, Bohnen NI, et al. Update on appropriate use criteria for amyloid PET imaging: dementia experts, mild cognitive impairment, and education. Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging. Alzheimers Dement. 2013;9(4):e106-e109. doi:10.1016/j.jalz.2013.06.001 8. Shaw LM, Arias J, Blennow K, et al. Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease. Alzheimers Dement. 2018;14(11):1505-1521. doi:10.1016/j.jalz.2018.07.220 9. Kirmess KM, Meyer MR, Holubasch MS, et al. The PrecivityAD test: Accurate and reliable LC-MS/MS assays for quantifying plasma amyloid beta 40 and 42 and apolipoprotein E proteotype for the assessment of brain amyloidosis. Clin Chim Acta. 2021;519:267-275. doi:10.1016/j.cca.2021.05.011 10. West T, Kirmess KM, Meyer MR, et al. A blood-based diagnostic test incorporating plasma Abeta42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: findings from a multi cohort validity analysis. Mol Neurodegener. 2021;16(1):30. Published 2021 May 1. doi:10.1186/s13024-021-00451-6 11. Hu Y, Kirmess KM, Meyer MR, et al. Assessment of a plasma amyloid probability score to estimate amyloid positron emission tomography findings among adults with cognitive impairment. JAMA Netw Open. 2022;5(4):e228392. Published 2022 Apr 1. doi:10.1001/jamanetworkopen.2022.8392 12. Meyer MR, Kirmess KM, Eastwood S, et al. Clinical validation of the PrecivityAD2 blood test: A mass spectrometry-based test with algorithm combining %p-tau217 and Abeta42/40 ratio to identify presence of brain amyloid. Alzheimers Dement. Published online March 16, 2024. doi:10.1002/alz.13764 13. Jansen WJ, Janssen O, Tijms BM, et al. Prevalence estimates of amyloid abnormality across the Alzheimer disease clinical spectrum [published correction appears in JAMA Neurol. 2022 Mar 1;79(3):313]. JAMA Neurol. 2022;79(3):228-243. doi:10.1001/jamaneurol.2021.5216 14. Janelidze S, Barthelemy NR, He Y, Bateman RJ, Hansson O. Mitigating the associations of kidney dysfunction with blood biomarkers of Alzheimer disease by using phosphorylated tau to total tau ratios [published correction appears in JAMA Neurol. 2023 Aug 1;80(8):873]. JAMA Neurol. 2023;80(5):516-522. doi:10.1001/jamaneurol.2023.0199 15. Pichet Binette A, Janelidze S, Cullen N, et al. Confounding factors of Alzheimer's disease plasma biomarkers and their impact on clinical performance. Alzheimers Dement. 2023;19(4):1403-1414. doi:10.1002/alz.12787 16. Mahley RW, Rall SC Jr. Apolipoprotein E:

far more than a lipid transport protein. Annu Rev Genomics Hum Genet. 2000;1:507-537. doi:10.1146/annurev.genom.1.1.507 17. Verghese PB, Castellano JM, Holtzman DM. Apolipoprotein E in Alzheimer's disease and other neurological disorders. Lancet Neurol. 2011;10(3):241-252. doi:10.1016/S1474-4422(10)70325-2 18. Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. Neuron. 2009;63(3):287-303. doi:10.1016/j.neuron.2009.06.026 19. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993;261(5123):921-923. doi:10.1126/science 20. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology. 1993;43(8):1467-1472. doi:10.1212/wnl.43.8.1467 21. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy [published correction appears in Nat Rev Neurol. 2013. doi:10.1038/nmeurol.2013.32. Liu, Chia-Chan [corrected to Liu, Chia-Chen]]. Nat Rev Neurol. 2013;9(2):106-118. doi:10.1038/nrneurol.2012.263 22. Roses AD. Apolipoprotein E alleles as risk factors in Alzheimer's disease. Annu Rev Med. 1996;47:387-400. doi:10.1146/annurev.med.47.1.387

PERA
621166

Preeclampsia sFlt-1/PIGF (Soluble fms-Like Tyrosine Kinase 1/ Placental Growth Factor) Ratio, Serum

Clinical Information: Preeclampsia (PE) is a complication of pregnancy that affects approximately 5% of women worldwide. Preeclampsia is a serious hypertensive condition occurring at mid-pregnancy. Clinical signs of PE, such as the onset of hypertension, are typically observed after 20 weeks of gestation. Clinically, PE may vary from mild to severe forms, and may require premature delivery. The severe form of PE, which may include symptoms of the life-threatening HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, occurs in about 20% of women presenting with PE. While early-onset PE (which develops before 34 weeks of gestation) is less prevalent than late-onset PE (which develops at 34 weeks of gestation or later), early onset PE is associated with a greater risk of adverse outcome. Although the cause of PE remains unclear, the syndrome may be initiated by an imbalance of placental factors that induce endothelial dysfunction. Soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PIGF) are both associated with placental dysfunction and risk of PE during pregnancy. Women with PE have been reported to have increased circulating concentrations of sFlt-1, an antiangiogenic protein largely produced in the placenta, which is associated with inhibition of vascular endothelial growth factor and PlGF. During pregnancy, PlGF concentrations typically increase progressively in the first and second trimester and then decrease towards full term. In contrast, in cases of clinical PE, sFlt-1 concentrations are significantly increased versus concentrations observed in normal pregnancies, while concentrations of circulating free PlGF are significantly decreased relative to normal pregnancy. The use of the sFlt-1/PIGF ratio has been shown to be a useful tool to aid in risk assessment of patients with clinical signs and symptoms consistent with development of PE with severe features (as defined by American College of Obstetricians and Gynecologists guidelines)(1). Based on the data collected during the PRAECIS clinical study, the prognostic performance of the sFlt-1/PIGF ratio using a ratio cut-off of 40 (where if the ratio is greater than or equal to 40, there is a high risk for progression to PE with severe features), exhibited a sensitivity of 94%, and specificity of 75% for the development of PE with severe features within 2 weeks. The performance of the sFlt-1/PlGF ratio to predict development of PE with severe features within two weeks was statistically higher than the prognostic performance of other commonly used clinical (highest systolic blood pressure, highest diastolic blood pressure) and laboratory (eg, aspartate aminotransferase, alanine aminotransferase, creatinine, and platelets) markers associated with PE.

Useful For: Aiding in risk assessment of patients with clinical signs and symptoms consistent with development of preeclampsia with severe features This test is not intended for making a diagnosis of preeclampsia or preeclampsia with severe features. This test is not a stand-alone test for monitoring of hypertensive disorders of pregnancy or for changing treatment, including medication.

Interpretation: A sFlt-1/PlGF (soluble fms-like tyrosine kinase 1/placental growth factor) ratio will be

reported as a unitless whole number. sFlt-1 and PlGF concentrations will not be individually reported. The sFlt-1/PlGF ratio is indicated to be used as an aid in the management of the patient and are prognostic assays intended to stratify hospitalized patients in two risk groups (low risk and high risk of progression to preeclampsia with severe features within two weeks from presentation). If the result of the sFlt-1/PlGF ratio is greater than or equal to 40, the pregnant woman is at high risk for progression to preeclampsia with severe features within 2 weeks of presentation. If the result of the sFlt-1/PlGF ratio is less than 40, the pregnant woman is at low risk for progression to preeclampsia with severe features within 2 weeks of presentation. The sFlt-1/PlGF ratio results should be used in conjunction with information available from clinical evaluations and other standard of care procedures. The test result is not to be used to replace clinical judgement. The clinical management should be dependent on the patient's healthcare provider's recommendations as inferred from their clinical status. Therefore, the test results should not be used as a deciding factor to change management plans, and especially not for decisions of pregnancy delivery or for patient discharge from hospital.

Reference Values:
<40

Clinical References: 1. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gyneco. 2020;135(6):e237-e260 2. Thadhani R, Lemoine E, Rana S, et al. Circulating angiogenic factor levels in hypertensive disorders of pregnancy. NEJM. 2022;1(12). doi:10.1056/EVIDoa2200161 3. Zeisler H, Llurba E, Chantraine F, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med. 2016;374(1):13-22. doi:10.1056/NEJMoa1414838 4. Dathan-Stumpf A, Rieger A, Verlohren S, Wolf C, Stepan H. sFlt-1/PlGF ratio for prediction of preeclampsia in clinical routine: A pragmatic real-world analysis of healthcare resource utilisation. PLoS One. 2022;17(2):e0263443. Published 2022 Feb 24. doi:10.1371/journal.pone.0263443

PGN
65119

Pregabalin, Serum

Clinical Information: Pregabalin (Lyrica) is an anticonvulsant drug used to treat partial seizures in patients and is a more potent successor to gabapentin. Pregabalin is commonly used for neuropathic pain and fibromyalgia. This test can be used by healthcare providers to assess compliance and may be clinically useful in patients with kidney failure who generally require lower dosages. Therapeutic and toxic ranges are not well defined. Therapeutic concentrations are reportedly 2 to 5 mcg/mL, while toxicity may occur at concentrations above 10 mcg/mL.

Useful For: Monitoring serum pregabalin (Lyrica) concentrations, assessing compliance, and adjusting dosage in patients

Interpretation: The serum concentration should be interpreted in the context of the patient's clinical response and other clinical tests. This may provide useful information for patients showing poor response, noncompliance, or adverse effects. Toxicity can occur with concentrations greater than or equal to 10 mcg/mL.

Reference Values:
2.0-5.0 mcg/mL

Clinical References: 1. Baselt R: Disposition of Toxic Drugs and Chemicals in Man. 10th ed. Biomedical Publications; 2014 2. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry, 2018;51(1-02):9-62

17PRN
88646

Pregnenolone and 17-Hydroxypregnenolone, Serum

Clinical Information: Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. Deficiencies in several enzymes can cause CAH, including 21-hydroxylase (CYP21A2 variants; 90% of cases), 11-hydroxylase (CYP11A1 variants; 5%-8%), 3-beta-hydroxysteroid dehydrogenase (3-beta-HSD) (HSD3B2 variants; <5%), and 17-alpha-hydroxylase (CYP17A1 variants; <1%). The resulting hormone imbalances (reduced glucocorticoids and mineralocorticoids; and elevated steroid intermediates and androgens) can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. The adrenal glands, ovaries, testes, and placenta produce steroid intermediates, which are hydroxylated at position 21 (by 21-hydroxylase) and position 11 (by 11-hydroxylase) to produce cortisol. Deficiency of either 21-hydroxylase or 11-hydroxylase results in decreased cortisol synthesis and loss of feedback inhibition of adrenocorticotropic hormone (ACTH) secretion. The consequent increased pituitary release of ACTH drives increased production of steroid intermediates. The steroid intermediates are oxidized at position 3 by 3-beta-HSD. The 3-beta-HSD enzyme allows formation of 17-hydroxyprogesterone (17-OHPG) from 17-hydroxypregnenolone and progesterone from pregnenolone. When 3-beta-HSD is deficient, cortisol is decreased, 17-hydroxypregnenolone and pregnenolone levels may increase, and 17-OHPG and progesterone levels, respectively, are low. Dehydroepiandrosterone is also converted to androstenedione by 3-beta-HSD and may be elevated in patients affected with 3-beta-HSD deficiency. The best screening test for CAH, most often caused by either 21- or 11-hydroxylase deficiency, is the analysis of 17-OHPG (along with cortisol and androstenedione). CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydoxylase Deficiency, Serum allows the simultaneous determination of these 3 analytes. Alternately, these tests may be ordered individually: OHPG / 17-Hydroxyprogesterone, Serum; CINP / Cortisol, Mass Spectrometry, Serum; and ANST / Androstenedione, Serum. If both 21- and 11-hydroxylase deficiency have been ruled out, analysis of 17-hydroxypregnenolone and pregnenolone may be used to confirm the diagnosis of 3-beta-HSD or 17-alpha-hydroxylase deficiency. For more information see Steroid Pathways.

PREGN
88645

Pregnenolone, Serum

Clinical Information: Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. Deficiencies in several enzymes can cause CAH, including 21-hydroxylase (CYP21A2 variants; 90% of cases), 11-hydroxylase (CYP11A1 variants; 5%-8%), 3-beta-hydroxysteroid dehydrogenase (3-beta-HSD) (HSD3B2 variants; <5%), and 17-alpha-hydroxylase (CYP17A1 variants; 125 cases reported to date). The resulting hormone imbalances (reduced glucocorticoids and mineralocorticoids; elevated steroid intermediates and androgens) can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. The adrenal glands, ovaries, testes, and placenta produce steroid intermediates, which are hydroxylated at the position 21 (by 21-hydroxylase) and position 11 (by 11-hydroxylase) to produce cortisol. Deficiency of either 21-hydroxylase or 11-hydroxylase results in decreased cortisol synthesis and loss of feedback inhibition of adrenocorticotropic hormone (ACTH) secretion. The consequent increased pituitary release of ACTH drives increased production of steroid intermediates. The steroid intermediates are oxidized at position 3 by 3-beta-HSD. The 3-beta-HSD enzyme allows formation of 17-hydroxyprogesterone (17-OHPG) from 17-hydroxypregnenolone and progesterone from pregnenolone. When 3-beta-HSD is deficient, cortisol is decreased, 17-hydroxypregnenolone and pregnenolone levels may increase, and 17-OHPG and progesterone levels are low. Dehydroepiandrosterone is also converted to androstenedione by 3-beta-HSD and may be elevated in patients affected with 3-beta-HSD deficiency. The best screening test for CAH, most often caused by either 21- or 11-hydroxylase deficiency, is the analysis of 17-OHPG, along with cortisol and androstenedione. CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency, Serum allows the simultaneous determination of these 3 analytes. Alternatively, these tests may be ordered individually: OHPG / 17-Hydroxyprogesterone, Serum; CINP / Cortisol, Mass Spectrometry, Serum; and ANST / Androstenedione, Serum. If both 21- and 11-hydroxylase deficiency have been ruled out, analysis of 17-hydroxypregnenolone and pregnenolone may be used to confirm the diagnosis of 3-beta-HSD or 17-alpha-hydroxylase deficiency. For more information see Steroid Pathways.

Useful For: An ancillary test for congenital adrenal hyperplasia, particularly in situations in which a

diagnosis of both 21- and 11-hydroxylase deficiency have been ruled out Confirming a diagnosis of 3-beta-hydroxy dehydrogenase deficiency

Interpretation: The diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always require the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) variants usually have very high levels of androstenedione, often 5-fold to 10-fold elevations. 17-Hydroxyprogesterone (17-OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. For the HSD3B2 variant, cortisol, 17-OHPG, and progesterone levels will be decreased; 17-hydroxypregnenolone, pregnenolone, and dehydroepiandrosterone (DHEA) levels will be increased. In the much less common CYP11A1 variant, androstenedione levels are elevated to a similar extent as in CYP21A2 variant, and cortisol is also low, but OHPG is only mildly, if at all, elevated. In the very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors (particularly pregnenolone, 11-dexycorticosterone, corticosterone, and 18-hydroxycorticosterone) are increased. For more information see Steroid Pathways.

Reference Values:

CHILDREN/ADOLESCENTS*

Males
0-6 years: Not established
7-9 years: <206 ng/dL
10-12 years: <152 ng/dL
13-15 years: 18-197 ng/dL
16-17 years: 17-228 ng/dL
Tanner Stages
Stage I: <157 ng/dL
Stage II: <144 ng/dL
Stage III: <215 ng/dL
Stage IV-V: 19-201 ng/dL

Females
0-6 years: Not established
7-9 years: <151 ng/dL
10-12 years: 19-220 ng/dL
13-15 years: 22-210 ng/dL
16-17 years: 22-229 ng/dL
Tanner Stages
Stage I: <172 ng/dL
Stage II: 22-229 ng/dL
Stage III: 34-215 ng/dL
Stage IV-V: 26-235 ng/dL

*Kushnir MM, Rockwood AL, Roberts WL, et al. Development and performance evaluation of a tandem mass spectrometry assay for 4 adrenal steroids. Clin Chem. 2006;52(8):1559-1567

ADULTS
> or =18 years: 33-248 ng/dL

To convert to nmol/L, multiply the value in ng/dL by 0.03159757.

Clinical References: 1. Wudy S A, Hartmann M, Svoboda M. Determination of 17-hydroxyprogesterone in plasma by stable isotope dilution/benchtop liquid chromatography-tandem

mass spectrometry. Horm Res. 2000;53(2):68-71 2. Therrell BL. Newborn screening for congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. 2001:30(1):15-30 3. Bachega TA, Billerbeck AE, Marcondes JA, et al. Influence of different genotypes on 17-hydroxyprogesterone levels in patients with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Clin Endocrinol (Oxf). 2000:52(5):601-607 4. Kao P, Machacek DA, Magera MJ at al. Diagnosis of adrenal cortical dysfunction by liquid chromatography-tandem mass spectrometry. Ann Clin Lab Sci. 2001;31(2):199-204 5. Kushnir MA, Rockwood AL, Roberts WL, et al: Development and performance evaluation of a tandem mass spectrometry assay for 4 adrenal steroids. Clinical Chemistry 2006;52(8):1559-1567 6. Collett-Solberg PF. Congenital adrenal hyperplasia: from genetics and biochemistry to clinical practice, Part 1. Clin Pediatr (Phila). 2001:40(1):1-16 7. Chormanski D, Muzio MR. C 17 hydroxylase deficiency. In: StatPearls [Internet]. StatPearls Publishing; 2021. Updated January 3, 2023. Accessed May 29, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK546644/

PADF
35313

Prenatal Aneuploidy Detection, FISH

Clinical Information: Up to 95% of chromosomal abnormalities diagnosed prenatally involve aneuploidy (gain or loss of whole chromosome) of chromosomes 13, 18, 21, X, and Y. In liveborn infants, about 8 to 1000 have a major chromosome anomaly, of which 6.5 to 1000 involve aneuploidy of the 5 chromosomes analyzed by this test. Therefore, aneuploidy of chromosomes 13, 18, 21, X, and Y accounts for 81% to 95% of major chromosome anomalies in liveborn infants. Techniques to detect aneuploidy include standard chromosome analysis and fluorescence in situ hybridization (FISH). Standard chromosome analysis from amniotic fluid cells or chorionic villi requires 5 to 9 days for culture, harvest, and analysis. FISH, which uses DNA probes and can be performed on cultured and uncultured cells, can rapidly detect aneuploidy of 13, 18, 21, X, and Y in uncultured amniotic fluid cells or chorionic villi. FISH-based analysis may be helpful in medically urgent evaluations of newborn infants suspected to have aneuploidy of any of these chromosomes.

Useful For: Screening for chromosomal aneuploidies of chromosomes 13, 18, 21, X, and Y in prenatal specimens

Interpretation: When no significant abnormalities are detected by the targeted fluorescence in situ hybridization (FISH) probes, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, recommendations for additional testing, and contact information for the laboratory if there are additional questions. A normal result does not rule out the possibility of birth defects, such as those caused by non-targeted chromosome abnormalities, submicroscopic cytogenetic abnormalities, pathogenic molecular variants, and environmental factors (ie, teratogen exposure). For these reasons, clinicians should inform their patients of the technical limitations of FISH analysis before the procedure is performed, so that patients may make an informed decision about pursuing the procedure. It is recommended that a qualified professional in Medical Genetics communicate all results to the patient.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Committee opinion No.682 summary: Microarrays and next-generation sequencing technology: The use of advanced genetic diagnostic tools in obstetrics and gynecology. Obstet Gynecol. 2016;128(6):1462-1463 2. American College of Obstetricians and Gynecologists. (2007). ACOG Practice Bulletin No. 88, December 2007. Invasive prenatal testing for aneuploidy. Obstet Gynecol. 2007;110(6):1459-1467 3. Ward BE, Gersen SL, Carelli MP, et al. Rapid prenatal diagnosis of chromosomal aneuploidies by fluorescence in situ hybridization: Clinical experience with 4,500 specimens. Am J Hum Genet. 1993;52(5):854-865 4. Sheets KB, Crissman BG, Feist CD, et al. Practice

guidelines for communicating a prenatal or postnatal diagnosis of Down syndrome: recommendations of the national society of genetic counselors. J Genet Couns. 2011;20(5):432-444

PHSP
5566

Prenatal Hepatitis Evaluation, Serum

Clinical Information: Hepatitis B: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (ie, blood transfusion, sharing of needles among injection drug users). The virus is found in virtually every type of human body fluid and is spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. Infection of the infant can occur if the mother is a chronic hepatitis B surface antigen carrier or has an acute HBV infection at the time of delivery. Transmission is rare if an acute infection occurs in either the first or second trimester of pregnancy. After a course of acute illness, HBV persists in about 10% of patients who were infected during adulthood. Some carriers are asymptomatic, while others may develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus recognized as the cause of most cases of posttransfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Laboratory testing for HCV infection usually begins by screening for the presence of HCV-specific antibodies in serum, using an US Food and Drug Administration approved screening test. Specimens that are repeatedly reactive by screening tests should be confirmed with HCV tests with higher specificity, such as direct detection of HCV RNA by reverse transcriptase-polymerase chain reaction or HCV-specific antibody confirmatory tests. HCV antibodies are usually not detectable during the first 2 months following infection but are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies neither neutralize the virus nor provide immunity against this viral infection. Decrease in the HCV antibody level in serum may occur following resolution of infection. Current serologic screening tests to detect HCV antibodies include enzyme and chemiluminescence immunoassays. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing exist: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable HCV-specific antibodies -False-reactive screening test results can occur -A reactive screening test result does not distinguish between past (resolved) and present HCV infection -Serologic tests cannot provide information on clinical response to anti-HCV therapy Reactive screening test results should be followed by a supplemental or confirmatory test, such as a nucleic acid test for HCV RNA or HCV antibody confirmatory test. Nucleic acid tests provide a very sensitive and specific approach for the direct detection of HCV RNA.

Useful For: Screening pregnant women for chronic hepatitis B and hepatitis C in primary care settings, with or without risk factors for hepatitis C Determining the level of infectivity of chronic hepatitis B in pregnant women This test is not useful for diagnosis of hepatitis B during the "window period" of acute hepatitis B virus infection (ie, after disappearance of hepatitis B surface antigen and prior to appearance of hepatitis B surface antibody). This test should not be used as a screening test for hepatitis C in blood or human cells/tissue donors. This test profile is not useful for detection or diagnosis of acute hepatitis C virus (HCV) in pregnancy, since HCV antibodies may not be detectable until after 2 months following exposure, and HCV RNA testing is not performed on specimens with negative HCV antibody screening test results.

Interpretation: Hepatitis B virus surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 8 weeks following hepatitis B virus (HBV) infection. A confirmed positive result for HBsAg is indicative of acute or chronic hepatitis B. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either a chronic carrier state or chronic liver disease. HBs antibody (anti-HBs) appears with the resolution of HBV infection after the disappearance of HBsAg. Hepatitis B e antigen (HBeAg) appears at approximately the same time as HBsAg and indicates that the virus is replicating and the

individual is infectious. Appearance of anti-HBe after the disappearance of HBsAg and HBeAg usually indicates recovery and loss of infectivity. Reactive hepatitis C virus (HCV) antibody screening results with cutoff index (COI) at or below 20.0 are not predictive of the true HCV antibody status; additional testing is recommended to confirm HCV antibody status. Reactive results with COI greater than 20.0 are highly predictive (95% or greater probability) of the true HCV antibody status, but additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to, or infection with, HCV. Negative screening test results in individuals with prior exposure to HCV may be due to low antibody levels that are below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with acute or recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks). Testing for HCV RNA using HCVRP / Hepatitis C Virus (HCV) RNA Detection and Quantification, Real-Time Reverse Transcription-PCR, Prenatal, Serum is recommended for detection of HCV infection in such patients.

Reference Values:

HEPATITIS B VIRUS SURFACE ANTIGEN
Negative

HEPATITIS C VIRUS ANTIBODY
Negative

See Viral Hepatitis Serologic Profiles

Clinical References: 1. World Health Organization. Guidelines on hepatitis B and C testing. World Health Organization; 2017. Accessed October 7, 2024. Available at www.who.int/publications/i/item/9789241549981 2. Society for Maternal-Fetal Medicine. Hepatitis C in pregnancy: screening, treatment, and management. Am J Obstet Gynecol. 2017; 217(5):B2-B12 3. American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA): HCV guidance: Recommendations for testing, managing, and treating hepatitis C. AASLD, IDSA; Updated December 19, 2023. Accessed October 7, 2024. Available at www.hcvguidelines.org/contents 4. US Preventive Services Task Force. Screening for hepatitis C virus infection in adolescents and adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2020;323(10):970-975. doi:10.1001/jama.2020.1123 5. Centers for Disease Control and Prevention. Screening and Testing for HIV, Viral Hepatitis, STD and Tuberculosis in Pregnancy. CDC; Updated January 25, 2024. Accessed October 8, 2024. Available at www.cdc.gov/pregnancy-hiv-std-tb-hepatitis/php/screening/?CDC_AAref_Val 6. Centers for Disease Control and Prevention. Screening and testing for hepatitis B virus infection: CDC Recommendations – United States, 2023. MMWR Recomm Rep 2023;72(No. RR-1):1-25. Available at www.cdc.gov/mmwr/volumes/72/rr/rr7201a1.htm?s_cid=rr7201a1_w

PHEPU
620973

Previous Viral Hepatitis (Unknown Type), Serum

Clinical Information: Hepatitis A: Hepatitis A virus (HAV) is an RNA virus that accounts for 20% to 25% of viral hepatitis in adults in the United States. HAV infection is spread by the oral/fecal route and produces acute hepatitis that follows a benign, self-limited course. Spread of the disease is usually associated with contaminated food or water caused by poor sanitary conditions. Outbreaks frequently occur in overcrowded situations and institutions or high-density centers such as prisons and healthcare centers. Epidemics may occur following floods or other disaster situations. Chronic carriers of HAV have never been observed. Hepatitis B: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles among injection drug users). The virus is found in various human body fluids and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly

transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some chronic carriers are asymptomatic, while others develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus recognized as the cause of most cases of posttransfusion hepatitis that is a significant cause of morbidity and mortality worldwide. HCV is transmitted through contaminated blood or blood products or close, personal contact. HCV shows a high rate of progression (~75%) to chronic disease. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Cirrhosis and hepatocellular carcinoma are sequelae of chronic HCV.

Useful For: Determining if an individual has been infected following exposure to an unknown type of viral hepatitis virus Obtaining baseline serologic markers of an individual exposed to a source with an unknown type of hepatitis Determining immunity to hepatitis A and B viral infections

Interpretation: Interpretation depends on clinical setting. For more information see Viral Hepatitis Serologic Profiles. Hepatitis A: Hepatitis A virus (HAV)-specific total antibodies are almost always detectable by the onset of symptoms of acute hepatitis A (usually 15 to 45 days after exposure). The initial antibody consists almost entirely of the IgM subclass of antibody. Anti-HAV IgM usually falls to undetectable levels 3 to 6 months after infection. Anti-HAV IgG levels rise quickly once the virus is cleared and persist for many years. Hepatitis B: Hepatitis B virus surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 8 weeks following hepatitis B virus (HBV) infection. A confirmed positive result for HBsAg is indicative of acute or chronic hepatitis B. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Anti-HBs appears with the resolution of HBV infection after the disappearance of HBsAg. Anti-HBs also appears as the immune response following a course of inoculation with the hepatitis B vaccine. Hepatitis B virus core antibody (anti-HBc) appears shortly after the onset of symptoms of HBV infection and may be the only serologic marker remaining years after exposure to hepatitis B. Hepatitis C: Hepatitis C virus-specific antibodies are usually not detectable during the first 2 months after exposure, but they are almost always detectable by the late convalescent stage of infection. HCV antibodies are not neutralizing and do not provide immunity.

Reference Values:

HEPATITIS B VIRUS SURFACE ANTIGEN
Negative

HEPATITIS B VIRUS SURFACE ANTIGEN CONFIRMATION
Negative

HEPATITIS B VIRUS SURFACE ANTIBODY, QUALITATIVE/QUANTITATIVE
Hepatitis B Surface Antibody
Unvaccinated: Negative
Vaccinated: Positive

HEPATITIS B VIRUS SURFACE ANTIBODY, QUANTITATIVE
Unvaccinated: <8.5 mIU/mL
Vaccinated: > or =11.5 mIU/mL

HEPATITIS B VIRUS CORE TOTAL ANTIBODIES
Negative

HEPATITIS A VIRUS TOTAL ANTIBODY
Unvaccinated: Negative
Vaccinated: Positive

HEPATITIS C VIRUS ANTIBODY

Negative

HEPATITIS C VIRUS RNA DETECTION and QUANTIFICATION by REAL-TIME RT-PCR
Undetected

Interpretation depends on clinical setting. For more information see Viral Hepatitis Serologic Profiles.

Clinical References:

PBCPN
620737

Primary Biliary Cholangitis Antibody Panel, Serum

Clinical Information:

Useful For: Evaluation of at-risk or previously diagnosed primary biliary cholangitis patients with new features of other liver diseases or systemic autoimmune diseases

Interpretation: Positive results of anti-mitochondrial antibody, anti-Sp100 and/or anti-gp210 antibodies associated with features of cholestatic liver disease is highly suggestive of primary biliary cholangitis. Antinuclear antibody positivity for non-primary biliary cholangitis associated pattern may suggest a coexisting disease requiring additional testing for confirmation.

Reference Values:

MITOCHONDRIAL AB, M2
Negative: <0.1 Units
Borderline: 0.1-0.3 Units
Weakly positive: 0.4-0.9 Units
Positive: > or =1.0 Units
Reference values apply to all ages.

SP100 Antibody, IgG
Negative: < or =20.0 Units
Equivocal: 20.1-24.9 Units
Positive: > or =25.0 Units

GP210 Antibody, IgG
Negative: < or =20.0 Units
Equivocal: 20.1-24.9 Units
Positive: > or =25.0 Units

ANTINUCLEAR AB, HEP-2 SUBSTRATE
Negative: <1:80

Clinical References: 1. Younossi ZM, Bernstein D, Shiffman ML, et al. Diagnosis and management of primary biliary cholangitis. Am J Gastroenterol. 2019;114(1):48-63 2. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance update from the American Association for the Study of Liver Diseases. Hepatology. Hepatology. 2019;69(1):394-419 3. International Consensus on ANA Patterns. AC-20 Cytoplasmic fine speckled. ICAP; 2015. Accessed September 15, 2023. Available at www.anapatterns.org/view_pattern.php?pattern=20 4. Zhang Q, Liu Z, Wu S, et al. Meta-analysis of antinuclear antibodies in the diagnosis of antimitochondrial antibody-negative primary biliary cholangitis. Gastroenterol Res Pract. 2019;2019:8959103 5. Dahlqvist G, Gaouar F, Carrat F, et al. Large-scale characterization study of patients with antimitochondrial antibodies but nonestablished primary biliary cholangitis. Hepatology. 2017;65(1):152-163 6. Trivella J, John BV, Levy

C. Primary biliary cholangitis: Epidemiology, prognosis, and treatment. Hepatol Commun. 2023;7(6):e0179 7. Nakamura M, Kondo H, Mori T, et al. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. Hepatology. 2007;45(1):118-127 8. Favoino E, Grapsi E, Barbuti G, et al. Systemic sclerosis and primary biliary cholangitis share an antibody population with identical specificity. Clin Exp Immunol. 2023;212(1):32-38 9. Wei Q, Jiang Y, Xie J, et al. Investigation and analysis of HEp 2 indirect immunofluorescence titers and patterns in various liver diseases [published correction appears in Clin Rheumatol. 2021 Apr;40(4):1667]. Clin Rheumatol. 2020;39(8):2425-2432 10. Munoz-Sanchez G, Perez-Isidro A, Ortiz de Landazuri I, et al. Working algorithms and detection methods of autoantibodies in autoimmune liver disease: A nationwide study. Diagnostics (Basel). 2022;12(3):697

PCDGG
617421

Primary Ciliary Dyskinesia Gene Panel, Varies

Clinical Information: Primary ciliary dyskinesia (PCD) is a condition characterized by motile ciliary dysfunction due to structural or biogenesis defects of the cilia.(1,2) The primary clinical manifestation of PCD is chronic upper and lower respiratory disease (including neonatal respiratory distress, chronic cough, chronic nasal congestion, chronic pansinusitis, recurrent pulmonary infections, and bronchiectasis) leading to respiratory failure.(1-3) Other common features of PCD include laterality (situs) defects and infertility.(1-3) When laterality defects are present in addition to respiratory manifestations, the condition may be described as Kartagener syndrome.(4) Diagnostic workup for suspected PCD can include ciliary ultrastructure analysis via transmission electron microscopy, high-speed video microscopy with ciliary beat pattern analysis, nasal nitric oxide level measurement, immunofluorescence imaging of axonemal proteins, and molecular genetic testing.(1,2) Genetic testing can be diagnostic when other analyses have normal or ambiguous results.(2) The prevalence of PCD is not established and estimates of prevalence have ranged from 1:2200 to 1:40,000 births.(4) In individuals with well-supported PCD diagnoses via clinical and ciliary analyses, it is estimate that a genetic etiology can be identified in up to 80% of cases.(3) In most cases, PCD follows an autosomal recessive pattern of inheritance. Rarely, PCD can follow an autosomal dominant or X-linked pattern of inheritance.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of primary ciliary dyskinesia Establishing a diagnosis of primary ciliary dyskinesia

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Shapiro AJ, Davis SD, Polineni D, et al. Diagnosis of primary ciliary dyskinesia. An official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;197(12):e24-e39. doi:10.1164/rccm.201805-0819ST 2.Shapiro AJ, Zariwala MA, Ferkol T, et al. Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD foundation consensus recommendations based on state of the art review. Pediatr Pulmonol. 2016;51(2):115-132. doi:10.1002/ppul.23304 3. Zariwala MA, Knowles MR, Leigh MW. Primary ciliary dyskinesia. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews [Internet]. University of Washington, Seattle; 2007. Updated December 5, 2019. Accessed January 23, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1122/ 4. Mirra V, Werner C, Santamaria F. Primary ciliary dyskinesia: An update on clinical aspects, genetics, diagnosis, and future treatment strategies. Front Pediatr. 2017;5:135. doi:10.3389/fped.2017.00135 5. Richards S, Aziz N, Bale S, et al. Standards and

guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

HLHGP
619830

Primary Hemophagocytic Lymphohistiocytosis Gene Panel, Varies

Clinical Information: Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening disorder characterized by fever, cytopenias, coagulopathy, hepatosplenomegaly, neurologic symptoms, and hemophagocytosis in the bone marrow, spleen, lymph nodes, or liver. Patients often have elevated ferritin and soluble interleukin-2 receptor concentrations, as well as low fibrinogen levels. The Histiocyte Society established criteria for HLH for the HLH-2004 clinical trial, and these criteria are often referred to by physicians considering a diagnosis of HLH.(1) Primary HLH, also known as familial HLH (F-HLH), is caused by disease-causing variants in several genes. Secondary or acquired HLH can be triggered by infection, malignancy, transplant, autoimmune disorders, or drugs. While the terms "primary" and "secondary" have been in use for some time, the North American Consortium for Histiocytosis recommended a new classification system that divides HLH into forms that respond to immunosuppressive treatment, which are referred to as "HLH disease" and forms that do not respond to immunosuppressives, which are referred to as "HLH mimics."(2) In the pediatric population, the incidence of HLH is thought to range from 1 to 225 per 300,000 live births, equally distributed between male and female infants, with the mean age of occurrence of 1.8 years. The epidemiology among adults is less well-studied; however, the incidence is estimated to be 1 of every 2000 adult admissions to tertiary medical centers, with the mean age at presentation of approximately 50 years. Many genes have been identified in association with F-HLH. In a pediatric population, genetic variants in PRF1 account for approximately 25% of cases, while STXBP2 and UNC13D are each responsible for approximately 20% of cases, and XIAP accounts for 10% of cases. Disease-causing variants in PRF1, UNC13D, STX11, and STXBP2 prevent the release of cytotoxic granules into the immunological synapse, resulting in an inability to kill target cells. Pigment disorders, including Griscelli syndrome type 2, Chediak-Higashi syndrome, and Hermansky-Pudlak syndrome type 2 (due to variants in RAB27A, LYST, and AP3B1, respectively) also are associated with HLH. Due to significant granule trafficking defects, patients may also have bleeding tendencies, neutropenia, and neurological symptoms. X-linked lymphoproliferative disorders and Epstein-Barr virus susceptibility disorders are also associated with HLH. While most forms of F-HLH are inherited in an autosomal recessive pattern, there are autosomal dominant and X-linked forms.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of familial hemophagocytic lymphohistiocytosis (F-HLH) Establishing a diagnosis of F-HLH, allowing for appropriate management and surveillance for disease features based on the gene and/or variant involved Identifying variants within genes known to be associated with F-HLH, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124-131. doi:10.1002/pbc.21039 2. Jordan MB, Allen CE, Greenberg J, et al. Challenges in the diagnosis of

hemophagocytic lymphohistiocytosis: Recommendations from the North American Consortium for Histiocytosis (NACHO). Pediatr Blood Cancer. 2019;66(11):e27929. doi:10.1002/pbc.27929 3. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 4. Gadoury-Levesque V, Dong L, Su R, et al. Frequency and spectrum of disease-causing variants in 1892 patients with suspected genetic HLH disorders. Blood Adv. 2020;4(12):2578-2594 5. Canna SW, Marsh RA. Pediatric hemophagocytic lymphohistiocytosis. Blood. 2020;135(16):1332-1343 6. Ponnatt TS, Lilley CM, Mirza KM. Hemophagocytic lymphohistiocytosis. Arch Pathol Lab Med. 2022;146(4):507-519 7. Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507. doi:10.1007/s10875-022-01289-3

PMND1
609778

Primary Membranous Nephropathy Diagnostic Cascade, Serum

Clinical Information: Membranous nephropathy (MN) is a rare disease in which immune complexes deposit at the glomerular basement membrane, causing damage to the filtration barrier, resulting in proteinuria. Recent studies have shown that in approximately 70% of patients with primary MN (pMN), the immune complexes consist of autoantibodies against the podocyte protein M-type phospholipase A2 receptor (PLA2R).(1) There is also evidence that levels of anti-PLA2R autoantibodies correlate well with disease activity and progression.(2) The presence of anti-PLA2R antibodies could also potentially be used to differentiate pMN from other causes of nephrotic syndrome if a biopsy is not possible. Among patients with chronic kidney disease awaiting kidney transplantation, higher levels of anti-PLA2R could predict those more likely to recur after transplantation.(2) Mayo Clinic Laboratory data suggest that there is a high-concordance between the enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence assay PLA2R results; however, the ELISA assay alone may be preferred for monitoring patients with membranous nephropathy over time for trends in anti-PLA2R antibody levels. In the remaining 30% of patients with MN who are PLA2R-negative, anti-thrombospondin type-1 domain-containing 7A (THSD7A) was shown to have an approximate 10% prevalence (ie, about 3% of all primary MN patients).(3) Mouse podocytes express THSD7A and introduction of anti-THSD7A autoantibodies induces MN in murine models. Mouse podocytes do not express PLA2R so exogenous administration of anti-PLA2R does not recapitulate MN in mice.(4) Additionally, THSD7A has been described as a potential tumor antigen and, thus, it has been suggested that THSD7A-positive patients merit a thorough cancer screening.(5)

Useful For: Distinguishing primary from secondary membranous nephropathy using an algorithmic approach Monitoring patients with membranous nephropathy at very low antibody titers Screening for anti-phospholipase A2 receptor antibodies

Interpretation: Therapy outcome can be monitored by measuring the anti-phospholipase A2 receptor (PLA2R) antibody titer. A titer increase, decrease, or disappearance generally precedes a change in clinical status. Thus, the determination of the antibody titer has a high predictive value with respect to clinical remission, relapse, or risk assessment after kidney transplantation. According to the manufacturer's package insert, the EUROIMMUN Anti-PLA2R indirect immunofluorescence assay (IFA) was positive in 77.1% of patients with biopsy proven primary membranous nephropathy (pMN).(6) This corresponds well with published literature that approximately 70% of patients with pMN will have anti-PLA2R antibodies.

Reference Values:
ANTI-PHOSPHOLIPASE A2 RECEPTOR (PLA2R) ENZYME-LINKED IMMUNOSORBENT ASSAY:

<14 RU/mL: Negative
14 to 19 RU/mL: Borderline
> or =20 RU/mL: Positive

PLA2R IMMUNOFLUORESCENCE:
Negative

THROMBOSPONDIN TYPE-1 DOMAIN-CONTAINING 7A ANTIBODIES:
Negative

Clinical References: 1. Beck Lh Jr, Bonegio RGB, Lambeau G, et al: M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009 Jul 2;361(1):11-21 2. Schlumberger W, Hornig N, Lange S, et al: Differential diagnosis of membranous nephropathy with autoantibodies to phospholipase A2 receptor 1. Autoimmun Rev. 2014 Feb;13(2)108-113 3. Tomas NM, Beck LH Jr, Meyer-Schwesinger C, et al: Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med. 2014 Dec 11;371(24):2277-2287. doi: 10.1056/NEJMoa1409354 4. Tomas NM, Hoxha E, Reinicke AT, et al: Autoantibodies against thrombospondin type 1 domain-containing 7A induce membranous nephropathy. J Clin Invest. 2016 Jul 1;126(7):2519-2532. doi: 10.1172/JCI85265 5. Stahl PR, Hoxha E, Wiech T, Schroder C, Simon R, Stahl RAK: THSD7A expression in human cancer. Genes Chromosomes Cancer. 2017 Apr;56(4):314-327. doi: 10.1002/gcc.22440 6. Package insert: EUROIMMUN Anti-PLA2R IFA Kit, EUROIMMUN US; V 09/24/2018

PRMB
37053

Primidone and Phenobarbital, Serum

Clinical Information: Primidone is used for control of grand mal seizures that are refractory to other antiepileptics and seizures of psychomotor or focal origin. Primidone is initially dosed in progressively increasing amounts starting with 100 mg at bedtime to 250 mg 3 times a day after 10 days of therapy in adults. Primidone exhibits a volume of distribution of 0.6 L/kg and a half-life of 8 hours. When monitoring primidone and phenobarbital levels simultaneously, the specimen should be drawn just before the next dose is administered. Primidone is not highly protein bound, approximately 10%. Phenobarbital is a metabolite of primidone. Like phenobarbital, there are no known major drug-drug interactions that affect the pharmacology of primidone. Toxicity associated with primidone is primarily due to the accumulation of phenobarbital. Diagnosis and treatment are as described for PBAR / Phenobarbital, Serum.

Useful For: Assessing compliance Monitoring for appropriate therapeutic levels of primidone and phenobarbital Assessing toxicity

Interpretation: At steady-state, which is achieved approximately 2 weeks after therapy is initiated, blood levels of primidone that correlate with optimal response to the drug range from 9.0 to 12.5 mcg/mL for adults and 7.0 to 10.0 mcg/mL for children younger than 5 years. The corresponding levels for phenobarbital are 20.0 to 40.0 mcg/mL for adults and 15.0 to 30.0 mcg/mL for children younger than 5 years. Dosage adjustment based on blood level information is the best way to obtain optimal response to the drug.

Reference Values:
Primidone
Therapeutic: 5.0-12.0 mcg/mL
Critical value: > or =15.0 mcg/mL

Phenobarbital

Therapeutic: 10.0-40.0 mcg/mL
Critical value: > or =60.0 mcg/mL

Clinical References: 1. Lenkapothula N, Cascella M. Primidone. In: StatPearls [Internet]. StatPearls Publishing; 2024. Updated July 24, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK562297/ 2. Aronson J. Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions. 16th ed. Elsevier; 2016:927-932. doi.org/10.1016/B978-0-444-53717-1.01336-6

PTRE
82784

Privet Tree, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to privet tree Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PRKSG 617435 PRKAR1A Full Gene Sequencing with Deletion/Duplication, Varies

Clinical Information:

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of Carney Complex (CNC) or acrodysostosis-1 with hormone resistance Establishing a diagnosis of CNC or acrodysostosis-1 with hormone resistance

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Maleszewski JJ, Larsen BT, Kip NS, et al. PRKAR1A in the development of cardiac myxoma: a study of 110 cases including isolated and syndromic tumors. Am J Surg Pathol. 2014;38(8):1079-1087. doi:10.1097/PAS.0000000000000202 2. Rhayem Y, Le Stunff C, Abdel Khalek W, et al. Functional characterization of PRKAR1A mutations reveals a unique molecular mechanism causing acrodysostosis but multiple mechanisms causing Carney complex. J Biol Chem. 2015;290(46):27816-27828. doi:10.1074/jbc.M115.656553 3. Salpea P, Horvath A, London E, et al. Deletions of the PRKAR1A locus at 17q24.2-q24.3 in Carney complex: genotype-phenotype correlations and implications for genetic testing. J Clin Endocrinol Metab. 2014;99(1):E183-E188. doi:10.1210/jc.2013-3159 4. Stratakis CA, Raygada M. Carney complex. In: Adam MP, Ardinger HH, Pagon RA, et al. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated September 21, 2023. Accessed January 7, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1286/ 5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 6. Nagasaki K, Iida T, Sato H, et al. PRKAR1A mutation affecting cAMP-mediated G protein-coupled receptor signaling in a patient with acrodysostosis and hormone resistance. J Clin Endocrinol Metab. 2012;97(9):E1808-E1813. doi:10.1210/jc.2012-1369

GAL2 606833 Probability of Hepatocellular Carcinoma, Serum

Clinical Information: Biomarkers of hepatocellular carcinoma (HCC) include alpha-fetoprotein (AFP), third electrophoretic form of lentil lectin-reactive AFP (AFP-L3), and des-carboxy-prothrombin (DCP). The GALAD (gender, age, AFP-L3, AFP, des-gamma-carboxy prothrombin) model combines these three biomarkers with the patient's gender and age to estimate the risk of HCC in patients with chronic liver disease based on the following equation: Z = -10.08 + 0.09 x age + 1.67 x sex + 2.34 log(10) (AFP) + 0.04 x AFP - L3 + 1.33 x log(10) (DCP), where sex = 1 for males, 0 for females. The GALAD score is calculated using the lower limit of quantitation (LLOQ) when one or more of the following values are below the LLOQ: %L3, Total AFP, or Des-Gamma-Carboxy Prothrombin. In the event this occurs, the GALAD score is resulted as (<)GALAD score. The GALAD model has been demonstrated to have

higher diagnostic accuracy for the detection of HCC when compared to the use AFP, AFP-L3, and DCP markers alone or in combination. The performance of the GALAD score has also been reported to be superior to ultrasound for HCC detection.

Useful For: Calculation of the risk for patients with chronic liver disease to develop hepatocellular carcinoma

Interpretation: Higher GALAD (gender, age, AFP-L3, AFP, des-gamma-carboxy prothrombin) model scores correlate with increased risk of hepatocellular carcinoma (HCC). The area under the curve (AUC) of a receiver operating characteristic curve of the GALAD score was 0.95 for all HCC detection and 0.92 for the detection of early-stage HCC. Additionally, the AUC of the GALAD score (0.95) was higher than that of ultrasound alone for all HCC detection (AUC of 0.82, P <0.01). The sensitivity and specificity performance characteristics of the GALAD score for HCC will be influenced by the selected GALAD score cut-off. For example, at an optimal AUC cutoff of 0.76, the GALAD score had 91% sensitivity and 85% specificity for HCC detection. At a more specific GALAD score cutoff of 0.88, the observed sensitivity was 80% for HCC detection with an observed specificity of 97%. The GALAD model was developed and validated in patient cohorts with a prevalence of HCC ranging from 35% to 49%. The performance of the model may be altered in populations with different HCC prevalence. In addition, the clinical performance of the GALAD score varies by etiology of HCC and, therefore, may be different in different regions of the world.

Reference Values:
Only orderable as part of a profile. For more information see HCCGS / Hepatocellular Carcinoma Risk Panel with GALAD Score, Serum

Not applicable

Clinical References: 1. Johnson P, Pirrie S, Cox T, et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev. 2014;23(1):144-153 2. Berhane S, Toyota H, Tada T, et al. Role of the GALAD and BALAD-2 serologic models in diagnosis of hepatocellular carcinoma and prediction of survival in patients. Clin Gastroenterol Hepatic. 2016;14(6):875-886 3. Yang JD, Addissie BD, Mara KC, et al. GALAD score for hepatocellular carcinoma detection in comparison with liver ultrasound and proposal of GALADUS score. Cancer Epidemiol Biomarkers Prev. 2019;28(3):531-538 doi:10.1158/1055-9965 4. Leerapun A, Suravarapu S, Bida JP, et al. The utility of serum AFP-L3 in the diagnosis of hepatocellular carcinoma: Evaluation in a U.S. referral population. Clin Gastroenterol Hepatol. 2007;5(3):394-402 5. Durazo FA, Blatt LM, Corey WG, et al. Des-gamma-carboxyprothrombin, alpha-fetoprotein and AFP-L3 in patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma. J Gastroenterol Hepatol. 2008;23:1541-1548 6. Chaiteerakij R, Addissie BD, Roberts LR. Update on biomarkers of hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2015;13(2):237-245 doi:10.1016/j.cgh.2013.10.038

PA
8683

Procainamide and N-Acetylprocainamide, Serum

Clinical Information: Procainamide (PA) is indicated in the treatment of life-threatening ventricular arrhythmias. PA is metabolized to an active metabolite, N-acetylprocainamide (NAPA), with metabolism controlled by genetically determined enzymes. In patients with normal kidney function, fast metabolizers will have a PA:NAPA ratio less than 1 at 3 hours after the dose is administered. Slow acetylators (PA:NAPA ratio >2 after 3 hours) are more likely to present with systemic lupus erythematosus-like symptoms and may test positive for antinuclear antibodies. Patients who have prolonged exposure to procainamide levels above 12.0 mcg/mL or a NAPA concentration of 40.0 mcg/mL or higher are very likely to exhibit symptoms of toxicity, which are characterized by

hypotension, ventricular fibrillation, widened QRS complex (intraventricular conduction delay), junctional tachycardia, oliguria, confusion, nausea, and vomiting. Kidney disease, liver disease, cardiac failure, and states of low cardiac output reduce the metabolism and clearance of PA and NAPA. Coadministration of histamine H2 receptor antagonists, such as cimetidine and ranitidine reduce renal clearance of PA and NAPA resulting in higher plasma concentrations of each.

Useful For: Monitoring therapy with procainamide Assessing compliance Evaluating procainamide toxicity

Interpretation: Administration of a dose of 50 mg/kg will usually yield the optimal trough concentration in the range of 4.0 to 10.0 mcg/mL for procainamide and 12.0 to 18.0 mcg/mL for N-acetylprocainamide.

Reference Values:

Procainamide
Therapeutic: 4.0-10.0 mcg/mL
Critical value: >12.0 mcg/mL

N-acetylprocainamide
Therapeutic: 12.0-18.0 mcg/mL
Critical value: > or =40.0 mcg/mL

Clinical References: 1. Milone MC, Shaw LM. Chapter 42: Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453.e9 2. Brunton LL, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 14th ed. McGraw-Hill Education, 2023

PRCAL
602598

Procalcitonin, Serum

Clinical Information: Procalcitonin (PCT) is a biomarker associated with the inflammatory response to bacterial infection and aids in the risk assessment of critically ill patients on their first day of admission to the intensive care unit (ICU), or when obtained in the emergency department or other medical wards prior to ICU admission, for progression to severe sepsis and septic shock. The percent change in PCT level over time aids in the prediction of cumulative 28-day mortality in patients with severe sepsis and septic shock. A PCT level that declines 80% or less from the day that severe sepsis or septic shock was clinically diagnosed (day 0) to 4 days after clinical diagnosis (day 4) is associated with higher cumulative 28-day risk of all-cause mortality than a decline above 80%. The PCT level on day 1 (the day after severe sepsis or septic shock is first clinically diagnosed) can be used to calculate the percent change in PCT level at day 4 if the day 0 measurement is unavailable.

Useful For: Monitoring antibiotic therapy and all-cause mortality for patients diagnosed with severe sepsis or septic shock in the Intensive Care Unit (ICU) or when obtained in the emergency department or other medical wards prior to ICU admission

Interpretation: Systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock were categorized according to the criteria of the consensus conference of the American College of Chest Physicians/Society of Critical Care Medicine.(1) The change of procalcitonin (PCT) concentration over time provides prognostic information about the risk of mortality(2) within 28 days for patients diagnosed with severe sepsis or septic shock coming from the emergency department, intensive care unit, other medical wards, or directly from outside the hospital. Data support the use of procalcitonin determinations from the day severe sepsis or septic shock is first diagnosed (day 0) or the day thereafter (day 1) and the fourth day after diagnosis (day 4) for the classification of patients into higher and lower risk for mortality

within 28 days. Change in procalcitonin of 80% or less: A decrease of PCT levels below or equal to 80% defines a positive change in PCT test result representing a higher risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock. Change in procalcitonin above 80%: A decrease of PCT levels of more than 80% defines a negative change in PCT result representing a lower risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock. Positive results: Procalcitonin greater than or equal to 0.25 ng/mL may indicate bacteremia or bacterial pneumonia; however, it is a non-specific biomarker. False positives can be seen in patients with a variety of illnesses, including but not limited to severe trauma, shock, recent surgery, burns, renal insufficiency, severe liver disease, COVID-19, and certain malignancies. Negative results: Procalcitonin less than 0.25 ng/mL may indicate lower probability of bacteremia or bacterial pneumonia. Intracellular bacteria, viruses, and fungi do not cause elevation of procalcitonin, so low values (<0.25 ng/mL) do not rule out other infections.

Reference Values:
0.00-0.24 ng/mL

Clinical References: 1. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20(6):864-874 2. Schuetz P, Maurer P, Punjabi V, Desai A, Amin DN, Gluck E. Procalcitonin decrease over 72 hours in US critical care units predicts fatal outcome in sepsis patients. Crit Care. 2013;17(3):R115. doi:10.1186/cc12787 3. Peyro Saint Paul L, Debruyne D, Bernard D, Mock DM, Defer GL. Pharmacokinetics and pharmacodynamics of MD1003 (high-dose biotin) in the treatment of progressive multiple sclerosis. Expert Opin Drug Metab Toxicol. 2016;12(3):327-344. doi:10.1517/17425255.2016.1136288 4. Grimsey P, Frey N, Bendig G, et al. Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. J Pharmacokinet Pharmacodyn. 2017;2(4):247-256. doi:10.4155/ipk-2017-0013 5. Chambliss AB, Patel K, Colon-Franco JM, et al. AACC guidance document on the clinical use of procalcitonin. J Appl Lab Med. 2023;8(3):598-634. doi:10.1093/jalm/jfad007

PINP
61695

Procollagen I Intact N-Terminal, Serum

Clinical Information: Procollagen type I propeptides are derived from collagen type I, which is the most common collagen type found in mineralized bone. In bone, collagen is synthesized by osteoblasts in the form of procollagen. This precursor contains a short signal sequence and terminal extension peptides: amino-terminal propeptide (PINP) and carboxy-terminal propeptide. These propeptide extensions are removed by specific proteinases before the collagen molecules form. Both propeptides can be found in the circulation and their concentration reflects the synthesis rate of collagen type I. Although collagen type I propeptides may also arise from other tissues (such as the skin, vessels, fibrocartilage, and tendons), most nonskeletal tissues exhibit a slower turnover than bone and contribute very little to the circulating pool of PINP. PINP is considered the most sensitive marker of bone formation, and it is particularly useful for monitoring bone formation therapies and antiresorptive therapies; it is recommended that the test be performed at baseline before starting osteoporosis therapy and performed again 3 to 6 months later.

Useful For: Aiding in monitoring antiresorptive and anabolic therapy in patients with osteoporosis An adjunct in the assessment of conditions associated with increased bone turnover, such as Paget disease This test should not be used as a screening test for osteoporosis in the general population.

Interpretation: This assay is specific for the intact trimeric form of procollagen type I N-terminal propeptide (PINP). When monitoring response to osteoporosis treatment, a change of greater or equal to 21% (least significant change) from baseline PINP levels (ie, prior to the start of therapy), 3 to 6 months

after initiation of therapy indicates an adequate therapeutic response. The direction of the change in PINP levels (decrease or increase) will depend on the type of osteoporosis treatment. In patients taking bisphosphonates, PINP levels have been shown to decrease up to 70% from baseline after 6 months of therapy. Treatment with hormone replacement therapy also shows a decrease in PINP levels but to a lesser degree than bisphosphonates therapy. In patients treated with teriparatide (recombinant human parathyroid hormone 1-34), PINP levels increase from baseline, reflecting the stimulatory effect of teriparatide on osteoblasts and bone formation. PINP levels have been shown to significantly increase as early as 1 month after teriparatide treatment, peaking at 6 months following treatment. Increases greater than 10 mcg/L have been reported in 77% to 79% of teriparatide-treated patients after 3 months of therapy and are considered a successful response.

Reference Values:

Adult male: 22-87 mcg/L
Adult female premenopausal: 19-83 mcg/L
Adult female postmenopausal: 16-96 mcg/L
Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Naylor KE, Jacques RM, Paggiosi M, et al. Response of bone turnover markers to three oral bisphosphonate therapies in postmenopausal osteoporosis: the TRIO study. Osteoporos Int. 2016;27(1):21-31. doi:10.1007/s00198-015-3145-7 2. McClung MR, San Martin J, Miller PD, et al. Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. Arch Intern Med. 2005;165(15):1762-1768 3. Eastell R, Krege JH, Chen P, et al. Development of an algorithm for using PINP to monitor treatment of patients with teriparatide. Curr Med Res Opin. 2006;22(1):61-66 4. Brown JP, Don-Wauchope A, Douville P, Albert C, Vasikaran SD. Current use of bone turnover markers in the management of osteoporosis. Clin Biochem. 2022;109-110:1-10. doi:10.1016/j.clinbiochem.2022.09.002

LDAI
621645

Progentec aiSLE DX Lupus Disease Activity Index, Plasma

Clinical Information:

Useful For: Aiding in the assessment of current systemic lupus erythematosus disease activity when used in conjunction with standard clinical assessment

Interpretation:

Reference Values:

C-X-C Motif Chemokine Ligand 10 (CXCL10/IP-10): 37-343 pg/mL
Interferon gamma (IFN-y): 0.34-7.80 pg/mL
Interleukin-15 (IL-15): 1.00-4.30 pg/mL
Interleukin-4 (IL-4): 1.000-3.200 pg/mL
Interferon alpha-2 (IFNa-2): 3.600-8.300 pg/mL
Interleukin-10 (IL-10): 1.20-9.50 pg/mL
Interleukin-7 (IL-7): 1.10-12.00 pg/mL
TNF-Related Apoptosis-Inducing Ligand (TRAIL): 26-120 pg/mL
B Lymphocyte Stimulator (BAFF)/BLys: 370-995 pg/mL
Osteopontin (OPN): 14,958-95,972 pg/mL

Clinical References: 1. Munroe M, Blankenship D, DeFreese D, et al. Abstract 0554: A refined disease activity immune index informed by select immune mediators that characterizes clinical disease activity in systemic lupus erythematosus. Arthritis Rheumatol. 2023;75(S9):1089-1092 2. Munroe M, DeJager W, Macwana S, et al. Abstract 1803: Ability of innate, adaptive, and TNF-superfamily immune

pathways to characterize disease activity and inform a refined lupus disease activity immune index in a confirmatory cohort of SLE patients. Arthritis Rheumatol. 2020;72(S10) 3. Munroe M, Guthridge J, Lu R, et al. Abstract 1693: Innate, adaptive, and TNF-Superfamily immune pathways inform a lupus disease activity immune index that characterizes disease activity in SLE. Arthritis Rheumatol. 2018;70(S9)

LFRI
621644

Progentec aiSLE DX Lupus Flare Risk Index, Plasma

Clinical Information:

Useful For: Aiding in the assessment of risk of flare in lupus patients when used in conjunction with standard clinical assessment

Interpretation: This test measures the concentrations of 11 blood plasma proteins. An algorithm is applied to these concentrations to calculate a flare risk index score that ranges from -30 to +30 with the magnitude indicating the likelihood of the patient experiencing a lupus flare in the next 12 weeks.

Reference Values:
Monocyte chemoattractant protein-1 (MCP1)/CCL2: 54-368 pg/mL
Interleukin-5 (IL-5): 0.260-2.000 pg/mL
Interleukin-17A (IL-17A): 2.100-11.000 pg/mL
Interleukin-7 (IL-7): 1.10-12.00 pg/mL
Interleukin-4 (IL-4): 1.000-3.200 pg/mL
Tumor necrosis factor-a (TNF-a): 1.80-12.00pg/mL
Monocyte chemoattractant protein-3 (MCP3)/CCL7: 0.82-16.00pg/mL
B Lymphocyte Stimulator (BAFF)/BLys: 370-995 pg/mL
Osteopontin (OPN): 14,958-95,972 pg/mL
Tumor necrosis factor receptor 1 (TNFR1)/TNFRSF1A: 617-1595 pg/mL
Tumor necrosis factor receptor 2 (TNFR2)/TNFRSF1B: 1079-3589 pg/mL

Clinical References: 1. Munroe ME, Blankenship D, DeFreese D, et al. A flare risk index informed by select immune mediators in systemic lupus erythematosus. Arthritis Rheumatol. 2023;75(5):723-735. doi:10.1002/art.42389 2. Thanou A, Jupe E, Purushothaman M, Niewold TB, Munroe ME. Clinical disease activity and flare in SLE: Current concepts and novel biomarkers. J Autoimmun. 2021;119:102615. doi:10.1016/j.jaut.2021.102615 3. Munroe ME, Vista ES, Merrill JT, Guthridge JM, Roberts VC, James JA. Pathways of impending disease flare in African-American systemic lupus erythematosus patients. J Autoimmun. 2017;78:70-78. doi:10.1016/j.jaut.2016.12.005 4. Munroe ME, Vista ES, Guthridge JM, Thompson LF, Merrill JT, James JA. Proinflammatory adaptive cytokine and shed tumor necrosis factor receptor levels are elevated preceding systemic lupus erythematosus disease flare. Arthritis Rheumatol. 2014;66(7):1888-1899. doi:10.1002/art.38573

PROG
70542

Progesterone Receptor (PR) Immunostain, Technical Component Only

Clinical Information: Progesterone receptor is a hormone receptor localized within the nucleus. It is highly expressed in the epithelial cells of the breast and endometrium, and smooth muscle cells of the uterus. This antibody is used along with that for estrogen receptor to assess hormonal responsiveness in breast cancer.

Useful For: Qualitative detection of progesterone receptor protein in a diagnostic setting

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Radzikowska E, Langfort R, Giedronowicz D. Estrogen and progesterone receptors in non small cell lung cancer patients. Ann Thorac Cardiovasc Surg. 2002;8(2):69-73 2. Wang C, Tran DA, Fu MZ, Chen W, Fu SW, Li X. Estrogen receptor, progesterone receptor, and HER2 receptor markers in endometrial cancer. J Cancer. 2020;11(7):1693-1701. doi:10.7150/jca.41943 3. Liao S, Mi HN, Chai LY, Wang HN. Effects of progesterone receptor on proliferation of uterine leiomyoma cells. J Biol Regul Homeost Agents. 2019;33(6):1685-1693. doi:10.23812/19-170-A 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PGSN
8141

Progesterone, Serum

Clinical Information: Sources of progesterone are the adrenal glands, corpus luteum, and placenta. Adrenal Glands: Progesterone synthesized in the adrenal glands is converted to other corticosteroids and androgens and, thus, is not a major contributor to circulating serum levels unless there is a progesterone-producing tumor present. Corpus Luteum: After ovulation, there is a significant rise in serum levels as the corpus luteum begins to produce progesterone in increasing amounts. This causes changes in the uterus, preparing it for implantation of a fertilized egg. If implantation occurs, the trophoblast begins to secrete human chorionic gonadotropin, which maintains the corpus luteum and its secretion of progesterone. If there is no implantation, the corpus luteum degenerates and circulating progesterone levels decrease rapidly, reaching follicular phase levels about 4 days before the next menstrual period. Placenta: By the end of the first trimester, the placenta becomes the primary secretor of progesterone.

Useful For: Ascertaining whether ovulation occurred in a menstrual cycle Assessment of infertility Evaluation of abnormal uterine bleeding Evaluation of placental health in high-risk pregnancy Determining the effectiveness of progesterone injections when administered to women to help support early pregnancy Workup of some patients with adrenal disorders

Interpretation: Ovulation results in a midcycle surge of luteinizing hormone followed by an increase in progesterone secretion, peaking between day 21 and 23. If no fertilization and implantation has occurred by then, supplying the corpus luteum with human chorionic gonadotropin-driven growth stimulus, progesterone secretion falls, ultimately triggering menstruation. Typically, day 21 to 23 serum progesterone concentrations of more than 10 ng/mL indicate normal ovulation and concentrations below 10 ng/mL suggest anovulation, inadequate luteal phase progesterone production, or inappropriate timing of specimen collection. Increased progesterone concentrations are occasionally seen with some ovarian cysts, molar pregnancies, rare forms of ovarian cancer, adrenal cancer, congenital adrenal hyperplasia, and testicular tumors. Increased progesterone may also be a result of overproduction by the adrenal glands. Low concentrations of progesterone may be associated with toxemia in late pregnancy, decreased ovarian function, amenorrhea, ectopic pregnancy, and miscarriage.

Reference Values:
<4 weeks: Not established
4 weeks-<12 months: < or =0.66 ng/mL (Confidence Interval: 0.63-0.94 ng/mL)
12 months-9 years: < or =0.35 ng/mL
10-17 years: Concentrations increase through adolescence and puberty
> or = 18 years: <0.20 ng/mL
Reference intervals are central 90th percentile of healthy population

Females:
<4 days old: Not established
4 days-<12 months: < or =1.3 ng/mL (Confidence Interval: 0.88-2.3 ng/mL)
12 months-9 years: < or =0.35 ng/mL
10-17 years: Adult concentrations are attained by puberty
> or = 18 years:
Reference intervals are central 90th percentile of healthy population
-Follicular phase: < or =0.89 ng/mL
-Ovulation: < or =12 ng/mL
-Luteal phase: 1.8-24 ng/mL
-Post-menopausal: < or =0.20 ng/mL
Pregnancy
-1st trimester: 11-44 ng/mL
-2nd trimester: 25-83 ng/mL
-3rd trimester: 58-214 ng/mL

Pediatric reference intervals adopted from the CALIPER study. https://caliperproject.ca/caliper/database/

For International System of Units (SI) conversion for Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Lippe BM, LaFranchi SH, Lavin N, et al. Serum 17-alpha-hydroxyprogesterone, progesterone, estradiol, and testosterone in the diagnosis and management of congenital adrenal hyperplasia. J Pediatr. 1974;85(6):782-7. doi:10.1016/s0022-3476(74)80340-9 2. Haymond S, Gronowski AM. In Burtis CA, Ashwood ER, Bruns DE, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 4th ed. Elsevier; 2006: 2097-2152 3. CALIPER Database. The Hospital for Sick Children. Available at: https://caliperproject.ca/caliper/database/ 4. Cole T. Hormones. In: Rifai N, Chiu RWK, Young I, Burnham CA, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 38

22C3
603762

Programmed Death-Ligand 1 (PD-L1) (22C3), Semi-Quantitative Immunohistochemistry, Manual

Clinical Information: Programmed cell death 1-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) or CD274, is a transmembrane protein involved in the regulation of cell-mediated immune responses through interaction with the receptor programmed death protein-1 (PD-1). PD-L1 has been identified as both a prognostic and theranostic marker in a variety of neoplasms. Overexpression of PD-L1 has been observed in carcinomas of the urinary bladder, lung, gastric and gastroesophageal junction, thymus, colon, pancreas, ovary, breast, kidney, and in melanoma and glioblastoma.

Useful For: Identification of neoplasms expressing programmed cell death 1-ligand 1 (clone 22C3)

Interpretation: The results of the test will be reported in form of scores. The scoring system is based on type and origin of tumor. If additional interpretation or analysis is needed, order PATHC / Pathology Consultation along with this test.

Clinical References: 1. Rimm DL, Han G, Taube JM, et al. A prospective, multi-institutional, pathologist-based assessment of 4 immunohistochemistry assay for PD-L1 expression in non-small cell lung cancer. JAMA Oncol. 2017;3(8):1051-1058. doi:10.1001/jamaoncol.2017.0013 2. Gaule P, Smithy JW, Toki M, et al. A quantitative comparison of antibodies to programmed cell death 1 Ligand 1.

JAMA Oncol. 2017;3(2):256-259. doi:10.1001/jamaoncol.2016.3015 3. Sunshine JC, Nguyen P, Kaunitz G, et al. PD-L1 expression in melanoma: A quantitative immunohistochemical antibody comparison. Clin Can Res. 2017;23(16):4938-4944. doi:10.1158/1078-0432.CCR-16-1821 4. D'Incecco A, Andreozzi M, Ludovini V, et al. PD-1 and PD-L1 expression in molecularly selected non-small-cell lung cancer patients. Br J Cancer. 2015;112(1):95-102. doi:10.1038/bjc.2014.555 5. Mansfield AS, Roden AC, Peikert T, et al. B7-H1 expression in malignant pleural mesothelioma is associated with sarcomatoid histology and poor prognosis. J Thorac Oncol. 2014;9(7):1036-1040. doi:10.1097/JTO.0000000000000177 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

288PD 609994 Programmed Death-Ligand 1 (PD-L1) (28-8), Semi-Quantitative Immunohistochemistry, Manual

Clinical Information: Programmed cell death 1-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) or CD274, is a transmembrane protein involved in the regulation of cell-mediated immune responses through interaction with the receptor programmed death protein-1. PD-L1 has been identified as both a prognostic and theranostic marker in a variety of neoplasms. Overexpression of PD-L1 has been observed in carcinomas of the bladder, lung, gastric and gastroesophageal junction, colon, ovary, breast, kidney, and melanoma.

Useful For: Identification of neoplasms expressing programmed cell death 1-ligand 1(clone 28-8)

Interpretation: The results of the test will be reported in form of scores. The scoring system is based on type and origin of tumor. If additional interpretation or analysis is needed, order PATHC / Pathology Consultation along with this test.

Clinical References: 1. Garcia A, Recondo G, Greco M et al. Correlation between PD-L1 expression (clones 28-8 and SP263) and histopathology in lung adenocarcinoma. Heliyon. 2020;6(6):e04117 2. Kintslera S, Cassataroa MA, Drosch M, Holenya P, Knuechel R, Braunschweig T. Expression of programmed death ligand (PD-L1) in different tumors. Comparison of several current available antibody clones and antibody profiling. Ann Diagn Pathol. 2019;41:24-37 3. O'Malley DP, Yang Y, Boisot S, et al. Immunohistochemical detection of PD-L1 among diverse human neoplasms in a reference laboratory: observations based upon 62,896 cases. Mod Pathol. 2019;32(7):929-942 4. Koppel C, Schwellenbach H, Zielinski D, et al. Optimization and validation of PD-L1 immunohistochemistry staining protocols using the antibody clone 28-8 on different staining platforms. Mod Pathol. 2018;31(11):1630-1644 5. Phillips T, Simmons P, Inzunza HD, et al. Development of an automated PD-L1 immunohistochemistry (IHC) assay for non-small cell lung cancer. Appl Immunohistochem Mol Morphol. 2015;23(8):541-549 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

SP142 603769 Programmed Death-Ligand 1 (PD-L1) (SP142), Semi-Quantitative Immunohistochemistry, Manual

Clinical Information: Programmed cell death 1-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) or CD274, is a transmembrane protein involved in the regulation of cell-mediated immune responses through interaction with the receptor programmed death protein-1. PD-L1 has been identified as both a prognostic and theranostic marker in a variety of neoplasms. Overexpression of PD-L1 has been observed in carcinomas of the urinary bladder, lung, thymus, colon, pancreas, ovary, breast, kidney, and in melanoma and glioblastoma.

Useful For: Identification of neoplasms expressing programmed cell death 1-ligand 1 (clone SP142)

Interpretation: The results of the test will be reported in form of scores. The scoring system is based on type and origin of tumor. If additional interpretation or analysis is needed, order PATHC / Pathology Consultation along with this test.

Clinical References: 1. Rimm DL, Han G, Taube JM, et al. A prospective, multi-institutional, pathologist-based assessment of 4 immunohistochemistry assay for PD-L1 expression in non-small cell lung cancer. JAMA Oncol. 2017;3(8):1051-1058. doi: 10.1001/jamaoncol.2017.0013 2. Gaule P, Smithy JW, Toki M, et al. A quantitative comparison of antibodies to programmed cell death 1 Ligand 1. JAMA Oncol. 2017;3(2):256-259. doi: 10.1001/jamaoncol.2016.3015 3. Sunshine JC, Nguyen P, Kaunitz G, et al. PD-L1 expression in melanoma: A quantitative immunohistochemical antibody comparison. Clin Can Res. 2017;23(16):4938-4944. doi:10.1158/1078-0432.CCR-16-1821 4. D'Incecco A, Andreozzi M, Ludovini V, et al. PD-1 and PD-L1 expression in molecularly selected non-small-cell lung cancer patients. Br J Cancer. 2015;112(1):95-102. doi: 10.1038/bjc.2014.555 5. Mansfield AS, Roden AC, Peikert T, et al. B7-H1 expression in malignant pleural mesothelioma is associated with sarcomatoid histology and poor prognosis. J Thorac Oncol. 2014;9(7):1036-1040. doi: 10.1097/JTO.0000000000000177 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

SP263 603755 Programmed Death-Ligand 1 (PD-L1) (SP263), Semi-Quantitative Immunohistochemistry, Manual

Clinical Information: Programmed cell death 1-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) or CD274, is a transmembrane protein involved in the regulation of cell-mediated immune responses through interaction with the receptor programmed death protein-1. PD-L1 has been identified as both a prognostic and theranostic marker in a variety of neoplasms. Overexpression of PD-L1 has been observed in carcinomas of the urinary bladder, lung, thymus, colon, pancreas, ovary, breast, kidney, and in melanoma and glioblastoma.

Useful For: Identification of neoplasms expressing programmed cell death 1-ligand 1 (clone SP263)

Interpretation: The results of the test will be reported in form of scores. The scoring system is based on type and origin of tumor. If additional interpretation or analysis is needed, order PATHC / Pathology Consultation along with this test.

Clinical References: 1. Rimm DL, Han, G, Taube JM, et al. A prospective, multi-institutional, pathologist-based assessment of 4 immunohistochemistry assay for PD-L1 expression in non-small cell lung cancer. JAMA Oncol. 2017;3(8):1051-1058 2. Gaule P, Smithy JW, Toki M, et al. A quantitative comparison of antibodies to programmed cell death 1 Ligand 1. JAMA Oncol. 2017;3(2):256-259 3. Sunshine JC, Nguyen P, Kaunitz G, et al. PD-L1 expression in melanoma: A quantitative immunohistochemical antibody comparison. Clin Can Res. 2017;23(16):4938-4944 4. D'Incecco A, Andreozzi M, Ludovini V, et al. PD-1 and PD-L1 expression in molecularly selected non-small-cell lung cancer patients. Br J Cancer. 2015;112(1):95-102 5. Mansfield AS, Roden AC, Peikert T, et al. B7-H1 expression in malignant pleural mesothelioma is associated with sarcomatoid histology and poor prognosis. J Thorac Oncol. 2014;9(7):1036-1040 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PINS
80908

Proinsulin, Plasma

Clinical Information: Proinsulin is the precursor of insulin and C-peptide (connecting peptide). Following synthesis, proinsulin is packaged into secretory granules, where it is processed to C-peptide and insulin by prohormone convertases (PC1/3 and PC2) and carboxypeptidase E. Only 1% to 3% of proinsulin is secreted intact. However, because proinsulin has a longer half-life than insulin, circulating proinsulin concentrations are in the range of 5% to 30% of circulating insulin concentrations on a molar basis, with the higher relative proportions seen after meals and in patients with insulin resistance or early type 2 diabetes. Proinsulin can bind to the insulin receptor and exhibits 5% to 10% of the metabolic activity of insulin. Proinsulin levels might be elevated in patients with insulin-producing islet cell tumors (insulinomas). These patients suffer from hypoglycemic attacks due to inappropriate secretion of insulin by the tumors. The biochemical diagnosis rests primarily on demonstrating nonsuppressed insulin levels in the presence of hypoglycemia (blood glucose <45 mg/dL). The diagnosis can be difficult, as tumors might be small or secrete insulin only episodically. Insulin injections or hypoglycemic drugs can also mimic insulinoma. Evaluation of these patients frequently requires a prolonged fast (72 hours) as well as supplementary tests in addition to insulin and glucose measurements, including a sulfonylurea screen and measurement of C-peptide, proinsulin, and beta-hydroxybutyrate. The inappropriate oversecretion of insulin by insulinomas causes the release of an increased numbers of secretory granules with incompletely processed insulin, resulting in elevated serum/plasma proinsulin concentrations. This oversecretion of proinsulin in insulinomas is accentuated during fasting, when proinsulin normally does not account for more than 5% of the insulin concentrations. Proinsulin is strikingly elevated in PC1/3 deficiency. These patients have defects in the processing of multiple peptide hormones and suffer from diabetes, adrenal insufficiency, infertility, and obesity. Affected individuals typically have red hair regardless of racial background. Variants in the proinsulin molecule have been reported that affect PC cleavage efficiency or subsequent proinsulin metabolism. These variants can also lead to markedly elevated proinsulin levels but are usually not accompanied by diabetes or any other hormonal abnormalities.

Useful For: As part of the diagnostic workup of suspected insulinoma As part of the diagnostic workup of patients with suspected prohormone convertase 1/3 deficiency As part of the diagnostic workup of patients with suspected proinsulin variations

Interpretation: Normal individuals will have proinsulin concentrations below the upper limit of the normal fasting reference range (22 pmol/L) when hypoglycemic (blood glucose <60 mg/dL). Conversely, most (>80%) insulinoma patients will have proinsulin concentrations above the upper limit of the reference range. The sensitivity and specificity for a diagnosis of insulinoma during hypoglycemia are approximately 75% and near 100%, respectively, at the 22 pmol/L cutoff. A higher sensitivity (>95%) can be achieved using a 5 pmol/L cutoff, which is recommended by Mayo Clinic's highly-experienced hypoglycemia team to avoid missing cases. However, the lower cutoff results in reduced specificity (approximately 40%), emphasizing the need for a combination of different tests to assure accurate biochemical diagnosis. Patients with prohormone convertase 1/3 deficiency have low, or sometimes undetectable, insulin levels and substantially elevated proinsulin levels, exceeding the upper limit of the reference range substantially in the fasting state and rising even higher after food intake. Many other hormonal abnormalities are also present, including cortisol deficiency (because of lack of processing of pro-opiomelanocortin to adrenocorticotropic hormone and other peptides), infertility, and, often, obesity.

Reference Values:
3.6-22 pmol/L

Clinical References: 1. Murtha TD, Lupsa BC, Majumdar S, Jain D, Salem RR. A systematic review of proinsulin-secreting pancreatic neuroendocrine tumors. J Gastrointest Surg. 2017;21(8):1335-1341 2. Placzkowski KA, Vella A, Thompson GB, et al. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987-2007. J Clin Endocrinol Metab. 2009;94(4):1069-1073 3. Vezzosi D, Bennet A., Fauvel J, Caron P. Insulin, C-peptide and proinsulin for the biochemical diagnosis of hypoglycemia related to endogenous hyperinsulinism. Eur

J Endocrinol. 2007;157(1):75-83 4. Service FJ. Hypoglycemic disorders. N Engl J Med. 1995;322(17):1144-1152 5. Steiner DF. The proprotein convertases. Curr Opin Chem Biol. 1998;2(1):31-39

PRLI
70541

Prolactin (PRL) Immunostain, Technical Component Only

Clinical Information: Prolactin is a pituitary hormone involved in the stimulation of milk production, salt and water regulation, growth, development, and reproduction. Prolactin-producing cells constitute approximately 20% of the cells of the normal anterior pituitary. Antibodies to prolactin are used in a panel to subclassify pituitary adenomas.

Useful For: Subclassification of pituitary adenomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Ezzat S, Asa SL, Couldwell WT, et al. The prevalence of pituitary adenomas. A sytematic review. Cancer. 2004;101:613-619 2. Hamid Z, Mrak RE, Ijaz M, Faas FH. Sensitivity and specificity of immunohistochemistry in pituitary adenomas. The Endocrinologist. 2009;19:38-43 3. Osamura RY, Kajiva H, Takei M, et al. Pathology of the human pituitary adenomas. Histochem Cell Biol. 2008;130(3):495-507 4. Zada G, Woodmansee WW, Ramkissoon R, et al. Atypical pituitary adenomas: incidence, clinical characteristics, and implications. J Neurosurg. 2011;114:336-344 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PLPMA
35090

Prolactin, Pituitary Macroadenoma, Serum

Clinical Information: Prolactin-secreting macroadenomas (>10 mm in diameter) can sometimes produce exceedingly high serum prolactin concentrations that may paradoxically result in falsely low prolactin concentrations when measured by immunometric assays. In such situations, very high concentrations of prolactin saturate both the capture and signal antibodies in the assay, block formation of the capture antibody-prolactin-signal antibody "sandwich," and result in falsely decreased prolactin results (referred to as the high-dose hook effect). With such tumors, serum prolactin levels may be falsely decreased into the normal reference interval, potentially resulting in inappropriate patient management. Dilution of the specimen eliminates the analytic artifact in these cases. Prolactin is secreted by the anterior pituitary gland and controlled by the hypothalamus. The major chemical controlling prolactin secretion is dopamine, which inhibits prolactin secretion from the pituitary. Prolactin is released from the pituitary in response to thyrotropin-releasing hormone and other factors. Prolactin is the principal hormone that controls the initiation and maintenance of lactation. In normal individuals, prolactin concentrations increase in response to physiologic stimuli such as sleep, stress, exercise, sexual intercourse, and hypoglycemia, and are also elevated during pregnancy, lactation, postpartum, and in the newborn infant. Hyperprolactinemia is the most common hypothalamic-pituitary disorder encountered in clinical endocrinology. Pathologic causes of hyperprolactinemia include prolactin-secreting pituitary adenoma (prolactinoma, which is more frequent in females than males, and accounts for approximately 40% of all pituitary tumors), functional and organic disease of the hypothalamus, primary hypothyroidism, compression of the pituitary stalk, chest wall lesions, renal insufficiency, polycystic ovarian disease, and ectopic tumors. In general, serum prolactin concentrations parallel tumor size in patients with prolactinomas. Macroadenomas (>10 mm in diameter) are typically

associated with serum prolactin concentrations >250 ng/mL and a concentration >500 ng/mL is diagnostic of a macroprolactinoma. Moderately increased concentrations of serum prolactin are not a reliable guide for determining whether a prolactin-producing pituitary adenoma is present. Multiple medications can cause increased prolactin concentration including estrogens, dopamine receptor blockers (eg, phenothiazines), dopamine antagonists (eg, metoclopramide, domperidone), alpha-methyldopa, cimetidine, opiates, antihypertensive medications, and other antidepressants and antipsychotics. Hyperprolactinemia often results in loss of libido, galactorrhea, oligomenorrhea or amenorrhea, and infertility in premenopausal females; and loss of libido, impotence, infertility, and hypogonadism in males. Postmenopausal and premenopausal women, as well as men, can also suffer from decreased muscle mass and osteoporosis. Prolactinomas may rarely present in childhood or adolescence. In girls, disturbances in menstrual function and galactorrhea may be seen, whereas in boys, delayed pubertal development and hypogonadism are often present. The treatment options are the same as in adult patients.

PRL
85670

Prolactin, Serum

Clinical Information: Prolactin is secreted by the anterior pituitary gland and controlled by the hypothalamus. The major chemical controlling prolactin secretion is dopamine, which inhibits prolactin secretion from the pituitary. Prolactin is released from the pituitary in response to thyrotropin-releasing hormone and other factors. Prolactin is the principal hormone that controls the initiation and maintenance of lactation. In normal individuals, prolactin concentrations increase in response to physiologic stimuli such as sleep, stress, exercise, sexual intercourse, and hypoglycemia, and concentrations are also elevated during pregnancy, lactation, postpartum, and in a newborn infant. Hyperprolactinemia is the most common hypothalamic-pituitary disorder encountered in clinical endocrinology. Pathologic causes of hyperprolactinemia include prolactin-secreting pituitary adenoma (prolactinoma, which is more frequent in females than males and accounts for approximately 40% of all pituitary tumors), functional and organic disease of the hypothalamus, primary hypothyroidism, compression of the pituitary stalk, chest wall lesions, renal insufficiency, polycystic ovarian disease, and ectopic tumors. Hyperprolactinemia often results in loss of libido, galactorrhea, oligomenorrhea or amenorrhea, and infertility in premenopausal females, and loss of libido, impotence, infertility, and hypogonadism in males. Postmenopausal and premenopausal women, as well as men, can also suffer from decreased muscle mass and osteoporosis. Prolactinomas may rarely present in childhood or adolescence. In girls, disturbances in menstrual function and galactorrhea may be seen, whereas in boys, delayed pubertal development and hypogonadism are often present. The treatment options are the same as in adult patients.

Useful For: Aiding in evaluation of pituitary tumors, amenorrhea, galactorrhea, infertility, and hypogonadism Monitoring therapy of prolactin-producing tumors

Interpretation: In general, serum prolactin concentrations parallel tumor size in patients with prolactinomas. Macroadenomas (>10 mm in diameter) are typically associated with serum prolactin concentrations above 250 ng/mL, and a concentration above 500 ng/mL is diagnostic of a macroprolactinoma. Moderately increased concentrations of serum prolactin are not a reliable guide for determining whether a prolactin-producing pituitary adenoma is present. After initiation of medical therapy of prolactinomas, prolactin levels should decrease substantially in most patients; in 60% to 80% of patients, normal levels should be reached. Failure to suppress prolactin levels may indicate tumors resistant to the usual central-acting dopamine agonist therapies; however, a subset of patients will show tumor shrinkage despite persistent hyperprolactinemia. Patients who show neither a decrease in prolactin levels nor tumor shrinkage might require additional therapeutic measures. In patients where a discrepancy between pituitary tumor size and prolactin elevation is observed, a test for false-low serum prolactin (hook effect) should be performed by serial dilution. See PLPMA / Prolactin, Pituitary Macroadenoma, Serum. This assay should demonstrate no high-dose hook effect at prolactin concentrations up to approximately 12,500 ng/mL.(1) Multiple medications can cause increased prolactin concentration including estrogens, dopamine receptor blockers (eg, phenothiazines), dopamine antagonists (eg, metoclopramide, domperidone), alpha-methyldopa, cimetidine, opiates, antihypertensive medications, and other antidepressants and antipsychotics. In patients with asymptomatic hyperprolactinemia, assessment for macroprolactin (prolactin bound to immunoglobulin) is suggested. Macroprolactin is detected by differing degrees depending on the immunoassay used to measure prolactin. This assay shows low

reactivity with most forms of macroprolactin. Macroprolactin should be evaluated in asymptomatic hyperprolactinemic subjects or when pituitary imaging studies are not informative. See MCRPL / Macroprolactin, Serum.

Reference Values:

Males
<18 years: not established
> or =18 years: 4.0-15.2 ng/mL

Females:
<18 years: not established
> or =18 years: 4.8-23.3 ng/mL

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

APRI
603183

Prolonged Clot Time Profile Interpretation

Clinical Information: When coagulation screening tests are performed to verify normal function of the coagulation system (eg, preoperative, routine examination), they sometimes indicate an abnormality that may be unexplained (ie, prolonged clotting times). This consultation provides validation of the prolongation and as comprehensive a workup as needed to define the abnormality. Possibilities for a cause of prolongation include: -Artifactual due to high hematocrit (dilution of specimen by anticoagulant if patient hematocrit is 55% or greater) -Factor deficiencies, congenital or acquired -Factor inhibitors eg, factor VIII inhibitors (bleeding disorder) -Lupus anticoagulant (risk for thrombosis or recurrent miscarriage) -Anticoagulant drug effect eg, (including warfarin [Coumadin or Jantoven], oral anti-Xa inhibitors, oral direct thrombin inhibitors), heparin.

Useful For: Interpretation of testing performed as part of a profile to determine the cause of prolongation of prothrombin time or activated partial thromboplastin time Interpretation of testing performed as part of a profile for screening for prolonged clotting times and determining the presence of factor deficiencies or inhibitor (eg, factor-specific, lupus-like, or the presence of heparin)

Interpretation: An interpretive report will be provided when testing is completed, noting a presence or absence of a prolonged bleeding disease state.

Reference Values:

Only orderable as part of a profile. For more information see APROL / Prolonged Clot Time Profile, Plasma.

An interpretive report will be provided.

Clinical References: 1. Clinical and Laboratory Standards Institute. Collection, transport, and processing of blood specimens for testing plasma-based coagulation assays and molecular hemostasis assays; approved guideline-fifth edition. CLSI document H21-A5. CLSI; 2008 2. Kamal AH, Tefferi A, Pruthi RK. How to interpret and pursue an abnormal prothrombin time, activated partial thromboplastin time, and bleeding time in adults. Mayo Clin Proc. 2007;82(7):864-873 3. Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. Humana Press; 2017

APROL
603308

Prolonged Clot Time Profile, Plasma

Clinical Information: When coagulation screening tests are performed to verify normal function of the coagulation system (eg, preoperative, routine examination), they sometimes indicate an abnormality that may be unexplained (ie, prolonged clotting times). This consultation provides validation of the prolongation and as comprehensive a workup as needed to define the abnormality. Possibilities for a cause of prolongation include: -Artifactual due to high hematocrit (dilution of specimen by anticoagulant if patient hematocrit is 55% or greater) -Factor deficiencies, congenital or acquired -Factor inhibitors eg, factor VIII inhibitors (bleeding disorder) -Lupus anticoagulant (risk for thrombosis or recurrent miscarriage) -Anticoagulant drug effect eg, (including warfarin [Coumadin or Jantoven], oral anti-Xa inhibitors, oral direct thrombin inhibitors), heparin.

Useful For: Determining the cause of prolongation of prothrombin time or activated partial thromboplastin time Screening for prolonged clotting times and determining the presence of factor deficiencies or inhibitor (eg, factor-specific, lupus-like, or the presence of heparin)

Interpretation: An interpretive report will be provided when testing is completed, noting a presence or absence of a prolonged bleeding disease state.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Clinical and Laboratory Standards Institute. Collection, transport, and processing of blood specimens for testing plasma-based coagulation assays and molecular hemostasis assays; approved guideline-fifth edition. CLSI document H21-A5. CLSI; 2008 2. Kamal AH, Tefferi A, Pruthi RK. How to interpret and pursue an abnormal prothrombin time, activated partial thromboplastin time, and bleeding time in adults. Mayo Clin Proc. 2007;82(7):864-873 3. Kottke-Marchant K, ed. Laboratory Hematology Practice. Wiley Blackwell Publishing; 2012 4. Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. Humana Press; 2017

PHD2
61683

Prolyl Hydroxylase Domain-2 (PHD2/EGLN1) Gene Sequencing, Whole Blood

Clinical Information: Erythrocytosis (ie, increased red blood cell [RBC] mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, kidney cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases are associated with pheochromocytoma or paraganglioma formation. Hereditary erythrocytosis is caused by variants in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new alterations to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (see Table). The true prevalence of hereditary erythrocytosis-causing alterations is unknown. The hemoglobin genes, HBA1/HBA2 and HBB, are not assayed in this profile. Table. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum EPO JAK2 V617F Acquired Decreased JAK2 exon 12 Acquired Decreased EPOR Dominant Decreased PHD2/EGLN1 Dominant Normal level BPGM Recessive Normal level Beta Globin Dominant

Normal level to increased Alpha Globin Dominant Normal level to increased HIF2A/EPAS1 Dominant Normal level to increased VHL Recessive Normal level to increased The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the PHD2 (EGLN1) gene. Genetic variants resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants in PHD2/EGLN1 and HIF2A/EPAS1 have also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating variants in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known variants have been localized to exon 8 and are heterozygous truncating variants. EPOR variants are associated with decreased to normal EPO levels values (see Table).

Useful For: Assessing PHD2/EGLN1 in the evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased red blood cell (RBC) mass, elevated RBC count, hemoglobin, or hematocrit

Interpretation: An interpretive report will be provided as a part of the HEMP / Hereditary Erythrocytosis Mutations, Whole Blood and will include specimen information, assay information, and whether the specimen was positive for any variants in the gene. If positive, the variant will be correlated with clinical significance, if known.

Reference Values:
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations, Whole Blood.

An interpretive report will be provided.

Clinical References: 1. Patnaik MM, Tefferi A: The complete evaluation of erythrocytosis: congenital and acquired. Leukemia. 2009 May;23(5):834-844. doi: 10.1038/leu.2009.54 2. McMullin MF: The classification and diagnosis of erythrocytosis. Int J Lab Hematol. 2008 Dec;30(6):447-459 3. Percy MJ, Lee FS: Familial erythrocytosis: molecular links to red blood cell control. Haematologica. 2008 Jul;93(7):963-967. doi: 10.3324/haematol.13250 4. Huang LJ, Shen YM, Bulut GB: Advances in understanding the pathogenesis of primary familial and congenital polycythaemia. Br J Haematol. 2010 Mar;148(6):844-852 5. Maran J, Prchal J: Polycythemia and oxygen sensing. Pathologie Biologie. 2004 Jun;52(5):280-284 6. Lee F: Genetic causes of erythrocytosis and the oxygen-sensing pathway. Blood Rev. 2008 Nov;22(6):321-332 7. Merchant SH, Oliveira JL, Hoyer JD, Viswanatha DS: Erythrocytosis. In: His ED, ed. Hematopathology. 2nd ed. Elsevier Saunders; 2012:22-723 8. Zhuang Z, Yang C, Lorenzo F, et al: Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. N Engl J Med. 2012 Sep 6;367(10):922-930 9. Ladroue C, Carcenac R, Leporrier M, et al: PHD2 mutation and congenital erythrocytosis with paraganglioma. N Engl J Med. 2008 Dec 18;359(25):2685-2692 10. Lorenzo FR, Yang C, Ng Tang Fui M, et al: A novel EPAS1/HIF2A germline mutation in congenital polycythemia with paraganglioma. J Mol Med. 2013 Apr;91(4):507-512 11. Tarade D, Robinson CM, Lee JE, Ohh M: HIF-2alpha-pVHL complex reveals broad genotype-phenotype correlations in HIF-2aalpha-driven disease. Nat Commun. 2018 Aug 22;9(1):3359 12. Oliveira JL: Algorithmic evaluation of hereditary erythrocytosis: Pathways and caveats. Int J Lab Hematol. 2019 May;41 Suppl 1:89-94. doi: 10.1111/ijlh.13019

FPHEG
90101

Promethazine (Phenergan)

Reference Values:
Reference Range: < 150 ng/mL

FIBDD
57459

PROMETHEUS IBD sgi Diagnostic

Clinical Information: Combines serologic, genetic, and inflammation markers to help differentiate Inflammatory Bowel Disease (IBD) vs non-IBD and ulcerative colitis (UC) vs Crohn's disease (CD). The PROMETHEUS IBD sgi Diagnostic is the 4th-generation IBD diagnostic test and the first and only test to combine serologic, genetic, and inflammation markers in the proprietary Smart Diagnostic Algorithm for added diagnostic clarity. This test aids healthcare providers in differentiating IBD vs non-IBD and CD vs UC in one comprehensive blood test. This assay includes 9 serological markers ASCA IgA, ASCA IgG and proprietary markers anti-Fla-X, anti-A4-Fla2, anti-CBir1, anti-OMPC, and DNAse-sensitive pANCA that helps identify patients with IBD and utilizes Smart Diagnostic Algorithm Technology to improve the predictive accuracy. Genetic susceptibility influences immune responses, and this assay includes evaluation of ATG16L1, STAT3, NKX2-3, and ECM1. Inflammatory markers include VEGF, ICAM-1, VCAM-1, CRP, SAA. While most other labs only offer assay values, PROMETHEUS IBD sgi Diagnostic provides added clarity in diagnosing IBD, UC, and CD.

Reference Values:
Testing is complete. Final report has been sent to the referring laboratory.

FPLAC
91783

PROMETHEUS LactoTYPE

Reference Values:
A final report will be attached in MayoAccess.

PFN
80295

Propafenone, Serum

Clinical Information: Propafenone (Rythmol) is a class 1C cardiac antiarrhythmic used to treat ventricular arrhythmias (ventricular tachycardia, supraventricular tachycardia, and ventricular premature contractions). Propafenone undergoes extensive first metabolism (half-life is approximately 2-10 hours). Its clinical efficacy is maintained through the formation of a metabolite (5-hydroxypropafenone) that is more pharmacologically active than the parent drug and has a longer half-life. Specimens should only be collected after patient has been receiving propafenone orally for at least 3 days. Trough concentrations should be collected just before administration of the next dose. The therapeutic concentration is 0.5 to 2.0 mcg/mL; concentrations less than 0.5 mcg/mL likely indicate inadequate therapy, and propafenone above 2.0 mcg/mL indicates excessive therapy. Adverse side effects are seen in the central nervous system, skin, and gastrointestinal tract.

Useful For: Monitoring propafenone therapy Assessing potential propafenone toxicity

Interpretation: The therapeutic concentration is 0.5 to 2.0 mcg/mL; concentrations below 0.5 mcg/mL likely indicate inadequate therapy and propafenone above 2.0 mcg/mL indicates excessive therapy.

Reference Values:
Trough Value
0.5-2.0 mcg/mL: Therapeutic concentration

>2.0 mcg/mL: Toxic concentration

Clinical References: 1. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453 2. Josephson ME, Buxton AE, Marchlinski FE. The tachyarrhythmias: tachycardias. In: Wilson JD, Braunwald E, Isselbacher KJ, et al, eds. Harrison's Principles of Internal Medicine. 12th ed. McGraw-Hill Book Company; 1991:915 3. Valdes R Jr, Jortani SA, Gheorghiade M. Standards of laboratory practice: cardiac drug monitoring. National Academy of Clinical Biochemistry. Clin Chem. 1998;44(5):1096-1099 4. Joseph SP, Holt DW. Electrophysiological properties of mexiletine assessed with respect to plasma concentrations. Eur J Cardiol. 1980;11(2):115-121

FPROS
75902

Prostaglandin D2 (PG D2), Random Urine

Clinical Information: Prostaglandins are fatty acids derived from arachidonic acid metabolism. They are closely related to the Thromboxanes and Leukotrienes. Prostaglandin D2 is derived mainly from Prostaglandin H2 and is metabolized to Dihydroketo Prostaglandin D2. Prostaglandin D2 is excreted directly into the urine. The sites of highest Prostaglandin D2 activity are the brain, spinal cord, intestines, and stomach. Prostaglandin D2 is the major Prostaglandin produced by uterine tissue. Prostaglandin D2 is a potent bronchoconstrictor, neuromodulator, and anti-antithrombin agent. It also stimulates the secretion of Pancreatic Glucagon. Prostaglandin D2 has been found to have an anti-metastatic effect on many malignant tumor cells. Prostaglandin D2 production and circulating levels are drastically suppressed by aspirin and indomethacin.

Reference Values:
Up to 175 ng/g Creatinine

FPDPG
75900

Prostaglandin D2 (PGD2)

Clinical Information: Prostaglandins are fatty acids derived from arachidonic acid metabolism. They are closely related to the Thromboxanes and Leukotrienes. Prostaglandin D2 is derived mainly from Prostaglandin H2, and is metabolized to Dihydroketo Prostaglandin D2. Prostaglandin D2 is excreted directly into the urine. The sites of highest Prostaglandin D2 activity are the brain, spinal cord, intestines, and stomach. Prostaglandin D2 is the major Prostaglandin produced by uterine tissue. Prostaglandin D2 is a potent bronchoconstrictor, neuromodulator, and anti-antithrombin agent. It also stimulates the secretion of Pancreatic Glucagon. Prostaglandin D2 has been found to have an anti-metastatic effect on many malignant tumor cells. Prostaglandin D2 production and circulating levels are drastically suppressed by aspirin and Indomethacin.

Reference Values:
35 - 115 pg/mL
No pediatric reference ranges available for this test.

PHI11
113000

Prostate Health Index Reflex, Serum

Clinical Information: Prostate-specific antigen (PSA) is a glycoprotein produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. In conditions of increased glandular size and tissue damage, PSA is released into circulation. Measurement of serum PSA is useful for determining the extent of prostate cancer and assessing the response to prostate cancer treatment. PSA is also used as a screening tool for prostate cancer detection,

although its use in screening has become controversial in recent years. While an elevated serum PSA is associated with prostate cancer, a number of benign conditions, such as benign prostatic hyperplasia and prostatitis might lead to elevated serum PSA concentrations. As a consequence, PSA lacks specificity for prostate cancer detection. Several PSA isoforms have been identified that can further increase the specificity of PSA for prostate cancer. In particular, the [-2] form of proPSA (p2PSA) shows improved performance over either total or free PSA for prostate cancer detection on biopsy. The prostate health index (phi) is a formula that combines all 3 PSA forms (total PSA, free PSA, and p2PSA) into a single score. phi is calculated using the following formula: (p2PSA/free PSA) x square root of PSA. In a multicenter study that compared the performance of total PSA, free PSA, p2PSA, and phi in men undergoing prostate biopsy due to a serum PSA concentration between 4.0 and 10.0 ng/mL, phi was the best predictor of any prostate cancer, high-grade cancer, and clinically significant cancer. At 95% clinical sensitivity, the clinical specificity of phi was 16.0%, compared to 8.4% for free PSA and 6.5% for total PSA.

Useful For: As an aid in distinguishing prostate cancer from benign prostatic conditions in men aged 50 years and older with total PSA between 4.0 and 10.0 ng/mL and digital rectal examination findings that are not suspicious for cancer

Interpretation: The prostate health index (phi) may be used to determine the probability of prostate cancer on biopsy in men aged 50 years and older with total prostate-specific antigen (PSA) in the 4.0 to 10.0 ng/mL range. Low phi scores are associated with a lower probability of finding prostate cancer on biopsy, and higher phi scores are associated with an increased probability of finding prostate cancer on biopsy. The choice of an appropriate phi score to be used in guiding clinical decision-making may vary for each patient and may depend on other clinical factors or family history. The table below indicates the probability of finding prostate cancer on biopsy when total PSA is in the range of 4.0 to 10.0 ng/mL and may be used as guidance for interpreting the phi score. phi range Probability of cancer 95% Confidence interval 0-26.9 9.8% 5.2%-15.4% 27.0-35.9 16.8% 11.3%-22.2% 36.0-54.9 33.3% 26.8%-39.9% 55.0+ 50.1% 39.8%-61.0%

Reference Values:

Females: Not applicable PROSTATE-SPECIFIC ANTIGEN (PSA) MALES: Age	**Reference range**
	< or =2.0 ng/mL
40-49 years	< or =2.5 ng/mL
50-59 years	< or =3.5 ng/mL
60-69 years	< or =4.5 ng/mL
70-79 years	< or =6.5 ng/mL
> or =80 years	< or =7.2 ng/mL
PERCENT FREE PSA MALES: When PSA is in the range of 4.0-10.0 ng/mL % Free PSA	Probability of cancer
< or =10%	56%
11-15%	28%
16-20%	20%
21-25%	16%

>25%	8%
PROSTATE HEALTH INDEX (phi) MALES: When PSA is in the range of 4.0-10.0 ng/mL phi range	Probability of cancer
0-26.9	9.8%
27.0-35.9	16.8%
36.0-54.9	33.3%
> or =55.0	50.1%

Clinical References: 1. Catalona WJ, Partin AW, Sanda MG, et al. A multicenter study of [-2]pro-prostate-specific antigen combined with prostate-specific antigen and free prostate-specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/mL prostate-specific antigen range. J Urol. 2011;185(5):1650-1655 2. Pecoraro V, Roli L, Plebani M, Trenti T. Clinical utility of the (-2)proPSA and evaluation of the evidence: a systematic review. Clin Chem Lab Med. 2016;54(7):1123-1132. doi:10.1515/cclm-2015-0876 3. Loeb S, Catalona WJ: The Prostate Health Index: a new test for the detection of prostate cancer. Ther Adv Urol. 2014 Apr;6(2):74-77. doi: 10.1177/1756287213513488

PSAIM
70543

Prostate Specific Antigen (PSA) Immunostain, Technical Component Only

Clinical Information: Prostate specific antigen is present within the cytoplasm of glandular epithelium in normal prostate, as well as in prostate cancer. It is useful diagnostically for identification of adenocarcinoma of the prostate in metastatic sites and for differentiating prostatic adenocarcinoma from urothelial carcinoma.

Useful For: Marker of glandular epithelium in normal and neoplastic prostate

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Aihara M, Lebovitz RM, Wheeler TM, et al. Prostate specific antigen and gleason grade: an immunohistochemical study of prostate cancer. J Urol. 1004;151(6):1558-1564 2. Bostwick DG. Prostate-specific antigen. Current role in diagnostic pathology of prostate cancer. Am J Clin Pathol. 1994;102(4 Suppl 1):S31-S37 3. Hameed O, Humphrey PA. Immunohistochemistry in diagnostic surgical pathology of the prostate. Semin Diagn Pathol. 2005;22(1):88-104 4. Hammerich KH, Ayala GE, Wheeler TM. Application of immunohistochemistry to the genitourinary system (prostate, urinary bladder, testis, and kidney). Arch Pathol Lab Med. 2008;132:432-440 5. Varma M, Berney DM, Rhodes A. Technical variations in prostatic immunohistochemistry: need for standardisation and stringent quality assurance in PSA and PSAP immunostaining. J Clin Pathol. 2004;57:687-690 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An Introduction to the Performance of Immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PTRIP
610456

Prostate Triple (P63/KRT/P504S), Technical Component Only

Clinical Information: The prostate triple assay consists of 3 antibodies P63, HMW KRT (34betaE12), and P504S. This multiplex is used in the diagnosis of high-grade prostatic intraepithelial neoplasia (PIN) and prostate cancer. P63 (nuclear) and HMW KRT (cytoplasmic) are expressed in normal myoepithelial cells that surround the prostatic epithelial cells (detected with 3,3'-diaminobenzidine chromogen). This myoepithelial layer is lost in carcinoma. P504S (cytoplasmic) is abnormally expressed in high-grade PIN and prostate cancer epithelial cells (detected with fast red chromogen).

Useful For: Aiding in the identification of high-grade prostatic intraepithelial neoplasia and prostate cancer

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Rathod SG, Jaiswal DG, Bindu RS. Diagnostic utility of triple antibody (AMACR, HMWCK and P63) stain in prostate neoplasm. J Family Med Prim Care. 2019; 8(8):2651-2655. doi:10.4103/jfmpc.jfmpc_432_19 2. Ng VW, Koh M, Tan SY, Tan PH. Is triple immunostaining with 34betaE12, p63, and racemase in prostate cancer advantageous? A tissue microarray study. Am J Clin Pathol. 2007;127(2):248-253. doi:10.1309/JCFW75KGFWQUHVQD 3. Jiang Z, Li C, Fischer A, et al. Using an AMACR (P504S)/34betaE12/p63 cocktail for the detection of small focal prostate carcinoma in needle biopsy specimens. Am J Clin Pathol. 2005;123(2):231-236. doi:10.1309/1g1nk9dbgfnb792l 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PSA
9284

Prostate-Specific Antigen (PSA) Diagnostic, Serum

Clinical Information: Prostate-specific antigen (PSA) is a glycoprotein produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. Increases in glandular size and tissue damage caused by benign prostatic hypertrophy, prostatitis, or prostate cancer may increase circulating PSA levels. In patients with previously diagnosed prostate cancer, PSA testing is advocated as an early indicator of tumor recurrence and as an indicator of response to therapy. The role of PSA in early detection of prostate cancer is controversial. The American Cancer Society recommends annual examination with digital rectal examination and serum PSA beginning at age 50 and for men with a life expectancy of at least 10 years after detection of prostate cancer. For men in high-risk groups, such as African Americans or men with a first-degree relative diagnosed at a younger age, testing should begin at a younger age. It is generally recommended that information be provided to patients about the benefits and limitations of testing and treatment so they can make informed decisions.

Useful For: As an aid in the detection of prostate cancer when used in conjunction with a digital rectal exam in men 50 years and older To aid in the prognosis and management of individuals diagnosed with prostate cancer

Interpretation: Prostate-specific antigen (PSA) values are reported with the 95th percentile limits by decade of age. These reference limits include men with benign prostatic hyperplasia. They exclude all cases with proven cancer. PSA values exceeding the age-specific limits are suspicious for prostate disease, but additional testing, such as prostate biopsy, is needed to diagnose prostate pathology. The minimal reporting value is 0.1 ng/mL. Values above 0.2 ng/mL are considered evidence of biochemical

recurrence of cancer in men after prostatectomy.

Reference Values:

Males: Age (Years)	PSA Upper Limit (ng/mL)
	< or =2.0
40-49	< or =2.5
50-59	< or =3.5
60-69	< or =4.5
70-79	< or =6.5
> or =80	< or =7.2

Clinical References:

SPSA
82023

Prostate-Specific Antigen (PSA) Screen, Serum

Clinical Information: Prostate-specific antigen (PSA) is a glycoprotein produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. Increases in glandular size and tissue damage caused by benign prostatic hypertrophy, prostatitis, or prostate cancer may increase circulating PSA levels. In patients with previously diagnosed prostate cancer, PSA testing is advocated as an early indicator of tumor recurrence and as an indicator of response to therapy. The role of PSA in early detection of prostate cancer is controversial. The American Cancer Society recommends annual examination with digital rectal examination and serum PSA beginning at age 50 and for men with a life expectancy of at least 10 years after detection of prostate cancer. For men in high-risk groups, such as African Americans or men with a first-degree relative diagnosed at a younger age, testing should begin at a younger age. It is generally recommended that information be provided to patients about the benefits and limitations of testing and treatment so they can make informed decisions.

Useful For: As a screening aid in the detection of prostate cancer when used in conjunction with a digital rectal exam in men 50 years or older Screening to aid in the prognosis and management of individuals diagnosed with prostate cancer

Interpretation: Prostate-specific antigen (PSA) values are reported with the 95th percentile limits by decade of age. These reference limits include men with benign prostatic hyperplasia. They exclude all cases with proven cancer. PSA values exceeding the age-specific limits are suspicious for prostate disease, but additional testing, such as prostate biopsy, is needed to diagnose prostate pathology. The minimal reporting value is 0.1 ng/mL. Values above 0.2 ng/mL are considered evidence of biochemical recurrence of cancer in men after prostatectomy.

Reference Values:

Males: Age (years)	PSA upper limit (ng/mL)
	< or =2.0
40-49	< or =2.5
50-59	< or =3.5
60-69	< or =4.5
70-79	< or =6.5
> or =80	< or =7.2

Clinical References: 1. Grimsey P, Frey N, Bendig G, et al. Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. J Pharmacokinet Pharmacodyn. 2017 Sept;2(4):247-256. doi:10.4155/ipk-2017-0013 2. Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA. 1993;270(7):860-864 3. Saint Paul LP, Debruyne D, Bernard D, Mock DM, Defer GL. Pharmacokinetics and pharmacodynamics of MD1003 (high-dose biotin) in the treatment of progressive multiple sclerosis. Expert Opin Drug Metab Toxicol. 2016;12(3):324-344. doi:10.1517/17425255.2016.1136288 4. Smith RA, Cokkinides V, von Eschenbach A, et al. American Cancer Society guidelines for the early detection of cancer. CA Cancer J Clin. 2002;52(1):8-22. doi:10.3322/canjclin.52.1.8 5. Barry MJ, Albertsen PC, Bagshaw MA, et al. Outcomes for men with clinically nonmetastatic prostate carcinoma managed with radical prostatectomy, external beam radiotherapy, or expectant management: a retrospective analysis. Cancer. 2001;91(12):2302-2314. doi:10.1002/1097-0142(20010615)91:12<2302::aid-cncr1262>3.3.co;2-g 6. Blute ML, Bergstralh EJ, Iocca A, Scherer B, Zincke H. Use of Gleason score, prostate specific antigen, seminal vesicle and margin status to predict biochemical failure after radical prostatectomy. J Urol. 2001;165(1):119-125. doi:10.1097/00005392-200101000-00030 7. Netto GJ, Epstein JI. Immunohistology of the prostate. In: Dabbs DJ, ed. Diagnostic Immunohistochemistry. 5th ed. Elsevier; 2019:588-623 8. Ilic D, Djulbegovic M, Jung JH, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. BMJ. 2018;362:k3519. doi:10.1136/bmj.k3519

PSAU
64061

Prostate-Specific Antigen (PSA) Ultrasensitive, Serum

Clinical Information: Prostate-specific antigen (PSA) is the most widely used method to detect prostate cancer recurrence after radical prostatectomy (RP). Approximately 20% to 35% of patients develop a rising PSA following RP for clinically localized prostate cancer. Biochemical recurrence (BCR) is defined as an increase in PSA after curative therapy without clinical or radiological evidence of disease. The median time to BCR could vary between 2 to 3 years. A standard PSA cutpoint to indicate BCR has yet to be established. For example, the American Urological Association and the American Society for Radiation Oncology defined BCR after surgery as initial and confirmatory PSA concentrations of 0.2 ng/mL or greater. However, a BCR definition of 0.4 ng/mL PSA has also been proposed. Assays that measure PSA to concentrations below 0.1 ng/mL are denoted ultrasensitive PSA (USPSA). The use of USPSA cutpoints below currently recommended PSA thresholds may be helpful in identifying cases of early biochemical recurrence and for selecting patients with adverse clinicopathologic risk factors for secondary therapy. However, some authors believe that USPSA assays offers minimal advantages and could lead to increased anxiety in patients who have clinically meaningless rises of PSA and might lead to overtreatment.

Useful For: As an aid in the detection of prostate cancer when used in conjunction with a digital rectal exam in men ages 50 years and older To aid in the prognosis and management of individuals diagnosed with prostate cancer Monitoring disease after radical prostatectomy This test should not be used for initial prostate cancer screening.

Interpretation: An undetectable (<0.01 ng/mL) ultrasensitive prostate-specific antigen (USPSA) concentration after radical prostatectomy is reassuring and may aid in postoperative risk stratification of patients. A detectable USPSA concentration (> or =0.01 ng/mL) after radical prostatectomy (RP) does not necessarily translate into disease progression or recurrence. Interpretation of a detectable USPSA needs to be made in conjunction with other clinicopathologic risk factors. The cutpoint for interpretation of USPSA assays remains controversial and has ranged from 0.01 to 0.05 ng/mL. For example, in a study that included 754 men after RP, a cutpoint of 0.01 ng/mL was an independent predictor of biochemical recurrence (BCR). BCR-free survival at 5 years was 92.4% for patients with an USPSA post-RP of less than 0.01 ng/mL and 56.8% for patients with an USPSA post-RP of 0.01 ng/mL or higher.(1) In the same study a cutoff of 0.03 ng/ml also predicted BCR independent of clinicopathological factors and BCR-free survival at 5 yrs was 90.8% for patients with an USPSA post-RP of less than 0.03 ng/mL and 26.9% for patients with a PSA post-RP of greater or equal to 0.03 ng/mL.(1)

Reference Values:

Males: Age (years)	PSA upper limit (ng/mL)
	< or =2.0
40-49	< or =2.5
50-59	< or =3.5
60-69	< or =4.5
70-79	< or =6.5
> or =80	< or =7.2

Clinical References: 1. Sokoll LJ, Zhang Z, Chan DW, et al. Do ultrasensitive prostate specific antigen measurements have a role in predicting long-term biochemical recurrence-free survival in men after radical prostatectomy? J Urol. 2016;195(2):330-336. doi:10.1016/j.juro.2015.08.080 2. Saint Paul LP, Debruyne D, Bernard D, Mock DM, Defer GL. Pharmacokinetics and pharmacodynamics of MD1003 (high-dose biotin) in the treatment of progressive multiple sclerosis. Expert Opin Drug Metab Toxicol. 2016;12(3):324-344. doi:10.1517/17425255.2016.1136288 3. Grimsey P, Frey N, Bendig G, et al. Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. J Pharmacokinet Pharmacodyn. 2017 Sept;2(4):247-256. doi:10.4155/ipk-2017-0013 4. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO guideline. J Urol. 2013;190(2):441-449. doi:10.1016/j.juro.2013.05.032 5. Mir MC, Li J, Klink JC, Kattan Mw, Klein EA, Stephenson A. Optimal definition of biochemical recurrence after radical prostatectomy depends on pathologic risk factors: Identifying candidates for early salvage therapy. Eur Urol. 2014;66(2):204-210. doi:10.1016/j.eururo.2013.08.022

PSAFT 81944 Prostate-Specific Antigen (PSA), Total and Free, Serum

Clinical Information: Prostate-specific antigen (PSA) is a glycoprotein produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. Increases in glandular size and tissue damage caused by benign prostatic hypertrophy, prostatitis, or prostate cancer may increase circulating PSA levels. PSA exists in serum in multiple forms: complexed to alpha-1-anti-chymotrypsin (PSA-ACT complex), unbound (free PSA), and enveloped by alpha-2-macroglobulin (not detected by immunoassays). Higher total PSA levels and lower percentages of free PSA are associated with higher risks of prostate cancer. Most prostate cancers are slow growing, so the utility of prostate cancer screening is marginal in most men with a life expectancy of less than 10 years.

Useful For: As an aid in distinguishing prostate cancer from benign prostatic conditions in men aged 50 years and older with total PSA between 4.0 and 10.0 ng/mL with digital rectal examination findings that are not suspicious for cancer

Interpretation: When total prostate-specific antigen (PSA) concentration is below 2.0 ng/mL, the probability of prostate cancer in asymptomatic men is low, further testing and free PSA may provide little additional information. When total PSA concentration is above 10.0 ng/mL, the probability of cancer is high and prostate biopsy is generally recommended. The total PSA range of 4.0 to 10.0 ng/mL has been described as a diagnostic "gray zone," in which the free PSA:total PSA ratio helps to determine the relative risk of prostate cancer (see table). Therefore, some urologists recommend using the free PSA:total ratio to help select which men should undergo biopsy. However, even a negative result of prostate biopsy does not rule-out prostate cancer. Up to 20% of men with negative biopsy results have subsequently been found to have cancer. Based on free PSA:total PSA ratio: the percent probability of finding prostate cancer on a needle biopsy by age in years: Free PSA:total PSA ratio 50-59 years 60-69 years 70 years and older < or =0.10 49% 58% 65% 0.11-0.18 27% 34% 41% 0.19-0.25 18% 24% 30% >0.25 9% 12% 16%

Clinical References: 1. Saint Paul LP, Debruyne D, Bernard D, Mock DM, Defer GL. Pharmacokinetics and pharmacodynamics of MD1003 (high-dose biotin) in the treatment of progressive multiple sclerosis. Expert Opin Drug Metab Toxicol. 2016;12(3):327-344. doi:10.1517/17425255.2016.1136288 2. Grimsey P, Frey N, Bendig G, et al. Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. Int J Pharmacokinet. 2017 Sept;2(4):247-256. doi:10.4155/ipk-2017-00131. 3. Catalona WJ, Smith DS, Wolfert RL, et al. Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening. JAMA. Oct:274(15);214-1220 4. Oesterling JE, Jacobsen SJ, Klee GG, et al. Free, complexed and total serum prostate specific antigen: the establishment of appropriate reference ranges for their concentrations and ratios. J Urol. 1995 Sep;154(3):1090-1095. doi:10.1016/s0022-5347(01)66984-2 5. Duffy MJ. Biomarkers for prostate cancer: prostate-specific antigen and beyond. Clin Chem Lab Med. 2020 Feb 25;58(3):326-339. doi: 10.1515/cclm-2019-0693 6. Catalona WJ: Prostate cancer screening. Med Clin North Am. 2018 Mar;102(2):199-214. doi:10.1016/j.mcna.2017.11.001 7. Catalona WJ, Smith DS, Wolfert RL, et al. Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening. JAMA. 1995:274(15);214-1220 8. Ilic D, Djulbegovic M, Jung JH, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. BMJ. 2018;362:k3519. doi:10.1136/bmj.k3519

PACPI 70531 Prostatic Acid Phosphatase (PACP) Immunostain, Technical Component Only

Clinical Information: Prostatic acid phosphatase (PACP) is a cytoplasmic enzyme produced in normal prostatic epithelium and prostatic adenocarcinoma. PACP is a useful adjunct to the immunostain for prostate-specific antigen; if 1 of these 2 markers is immunoreactive, a tumor of prostatic origin is likely. Bladder epithelium and certain neuroendocrine tumors such as rectal carcinoid may be weakly

immunoreactive.

Useful For: Identification of normal prostatic epithelium and prostatic adenocarcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1.Hameed O, Humphrey PA. Immunohistochemistry in diagnostic surgical pathology of the prostate. Semin Diagn Pathol. 2005;22(1):88-104 2. Hammerich KH, Ayala GE, Wheeler TM. Application of immunohistochemistry to the genitourinary system (prostate, urinary bladder, testis, and kidney). Arch Pathol Lab Med. 2008;132:432-440 3. Varma M, Berney DM, Rhodes A. Technical variations in prostatic immunohistochemistry: Need for standardisation and stringent quality assurance in PSA and PSAP immunostaining. J Clin Pathol. 2004;57:687-690 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PACP
8019

Prostatic Acid Phosphatase, Serum

Clinical Information: Prostatic acid phosphatase (PAP), a glycoprotein synthesized by the prostate gland, is a member of a diverse group of isoenzymes that are capable of hydrolyzing phosphate esters in acidic medium. They are classified based on their electrophoretic mobilities. PAP was a major tumor marker for prostate cancer for more than 50 years.(1) However, PAP is no longer used to screen for or stage prostate cancer. In most instances, serum prostate specific antigen (PSA) is used instead. PAP usefulness is now limited to niche applications. Pre-treatment PAP measurement may add unique, clinically useful prognostic information for predicting recurrence in men who are undergoing radical prostatectomy for clinically localized prostate cancer. PAP also may be useful for following the progression of disease response to therapy in men treated by androgen ablation. However, for both applications, PSA provides more information and also should be utilized.

Useful For: Aiding in predicting recurrence after radical prostatectomy for clinically localized prostate cancer Following response to androgen ablation therapy, when used in conjunction with prostate-specific antigen

Interpretation: Prostatic acid phosphatase (PAP) levels above the reference range may indicate prostate cancer but can be due to many other factors, see Cautions. A rise in PAP levels in patients with known prostate cancer can indicate tumor progression or recurrence. However, there is considerable intra-subject biological variability, limiting the usefulness of this test.

Reference Values:
< or =2.1 ng/mL

Clinical References: 1. Moul JW, Connelly RR, Perahia B, McLeod DG. The contemporary value of pretreatment prostatic acid phosphatase to predict pathological stage and recurrence in radical prostatectomy cases. J Urol. 1998;159:935-940 2. Beaver TR, Schultz AL, Fink LM, et al. Discordance between concentration of prostate-specific antigen and acid phosphatase in serum of patients with adenocarcinoma of the prostate. Clin Chem. 1988;34:1524 3. Velonas VM, Woo HH, dos Remedios CG, Assinder SJ. Current status of biomarkers for prostate cancer. Int J Mol Sci. 2013;14(6):11034-60. doi:10.3390/ijms140611034 4. Kong HY, Byun J. Emerging roles of human prostatic acid phosphatase. Biomol Ther (Seoul). 2013;21(1):10-20. doi: 10.4062/biomolther.2012.095

CFX
9339

Protein C Activity, Plasma

Clinical Information: Physiology: Protein C is a vitamin K-dependent anticoagulant proenzyme. It is synthesized in the liver and circulates in the plasma. The biological half-life of plasma protein C is approximately 6 to 10 hours, similar to the relatively short half-life of coagulation factor VII. Protein C is activated by thrombin, in the presence of an endothelial cell cofactor (thrombomodulin), to form the active enzyme activated protein C (APC). APC functions as an anticoagulant by proteolytically inactivating the activated forms of coagulation factors V and VIII (factors Va and VIIIa). APC also enhances fibrinolysis by inactivating plasminogen activator inhibitor. Expression of the anticoagulant activity of APC is enhanced by a cofactor, protein S, another vitamin K-dependent plasma protein. Pathophysiology: Congenital homozygous protein C deficiency results in a severe thrombotic diathesis, evident in the neonatal period and resembling purpura fulminans. Congenital heterozygous protein C deficiency may predispose to thrombotic events, primarily venous thromboembolism; arterial thrombosis (stroke, myocardial infarction, etc.) may occur. Some individuals with hereditary heterozygous protein C deficiency may have no personal or family history of thrombosis and may or may not be at increased risk. Congenital heterozygous protein C may predispose to development of coumarin-associated skin necrosis. Skin necrosis has occurred during the initiation of oral anticoagulant therapy. Two types of hereditary heterozygous protein C deficiency are recognized: -Type I (concordantly decreased protein C function and antigen) -Type II (decreased protein C function with normal antigen level) Acquired deficiencies of protein C may occur in association with: -Vitamin K deficiency -Oral anticoagulation with coumarin compounds -Liver disease -Intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (ICF/DIC) The clinical hemostatic significance of acquired protein C deficiency is uncertain. Assay of protein C functional activity is recommended for the initial laboratory evaluation of patients suspected of having congenital protein C deficiency (personal or family history of thrombotic diathesis), rather than assay of protein C antigen.

Useful For: As an initial test for evaluating patients suspected of having congenital protein C deficiency, including those with personal or family histories of thrombotic events Detecting and confirming congenital type I and type II protein C deficiencies Detecting and confirming congenital homozygous protein C deficiency Identifying decreased functional protein C of acquired origin (eg, due to oral anticoagulant effect, vitamin K deficiency, liver disease, intravascular coagulation and fibrinolysis/disseminated intravascular coagulation)

Interpretation:

Reference Values:
70-150%

Clinical References: 1. Mannucci PM, Owen WG: Basic and clinical aspects of proteins C and S. In: Bloom AL, Thomas DP, eds. Haemostasis and Thrombosis. 2nd ed. Churchill Livingstone; 1987:452-464 2. Marlar RA, Mastovich S. Hereditary protein C deficiency: a review of the genetics, clinical presentation, diagnosis and treatment. Blood Coagul Fibrinolysis. 1990;1(3):319-330 3. Marlar RA, Montgomery RR, Broekmans AW. Diagnosis and treatment of homozygous protein C deficiency. Report of the Working Party on Homozygous Protein C Deficiency of the Subcommittee on Protein C and Protein S, International Committee on Thrombosis and Haemostasis. J Pediatr. 1989;114(4 Pt 1):528-534 4. Miletich J, Sherman L, Broze G Jr. Absence of thrombosis in subjects with heterozygous protein C deficiency. N Engl J Med. 1987;317(16):991-996 5. Pabinger I, Allaart CF, Hermans J, Briet E, Bertina RM. Hereditary protein C-deficiency: laboratory values in transmitters and guidelines for the diagnostic procedure. Report on a study of the SSC Subcommittee on Protein C and Protein S. Protein C Transmitter Study Group. Thromb Haemost. 1992;68(4):470-474 6. Cooper PC, Pavlova A, Moore GA, Hickey KP, Marlar RA. Recommendations for clinical laboratory testing for protein C deficiency, for the subcommittee on plasma coagulation inhibitors of the ISTH. J Thromb Haemost. 2020;18(2):271-277 7. Baron JM, Johnson SM, Ledford-Kraemer MR, Hayward CP, Meijer P, Van Cott EM. Protein C assay performance: an analysis of North American specialized coagulation laboratory association proficiency

testing results. Am J Clin Pathol. 2012;137(6):909-15. doi:10.1309/AJCP8MWU4QSTCLPU 8. Roshan TM, Stein N, Jiang XY. Comparison of clot-based and chromogenic assay for the determination of protein c activity. Blood Coagul Fibrinolysis. 2019;30(4):156-160. doi:10.1097/MBC.0000000000000806

PCAG
9127

Protein C Antigen, Plasma

Clinical Information: Protein C is a vitamin K-dependent anticoagulant proenzyme. It is synthesized in the liver and circulates in the plasma. The biological half-life of plasma protein C is approximately 6 to 10 hours, similar to the relatively short half-life of coagulation factor VII. Protein C is activated by thrombin, in the presence of an endothelial cell cofactor (thrombomodulin), to form the active enzyme, activated protein C (APC). APC functions as an anticoagulant by proteolytically inactivating the activated forms of coagulation factors V and VIII (factors Va and VIIIa). APC also enhances fibrinolysis by inactivating plasminogen activator inhibitor type 1 (PAI-1). Expression of the anticoagulant activity of APC is enhanced by a cofactor, protein S, another vitamin K-dependent plasma protein. Congenital homozygous protein C deficiency results in a severe thrombotic diathesis, evident in the neonatal period and resembling purpura fulminans. Congenital heterozygous protein C deficiency may predispose the patient to thrombotic events, primarily venous thromboembolism. Arterial thrombosis (stroke, myocardial infarction, etc) may occur. Some individuals with hereditary heterozygous protein C deficiency may have no personal or family history of thrombosis and may or may not be at increased risk. The 2 types of hereditary heterozygous protein C deficiencies that are recognized are: -Type I (concordantly decreased protein C function and antigen) -Type II (decreased protein C function with normal antigen) Acquired deficiency of protein C may occur in association with: -Vitamin K deficiency -Oral anticoagulation with Coumadin (warfarin) compounds -Liver disease -Intravascular coagulation and fibrinolysis/disseminated intravascular coagulation

Useful For: Differentiating congenital type I protein C deficiency from type II deficiency Evaluating the significance of decreased functional protein C, especially when decreased protein C activity might be congenital rather than acquired (eg, due to oral anticoagulant effect, vitamin K deficiency, liver disease, or intravascular coagulation and fibrinolysis/disseminated intravascular coagulation) This test is not useful for predicting a thrombotic event.

Interpretation: Values less than 70% to 75% may represent a congenital deficiency state, if acquired deficiencies can be excluded. Protein C antigen and activities generally are undetectable in individuals with severe, homozygous protein C deficiency. Acquired protein C deficiency is of uncertain clinical hemostatic significance. The clinical significance of increased protein C is unknown.

Reference Values:
Adults: 72%-160%
Normal, full-term newborn infants or healthy premature infants may have decreased levels of protein C antigen (15%-50%), which may not reach adult levels until later in childhood or early adolescence.*
*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing.

Clinical References: 1. Mannucci PM, Owen WG. Basic and clinical aspects of proteins C and S. In: Bloom AL, Thomas DP, eds. Haemostasis and Thrombosis. 2nd ed. Edinburgh, Churchill Livingstone; 1987:452-464 2. Marlar RA, Mastovich S. Hereditary protein C deficiency: a review of the genetics, clinical presentation, diagnosis and treatment. Blood Coagul Fibrinolysis. 1990;1(3):319-330 3. Marlar RA, Montgomery RR, Broekmans AW. Diagnosis and treatment of homozygous protein C deficiency. Report of the Working Party on Homozygous Protein C Deficiency of the Subcommittee on Protein C and Protein S, International Committee on Thrombosis and Haemeostasis. J Pediatr. 1989;114(4 Pt 1):528-534 4. Miletrich J, Sherman L, Broze G Jr. Absence of thrombosis in subjects

with heterozygous protein C deficiency. N Engl J Med. 1987;317(16):991-996 5. Cooper PC, Pavlova A, Moore GW, Hickey KP, Marlar RA. Recommendations for clinical laboratory testing for protein C deficiency, for the subcommittee on plasma coagulation inhibitors of the ISTH. J Thromb Haemost. 2020;18(2):271-277

GNPRC 619173 Protein C Deficiency, PROC Gene, Next-Generation Sequencing, Varies

Clinical Information:

Useful For: Evaluating protein C deficiency in patients with a personal or family history suggestive of this hereditary thrombophilia Confirming a diagnosis of autosomal dominant protein C deficiency with the identification of a known or suspected disease-causing alteration in the PROC gene Confirming a diagnosis of autosomal recessive severe protein C deficiency with the identification of homozygous or compound heterozygous disease-causing alteration(s) in the PROC gene Determining the disease-causing alteration(s) within the PROC gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of protein C deficiency Prognosis and risk assessment based on the genotype-phenotype correlations Ascertaining the variant status of family members related to an individual with a confirmed PROC variant for the purposes of informing clinical management and genetic counseling Carrier testing for close family members of an individual with a diagnosis of autosomal recessive severe protein C deficiency This test is not intended for prenatal diagnosis.

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Cooper PC, Hill M, Maclean RM: The phenotypic and genetic assessment of protein C deficiency. Int J Lab Hematol. 2012 Aug;34(4):336-346 2. Dinarvand P, Moser KA: Protein C Deficiency. Arch Pathol Lab Med. 2019 Oct;143(10):1281-1285 3. Mustafa S, Mannhalter C, Rintelen C: Clinical features of thrombophilia in families with gene defects in protein C or protein S combined with factor V Leiden. Blood Coagul Fibrinolysis. 1998 Jan;9(1):85-89 4. Minford A, Brandao LR, Othman M: Diagnosis and management of severe congenital protein C deficiency (SCPCD): Communication from the SSC of the ISTH. J Thromb Haemost. 2022 Jul;20(7):1735-1743 5. Varga EA, Kujovich JL: Management of inherited thrombophilia: guide for genetics professionals. Clin Genet. 2012 Jan;81(1):7-17 6. Arachchillage DJ, Mackillop L, Chandratheva A: Thrombophilia testing: A British Society for Haematology guideline. Br J Haematol. 2022 Aug;198(3):443-458 7. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

SFX 617792 Protein S Activity, Plasma

Clinical Information:

Useful For: Second-order testing for diagnosis of congenital or acquired protein S deficiency, ie, as an adjunct to initial testing based on results of protein S antigen assay (free protein S antigen, with or without

total protein S antigen assay) Evaluating patients with a history of venous thromboembolism

Interpretation: In type I and type III congenital deficiency, free protein S antigen is decreased, and protein S functional activity is similarly decreased. In type II congenital (dysfunctional) protein S deficiency, total and free protein S antigen levels are normal, but functional activity is decreased. Patients with acquired free protein S deficiency associated with inflammation-related increase of C4b-binding protein typically have decreased free protein S antigen and protein S activity with normal (or elevated) total protein S antigen. Acquired protein S deficiency is of uncertain clinical hemostatic significance and is associated with a variety of conditions. Elevated protein S levels are of uncertain clinical significance.

Reference Values:

Males: 65-150%
Females
<50 years: 50-150%
> or =50 years: 65-150%
Newborn infants have normal or near-normal free protein S antigen (> or =50%), although total protein S antigen is usually below the adult reference range. There are insufficient data concerning protein S activity in normal neonates, infants, and children; but normal or near-normal activity (> or =50%) probably is present by age 3 to 6 months.

Clinical References:

PSF
80338

Protein S Antigen, Free, Plasma

Clinical Information: Protein S is a vitamin K-dependent glycoprotein present in platelets and synthesized within the liver and endothelial cells. Protein S works as part of the natural anticoagulant system by acting as a cofactor to activated protein C (APC) in the proteolytic inactivation of procoagulant factors Va and VIIIa. In addition, protein S has direct APC-independent anticoagulant activity by inhibiting formation of the prothrombin and tenase complexes, possibly due to its high affinity for anionic phospholipid membranes. In human plasma, protein S forms a complex with the compliment regulatory protein, C4b-binding protein (C4bBP). Of the total plasma protein S, approximately 60% circulates bound to C4bBP while the remaining 40% circulates as "free" protein S. Only free protein S has anticoagulant function. C4bBP is composed of 6 or 7 alpha-chains and 1 or no beta-chain (C4bBP-beta). Different C4bBP isoforms are present in plasma, but only C4bBP-beta binds protein S. Congenital protein S deficiency is an autosomal dominant disorder that is present in 2% to 6% of patients with venous thrombosis. Patients with protein S deficiency have an approximately 10-fold increased risk of venous thrombosis. In addition, they may also experience recurrent miscarriage, complications of pregnancy (preeclampsia, abruptio placentae, intrauterine growth restriction, and stillbirth) and possibly arterial thrombosis. Three types of protein S deficiency have been described according to the levels of total protein S antigen, free protein S antigen, and protein S activity in plasma. Types I and III protein S deficiency are much more common than type II (dysfunctional) protein S deficiency. Type III protein S deficiency appears to be partly due to mutations within the protein S binding region for C4bBP-beta. Homozygous protein S deficiency is rare but can present as neonatal purpura fulminans, reflecting severe disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) caused by the absence of plasma protein S. Acquired deficiency of protein S has causes that are generally of unknown hemostatic significance (ie, uncertain thrombosis risk), and is much more common than hereditary protein S deficiency. Acquired protein S deficiency can present through vitamin K deficiency, oral anticoagulant therapy, liver disease, DIC/ICF, thrombotic thrombocytopenia purpura, pregnancy or estrogen therapy, nephritic syndrome, and sickle cell anemia. As an acute-phase reactant, plasma C4bBP levels increase with acute illness and may cause acquired free protein S deficiency. Measurement of plasma free

protein S antigen is performed as the initial testing for protein S deficiency. When the free protein S antigen level is below the age- and sex-adjusted normal range, reflexive testing will be performed for total plasma protein S antigen.

Useful For: As part of an investigation of patients with a history of thrombosis

Interpretation: Protein S values vary widely in the normal population and are age- and sex-dependent. Table. Types of Heterozygous Protein S Deficiency Type Protein S antigen free Protein S antigen total Protein S activity I Low Low Low II Normal Normal Low III Low Normal Low Protein S and C4b-binding protein (C4bBP) are coordinately regulated, and an increased total protein S antigen and low free protein S antigen most commonly reflect acute or chronic inflammation or illness with an associated increase in plasma C4bBP. For patients in whom hereditary protein S deficiency is strongly suspected and the free plasma protein S antigen level is normal, consideration should be given to testing of free protein S activity, SFX / Protein S Activity, Plasma, for detecting type II protein S deficiency (which is rare). An increased total protein S antigen is of uncertain clinical significance because free protein S antigen levels are usually normal, in such situations. However, the total protein S antigen level may be helpful in distinguishing acquired versus congenital protein S deficiency. High normal or increased total protein S antigen and reduced free protein S antigen suggests acquired protein S deficiency, as may be seen in pregnancy or inflammation. In contrast, low normal or decreased total protein S antigen and reduced free protein S antigen suggests vitamin K deficiency or a warfarin effect, but also could reflect congenital protein S deficiency (type I or III). Vitamin K deficiency, oral anticoagulant therapy, presence of liver disease, or disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) are common acquired causes of protein S deficiency, which is of uncertain significance when such conditions are present. Concomitant assay of coagulation factor II activity may be helpful in differentiating congenital protein S deficiency from oral anticoagulation effects, but supportive data are currently suboptimal. Differentiation of congenital and acquired protein S deficiency requires clinical correlation and may require repeated laboratory study of the patient and selected family members in some instances. DNA-based testing may be helpful; see GNPRS / Protein S Deficiency, PROS1 Gene, Next-Generation Sequencing, Varies.

Reference Values:
Only orderable as part of a profile, see PSTF / Protein S Antigen, Plasma.

Males: 65-160%
Females:
<50 years: 50-160%
> or =50 years: 65-160%
Normal, full-term newborn infants or healthy premature infants may have decreased levels of total protein S (15%-50%), but because of low levels of C4bBP, free protein S may be normal or near the normal adult level (> or =50%). Total protein S reaches adult levels by 90-180 days postnatal.*

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing

Clinical References: 1. Borgel D, Gandrille S, Aiach M. Protein S deficiency. Thromb Haemost. 1997;78(1):351-356 2. De Stefano V, Finazzi G, Mannucci PM. Inherited thrombophilia: pathogenesis, clinical syndromes, and management. Blood. 1996;87(9):3531-3544 3. Zoller B, Garcia de Frutos P, Dahlback B. Evaluation of the relationship between protein S and C4b-binding protein isoforms in hereditary protein S deficiency demonstrating type I and type III deficiencies to be phenotypic variants of the same genetic disease. Blood. 1995;85(12):3524-3531 4. Grandrille S, Borgel D, Ireland H, et al. Protein S deficiency: a database of mutations. For the Plasma Coagulation Inhibitors Subcommittee for the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost. 1997;77(6):1201-1214 5. Wolf M, Boyer-Neumann C, Peynaud-Debayle E, Marfaing-Koka A, Amiral J, Meyer D. Clinical applications of a direct assay of free protein S antigen

using monoclonal antibodies. A study of 59 cases. Blood Coagul Fibrinolysis. 1994;5(2):187-192 6. Goodwin AJ, Rosendaal FR, Kottke-Marchant K, Bovill EG. A review of the technical, diagnostic, and epidemiologic considerations for protein S assays. Arch Pathol Lab Med. 2002;126(11):1349-1366 7. Serra J, Sales M, Chitolie A, et al: Multicentre evaluation of IL Test Free PS: a fully automated assay to quantify free protein S. Thromb Haemost. 2002;88(6):975-983 8. Marlar RA, Gausman JN, Tsuda H, Rollins-Raval MA, Brinkman HJM. Recommendations for clinical laboratory testing for S deficiency: Communication from the SCC committee plasma coagulation inhibitors of the ISTH. J Thromb Haemost. 2021;19(1):68-74

PSTF
83049

Protein S Antigen, Plasma

Clinical Information: Protein S is a vitamin K-dependent glycoprotein present in platelets and synthesized within the liver and endothelial cells. Protein S works as part of the natural anticoagulant system by acting as a cofactor to activated protein C (APC) in the proteolytic inactivation of procoagulant factors Va and VIIIa. In addition, protein S has direct APC-independent anticoagulant activity by inhibiting formation of the prothrombin and tenase complexes, possibly due to its high affinity for anionic phospholipid membranes. In human plasma, protein S forms a complex with the compliment regulatory protein, C4b-binding protein (C4bBP). Of the total plasma protein S, approximately 60% circulates bound to C4bBP while the remaining 40% circulates as "free" protein S. Only free protein S has anticoagulant function. C4bBP is composed of 6 or 7 alpha-chains and 1 or no beta-chain (C4bBP-beta). Different C4bBP isoforms are present in plasma, but only C4bBP-beta binds protein S. Congenital protein S deficiency is an autosomal dominant disorder that is present in 2% to 6% of patients with venous thrombosis. Patients with protein S deficiency have an approximately 10-fold increased risk of venous thrombosis. In addition, they may also experience recurrent miscarriage, complications of pregnancy (preeclampsia, abruptio placentae, intrauterine growth restriction, and stillbirth) and possibly arterial thrombosis. Three types of protein S deficiency have been described according to the levels of total protein S antigen, free protein S antigen, and protein S activity in plasma. Types I and III protein S deficiency are much more common than type II (dysfunctional) protein S deficiency. Type III protein S deficiency appears to be partly due to variants within the protein S binding region for C4bBP-beta. Homozygous protein S deficiency is rare but can present as neonatal purpura fulminans, reflecting severe disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) caused by the absence of plasma protein S. Acquired deficiency of protein S has causes that are generally of unknown hemostatic significance (ie, uncertain thrombosis risk) and is much more common than hereditary protein S deficiency. Acquired protein S deficiency can present through vitamin K deficiency, oral anticoagulant therapy, liver disease, DIC/ICF, thrombotic thrombocytopenia purpura, pregnancy, estrogen therapy, nephritic syndrome, and sickle cell anemia. As an acute-phase reactant, plasma C4bBP levels increase with acute illness and may cause acquired free protein S deficiency. Measurement of plasma free protein S antigen is performed as the initial testing for protein S deficiency. When the free protein S antigen level is below the age- and sex-adjusted normal range, reflexive testing will be performed for total plasma protein S antigen.

Useful For: Investigation of patients with a history of thrombosis

Interpretation: Protein S values vary widely in the normal population and are age- and sex-dependent. Table. Types of Heterozygous Protein S Deficiency Type Protein S antigen free Protein S antigen total Protein S activity I Low Low Low II Normal Normal Low III Low Normal Low Protein S and C4b-binding protein (C4bBP) are coordinately regulated, and an increased total protein S antigen and low free protein S antigen most commonly reflect acute or chronic inflammation or illness with an associated increase in plasma C4bBP. For patients in whom hereditary protein S deficiency is strongly suspected and the free plasma protein S antigen level is normal, consideration should be given to testing of free protein S activity, S_FX / Protein S Activity, Plasma, for detecting type II protein S deficiency (which is rare). An increased total protein S antigen is of uncertain clinical significance because free

protein S antigen levels are usually normal, in such situations. However, the total protein S antigen level may be helpful in distinguishing acquired versus congenital protein S deficiency. High normal or increased total protein S antigen and reduced free protein S antigen suggests acquired protein S deficiency, as may be seen in pregnancy or inflammation. In contrast, low normal or decreased total protein S antigen and reduced free protein S antigen suggests vitamin K deficiency or a warfarin (Coumadin) effect, but also could reflect congenital protein S deficiency (type I or III). Vitamin K deficiency, oral anticoagulant therapy, presence of liver disease, or disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) are common acquired causes of protein S deficiency, which is of uncertain significance when such conditions are present. Concomitant assay of coagulation factor II activity may be helpful in differentiating congenital protein S deficiency from oral anticoagulation effects, but supportive data are currently suboptimal. Differentiation of congenital and acquired protein S deficiency requires clinical correlation and may require repeated laboratory study of the patient and selected family members in some instances. DNA-based testing may be helpful; see PRSNG / Protein S Deficiency, PROS1 Gene, Next-Generation Sequencing, Varies.

Reference Values:

TOTAL
Males: 80-160%
Females
<50 years: 70-160%
> or =50 years: 80-160%

FREE
Males: 65-160%
Females
<50 years: 50-160%
> or =50 years: 65-160%

Normal, full-term newborn infants or healthy premature infants may have decreased levels of total protein S (15-50%); but because of low levels of C4b-binding protein, free protein S may be normal or near the normal adult level (> or =50%). Total protein S reaches adult levels by 90 to 180 days postnatal.*
*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing

Clinical References: 1. Borgel D, Gandrille S, Aiach M. Protein S deficiency. Thromb Haemost. 1997 July;78(1):351-356 2. De Stefano V, Finazzi G, Mannucci PM. Inherited thrombophilia: pathogenesis, clinical syndromes, and management. Blood. 1996 1;87(9):3531-3544 3. Zoller B, Garcia de Frutos P, Dahlback B. Evaluation of the relationship between protein S and C4b-binding protein isoforms in hereditary protein S deficiency demonstrating type I and type III deficiencies to be phenotypic variants of the same genetic disease. Blood. 1995;85(12):3524-3531 4. Grandrille S, Borgel D, Ireland H, et al. Protein S deficiency: a database of mutations. For the Plasma Coagulation Inhibitors Subcommittee for the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost. 1997;77(6):1201-1214 5. Wolf M, Boyer-Neumann C, Peynaud-Debayle E, Marfaing-Koka A, Amiral J, Meyer D. Clinical applications of a direct assay of free protein S antigen using monoclonal antibodies. A study of 59 cases. Blood Coagul Fibrinolysis. 1994;5(2):187-192 6. Laroche P, Plassart V, Amiral J. Rapid quantitative latex immunoassays for diagnosis of thrombotic disorders. Thromb Haemost. 1989:62:379 7. Goodwin AJ, Rosendaal FR, Kottke-Marchant K, Bovill EG. A review of the technical, diagnostic, and epidemiologic considerations for protein S assays. Arch Pathol Lab Med. 2002;126(11):1349-1366 8. Sales M, Begona A, Rosen S: IL Test Free Protein S: A diagnostic tool for protein S deficiency. Instrumentation Laboratories; Hemostasis Monograph 9. Serra J, Sales M, Chitolie A, et al: Multicentre evaluation of IL Test Free PS: a fully automated assay to quantify free protein S. Thromb Haemost. 2002;88(6):975-983 10. Marlar RA, Gausman JN, Tsuda H, Rollins-Raval MA, Brinkman HJM. Recommendations for clinical laboratory testing for S deficiency: Communication from the SCC committee plasma coagulation inhibitors of the ISTH. JThromb Haemost 2021;19:68-74

PST
80994

Protein S Antigen, Total, Plasma

Clinical Information: Protein S is a vitamin K-dependent glycoprotein present in platelets and synthesized within the liver and endothelial cells. Protein S works as part of the natural anticoagulant system by acting as a cofactor to activated protein C (APC) in the proteolytic inactivation of procoagulant factors Va and VIIIa. In addition, protein S has direct APC-independent anticoagulant activity by inhibiting formation of the prothrombin and tenase complexes, possibly due to its high affinity for anionic phospholipid membranes. In human plasma, protein S forms a complex with the compliment regulatory protein, C4b-binding protein (C4bBP). Of the total plasma protein S, approximately 60% circulates bound to C4bBP, while the remaining 40% circulates as free protein S. Only free protein S has anticoagulant function. C4bBP is composed of 6 or 7 alpha-chains and 1 or no beta-chain (C4bBP-beta). Different C4bBP isoforms are present in plasma, but only C4bBP-beta binds protein S. Congenital protein S deficiency is an autosomal dominant disorder that is present in 2% to 6% of patients with venous thrombosis. Patients with protein S deficiency have an approximately 10-fold increased risk of venous thrombosis. In addition they may also experience recurrent miscarriage, complications of pregnancy (preeclampsia, abruptio placentae, intrauterine growth restriction, and stillbirth) and possibly arterial thrombosis. Three types of protein S deficiency have been described according to the levels of total protein S antigen, free protein S antigen, and protein S activity in plasma. Types I and III protein S deficiency are much more common than type II (dysfunctional) protein S deficiency. Type III protein S deficiency appears to be partly due to mutations within the protein S binding region for C4bBP-beta. Homozygous protein S deficiency is rare, but can present as neonatal purpura fulminans, reflecting severe disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) caused by the absence of plasma protein S. Acquired deficiency of protein S has causes that are generally of unknown hemostatic significance (ie, uncertain thrombosis risk), and is much more common than hereditary protein S deficiency. Acquired protein S deficiency can present through vitamin K deficiency, oral anticoagulant therapy, liver disease, DIC/ICF, thrombotic thrombocytopenia purpura, pregnancy or estrogen therapy, nephritic syndrome, and sickle cell anemia. As an acute-phase reactant, plasma C4bBP levels increase with acute illness and may cause acquired free protein S deficiency. Measurement of plasma free protein S antigen is performed as the initial testing for protein S deficiency. When the free protein S antigen level is below the age- and sex-adjusted normal range, reflexive testing will be performed for total plasma protein S antigen.

Useful For: Aiding in the investigation of patients with a history of thrombosis

Interpretation: Protein S values vary widely in the normal population and are age- and sex-dependent. Table. Types of Heterozygous Protein S Deficiency Type Protein S antigen free Protein S antigen total Protein S activity I Low Low Low II Normal Normal Low III Low Normal Low Protein S and C4b-binding protein (C4bBP) are coordinately regulated, and an increased total protein S antigen and low free protein S antigen most commonly reflect acute or chronic inflammation or illness with an associated increase in plasma C4bBP. For patients in whom hereditary protein S deficiency is strongly suspected and the free plasma protein S antigen level is normal, consideration should be given to testing of free protein S activity, SFX / Protein S Activity, Plasma, for detecting type II protein S deficiency (which is rare). An increased total protein S antigen is of uncertain clinical significance because free protein S antigen levels are usually normal, in such situations. However, the total protein S antigen level may be helpful in distinguishing acquired versus congenital protein S deficiency. High normal or increased total protein S antigen and reduced free protein S antigen suggests acquired protein S deficiency, as may be seen in pregnancy or inflammation. In contrast, low normal or decreased total protein S antigen and reduced free protein S antigen suggests vitamin K deficiency or a warfarin effect, but also could reflect congenital protein S deficiency (type I or III). Vitamin K deficiency, oral anticoagulant therapy, the presence of liver disease, or disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) are common acquired causes of protein S deficiency, which is of uncertain significance when such conditions are present. Concomitant assay of coagulation factor II activity may be helpful in differentiating congenital protein S deficiency

from oral anticoagulation effects, but supportive data are currently suboptimal. Differentiation of congenital and acquired protein S deficiency requires clinical correlation and may require repeated laboratory study of the patient and selected family members in some instances. DNA-based testing may be helpful; see GNPRS / Protein S Deficiency, PROS1 Gene, Next-Generation Sequencing, Varies.

Reference Values:

Only orderable as part of a profile. For more information see PSTF / Protein S Antigen, Plasma.

Males: 80-160%
Females:
<50 years: 70-160%
> or =50 years: 80-160%
Normal, full-term newborn infants or healthy premature infants may have decreased levels of total protein S (15%-50%), but because of low levels of C4bBP, free protein S may be normal or near the normal adult level (> or =50%). Total protein S reaches adult levels by 90-180 days postnatal.*

*See Pediatric Hemostasis References section in Coagulation Guidelines for Specimen Handling and Processing

Clinical References: 1. Zoller B, Garcia de Frutos P, Dahlback B. Evaluation of the relationship between protein S and C4b-binding protein isoforms in hereditary protein S deficiency demonstrating type I and type III deficiencies to be phenotypic variants of the same genetic disease. Blood. 1995;85(12):3524-3531 2. Grandrille S, Borgel D, Ireland H, et al. Protein S deficiency: a database of mutations. For the Plasma Coagulation Inhibitors Subcommittee for the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost. 1997;77(6):1201-1214 3. Marlar RA, Gausman JN, Tsuda H, Rollins-Raval MA, Brinkman HJM. Recommendations for clinical laboratory testing for S deficiency: Communication from the SCC committee plasma coagulation inhibitors of the ISTH. J Thromb Haemost. 2021;19(1):68-74

GNPRS 619187 Protein S Deficiency, PROS1 Gene, Next-Generation Sequencing, Varies

Clinical Information:

Useful For: Evaluating protein S deficiency in patients with a personal or family history suggestive of this hereditary thrombophilia Confirming a diagnosis of autosomal dominant protein S deficiency with the identification of a known or suspected disease-causing alteration in the PROS1 gene Confirming a diagnosis of autosomal recessive severe protein S deficiency with the identification of homozygous or compound heterozygous disease-causing alteration(s) in the PROS1 gene Determining the disease-causing alteration(s) within the PROS1 gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of protein S deficiency Prognosis and risk assessment based on the genotype-phenotype correlations Ascertaining the variant status of family members related to an individual with a confirmed PROS1 variant for the purposes of informing clinical management and genetic counseling Carrier testing for close family members of an individual with a diagnosis of autosomal recessive severe protein S deficiency This test is not intended for prenatal diagnosis.

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:

An interpretive report will be provided.

Clinical References: 1. Gupta A, Tun AM, Gupta K: Protein S Deficiency. In: StatPearls [Internet]. StatPearls Publishing; Updated December 5, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK544344/ 2. ten Kate MK, van der Meer J: Protein S deficiency: a clinical perspective. Haemophilia. 2008 Nov;14(6):1222-1228 3. Garcia de Frutos P, Fuentes-Prior P, Hurtado B, Sala N: Molecular basis of protein S deficiency. Thromb Haemost. 2007 Sep;98(3):543-556 4. Beauchamp NJ, Dykes AC, Parikh N, Campbell Tait R, Daly ME: The prevalence of, and molecular defects underlying, inherited protein S deficiency in the general population. Br J Haematol. 2004 Jun;125(5):647-654 5. Arachchillage DJ, Mackillop L, Chandratheva A, Motawani J, MacCallum P, Laffan M.: Thrombophilia testing: A British Society for Haematology guideline. Br J Haematol. 2022 Aug;198(3):443-458 6. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

12PU1
614042

Protein, Total, 12 Hour, Urine

Clinical Information: Protein in urine normally consists of plasma proteins that have been filtered by glomeruli and not reabsorbed by the proximal tubule, and proteins secreted by renal tubules or other accessory glands. Increased amounts of protein in the urine may be due to: -Glomerular proteinuria: defects in permselectivity of the glomerular filtration barrier to plasma proteins (eg, glomerulonephritis or nephrotic syndrome) -Tubular proteinuria: incomplete tubular reabsorption of proteins (eg, interstitial nephritis) -Overflow proteinuria: increased plasma concentration of proteins that exceeds capacity for proximal tubular reabsorption (eg, multiple myeloma, myoglobinuria) -Urinary tract inflammation or tumor -Preeclampsia -Orthostatic proteinuria In pregnant women, a urinary protein excretion of more than 300 mg/24 hours is frequently cited as consistent with preeclampsia and 12-hour total protein excretion highly correlates with 24-hour values in this patient population.(1,2) Orthostatic proteinuria is characterized by increased protein excretion in the upright position but normal levels when supine. This condition can be detected by comparing urine protein levels in a collection split between day and night (see OPTU / Orthostatic Protein, Timed Collection, Urine). Orthostatic proteinuria is common in childhood and adolescence but rare after 30 years of age.

Useful For: Evaluation of renal disease Screening for monoclonal gammopathy Screening for postural (orthostatic) proteinuria In select clinical situations, collection of a 12-hour specimen may allow more rapid detection of proteinuria states (eg, screening pregnant patients for preeclampsia)

Interpretation: Total urine protein determined to be greater than 500 mg/24 hours should be evaluated by immunofixation to assess if there is a monoclonal immunoglobulin light chain and, if present, identify it as either kappa or lambda type. Urinary protein levels may rise to 300 mg/24 hours in healthy individuals after vigorous exercise. Low-grade proteinuria may be seen in inflammatory or neoplastic processes involving the urinary tract.

Reference Values:
<163 mg/12 hours (day or night collection)
Reference values have not been established for patients <18 years of age.

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1256-1323 2. Rinehart BK, Terrone DA, Larmon JE, et al: A 12-hour urine collection accurately assesses proteinuria in hospitalized hypertensive gravida. J Perinatol. 1999;19:556-558 3. Adelberg AM, Miller J, Doerzbacher M, Lambers DS: Correlation of quantitative protein measurements in 8-,

12-, and 24-hour urine samples for diagnosis of preeclampsia. Am J Obstet Gynecol. 2001 Oct;185(4):804-807 4. Robinson RR: Isolated proteinuria in asymptomatic patients. Kidney Int. 1980;18:395-406 5. Dube J , Girouard J, Leclerc P, Douville P: Problems with the estimation of urine protein by automated assays. Clin Biochem. 2005 May;38(5):479- 485 6. Koumantakis G, Wyndham, L. Fluorescein interference with urinary creatinine and protein measurements. Clin Chem. 1991 Oct;37(10 Pt 1):1799

PTU
614001

Protein, Total, 24 Hour, Urine

Clinical Information: Protein in urine is normally composed of a combination of plasma-derived proteins that have been filtered by glomeruli and have not been reabsorbed by the proximal tubules and proteins secreted by renal tubules or other accessory glands. Increased amounts of protein in the urine may be due to: -Glomerular proteinuria: caused by defects in permselectivity of the glomerular filtration barrier to plasma proteins (eg, glomerulonephritis or nephrotic syndrome) -Tubular proteinuria: caused by incomplete tubular reabsorption of proteins (eg, interstitial nephritis) -Overflow proteinuria: caused by increased plasma concentration of proteins (eg, multiple myeloma, myoglobinuria) -Urinary tract inflammation or tumor

Useful For: Evaluation of kidney disease using a 24-hour urine collection Screening for monoclonal gammopathy

Interpretation: Total protein greater than 500 mg/24 hours should be evaluated by immunofixation to determine if a monoclonal immunoglobulin light chain is present, and if so, identify it as either kappa or lambda type. Urinary protein levels may rise to 300 mg/24 hours in healthy individuals after vigorous exercise. Low-grade proteinuria may be seen in inflammatory or neoplastic processes involving the urinary tract.

Reference Values:
> or =18 years: <229 mg/24 hours
Reference values have not been established for patients <18 years of age.
Reference value applies to 24-hour collection.

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds. Textbook of Clinical Chemistry, 6th ed. Elsevier; 2018:1256-1323 2. Rinehart BK, Terrone DA, Larmon JE, et al: A 12-hour urine collection accurately assesses proteinuria in hospitalized hypertensive gravida. J Perinatol. 1999;19:556-558 3. Adelberg AM, Miller J, Doerzbacher M, Lambers DS: Correlation of quantitative protein measurements in 8-, 12-, and 24-hour urine samples for diagnosis of preeclampsia. Am J Obstet Gynecol. 2001 Oct;185(4):804-807 4. Robinson RR: Isolated proteinuria in asymptomatic patients. Kidney Int. 1980;18:395-406 5. Dube J, Girouard J, Leclerc P, et al: Problems with the estimation of urine protein by automated assays. Clin Biochem. 2005;38(5):479-485 6. Koumantakis G, Wyndham, L: Fluorescein Interference with Urinary Creatinine and Protein Measurements. Clin Chem. 1991;37(10):1799

TPBF
606619

Protein, Total, Body Fluid

Clinical Information: Pleural fluid: Pleural fluid is normally present within the pleural cavity surrounding the lungs, serving as a lubricant between the lungs and inner chest wall. Pleural effusion develops when the pleural cavity experiences an overproduction of fluid due to increased capillary hydrostatic and osmotic pressure that exceeds the ability of the lymphatic or venous system to return the fluid to circulation. Laboratory-based criteria are often used to classify pleural effusions as either exudative or transudative. Exudative effusions form due to infection or inflammation of the capillary

membranes allowing excess fluid into the pleural cavity. Patients with these conditions benefit from further investigation and treatment of the local cause of inflammation. Transudative effusions form due to systemic conditions such as volume overload, end stage kidney disease, and heart failure that can lead to excess fluid accumulation in the pleural cavity. Patients with transudative effusions benefit from treatment of the underlying condition.(1) Dr. Richard Light derived criteria in the 1970s that are still used today for patients with pleural effusions.(2) The criteria include the measurement of total protein and lactate dehydrogenase (LDH) in pleural fluid and serum. Exudates are defined as meeting 1 of the following criteria: 1. Pleural fluid to serum protein ratio above 0.5 2. Pleural fluid LDH above two-thirds the upper limit of normal serum LDH 3. Pleural fluid to serum LDH ratio above 0.6 Dr. Light's criteria were designed to be sensitive for detecting exudates at the expense of specificity.(3) Heart failure and recent diuretic use contribute to most misclassifications by Dr. Light's criteria (transudates falsely categorized as exudates). Serum-to-fluid protein gradient (serum protein minus fluid protein) may be calculated in these cases and when more than 3.1 g/dL suggests the patient has a transudative effusion. Peritoneal fluid: The pathologic accumulation of fluid within the peritoneal cavity is commonly referred to as ascites. The most common cause of ascites is liver cirrhosis. Differentiating cardiac from cirrhotic ascites is a common clinical conundrum as they are common conditions presenting with elevated serum ascites albumin gradient.(4) Heart failure leads to the development of high gradient ascites due to hepatic sinusoidal hypertension. Since the sinusoids are normal and have not been damaged from collagen deposition associated with cirrhosis, protein tends to "leak" more readily into ascites and is associated with higher total protein concentrations.

Useful For: Identification of exudative pleural effusions Differentiating hepatic from other causes of ascites that have elevated serum ascites albumin gradient using peritoneal fluid

Interpretation: A pleural fluid total protein to serum total protein ratio of above 0.5 is most consistent with exudative effusion.(2,5) A peritoneal fluid total protein of above 2.5 g/dL in patients with a high serum ascites albumin gradient can be caused by heart failure. A peritoneal fluid total protein of over 1.0 g/dL helps to differentiate secondary from spontaneous bacterial peritonitis in conjunction with other laboratory, imaging, and clinical findings.(6,7,8) The usefulness of measuring total protein in pericardial fluid is not well documented. Results may be interpreted in conjunction with serum or plasma total protein concentrations. The usefulness of measuring total protein in synovial fluid is limited as it has poor sensitivity and specificity for differentiating inflammatory vs noninflammatory causes and should be interpreted in conjunction with other clinical findings.(9) All other fluids: Total protein may be used to differentiate transudative from exudative effusions. The decision limits are not well defined in fluids other than pleural fluid and should be interpreted in conjunction with other clinical findings.(10)

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Block DR, Florkowski CM: Body fluids. In: Rifai N, Horvath AR, Wittwer CT. eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:chap 43 2. Light RW. The Light criteria: the beginning and why they are useful 40 years later. Clin Chest Med. 2013;34(1):21-26 3. Porcel JM. Identifying transudates misclassified by Light's criteria. Curr Opin Pulm Med. 2013;19(4):362-367 4. Block DR, Genzen JR: Diagnostic body fluid testing. In: Clarke W, ed. Contemporary Practice in Clinical Chemistry. 3rd ed. AACC Press; 2016:773-775 5. Sahn SA. Getting the most from pleural fluid analysis. Respirology. 2012;17(2):270-277 6. Runyon BA; AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology. 2013;57(4):1651-1653. doi:10.1002/hep.26359 7. McGibbon A, Chen GI, Peltekian KM, van Zanten SV. An evidence-based manual for abdominal paracentesis. Dig Dis Sci. 2007;52(12):3307-3315 8. Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving MA, McHutchison JG. The serum-ascites gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. Ann Intern Med. 1992;117(3):215-220 9. Shmerling RH, Delbanco TL,

Tosteson AN, Trentham DE. Synovial fluid tests: what should be ordered? JAMA. 1990;264(8):1009-1014 10. Brunzel NA: Pleural, pericardial, and peritoneal fluid analysis. In: Fundamentals of Urine and Body Fluid Analysis. WB Saunders Company; 1994:406

PRCON 617782 Protein, Total, Random, Urine

Clinical Information: Orthostatic proteinuria refers to the development of increased proteinuria that develops only when the person is upright and resolves when recumbent or supine. This condition is usually seen in children, adolescents, or young adults and accounts for the majority of cases of proteinuria in childhood. Orthostatic proteinuria usually does not indicate significant underlying renal pathology and is usually not associated with other urine abnormalities such as hypoalbuminemia, hematuria, red blood cell casts, fatty casts, etc. Orthostatic proteinuria typically resolves over time. This test evaluates for this condition by demonstrating either significant proteinuria, even while supine, or normal protein excretion. Significant proteinuria, even while supine, suggests that the patient does not have orthostatic proteinuria while normal protein excretion supports the diagnosis. This test is typically done on three consecutive mornings to provide more robust support for the diagnosis.

Useful For: Measurement of total protein for the assessment of orthostatic proteinuria

Interpretation: First-morning urine protein-to-creatinine ratio of less than 0.20 mg/mg creatinine supports the diagnosis of orthostatic proteinuria, while a result greater than 0.20 mg/mg creatinine does not support this diagnosis. Further investigation into other etiologies for proteinuria may be warranted.

Reference Values:
Not established

Clinical References: 1. Brunzel N: Chemical examination of urine. In: Fundamentals of Urine and Body Fluids. 4th ed. Saunders; 2018:92-94 2. Wilson DM, Anderson RL: Protein-osmolality ratio for the quantitative assessment of proteinuria from a random urinalysis sample. Am J Clin Pathol. 1993 Oct;100(4):419-424 3. Morgenstern BZ, Butani L, Wollan P, Wilson DM, Larson TS: Validity of protein-osmolality versus protein-creatinine ratios in the estimation of quantitative proteinuria from random samples of urine in children. Am J Kidney Dis. 2003 Apr;41(4):760-766 4. Rinehart BK, Terrone DA, Larmon JE, Perry KG Jr, Martin RW, Martin JN Jr: A 12-hour urine collection accurately assesses proteinuria in hospitalized hypertensive gravida. J Perinatol. 1999 Dec;19(8 Pt 1):556-558 5. Adelberg AM, Miller J, Doerzbacher M, Lambers DS: Correlation of quantitative protein measurements in 8-, 12-, and 24-hour urine samples for diagnosis of preeclampsia. Am J Obstet Gynecol. 2001 Oct;185(4):804-807 6. Robinson RR: Isolated proteinuria in asymptomatic patients. Kidney Int. 1980 Sep;18(3):395-406 7. Dube J, Girouard J, Leclerc P, Douville P: Problems with the estimation of urine protein by automated assays. Clin Biochem. 2005 May;38(5):479-485 8. Koumantakis G, Wyndham L: Fluorescein interference with urinary creatinine and protein measurements. Clin Chem. 1991 Oct;37(10 Pt 1):1799 9. Lamb EJ, Jones GRD: Kidney function tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:479-517

TP 8520 Protein, Total, Serum

Clinical Information: Plasma proteins are synthesized predominantly in the liver; immunoglobulins are synthesized by mononuclear cells of lymph nodes, spleen and bone marrow. The 2 general causes of alterations of serum total protein are a change in the volume of plasma water and a change in the concentration of 1 or more of the specific proteins in the plasma. Of the individual serum proteins, albumin is present in such high concentrations that low levels of this protein alone may cause hypoproteinemia. Hemoconcentration (decrease in the volume of plasma water) results in relative

hyperproteinemia; hemodilution results in relative hypoproteinemia. In both situations, concentrations of all the individual plasma proteins are affected to the same degree. Hyperproteinemia may be seen in dehydration due to inadequate water intake or to excessive water loss (eg, severe vomiting, diarrhea, Addison disease, and diabetic acidosis) or as a result of increased production of proteins. Increased polyclonal protein production is seen in reactive, inflammatory processes; increased monoclonal protein production is seen in some hematopoietic neoplasms (eg, multiple myeloma, Waldenstrom macroglobulinemia, monoclonal gammopathy of undetermined significance).

Useful For: Diagnosis and treatment of a variety of diseases involving the liver, kidney, or bone marrow, as well as other metabolic or nutritional disorders

Interpretation: Mild hyperproteinemia may be caused by an increase in the concentration of specific proteins normally present in relatively low concentration, eg, increases in acute phase reactants and polyclonalimmunoglobulins produced in inflammatory states, late-stage liver disease, and infections. Moderate-to-marked hyperproteinemia may also be due to multiple myeloma and other malignant paraproteinemias, although normal total protein levels do not rule out these disorders. A serum protein electrophoresis should be performed to evaluate the cause of the elevated serum total protein. Hypoproteinemia may be due to decreased production (eg, hypogammaglobulinemia) or increased protein loss (eg, nephrotic syndrome, protein-losing enteropathy). A serum protein electrophoresis should be performed to evaluate the cause of the decreased serum total protein. If a nephrotic pattern is identified, urine protein electrophoresis should also be performed.

Reference Values:
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients who are <12 months of age.

Clinical References: 1. Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier, 2018 2. Killingsworth LM: Plasma proteins in health and disease. Crit Rev Clin Lab Sci. 1979;11:1-30

TPSF
872

Protein, Total, Spinal Fluid

Clinical Information: Cerebrospinal fluid (CSF) proteins are those that remain in CSF following the ultrafiltration of plasma through the choroidal capillary wall. Some proteins that are unique to CSF are synthesized in the central nervous system. In general, diseases that interrupt the integrity of the capillary endothelial barrier lead to an increase in the total CSF protein. CSF protein is generally increased in all types of meningitis, cerebral infarction, brain abscess, meningovascular syphilis, subarachnoid hemorrhage, some brain tumors, trauma to the brain, some cases of multiple sclerosis, encephalomyelitis, and degenerative neurologic diseases. A decreased CSF protein may occur in water intoxication, CSF leak (CSF rhinorrhea or otorrhea), and hyperthyroidism.

Useful For: Detecting disruptions of the blood-brain barrier or intrathecal synthesis of immunoglobulins

Interpretation: Striking elevations of cerebrospinal fluid (CSF) total protein are noted in bacterial meningitis; smaller elevations occur in the other inflammatory diseases and with tumor or hemorrhage. The effect of any of these conditions is that the proportions of specific proteins in CSF increasingly resemble serum. In order to assess increased permeability or increased intrathecal production of proteins, simultaneous serum specimen and CSF specimens should be taken.

Reference Values:
> or =12 months: 0-35 mg/dL

Reference values have not been established for patients that are <12 months of age.

Clinical References: 1. Tietz Textbook of Clinical Chemistry. Fourth edition. Edited by CA Burtis, ER Ashwood, DE Bruns. Philadelphia, WB Saunders Company, 2006 2. Killingsworth LM: Clinical applications of protein determinations in biological fluids other than blood. Clin Chem 1982;28:1093-1103 3. Henry's Clinical Diagnosis and Management by Laboratory Methods. Cerebrospinal, synovial, and serous body fluids. Edited by McPherson and Pincus. Philadelphia, WB Saunders Co, 2007, 431-435

RPTU1
614004

Protein/Creatinine Ratio, Random, Urine

Clinical Information: Protein in urine is normally composed of a combination of plasma-derived proteins that have been filtered by glomeruli and have not been reabsorbed by the proximal tubules and proteins secreted by renal tubules or other accessory glands. Increased amounts of protein in the urine may be due to: -Glomerular proteinuria: Caused by defects in permselectivity of the glomerular filtration barrier to plasma proteins (eg, glomerulonephritis or nephrotic syndrome) -Tubular proteinuria: Caused by incomplete tubular reabsorption of proteins (eg, interstitial nephritis) -Overflow proteinuria: Caused by increased plasma concentration of proteins (eg, multiple myeloma, myoglobinuria)

Useful For: Evaluation of renal disease Screening for monoclonal gammopathy

Interpretation: Total protein of greater than 500 mg/24 hours should be evaluated by immunofixation to determine if a monoclonal immunoglobulin light chain is present and, if so, identify it as either kappa or lambda type. Urinary protein levels may rise to 300 mg/24 hours in healthy individuals after vigorous exercise. Low-grade proteinuria may be seen in inflammatory or neoplastic processes involving the urinary tract. In a random urine specimen, a protein:creatinine or protein:osmolality ratio can be used to roughly approximate 24-hour excretion rates. The normal protein-to-osmolality ratio is less than 0.42.(1) For patients younger than 18 years of age, no reference range has been established.

Reference Values:
> or =18 years: <0.18 mg/mg creatinine
Reference values have not been established for patients younger than 18 years of age.

Clinical References: 1. Brunzel N: Chemical examination of urine. In: Fundamentals of Urine and Body Fluids. 4th ed. Saunders; 2018:92-94 2. Wilson DM, Anderson RL: Protein-osmolality ratio for the quantitative assessment of proteinuria from a random urinalysis sample. Am J Clin Pathol. 1993 Oct;100(4):419-424 3. Morgenstern BZ, Butani L, Wollan P, Wilson DM, Larson TS: Validity of protein-osmolality versus protein-creatinine ratios in the estimation of quantitative proteinuria from random samples of urine in children. Am J Kidney Dis. 2003 Apr;41(4):760-766 4. Rinehart BK, Terrone DA, Larmon JE, Perry KG Jr, Martin RW, Martin JN Jr: A 12-hour urine collection accurately assesses proteinuria in hospitalized hypertensive gravida. J Perinatol. 1999 Dec;19(8 Pt 1):556-558 5. Adelberg AM, Miller J, Doerzbacher M, Lambers DS: Correlation of quantitative protein measurements in 8-, 12-, and 24-hour urine samples for diagnosis of preeclampsia. Am J Obstet Gynecol. 2001 Oct;185(4):804-807 6. Robinson RR: Isolated proteinuria in asymptomatic patients. Kidney Int. 1980 Sep;18(3):395-406 7. Dube J, Girouard J, Leclerc P, Douville P: Problems with the estimation of urine protein by automated assays. Clin Biochem. 2005 May;(38):479-485 8. Koumantakis G, Wyndham L: Fluorescein interference with urinary creatinine and protein measurements. Clin Chem. 1991 Oct;37(10 Pt 1):1799 9. Lamb EJ, Jones GRD: Kidney function tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:479-517

RATO2
617783

Protein/Creatinine, Random, Urine

Clinical Information: Orthostatic proteinuria refers to the development of increased proteinuria that develops only when the person is upright and resolves when recumbent or supine. This condition is usually seen in children, adolescents, or young adults, and accounts for the majority of cases of proteinuria in childhood. Orthostatic proteinuria usually does not indicate significant underlying renal pathology, and is usually not associated with other urine abnormalities such as hypoalbuminemia, hematuria, red blood cell casts, fatty casts, etc. Orthostatic proteinuria typically resolves over time. This test evaluates for this condition by demonstrating either significant proteinuria, even while supine, or normal protein excretion. Significant proteinuria, even while supine, suggests that the patient does not have orthostatic proteinuria while normal protein excretion supports the diagnosis. This test is typically done on three consecutive mornings to provide more robust support for the diagnosis.

Useful For: Calculation of total protein concentration per creatinine concentration

Interpretation: First-morning urine protein-to-creatinine ratio below 0.20 mg/mg creatinine supports the diagnosis of orthostatic proteinuria, while a result above 0.20 mg/mg creatinine does not support this diagnosis. Further investigation into other etiologies for proteinuria may be warranted.

Reference Values:
Only orderable as part of a profile. For more information see ORTHP / Orthostatic Proteinuria, Random, Urine.

> or =18 years: <0.18 mg/mg creatinine
Reference values have not been established for patients younger than 18 years of age.

Clinical References: 1. Brunzel N: Chemical examination of urine. In: Fundamentals of Urine and Body Fluids. 4th ed. Saunders; 2018:92-94 2. Wilson DM, Anderson RL: Protein-osmolality ratio for the quantitative assessment of proteinuria from a random urinalysis sample. Am J Clin Pathol. 1993 Oct;100(4):419-424 3. Morgenstern BZ, Butani L, Wollan P, Wilson DM, Larson TS: Validity of protein-osmolality versus protein-creatinine ratios in the estimation of quantitative proteinuria from random samples of urine in children. Am J Kidney Dis. 2003 Apr;41(4):760-766 4. Rinehart BK, Terrone DA, Larmon JE, Perry KG Jr, Martin RW, Martin JN Jr: A 12-hour urine collection accurately assesses proteinuria in hospitalized hypertensive gravida. J Perinatol. 1999 Dec;19(8 Pt 1):556-558 5. Adelberg AM, Miller J, Doerzbacher M, Lambers DS: Correlation of quantitative protein measurements in 8-, 12-, and 24-hour urine samples for diagnosis of preeclampsia. Am J Obstet Gynecol. 2001 Oct;185(4):804-807 6. Robinson RR: Isolated proteinuria in asymptomatic patients. Kidney Int. 1980 Sep;18(3):395-406 7. Dube J, Girouard J, Leclerc P, Douville P: Problems with the estimation of urine protein by automated assays. Clin Biochem. 2005 May;(38):479-485 8. Koumantakis G, Wyndham L: Fluorescein interference with urinary creatinine and protein measurements. Clin Chem. 1991 Oct;37(10 Pt 1):1799 9. Lamb EJ, Jones GRD: Kidney function tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:479-517

PR3
82965

Proteinase 3 Antibodies, IgG, Serum

Clinical Information: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides are characterized by a pauci-immune inflammation within the walls of small blood vessels.(1) There are 3 specific diseases which are identified as ANCA-associated vasculitides: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The serological hallmark of these disorders is the presence of ANCA, which are antibodies that bind to cytoplasmic antigens found in the granules of neutrophils.(2) Patients with GPA frequently have antibodies specific for proteinase 3 (PR3), while individuals with MPA or EGPA are more likely

to have antibodies that bind to myeloperoxidase (MPO). The presence of PR3-ANCA and MPO-ANCA can be detected using antigen-specific immunoassays or indirect immunofluorescence (IIF). IIF is typically performed using ethanol-fixed neutrophils. Using this substrate, anti-PR3 antibodies produce a granular cytoplasmic staining pattern, which is referred to as cANCA. In comparison, due to an artefact that is a result of the fixation process, anti-MPO antibodies display a perinuclear pattern (pANCA). Patients with suspected ANCA-associated vasculitis should be evaluated for the presence of PR3-ANCA, MPO-ANCA and ANCA by IIF. A consensus guideline published in 2017 recommends that patients with possible GPA or MPA be tested for PR3-ANCA and MPO-ANCA using antigen-specific immunoassays.(3) ANCA by IIF should then be used in cases where there is a high degree of suspicion for GPA or MPA, but the PR3-ANCA and MPO-ANCA testing is negative. To improve specificity of the testing, this guideline also suggests that ANCA be used in situations where a low-positive PR3-ANCA or MPO-ANCA level is detected. The classification criteria for MPA, GPA, and EGPA published by the American College of Rheumatology and the European Alliance of Associations for Rheumatology include PR3-ANCA and MPO-ANCA detected by either antigen-specific immunoassay or IIF.(4-6) These classification criteria incorporate serological ANCA testing along with clinical symptoms, imaging, and biopsy results to determine a score that allows for the classification of the various ANCA-associated vasculitides.

Useful For: Evaluating patients with clinical features of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, specifically granulomatosis with polyangiitis (GPA), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis Distinguishing between GPA and other forms of ANCA-associated vasculitis, in conjunction with myeloperoxidase antibody and cytoplasmic neutrophil antibody testing Following treatment response or monitoring disease activity in patients with proteinase 3 antibodies

Interpretation: Positive results for proteinase 3 (PR3) anti-neutrophil cytoplasmic antibodies (ANCA) by antigen-specific immunoassay and cytoplasmic ANCA by indirect immunofluorescence are consistent with the diagnosis of granulomatosis with polyangiitis (GPA), in patients with the appropriate clinical presentation. The reactivity of PR3-ANCA may decline with treatment of patients with GPA.

Reference Values:

<0.4 U (negative)
0.4-0.9 U (equivocal)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References: 1. Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. Nat Rev Dis Primers. 2020;6(1):71 2. Ramponi G, Folci M, De Santis M, et al. The biology, pathogenetic role, clinical implications, and open issues of serum anti-neutrophil cytoplasmic antibodies. Autoimmun Rev. 2021;20(3):102759 3. Bossuyt X, Cohen Tervaert JW, Arimura Y, et al. Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol. 2017;13(11):683-692 4. Suppiah R, Robson JC, Grayson PC, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. Ann Rheum Dis. 2022;81(3):321-326. doi:10.1136/annrheumdis-2021-221796 5. Robson JC, Grayson PC, Ponte C, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. Ann Rheum Dis. 2022;81(3):315-320. doi:10.1136/annrheumdis-2021-221795 6. Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. Ann Rheum Dis. 2022;81(3):309-314. doi:10.1136/annrheumdis-2021-221794

FPF12
75657

Prothrombin Fragment 1+2 MoAb

Reference Values:
<326 pmol/L
Pre-analytical conditions such as a difficult draw may spuriously increase test results.

PTNT
81742

Prothrombin G20210A Mutation, Blood

Clinical Information: The prothrombin (PT) F2 c.*97G>A (legacy G20210A) variant is a common variant within the 3' untranslated region of the prothrombin gene, affecting 1.5% to 3% of white Americans, especially persons of southern European ancestry. The F2 c.*97G>A variant is less common among African Americans (carrier frequency of 0.4%). The F2 c.*97G>A variant is associated with a 3-fold increased risk of venous thromboembolism due to increased plasma prothrombin activity among carriers.

Useful For: Patients with clinically suspected thrombophilia Determination of the duration of anticoagulation therapy of venous thromboembolism patients Screening for women contemplating hormone therapy

Interpretation: The results will be reported as: -Negative for the c.*97G>A variant -Heterozygous for the c.*97G>A variant -Homozygous for the c.*97G>A variant

Reference Values:
Negative

Clinical References: 1. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM: A common genetic variation in the 3'untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood. 1996;10:3698-3703 2. Makris M, Preston FE, Beauchamp NJ, et al: Co-inheritance of the 20210 A allele of the prothrombin gene increases the risk of thrombosis in subjects with familial thrombophilia. Thromb Haemost. 1997;78:1426-1429 3. De Stefano V, Martinelli I, Mannucci PM, et al: The risk of recurrent venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med. 1999;341:801-806 4. Freed J, Bauer KA: Thrombophilia: clinical and laboratory assessment and management. In: Kitchens CS, Kessler CM, Konkle BA, Streiff MB, Garcia DA, eds. Consultative Hemostasis and Thrombosis. 4th ed. Elsevier; 2019:242-265

PTSC
602171

Prothrombin Time (PT), Plasma

Clinical Information: This assay is used to monitor oral anticoagulant therapy to maintain a patient in a safe therapeutic range. In the absence of oral anticoagulant therapy, a prolonged prothrombin time indicates deficiency of one or more factors (I, II, V, VII, or X) or the presence of a coagulation inhibitor. The prothrombin time is also reported as the INR (International Normalized Ratio), based on the ISI (International Sensitivity Index) assigned to the thromboplastin and coagulometer. This assay is used for monitoring "stable" oral anticoagulation. A mixing test of patient and normal plasma (1:2) can be performed, if indicated, to differentiate coagulation factor deficiency from inhibition.

Useful For: Screening to identify a deficiency of one or more of the clotting factors of the extrinsic coagulation system (I, II, V, VII, X) due to hereditary deficiency or acquired conditions such as liver disease, vitamin K deficiency, or a specific factor inhibitor Monitoring patients on oral anticoagulant therapy to maintain a patient in a safe therapeutic range

Interpretation: Prolongation of the prothrombin time (PT) can occur as a result of deficiency of one or more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a "nonspecific" inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. PT mixing study, using equal volume patient and normal pool plasma, may be performed on specimens with a prolonged PT to assist in differentiating coagulation factor deficiencies from coagulation inhibitors. Correction of the PT mix to within the normal reference range usually indicates a coagulation factor deficiency (normal plasma in the mixture ensures at least 50% activity of all coagulation factors). If the prolonged PT is due to an inhibitor (eg, specific coagulation factor inhibitor, lupus anticoagulant, heparin), the PT mix typically fails to correct a prolonged PT. However, the presence of a weak inhibitor may be missed by the PT mixing study. Accurate interpretation of both PT and PT mixing study results may often require additional testing. For example, the thrombin time test is helpful for identifying or excluding the presence of heparin, the platelet neutralization procedure (using a modified activated partial thromboplastin time [APTT] method) for identifying or excluding lupus anticoagulant, the APTT and dilute Russell viper venom time for further assessment of the common procoagulant pathway, and coagulation factor assays to detect and identify deficient or abnormal factors. These assays are available as components of reflexive and interpretive testing panels in the Special Coagulation Laboratory (eg, APROL / Prolonged Clot Time Profile, Plasma).

Reference Values:

Clinical References: Favaloro EJ, Lippi G. eds. Hemostasis and Thrombosis, Methods and Protocols. Humana Press. 2017

PTMSC
602183

Prothrombin Time Mix 1:1, Plasma

Clinical Information: This test is only performed when the prothrombin time (PT) is abnormally prolonged. See PTSC / Prothrombin Time (PT), Plasma for an interpretation of results.

Useful For: Screening test to detect a deficiency of 1 or more of the clotting factors of the extrinsic coagulation system (I, II, V, VII, X) due to hereditary deficiency or acquired conditions such as liver disease, vitamin K deficiency, or a specific factor inhibitor Determining the cause of a prolonged prothrombin time, factor deficiency versus factor inhibitor

Interpretation: Prolongation of the prothrombin time (PT) can occur as a result of deficiency of 1 or more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a "nonspecific" inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. PT mixing study, using equal volume patient and normal pool plasma, may be performed on specimens with a prolonged PT to assist in differentiating coagulation factor deficiencies from coagulation inhibitors. Correction of the PT mix to within the normal reference range usually indicates a coagulation factor deficiency (normal plasma in the mixture ensures at least 50% activity of all coagulation factors). If the prolonged PT is due to an inhibitor (specific coagulation factor inhibitor, lupus anticoagulant, heparin, etc), the PT mix typically fails to correct a prolonged PT. However, the presence of a weak inhibitor may be missed by the PT mixing study. Accurate interpretation of both PT and PT mixing study results may often require additional testing. For example, the thrombin time test is helpful for identifying or excluding the presence of heparin, the platelet neutralization procedure (using a modified activated partial thromboplastin [APTT] method) for identifying or excluding lupus anticoagulant, the APTT and dilute Russell viper venom time for further assessment of the common procoagulant pathway, and coagulation factor assays to detect and identify deficient or abnormal factors. These assays are available as components of reflexive and interpretive testing panels in the Special Coagulation Laboratory: ALUPP / Lupus Anticoagulant Profile, Plasma ALBLD / Bleeding Diathesis Profile, Limited, Plasma AATHR / Thrombophilia Profile, Plasma and Whole Blood APROL / Prolonged Clot Time Profile, Plasma ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and

Fibrinolysis (DIC/ICF) Profile, Plasma

Reference Values:
Only orderable as a reflex. For more information see:
ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
AATHR / Thrombophilia Profile, Plasma and Whole Blood
APROL / Prolonged Clot Time Profile, Plasma
ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

9.4-12.5 seconds

Clinical References: Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. 1st ed. Humana Press; 2017

PTTP
40934

Prothrombin Time, Plasma

Clinical Information: Prothrombin is a plasma protein with a molecular weight of 68,700 Da. It is an unstable protein that can split easily into smaller compounds, one of which is thrombin. Prothrombin is formed continually by the liver, and it is continually being used throughout the body for blood clotting. If the liver fails to produce prothrombin, in a day or so the prothrombin concentration in the plasma falls to levels too low to provide normal blood coagulation. Vitamin K is required by the liver for normal activation of prothrombin as well as other clotting factors. Therefore, either lack of vitamin K or the presence of liver disease that prevents normal prothrombin formation can decrease the prothrombin concentration so low that a bleeding tendency results. Prothrombin time (PT) is used as a screening test to detect a deficiency of one or more of the clotting factors of the extrinsic coagulation system (I, II, V, VII, or X) due to a hereditary or acquired deficiency, liver disease, vitamin K deficiency, or presence of inhibitors. Inhibitors include specific coagulation factor inhibitors, Lupus-like anticoagulant inhibitors (eg, antiphospholipid antibodies), and nonspecific prothrombin time inhibitors (eg, monoclonal immunoglobulins, elevated fibrin degradation products). Mixing studies with normal plasma are useful in initial evaluation of prolonged PT when the cause is unknown (eg, not attributable to known oral anticoagulation or known coagulation factor deficiency). One of the following tests may be appropriate, depending on the clinical picture: -ALUPP / Lupus Anticoagulant Profile, Plasma -AATHR / Thrombophilia Profile, Plasma and Whole Blood -ALBLD / Bleeding Diathesis Profile, Limited, Plasma -APROL / Prolonged Clot Time Profile, Plasma PT results produced by different assays may vary significantly as there are differences in activity of the tissue factor and the instrument used to perform the test. Tissue factor is isolated from a variety of sources by assay manufacturers, and different batches may have different activity. Calculation of the international normalized ratio (INR) addresses this problem by normalizing the PT result. For this reason, INR is used to monitor oral anticoagulant therapy (warfarin or Coumadin). Warfarin inhibits the enzyme vitamin K epoxide reductase complex 1 (VKORC1), which is responsible for converting vitamin K to its active, reduced form. By inhibiting VKORC1, warfarin decreases the available active form of vitamin K in the tissues. Thus, when warfarin is given to a patient, the amounts of active prothrombin and factors VII, IX, and X, all formed by the liver degrade and are replaced by inactive factors. Although the coagulation factors continue to be produced, they have greatly decreased coagulant activity. Bleeding is the primary adverse reaction associated with warfarin use, and warfarin is among the top 10 drugs with the largest number of serious adverse events reported to the FDA. For these reasons, monitoring therapy closely and adjusting dose accordingly is critical. The international sensitivity index (ISI) is an experimentally derived measurement, usually provided by the thromboplastin manufacturer, reflecting thromboplastin (and PT) sensitivity to coagulation deficiencies. More sensitive thromboplastins have a low ISI (1.0-1.2), whereas less sensitive thromboplastins have a higher ISI (eg, 2.0-3.0). Calculation of the INR is as follows: INR=(Patient's PT/mean PT of reference range) ISI where: -INR=international normalized ratio

-ISI=international sensitivity index

Useful For: Screening assay to detect deficiencies of one or more coagulation factors (factors I, II, V, VII, X) Screening assay to detect coagulation inhibition Monitoring intensity of oral anticoagulant therapy when combined with INR reporting

Interpretation: Prothrombin time (PT) may be prolonged due to deficiencies of factors X, VII, V, and II of the extrinsic pathway, presence of inhibitors, or oral anticoagulation therapy. INR therapeutic ranges for orally administered drugs: -Standard-intensity warfarin therapeutic range: 2.0 to 3.0 -High-intensity warfarin therapeutic range: 2.5 to 3.5 Note: The INR should only be used for patients on stable oral anticoagulant therapy, though it is reported for all patients despite whether they are receiving oral anticoagulants.

Reference Values:
PROTHROMBIN TIME:
9.4-12.5 seconds

INTERNATIONAL NORMALIZED RATIO (INR):
0.9-1.1

Standard intensity warfarin therapeutic range: 2.0-3.0
High intensity warfarin therapeutic range: 2.5-3.5

Clinical References: 1. Hall JE: Hemostasis and blood coagulation. In: Guyton and Hall Textbook of Medical Physiology. 14th ed. Elsevier Sanders; 2021:447-488 2. Shin J, Kayser SR: Pharmacology of Vitamin K Antagonists. Fang MC, ed. Inpatient Anticoagulation. John Wiley-Blackwell; 2011:25-31 3. Clinical and Laboratory Standards institute (CLSI): One-stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin (APTT) Test. 2nd ed. CLSI document H47-A2, CLSI; 2008

PPFWE
31891

Protoporphyrins, Fractionation, Washed Erythrocytes

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma, and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing protoporphyrin fractions is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyria (XLDPP). Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors exacerbate symptoms, significantly impacting the severity and course of disease. Erythropoietic protoporphyria is caused by diminished ferrochelatase resulting in significantly increased free protoporphyrin levels in erythrocytes, plasma, and feces. X-linked dominant protoporphyria is caused by gain-of-function variants in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin, and total protoporphyrin in plasma and feces. Other possible causes of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron-deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria, a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria, a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing

Algorithm and Porphyria (Cutaneous) Testing Algorithm or call 800-533-1710 to discuss testing strategies. There are 2 test options: -PPFE / Protoporphyrins, Fractionation, Whole Blood -PPFWE / Protoporphyrins, Fractionation, Washed Erythrocytes The whole blood option is easiest for clients but requires that the specimen arrive at Mayo Clinic Laboratories within 7 days of collection. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

Useful For: Preferred test for analysis of erythrocyte protoporphyrin fractions Preferred test for evaluating patients with possible diagnoses of erythropoietic protoporphyria and X-linked dominant protoporphyria Establishing a biochemical diagnosis of erythropoietic protoporphyria, or X-linked dominant protoporphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:
FREE PROTOPORPHYRIN
<20 mcg/dL

ZINC-COMPLEXED PROTOPORPHYRIN
<60 mcg/dL

Clinical References: 1. Tortorelli S, Kloke K, Raymond K. Disorders of porphyrin metabolism. In: Dietzen DJ, Bennett MJ, Wong EDD, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:307-324 2. Phillips JD: Heme biosynthesis and the porphyrias. Mol Genet Metab. 2019;128(3):164-177. doi:10.1016/j.ymgme.2019.04.008 3. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-Linked sideroblastic anemia and the porphyrias. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 6, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225540906&bookid=2709 4. Whatley SD, Ducamp S, Gouya L, et al. C-terminal in the ALAS2 gene lead to gain of function and cause X-linked dominant protoporphyria without anemia or iron overload. Am J Hum Genet. 2008;83(3):408-414

PPFE
8739

Protoporphyrins, Fractionation, Whole Blood

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing protoporphyrin fractions is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyria (XLDPP). Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors exacerbate symptoms, significantly impacting the severity and course of disease. Erythropoietic protoporphyria is caused by diminished ferrochelatase resulting in significantly increased free protoporphyrin levels in erythrocytes, plasma, and feces. X-linked dominant protoporphyria is caused by gain-of-function variants in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin in erythrocytes, and total protoporphyrin levels in plasma and feces. Other possible causes of elevated

erythrocyte zinc-complexed protoporphyrin may include: -Iron-deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria, a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria, a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm or call 800-533-1710 to discuss testing strategies. There are 2 test options: -PPFE / Protoporphyrins, Fractionation, Whole Blood -PPFWE / Protoporphyrins, Fractionation, Washed Erythrocytes The whole blood option is easiest for clients but requires that the specimen arrive at Mayo Clinic Laboratories within 7 days of collection. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

Useful For: Evaluating patients with possible diagnoses of erythropoietic protoporphyria or X-linked dominant protoporphyria Establishing a biochemical diagnosis of erythropoietic protoporphyria and X-linked dominant protoporphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:
FREE PROTOPORPHYRIN
<20 mcg/dL

ZINC-COMPLEXED PROTOPORPHYRIN
<60 mcg/dL

Clinical References: 1. Tortorelli S, Kloke K, Raymond K. Disorders of porphyrin metabolism. In: Dietzen DJ, Bennett MJ, Wong EDD, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:307-324 2. Phillips JD. Heme biosynthesis and the porphyrias. Mol Genet Metab. 2019;128(3):164-177. doi:10.1016/j.ymgme.2019.04.008 3. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-Linked sideroblastic anemia and the porphyrias. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 6, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225540906&bookid=2709 4. Whatley SD, Ducamp S, Gouya L, et al. C-terminal in the ALAS2 gene lead to gain of function and cause X-linked dominant protoporphyria without anemia or iron overload. Am J Hum Genet. 2008;83(3):408-414

PROTR 9797 Protriptyline (Vivactyl)

Reference Values:
Reference Range: 50 - 170 ng/mL

PRSSZ 35532 PRSS1 Gene, Full Gene Analysis, Varies

Clinical Information: Hereditary pancreatitis (HP) is a rare autosomal dominant disorder associated with approximately 80% penetrance. HP is characterized by early onset acute pancreatitis during childhood or early adolescence. The acute pancreatitis in these patients generally progresses to chronic pancreatitis by adulthood and can eventually lead to both exocrine and endocrine pancreatic insufficiency. Patients with HP are also at an increased risk for developing pancreatic cancer. Studies have estimated the

lifetime risk of developing pancreatic cancer to be as high as 40%. Mutations in the protease serine 1 or cationic trypsinogen (PRSS1) gene are a common cause of HP. It has been reported that as many as 80% of patients with symptomatic hereditary pancreatitis have a causative PRSS1 mutation. HP cannot be clinically distinguished from other forms of pancreatitis. However, PRSS1 mutations are generally restricted to individuals with a family history of pancreatitis. PRSS1 mutations are infrequently found in patients with alcohol-induced and tropical pancreatitis. Although several mutations have been identified, the R122H, N29I and A16V mutations are the most common disease-causing mutations associated with HP. Data suggest that the R122H mutation results in more severe disease and earlier onset of symptoms than the A16V mutation. Although these 3 alterations account for >90% of mutations detected in the cationic trypsinogen gene, the inability to identify mutations in approximately 20% of families with HP suggests the involvement of other loci or unidentified mutations in the cationic trypsinogen gene. Mutations in other genes, such as SPINK1, CFTR and CTRC have been associated with hereditary and familial pancreatitis. Abnormalities in these genes are not detected by this assay. However, genetic testing for these genes simultaneously, including PRSS1, is available by ordering HPPAN / Hereditary Pancreatitis Panel.

Useful For: Confirmation of suspected clinical diagnosis of hereditary pancreatitis (HP) in patients with chronic pancreatitis Identification of familial PRSSI mutation to allow for predictive and diagnostic testing in family members

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424 2. Teich N, Mossner J: Hereditary chronic pancreatitis. Best Pract Res Clin Gastroenterol 2008;22(1):115-130 3. Rebours V, Levy P, Ruszniewski P: An overview of hereditary pancreatitis. Dig Liver Dis 2012;44(1):8-15 4. Ellis I: Genetic counseling for hereditary pancreatitis-the role of molecular genetics testing for the cationic trypsinogen gene, cystic fibrosis and serine protease inhibitor Kazal type 1. Gastroenterol Clin North Am 2004;33:839-854 5. Solomon S, Whitcomb DC, LaRusch J. PRSS1-Related Hereditary Pancreatitis. In: GeneReviews. Edited by RA Pagon, MP Adam, HH Ardinger HH, et al: University of Washington, Seattle. 1993-2014. 2012 Mar 1. Available at www.ncbi.nlm.nih.gov/books/NBK84399

PCHE1
606604

Pseudocholinesterase, Total, Serum

Clinical Information: Serum cholinesterase, often called pseudocholinesterase (PCHE), is distinguished from acetylcholinesterase, or "true cholinesterase," by both location and substrate. Acetylcholinesterase is found in erythrocytes, lungs and spleen, nerve endings, and gray matter of the brain. It is responsible for the hydrolysis of acetylcholine released at the nerve endings to mediate transmission of the neural impulse across the synapse. PCHE, the serum enzyme, is found in the liver, pancreas, heart, and white matter of the brain. Its biological role is unknown. The organophosphorus-containing insecticides and herbicides are potent inhibitors of the true cholinesterase and cause depression of PCHE. Low values of PCHE are also found in patients with liver disease. In general, patients with advanced cirrhosis and carcinoma with metastases will show a 50% to 70% decrease. Essentially normal values are seen in chronic hepatitis, mild cirrhosis, and obstructive jaundice. PCHE

metabolizes the muscle relaxants succinylcholine and mivacurium, and therefore, alterations in PCHE will influence the physiologic effect of these drugs. In normal individuals (approximately 94% of the population), certain drugs and other agents such as dibucaine and fluoride will almost completely inhibit the PCHE activity. A small number of individuals (<1% of the population) have been shown to have genetic variants of the enzyme and, therefore, cannot metabolize the muscle relaxants succinylcholine and mivacurium and experience prolonged apnea. These individuals generally have low levels of PCHE, which is not inhibited by dibucaine or fluoride. These individuals are either homozygous or compound heterozygous for an atypical gene controlling PCHE. Simple heterozygous individuals have also been identified who show intermediate enzyme values and inhibition.

Useful For: Monitoring exposure to organophosphorus insecticides and herbicides Monitoring patients with liver disease, particularly those undergoing liver transplantation Identifying patients who are homozygous or heterozygous for an atypical gene and have low levels of pseudocholinesterase This test is not useful for the differential diagnosis of jaundice.

Interpretation: Patients with normal pseudocholinesterase (PCHE) activity show 70% to 90% inhibition by dibucaine, while patients homozygous for the abnormal allele show little or no inhibition (0%-20%) and usually low levels of enzyme. Heterozygous patients have intermediate PCHE levels and response to inhibitors. The atypical gene is inherited in an autosomal recessive pattern. In a positive patient, family members should be tested. Decreasing or low levels may indicate exposure to organophosphorus insecticides or herbicides if liver disease and an abnormal allele have been ruled out.

Reference Values:

Males
5320-12,920 U/L

Females
0-15 years: 5320-12,920 U/L
16-39 years: 4260-11,250 U/L
40-41 years: 5320-12,920 U/L
> or =42 years: 5320-12,920 U/L
Note: Females aged 18-41 years who are pregnant or taking hormonal contraceptives, the reference interval is 3650-9120 U/L.

Clinical References: 1. Soliday FK, Conley YP, Henker R. Pseudocholinesterase deficiency: A comprehensive review of genetic, acquired, and drug influences. AANA J. 2010;78:313-320 2. Robles A, Michael M, McCallum R. Pseudocholinesterase deficiency: What the proceduralist needs to know. Am J Med Sci. 2019;357(3):263-267. doi:10.1016/j.amjms.2018.11.002 3. Lurati AR. Organophosphate exposure with pseudocholinesterase deficiency. Workplace Health and Saf. 2013;61(6):243-245. doi:10.1177/216507991306100602 4. den Blaauwen DH, Poppe WA, Tritschler W. Cholinesterase (EC 3.1.1.8) with butyrylthiocholine-iodide as substrate: References depending on age and sex with special reference to hormonal effects and pregnancy. J Clin Chem Clin Biochem. 1983;21:381-386

PSY
62235

Psychosine, Blood Spot

Clinical Information: Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive lysosomal storage disorder caused by an enzyme deficiency of galactocerebrosidase (GALC). GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates, galactosylceramide, lactosylceramide, and lactosylsphingosine. Krabbe disease is caused by variants in the GALC gene, and it has an estimated frequency of 1 in 100,000 births. The clinical course of Krabbe disease can be variable, even within the same family. Eighty-five percent to 90% of patients present before the first year of life with central nervous system impairment, including increasing irritability,

developmental delay, and sensitivity to stimuli. Rapid neurodegeneration, including white matter disease follows, with death usually occurring by 2 years of age. Late onset forms of the disease affect 10% to15% of individuals and are characterized by ataxia, vision loss, weakness, and psychomotor regression, typically presenting from age 6 months to the seventh decade of life. Newborn screening for Krabbe disease has been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed early, prior to onset of neurologic damage. Psychosine is 1 of 4 substrates degraded by GALC and is a neurotoxin at elevated concentrations. It has been shown to be elevated in patients with active Krabbe disease or with saposin A cofactor deficiency and, therefore, may be a useful biomarker for the presence of disease or disease progression. Reduced or absent GALC in leukocytes (GALCW / Galactocerebrosidase, Leukocytes) or dried blood spots (PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot) along with elevated psychosine levels can indicate a diagnosis of Krabbe disease. Molecular sequencing of the GALC gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, Varies) allows for detection of the disease-causing variants in affected patients and carrier detection in family members. Individuals with a disease phenotype similar to Krabbe disease may have saposin A cofactor deficiency. Saposin A cofactor deficiency also results in elevated psychosine levels. Testing for this condition via molecular analysis of the PSAP gene is useful in those with elevated psychosine and normal to reduced GALC activity with normal molecular genetic GALC sequencing.

Useful For: Aids in the biochemical detection of Krabbe disease and saposin A cofactor deficiency Second-tier testing or follow up testing after an abnormal newborn screening result in an infant for Krabbe disease This test is not capable of identifying carriers of Krabbe disease. This test is not intended for long-term monitoring of individuals being treated for Krabbe disease or for older children or adult patients at risk to develop Krabbe disease.

Interpretation: An interpretive report will be provided. An elevation of psychosine is indicative of symptomatic Krabbe disease or symptomatic saposin A cofactor deficiency. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
Normal <2 nmol/L

Clinical References: 1. Newborn Screening ACT Sheet [Decreased galactocerebrosidase, elevated psychosine] Krabbe Disease (infantile form). American College of Medical Genetics and Genomics; 2021. Updated May 2022. Accessed June 10, 2024. Available at www.acmg.net/PDFLibrary/Krabbe-Infantile.pdf 2. Newborn Screening ACT Sheet [Decreased galactocerebrosidase, mildly elevated psychosine] Krabbe Disease (late-onset form). American College of Medical Genetics and Genomics; 2021. Updated May 2022. Accessed June 10, 2024. Available www.acmg.net/PDFLibrary/Krabbe-Later-Onset.pdf 3. Orsini JJ, Morrissey MA, Slavin LN, et al. Implementation of newborn screening for Krabbe disease: population study and cutoff determination. Clin Biochem. 2009;42(9):877-884. doi:10.1016/j.clinbiochem.2009.01.022 4. Svennerholm L, Vanier MT, Mansson JE. Krabbe disease: A galactosylsphingosine (psychosine) lipidosis. J Lipid Res. 1980;21(1):53-64 5. Enns GM, Steiner RD, Cowan TM. Lysosomal disorders. In: Sarafoglou K, Hoffman G, Roth KS, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. McGraw-Hill Medical; 2009:744 6. Turgeon CT, Orsini JJ, Sanders KA, et al. Measurement of psychosine in dried blood spots--a possible improvement to newborn screening programs for Krabbe disease. J Inherit Metab Dis. 2015;38(5):923-929. doi:10.1007/s10545-015-9822-z 7. Wenger DA, Escolar ML, Luzi P, Rafi MA: Krabbe disease (globoid cell leukodystrophy). In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The

Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed August 30, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225546481&bookid=2709 8. Guenzel AJ, Turgeon CT, Nickander KK, et al. The critical role of psychosine in screening, diagnosis, and monitoring of Krabbe disease. Genet Med. 2020;22(6):1108-1118. doi:10.1038/s41436-020-0764-y 9. Thompson-Stone R, Ream MA, Gelb M, et al. Consensus recommendations for the classification and long-term follow up of infants who screen positive for Krabbe disease. Mol Genet Metab. 2021;134(1-2):53-59. doi:10.1016/j.ymgme.2021.03.016

PSYCF
606146

Psychosine, Spinal Fluid

Clinical Information: Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive lysosomal disorder caused by deficient activity of the enzyme galactocerebrosidase (GALC). GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates, galactosylceramide, lactosylceramide, and lactosylsphingosine. Krabbe disease is caused by variants in the GALC gene, and it has an estimated frequency of 1 in 100,000 births. The clinical course of Krabbe disease can be variable, even within the same family. Eighty-five percent to 90% of patients present before the first year of life with central nervous system impairment, including increasing irritability, developmental delay, and sensitivity to stimuli. Rapid neurodegeneration, including white matter disease follows, with death usually occurring by 2 years of age. Late onset forms of the disease affect 10% to15% of individuals and are characterized by ataxia, vision loss, weakness, and psychomotor regression, typically presenting from age 6 months to the seventh decade of life. Newborn screening for Krabbe disease has been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed prior to onset of neurologic damage. Psychosine is 1 of 4 substrates degraded by GALC and is a neurotoxin at elevated concentrations. It has been shown to be elevated in patients with active Krabbe disease or with saposin A cofactor deficiency and, therefore, may be a useful biomarker for the presence of disease or disease progression. Reduced or absent GALC in leukocytes (CBGC / Galactocerebrosidase, Leukocytes) or dried blood spots (PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot) along with elevated psychosine levels can indicate a diagnosis of Krabbe disease. Molecular sequencing of the GALC gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, Varies) allows for detection of the disease-causing variants in affected patients and carrier detection in family members. Individuals with a disease phenotype similar to Krabbe disease may have saposin A cofactor deficiency. Saposin A cofactor deficiency also results in elevated psychosine levels. Testing for this condition via molecular analysis of PSAP is useful in those with elevated psychosine and normal to reduced GALC activity with normal molecular genetic GALC sequencing.

Useful For: Aiding in the biochemical diagnosis of Krabbe disease using cerebrospinal fluid specimens Follow-up of individuals affected with Krabbe disease Follow-up testing after an abnormal newborn screening result for Krabbe disease Monitoring individuals at risk to develop late onset Krabbe disease Monitoring individuals with Krabbe disease after hematopoietic stem cell transplantation

Interpretation: An elevation of psychosine is indicative of Krabbe disease or saposin A cofactor deficiency.

Reference Values:
Normal < 0.04 nmol/L

Clinical References: 1. Kwon JM, Matern D, Kurtzberg J, et al. Consensus guidelines for newborn screening, diagnosis and treatment of infantile Krabbe disease. Orphanet J Rare Dis. 2018;13(1):30. doi: 10.1186/s13023-018-0766-x 2. Orsini JJ, Escolar ML, Wasserstein MP, et al. Krabbe disease. In: Adam

MP, Mirzaa GM, Pagon RA, eds. GeneReviews[Internet]. University of Washington, Seattle; 2000. Updated October 11, 2018. Accessed August 31, 2023. Available at: www.ncbi.nlm.nih.gov/books/NBK1238/ 3. Turgeon CT, Orsini JJ, Sanders KA, et al. Measurement of psychosine in dried blood spots--a possible improvement to newborn screening programs for Krabbe disease. J Inherit Metab Dis. 2015;38(5):923-929 4. Wenger DA, Escolar ML, Luzi P, Rafi MA: Krabbe disease (globoid cell leukodystrophy). In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed August 31, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225546481&bookid=2709 5. Guenzel AJ, Turgeon CT, Nickander KK, et al. The critical role of psychosine in screening, diagnosis, and monitoring of Krabbe disease. Genet Med. 2020;22(6):1108-1118 6. Thompson-Stone R, Ream MA, Gelb M, et al. Consensus recommendations for the classification and long-term follow up of infants who screen positive for Krabbe disease. Mol Genet Metab. 2021;134(1-2):53-59

PSYR
606145

Psychosine, Whole Blood

Clinical Information: Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive lysosomal disorder caused by deficient activity of the enzyme galactocerebrosidase (GALC). GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates, galactosylceramide, lactosylceramide, and lactosylsphingosine. Krabbe disease is caused by variants in the GALC gene, and it has an estimated frequency of 1 in 250,000 births. The clinical course of Krabbe disease can be variable, even within the same family. Eighty-five percent to 90% of patients present before the first year of life with central nervous system impairment, including increasing irritability, developmental delay, and sensitivity to stimuli. Rapid neurodegeneration, including white matter disease follows, with death usually occurring by 2 years of age. Late onset forms of the disease affect 10% to15% of individuals and are characterized by ataxia, vision loss, weakness, and psychomotor regression, typically presenting from age 6 months to the seventh decade of life. Newborn screening for Krabbe disease has been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed prior to onset of neurologic damage. Psychosine is 1 of 4 substrates degraded by GALC and is a neurotoxin at elevated concentrations. It has been shown to be elevated in patients with active Krabbe disease or with saposin A cofactor deficiency and, therefore, may be a useful biomarker for the presence of disease or disease progression. Reduced or absent GALC in leukocytes (GALCW / Galactocerebrosidase, Leukocytes) or dried blood spots (PLSD / Lysosomal and Peroxisomal Disorders Screen, Blood Spot) along with elevated psychosine levels can indicate a diagnosis of Krabbe disease. Molecular sequencing of the GALC gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, Varies) allows for detection of the disease-causing variants in affected patients and carrier detection in family members. Individuals with a disease phenotype similar to Krabbe disease may have saposin A cofactor deficiency. Saposin A cofactor deficiency also results in elevated psychosine levels. Testing for this condition via molecular analysis of PSAP is useful in those with elevated psychosine and normal to moderately reduced GALC activity with normal molecular genetic GALC sequencing.

Useful For: Aiding in the biochemical diagnosis of Krabbe disease using whole blood specimens Follow-up of individuals affected with Krabbe disease Follow-up testing after an abnormal newborn screening result for Krabbe disease Monitoring of individuals at risk to develop late onset Krabbe disease Monitoring of individuals with Krabbe disease after hematopoietic stem cell transplantation

Interpretation: An elevation of psychosine is indicative of Krabbe disease or saposin A cofactor deficiency.

Reference Values:
Normal <5 pmol/g Hb

Clinical References: 1. Newborn Screening ACT Sheet [Decreased galactocerebrosidase, elevated psychosine] Krabbe Disease (infantile form). American College of Medical Genetics and Genomics; 2021. Updated May 2022. Accessed June 10, 2024. Available at www.acmg.net/PDFLibrary/Krabbe-Infantile.pdf 2. Newborn Screening ACT Sheet [Decreased galactocerebrosidase, mildly elevated psychosine] Krabbe Disease (late-onset form). American College of Medical Genetics and Genomics; 2021. Updated May 2022. Accessed June 10, 2024. Available www.acmg.net/PDFLibrary/Krabbe-Later-Onset.pdf 3. Kwon JM, Matern D, Kurtzberg J, et al. Consensus guidelines for newborn screening, diagnosis and treatment of infantile Krabbe disease. Orphanet J Rare Dis. 2018;13(1):30. doi:10.1186/s13023-018-0766-x 4. Orsini JJ, Escolar ML, Wasserstein MP, et al. Krabbe disease. In: Adam MP, Mirzaa GM, Pagon R, eds. GeneReviews [Interntet]. University of Washington, Seattle; 2000. Updated October 11, 2018. Accessed August 31, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1238/ 5. Turgeon CT, Orsini JJ, Sanders KA, et al. Measurement of psychosine in dried blood spots-a possible improvement to newborn screening programs for Krabbe disease. J Inherit Metab Dis. 2015;38(5):923-929 6. Wenger DA, Escolar ML, Luzi P, Rafi MA. Krabbe disease (globoid cell leukodystrophy). In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed August 31, 2023. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225546481&bookid=2709 7. Guenzel AJ, Turgeon CT, Nickander KK, et al. The critical role of psychosine in screening, diagnosis, and monitoring of Krabbe disease. Genet Med. 2020;22(6):1108-1118. doi:10.1038/s41436-020-0764-y 8. Thompson-Stone R, Ream MA, Gelb M, et al. Consensus recommendations for the classification and long-term follow up of infants who screen positive for Krabbe disease. Mol Genet Metab. 2021;134(1-2):53-59. doi:10.1016/j.ymgme.2021.03.016

PSYQP
610060

Psychotropic Pharmacogenomics Gene Panel, Varies

Clinical Information: This panel provides a comprehensive analysis for multiple genes that have strong pharmacogenomic associations with medications used in the treatment of psychiatric disorders, including depression. Each sample is tested for specific variations with known functional impact. Pharmacogenomic data for the following specific variants are reviewed and reported (if present): -ADRA2A rs1800544 -ANKK1 (DRD2 associated) rs1800497 -CHRNA3 rs1051730 -COMT rs4680 -CYP1A2 *1F, *1K, *6, and *7 -CYP2B6 *4, *5, *6, *7, *8, *9, *11, *12, *13, *14, *15, *16 (also known as *18.002), *18, *19, *20, *22, *26, *27, , *35, *36, and *38 -CYP2C9 *2, *3, *4, *5, *6, *8, *9, *11, *12, *13, *14, *15, *16, *17, *18, *25, *26, *28, *30, *33, and *35 -CYP2C19 *2, *3, *4, *5, *6, *7, *8, *9, *10, *17, and *35 -CYP2D6 *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A (now known as *114), *14B (now known as *14),*15, *17, *29, *35, *36, *41, *59, *68, and CYP2D6 gene duplication; additional CYP2D6 variants may be detected through the reflex testing process -CYP3A4 *8, *11, *12, *13, *16, *17, *18, *22, and *26 -CYP3A5 *3, *6, *7, *8, and *9 -DRD2 rs1799978 -EPHX1 rs2234922 -GRIK4 rs1954787 -HLA-A*31:01 -HLA-B*15:02 -HTR2A rs7997012 -HTR2C rs3813929 and rs1414334 -MTHFR rs1801131 and rs1801133 -OPRM1 rs1799971 -SCN1A rs3812718 -SLC6A4 linked polymorphic region (LPR), a 44-base pair promoter insertion/deletion polymorphism -UGT2B15 rs1902023 Based on the results of each assay, a genotype is assigned, and a phenotype is predicted for each gene. Assessment of multiple genes may assist the ordering clinician with personalized drug recommendations, avoidance of adverse drug reactions, and optimization of drug treatment.

Useful For: Individualizing selection and dosage of medications prescribed for treatment of depression and other psychiatric disorders based on genetic variation Identifying genetic variation in genes known to be associated with response and/or risk of toxicity with psychotropic medications Evaluating patients who have failed therapy with selective serotonin reuptake inhibitors (SSRI) Evaluating patients with treatment-

resistant depression Predicting response time to improvement with SSRI

Interpretation: An interpretive report will be provided that focuses on medications and genes with published pharmacogenomic practice guidance by the Clinical Pharmacogenetics Implementation Consortium or other professional organizations,(1-3) where strong US Food and Drug Administration guidance has been issued in drug labels,(4) or where peer-reviewed literature strongly suggests that assessment of pharmacogenomic variants may enhance patient care.(5-8) For additional information regarding pharmacogenomic genes and their associated medications, see Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. PharmVar: Pharmacogene Variation Consortium. Updated November 5, 2024. Accessed November 14, 2024. Available at www.pharmvar.org/ 2. Clinical Pharmacogenetics Implementation Consortium (CPIC). Updated September 23, 2022. Accessed November 14, 2024.Available at https://cpicpgx.org/ 3. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical Pharmacogenetics Implementation Consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017;102(1):37-44. doi:10.1002/cpt.597 4. U.S National Library of Medicine: DailyMed. National Institutes of Health. Accessed November 14, 2024. Available at https://dailymed.nlm.nih.gov/dailymed/index.cfm 5. Bradley P, Shiekh M, Mehra V, et al. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: A randomized clinical trial demonstrating clinical utility. J Psychiatr Res. 2018;96:100-107 6. Brennan FX, Gardner KR, Lombard J, et al. A naturalistic study of the effectiveness of pharmacogenetic testing to guide treatment in psychiatric patients with mood and anxiety disorders. Prim Care Companion CNS Disord. 2015;17(2). doi:10.4088/PCC.14m01717 7. Perez V, Salavert A, Espadaler J, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. BMC Psychiatry. 2017;17(1):250 8. Reynolds GP, McGowan OO, Dalton CF. Pharmacogenomics in psychiatry: the relevance of receptor and transporter polymorphisms. Br J Clin Pharmacol. 2014;77(4):654-672 9. Crews KR, Monte AA, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther. 2021;110(4):888-896. doi:10.1002/cpt.2149

PTFIB
65820

PT-Fibrinogen, Plasma

Clinical Information: Fibrinogen, also known as factor 1, is a plasma protein that can be transformed by thrombin into a fibrin gel ("the clot"). Fibrinogen is synthesized in the liver and circulates in the plasma as a disulfide-bonded dimer of 3 subunit chains. The biological half-life of plasma fibrinogen is 3 to 5 days. An isolated deficiency of fibrinogen may be inherited as an autosomal recessive trait (afibrinogenemia or hypofibrinogenemia) and is one of the rarest of the inherited coagulation factor deficiencies. Acquired causes of decreased fibrinogen levels include acute or decompensated intravascular coagulation and fibrinolysis (disseminated intravascular coagulation), advanced liver disease, L-asparaginase therapy, and therapy with fibrinolytic agents (eg, streptokinase, urokinase, tissue plasminogen activator). Fibrinogen function abnormalities, dysfibrinogenemias, may be inherited (congenital) or acquired. Patients with dysfibrinogenemia are generally asymptomatic. However, the congenital dysfibrinogenemias are more likely than the acquired to be associated with bleeding or thrombotic disorders. While the dysfibrinogenemias are generally not associated with clinically significant hemostasis problems, they characteristically produce a prolonged thrombin time clotting test. Congenital dysfibrinogenemias usually are inherited as autosomal codominant traits. Acquired dysfibrinogenemias mainly occur in association with liver disease (eg, chronic hepatitis,

hepatoma) or kidney diseases associated with elevated fibrinogen levels. Fibrinogen is an acute-phase reactant, so a number of acquired conditions can result in an increase in its plasma level: -Acute or chronic inflammatory illnesses -Nephrotic syndrome -Liver disease and cirrhosis -Pregnancy or estrogen therapy -Compensated intravascular coagulation The finding of an increased level of fibrinogen in a patient with obscure symptoms suggests an organic rather than a functional condition. Chronically increased fibrinogen has been recognized as a risk factor for development of arterial and venous thromboembolism.

Useful For: Detecting increased or decreased fibrinogen (factor 1) concentration of acquired or congenital origin Differentiating hypofibrinogenemia from dysfibrinogenemia

Interpretation: This test assesses the level of total clottable fibrinogen (see Cautions).

Reference Values:
Only orderable as part of a coagulation reflex. For more information see:
ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
AATHR / Thrombophilia Profile, Plasma and Whole Blood
APROL / Prolonged Clot Time Profile, Plasma
ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

261-595 mg/dL
In normal full-term newborns and in healthy pre-mature infants (30-36 weeks gestation) fibrinogen is near adult levels (>150) and remains at adult levels throughout childhood.

Clinical References: Favaloro EJ, Lippi G. eds. Hemostasis and Thrombosis, Methods and Protocols. Humana Press 2017.

PTNZ
614586

PTEN Hamartoma Tumor Syndrome, PTEN Full Gene Analysis, Varies

Clinical Information: Germline variants in the PTEN gene are associated with a rare group of overlapping clinical syndromes collectively referred to as PTEN hamartoma tumor syndrome (PHTS). This includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, Proteus-like syndrome, and autism with macrocephaly.(1,2) PHTS is inherited in an autosomal dominant manner.(1) Between 10% to 48% of individuals with PHTS have a de novo PTEN variant.(3) Affected individuals have an increased risk of cancer, including cancers of the breast, endometrium, thyroid, kidney, and colon.(1) Individuals with PHTS also may present with macrocephaly, vascular lesions, trichilemmomas, mucocutaneous papillomatous papules, lipomatosis, hemangiomatosis, and pigmented macules on the glans penis.(1) Dysplastic gangliocytoma of the cerebellum, also known as Lhermitte-Duclos disease, is another hamartomatous tumor associated with PHTS.(1) Intellectual disability, developmental delay, and autism are commonly seen in individuals with PHTS.(1) Since it was reported that PTEN variants account for 10% to 20% of individuals with autism with macrocephaly, the American College of Medical Genetics and Genomics has recommended PTEN gene testing in individuals with both features.(4) The long-term clinical outcomes of individuals with PTEN-related autism with macrocephaly is not currently known.(1,2) As such, individuals with PTEN-related autism with macrocephaly should follow the same cancer screening recommendations provided for PHTS.(1,2) The National Comprehensive Cancer Network provides recommendations regarding the medical management of individuals with PHTS.(5)

Useful For: Evaluating patients with a personal or family history suggestive of PTEN hamartoma tumor syndrome (PHTS) Establishing a diagnosis of PHTS allowing for targeted cancer surveillance

based on associated risks Identifying variants within genes known to be associated with increased risk for PHTS allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Yehia L, Eng C. PTEN hamartoma tumor syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2001. Updated February 11, 2021. Accessed November 7, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1488/ 2. Yehia L, Keel E, Eng C. The clinical spectrum of PTEN mutations. Annu Rev Med. 2020;71:103-116 3. Mester J, Eng C. Estimate of de novo mutation frequency in probands with PTEN hamartoma tumor syndrome. Genet Med. 2012;14(9):819-822 4. Schaefer BG, Mendelsohn NJ; Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med. 2013;15(5):399-407 5. Daly MB, Pal T, Berry MP, et al. Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2021;19(1):77-102 6. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

FPTH
90182

PTH Antibody

Reference Values:
Negative

PU1
70545

PU.1 Immunostain, Technical Component Only

Clinical Information: PU.1 is an erythroblast transformation specific family transcription factor that regulates expression of immunoglobulin genes and other genes important in B-cell development. The nuclear protein is expressed in B cells in the germinal center and mantle zone. It is not expressed in plasma cells. PU.1 also plays a role in the differentiation of myeloid cells and is expressed in macrophages (strong staining), mast cells, early erythroid cells, and megakaryocytes. Expression of BOB.1, OCT-2, and PU.1 transcription factors are often downregulated in classical Hodgkin lymphoma. This property can be useful in lymphoma diagnosis.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Marafioti T, Mancini C, Ascani S, et al. Leukocyte-specific

phosphoprotein-1 and PU.1: two useful markers for distinguishing T-cell-rich B-cell lymphoma from lymphocyte-predominant Hodgkin's disease. Haematologica. 2004;89(8):957-964. 2. Torlakovic E, Tierens A, Dang HD, Delabie J. The transcription factor PU.1, necessary for B-cell development is expressed in lymphocyte predominance, but not classical Hodgkin's disease. Am J Pathol. 2001;159(5):1807-1814. doi:10.1016/S0002-9440(10)63027-1 3. Torlakovic E, Tierens A, Dang HD, Delabie J. The transcription factor PU.1, necessary for B-cell development is expressed in lymphocyte predominance, but not classical Hodgkin's disease. Am J Pathol. 2001;159(5):1807-1814. doi:10.1016/S0002-9440(10)63027-1 4. McCune RC, Syrbu SI, Vasef MA. Expression profiling of transcription factors Pax-5, Oct-1, Oct-2, BOB.1, and PU.1 in Hodgkin's and non-Hodgkin's lymphomas: a comparative study using high throughput tissue microarrays. Mod Pathol. 2006;19(7):1010-1018. doi:10.1038/modpathol.3800622 5. Loddenkemper C, Anagnostopoulos I, Hummel M, et al. Differential Emu enhancer activity and expression of BOB.1/OBF.1, Oct2, PU.1, and immunoglobulin in reactive B-cell populations, B-cell non-Hodgkin lymphomas, and Hodgkin lymphomas. J Pathol. 2004;202(1):60-69. doi:10.1002/path.1485 6. Lin J, Liu W, Luan T, et al. High expression of PU.1 is associated with Her-2 and shorter survival in patients with breast cancer. Oncol Lett. 2017;14(6):8220-8226. doi:10.3892/ol.2017.7204 7. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

PUSE
82362

Pumpkin Seed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to pumpkin seed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PUPYP
65151

Purines and Pyrimidines Panel, Plasma

Clinical Information: Purines (adenine, guanine, xanthine, hypoxanthine, uric acid) and pyrimidines (uracil, thymine, cytosine, orotic acid) are involved in all biological processes, providing the basis for storage, transcription, and translation of genetic information as RNA and DNA. Purines are required by all cells for growth and survival and play a role in signal transduction and translation. Purines and pyrimidines originate primarily from endogenous synthesis, with dietary sources contributing only a small amount. The end-product of purine metabolism is uric acid (2,6,8-trioxypurine), which must be excreted continuously to avoid toxic accumulation. Disorders of purine and pyrimidine metabolism can involve all organ systems at any age. The diagnosis of the specific disorders of purine and pyrimidine metabolism is based upon the clinical presentation of the patient, determination of specific concentration patterns of purine and pyrimidine metabolites, and confirmatory enzyme assays and molecular genetic testing. Over 35 inborn errors of purine and pyrimidine metabolism have been documented. Clinical features are dependent upon the specific disorder but represent a broad spectrum of clinical manifestations that may include immunodeficiency, developmental delay, nephropathy, and neurologic involvement. The most common disorder of purine metabolism is deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT), which usually results in classic Lesch-Nyhan syndrome. Lesch-Nyhan syndrome is an X-linked disorder characterized by crystals in urine, neurologic impairment, mild to severe intellectual disability, development of self-injurious behavior, and uric acid nephropathy. Treatments for Lesch-Nyhan syndrome include allopurinol, urine alkalinization and hydration for nephropathy, and supportive management of neurologic symptoms. For milder forms of HPRT deficiency, treatment that can mitigate the potentially devastating effects of these diseases are disorder dependent; therefore, early recognition through screening and subsequent confirmatory testing is highly desirable. Dihydropyrimidine dehydrogenase (DPD) deficiency can result in a severe disorder in infancy involving seizures, intellectual disability, microcephaly, and hypertonia. In its mildest form, however, individuals with DPD deficiency may be asymptomatic but are at risk for life-threatening toxic reactions to a certain class of drugs used to treat cancer called fluoropyrimidines (eg, 5-fluorouracil and capecitabine). If individuals with DPD deficiency ingest this medication, they can develop fluoropyrimidine toxicity. This drug toxicity can result in inflammation of the gastrointestinal tract and associated symptoms, as well as abnormal blood counts including neutropenia and thrombocytopenia.

Useful For: Evaluating patients with symptoms suspicious for disorders of purine and pyrimidine metabolism Monitoring patients with disorders of purine and pyrimidine metabolism Laboratory evaluation of primary and secondary hyperuricemias Assessing tolerance for fluoropyrimidine drugs used in cancer treatment Aiding in the diagnosis of individuals with suspected dihydropyrimidine dehydrogenase deficiency

Interpretation: Abnormal concentrations of measurable compounds will be reported along with an interpretation. The interpretation of an abnormal metabolite pattern includes an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnosis, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis), name, and phone number of contacts who may provide these studies, and a phone number of the laboratory directors in case the referring physician has additional questions.

Reference Values:

Age range	0-1 years	>1-4 years	5-18 years	>18 years
Uracil	< or =2	< or =2	< or =2	< or =2
Thymine	< or =2	< or =2	< or =2	< or =2
Adenine	< or =3	< or =3	< or =3	< or =3
Hypoxanthine	< or =35	< or =17	< or =15	< or =15
Xanthine	< or =6	< or =6	< or =6	< or =3
Dihydroorotic	< or =2	< or =2	< or =2	< or =2
Uric Acid	100-450	150-500	150-500	150-500
Deoxythymidine	< or =2	< or =2	< or =2	< or =2
Deoxyuridine	< or =2	< or =2	< or =2	< or =2
Uridine	< or =14	< or =9	< or =9	< or =9
Deoxyinosine	< or =2	< or =2	< or =2	< or =2
Deoxyguanosine	< or =2	< or =2	< or =2	< or =2
Inosine	< or =2	< or =2	< or =2	< or =2
Guanosine	< or =2	< or =2	< or =2	< or =2
Dihydrouracil	< or =3	< or =3	< or =3	< or =3
Dihydrothymine	< or =2	< or =2	< or =2	< or =2
N-carbamoyl- beta-alanine	< or =2	< or =2	< or =2	< or =2
N-carbamoyl- beta-aminoisobutryic acid	< or =2	< or =2	< or =2	< or =2

Clinical References: 1. Jinnah HA, Friedmann T. Lesch-Nyhan disease and its variants. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed January 4, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225089443 2. Nyhan WL, Hoffmann GF, Al-Aqeel AI, Barshop BA. Introduction to the disorders of purine and pyrimidine metabolism. Atlas of Inherited Metabolic Diseases. 4th ed. CRC Press; 2020:495-495 3. Balasubramaniam S, Duley JA,

Christodoulou J. Inborn errors of purine metabolism: clinical update and therapies. J Inherit Metab Dis. 2014;37:669-686 4. Balasubramaniam S, Duley JA, Christodoulou J. Inborn errors of pyrimidine metabolism: clinical update and therapy. J Inherit Metab Dis. 2014;37:687-698

PUPYU
41977

Purines and Pyrimidines Panel, Random, Urine

Clinical Information: Purines (adenine, guanine, xanthine, hypoxanthine) and pyrimidines (uracil, thymine, cytosine, orotic acid) are involved in all biological processes, providing the basis for storage, transcription, and translation of genetic information as RNA and DNA. Purines are required by all cells for growth and survival and play a role in signal transduction and translation. Purines and pyrimidines originate primarily from endogenous synthesis, with dietary sources contributing only a small amount. The end-product of purine metabolism is uric acid (2,6,8-trioxypurine), which must be excreted continuously to avoid toxic accumulation. Disorders of purine and pyrimidine metabolism can involve all organ systems at any age. The diagnosis of the specific disorders of purine and pyrimidine metabolism is based upon the clinical presentation of the patient, determination of specific concentration patterns of purine and pyrimidine metabolites, and confirmatory enzyme assays and molecular genetic testing. Numerous inborn errors of purine and pyrimidine metabolism have been documented. Clinical features are dependent upon the specific disorder but represent a broad spectrum of manifestations that may include immunodeficiency, developmental delay, nephropathy, and neurologic involvement. The most common disorder of purine metabolism is a deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT) which causes 3 overlapping clinical syndromes, depending on the amount of residual enzyme activity. The majority of patients with HPRT deficiency have classic Lesch-Nyhan syndrome, a severe X-linked disorder characterized by crystals in urine, neurologic impairment, mild to severe intellectual disability, development of self-injurious behavior, and uric acid nephropathy. Treatments for Lesch-Nyhan syndrome include allopurinol, urine alkalinization and hydration for nephropathy, and supportive management of neurologic symptoms. For milder forms of HPRT deficiency, treatment that can mitigate the potentially devastating effects of these diseases are disorder dependent; therefore, early recognition through screening and subsequent confirmatory testing is highly desirable. Urine S-sulfocysteine is elevated in 2 disorders with similar clinical phenotypes: molybdenum cofactor deficiency (MoCD) and isolated sulfite oxidase deficiency. Molybdenum is an important trace element that is biosynthesized into an important cofactor, which is essential for the proper functioning of the enzymes, xanthine oxidase, sulfite oxidase, and aldehyde oxidase, in addition to nitrogenases and nitrate reductase. Four genes are important in mediating the biosynthetic pathway to create molybdenum cofactor, MOCS1, MOCS2, MOCS3, and GPHN (gephyrin). The 3 clinical types of MoCD are autosomal recessive diseases resulting from 2 disease-causing variants in the respective causative gene. MoCDs result in a progressive neurodegenerative disease that manifests with seizures and brain abnormalities in the first weeks to months of life. The most common type of MoCD is MoCD A, caused by variants in MOCS1 and resulting in neonatal or infantile onset seizures and postnatal encephalopathy with rapidly progressive neurodegeneration. Infants with MoCD B (MOCS2 or MOCS3), and C (GPHN) have all been reported but are rare. Infants with MoCD have increased S-sulfocysteine and hypoxanthine and decreased uric acid concentrations in urine. The treatment for MoCD A only is cyclic pyranopterin monophosphate infusion and is most effective when initiated early. Isolated sulfite oxidase deficiency (ISOD) is an autosomal recessive disorder caused by deficiency of the enzyme sulfite oxidase, which results in progressive neurodegenerative disease in most cases. ISOD is the result of disease-causing variants in the SUOX gene. ISOD is a spectrum of disease ranging from severe, early onset disease that appears in the first days of life with seizures, feeding issues, and neurologic issues causing abnormal muscle tone, to mild, later onset disease manifesting after 6 months of age with developmental delay or regression, movement issues, which can be episodic, and ectopia lentis in some cases. Infants with ISOD have increased S-sulfocysteine and normal hypoxanthine concentrations in urine. Treatment is largely symptomatic, with medication for seizures and movement/neurologic issues. Unfortunately, no treatment for the underlying metabolic defect is currently available. Prevalence is unknown, but ISOD is likely underdiagnosed. Hereditary xanthinuria results in kidney stones and, less commonly, muscle pain and cramping caused

by accumulation of xanthine that forms crystals in the kidneys and muscle tissue. There are 2 types of hereditary xanthinuria: type I caused by deficiency of xanthine dehydrogenase resulting from disease-causing variants in the XDH gene, and type II caused by deficiency of molybdenum cofactor sulfurase resulting from variants in the MOCOS gene. Individuals with xanthinuria have increased xanthine and decreased uric acid concentrations in urine. The incidence of both types of hereditary xanthinuria is about 1 in 69,000 individuals.

Useful For: Evaluating patients with symptoms suspicious for disorders of purine and pyrimidine metabolism Monitoring patients with disorders of purine and pyrimidine metabolism Laboratory evaluation of primary and secondary hyperuricemias

Interpretation: Abnormal concentrations of measurable compounds will be reported along with an interpretation. The interpretation of an abnormal metabolite pattern includes an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnosis, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis), name and phone number of contacts who may provide these studies, and a phone number of the laboratory directors in case the referring physician has additional questions.

Reference Values:

Age range	0-3 years	4-6 years	7-12 years	13-18 years
Uracil	< or =50	< or =30	< or =25	< or =20
Thymine	< or =3	< or =3	< or =3	< or =3
Adenine	< or =3	< or =3	< or =3	< or =3
Hypoxanthine	< or =65	< or =30	< or =30	< or =30
Xanthine	< or =54	< or =21	< or =35	< or =15
Orotic	< or =4	< or =4	< or =3	< or =3
Dihydroorotic acid	< or =3	< or =3	< or =3	< or =3
Uric Acid	350-2500	200-2000	200-1400	150-700
Deoxythymidine	< or =3	< or =3	< or =3	< or =3
Deoxyuridine	< or =3	< or =3	< or =3	< or =3
Thymidine	< or =3	< or =3	< or =3	< or =3
Uridine	< or =10	< or =3	< or =3	< or =3
Deoxyadenosine	< or =3	< or =3	< or =3	< or =3
Deoxyinosine	< or =3	< or =3	< or =3	< or =3
Deoxyguanosine	< or =3	< or =3	< or =3	< or =3
Adenosine	< or =3	< or =3	< or =3	< or =3
Inosine	< or =6	< or =3	< or =3	< or =3
Guanosine	< or =4	< or =3	< or =3	< or =3
5-Aminoimidazole-4-carboxamide 1-beta-D-ribofuranoside (AICAR)	< or =3	< or =3	< or =3	< or =3
Succinyladenosine	< or =16	< or =3	< or =3	< or =3
S-Sulfocysteine	< or =11	< or =5	< or =5	< or =5

Dihydrouracil	< or =15	< or =6	< or =6	< or =6
Dihydrothymine	< or =11	< or =3	< or =3	< or =3
N-Carbamoyl-B-alanine	< or =30	< or =10	< or =10	< or =10
N-Carbamoyl-B-aminoisobutyric acid	< or =20	< or =3	< or =3	< or =3

Clinical References: 1. Jinnah HA, Friedmann T. Lesch-Nyhan disease and its variants. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed January 4, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225089443 2. Nyhan WL, Hoffmann GF, Al-Aqeel AI, Barshop BA. Introduction to the disorders of purine and pyrimidine metabolism. Atlas of Inherited Metabolic Diseases. 4th ed. CRC Press; 2020:495-495 3. Balasubramaniam S, Duley JA, Christodoulou J. Inborn errors of purine metabolism: clinical update and therapies. J Inherit Metab Dis. 2014;37(5):669-686 4.. Balasubramaniam S, Duley JA, Christodoulou J. Inborn errors of pyrimidine metabolism: clinical update and therapy. J Inherit Metab Dis. 2014;37(5):687-698 5. Misko AL, Liang Y, Kohl JB, Eichler F. Delineating the phenotypic spectrum of sulfite oxidase and molybdenum cofactor deficiency. Neurol Genet. 2020;6(4):e486

PC1TS
43437

Purkinje Cell Cytoplasmic Antibody Type 1 (PCA-1) Titer, Serum

Clinical Information: Purkinje cell antibody type 1 (PCA-1), also known as anti-Yo, binds to Purkinje cell cytoplasm in a characteristic pattern by indirect immunofluorescence. It is found in the serum, and usually cerebrospinal fluid, of patients with paraneoplastic cerebellar degeneration associated with gynecological or breast carcinoma. It is also found in some patients with sensory, sensorimotor neuropathy, or motor neuropathy with gynecologic cancer. Almost all (99%) seropositive patients are women.

Useful For: Identifying female patients whose subacute cerebellar degeneration or peripheral neuropathy is due to a remote (autoimmune) effect of gynecologic or breast carcinoma Reporting an end titer result from serum specimens

Interpretation: Purkinje cell antibody type 1 (PCA-1) has not been found in any healthy subject. It is rarely found in patients with neurologic diseases (including cerebellar disorders) without gynecologic or breast cancer. The ovarian cancers found in these patients are typically limited in metastatic spread and may not be detected by imaging procedures. If mammography is negative, exploratory laparotomy is advisable (as a "second look" in management of ovarian carcinoma). Breast carcinoma may coexist with a Mullerian cancer. PCA-1 is rarely found in patients with gynecologic cancer without neurologic dysfunction (<2%). PCA-1 is readily distinguished from PCA-Tr (a marker of Hodgkin lymphoma) and PCA-2 (a marker of small-cell lung carcinoma) by standardized staining criteria. PCA-1 rarely, if ever, has accompanying neuronal cytoplasmic or nuclear antibodies.

Reference Values:
Only orderable as a reflex. For further information see:
PAVAL / Paraneoplastic, Autoantibody Evaluation, Serum
ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum
AIAES / Axonal Neuropathy, Autoimmune/Paraneoplastic Evaluation, Serum

<1:240

Neuron-restricted patterns of IgG staining that do not fulfill criteria for Purkinje cell cytoplasmic antibody type 1 may be reported as "unclassified antineuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References: 1. Hetzel DJ, Stanhope CR, O'Neill BP, Lennon VA: Gynecologic cancer in patients with subacute cerebellar degeneration predicted by anti-Purkinje cell antibodies and limited in metastatic volume. Mayo Clin Proc. 1990 Dec;65(12):1558-1563 2. McKeon A, Tracy JA, Pittock SJ, Parisi JE, Klein CJ, Lennon VA. Purkinje cell cytoplasmic autoantibody type 1 accompaniments: the cerebellum and beyond. Arch Neurol. 2011 Oct;68(10):1282-9. doi: 10.1001/archneurol.2011.128 3. Vernino S, Lennon VA: New Purkinje cell antibody (PCA-2): Marker of lung cancer-related neurological autoimmunity. Ann Neurol. 2000 Mar;47(3):297-305 4. Yu Z, Kryzer TJ, Griesmann GE, et al: CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. Ann Neurol 2001 Feb;49(2):146-154 5. Pittock SJ, Kryzer TJ, Lennon VA: Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. Ann Neurol 2004 Nov;56(5):715-719 6. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res 2014 July;20(4):3862-3869

PC1TC
43446

Purkinje Cell Cytoplasmic Antibody Type 1 (PCA-1) Titer, Spinal Fluid

Clinical Information: Purkinje cell cytoplasmic autoantibody type 1 (PCA-1), also known as anti-Yo, binds to Purkinje cell cytoplasm in a characteristic pattern by indirect immunofluorescence. It is found in the serum, and usually cerebrospinal fluid, of patients with paraneoplastic cerebellar degeneration associated with gynecological or breast carcinoma. It is also found in some patients with sensory, sensorimotor, or motor neuropathy with some gynecologic cancer. Almost all (99%) seropositive patients are women.

Useful For: Identifying female patients whose subacute cerebellar degeneration or peripheral neuropathy is due to a remote (autoimmune) effect of gynecologic or breast carcinoma Reporting an end titer result from spinal fluid specimens

Interpretation: Purkinje cell cytoplasmic autoantibody type 1 (PCA-1) has not been found in any healthy subject. It is rarely found in patients with neurologic diseases (including cerebellar disorders) without gynecologic or breast cancer. The ovarian cancers found in these patients are typically limited in metastatic spread and may not be detected by imaging procedures. If mammography is negative, exploratory laparotomy is advised (as a "second look" in management of ovarian carcinoma). Breast carcinoma may coexist with a Mullerian cancer. PCA-1 is rarely found in patients with gynecologic cancer without neurologic dysfunction (<2%). PCA-1 is readily distinguished from PCA-Tr (a marker of Hodgkin lymphoma) and PCA-2 (a marker of small-cell lung carcinoma) by standardized staining criteria. PCA-1 rarely, if ever, has accompanying neuronal cytoplasmic or nuclear antibodies.

Reference Values:

Only orderable as a reflex. For more information see:

ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

<1:2

Neuron-restricted patterns of IgG staining that do not fulfill criteria for Purkinje cell cytoplasmic antibody type 1 may be reported as "unclassified antineuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References: 1. Hetzel DJ, Stanhope CR, O'Neill BP, Lennon VA: Gynecologic cancer in patients with subacute cerebellar degeneration predicted by anti-Purkinje cell antibodies and limited in metastatic volume. Mayo Clin Proc. 1990 Dec;65(12):1558-1563 2. McKeon A, Tracy JA, Pittock SJ, Parisi JE, Klein CJ, Lennon VA. Purkinje cell cytoplasmic autoantibody type 1 accompaniments: the cerebellum and beyond. Arch Neurol. 2011 Oct;68(10):1282-9. doi: 10.1001/archneurol.2011.128 3. Vernino S, Lennon VA: New Purkinje cell antibody (PCA-2): Marker of lung cancer-related neurological autoimmunity. Ann Neurol. 2000 Mar;47(3):297-305 4. Yu Z, Kryzer TJ, Griesmann GE, et al: CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. Ann Neurol. 2001 Feb;49(2):146-154 5. Pittock SJ, Kryzer TJ, Lennon VA: Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. Ann Neurol. 2004 Nov;56(5):715-719 6. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul;20[14]:3862-3869

PC2TS 43438 Purkinje Cell Cytoplasmic Antibody Type 2 (PCA-2) Titer, Serum

Clinical Information: Purkinje cell autoantibodies (PCA) are among the antineuronal autoantibodies (ANNA) recognized clinically as markers of a patient's immune response to specific cancers (paraneoplastic autoantibodies). In 1976, a PCA, defined by indirect immunofluorescence, was described by Dr. John Trotter and colleagues as a serological accompaniment of cerebellar ataxia related to Hodgkin lymphoma. That autoantibody is now known as anti-Tr or PCA-Tr. PCA-1 (or anti-Yo), first described in 1983, serves as a serological marker for a new or recurrent carcinoma of the ovary, other Mullerian tissue, or breast. PCA-1-positive patients are women in 99% of cases. They usually present with subacute cerebellar degeneration, but 10% have sensory or motor neuropathy. In 2000, the Mayo Clinic Neuroimmunology Laboratory described and named PCA-2, a new IgG marker of an immune response to small-cell lung carcinoma (SCLC) in patients presenting with a subacute paraneoplastic neurologic disorder. Other autoantibody markers of immune responses to SCLC include ANNA-1, ANNA-2, ANNA-3, amphiphysin, collapsin response-mediated protein-5 (CRMP-5)-IgG, anti-glial/neuronal nuclear antibody-type 1 (AGNA-1), neuronal calcium channel antibodies (N-type > P/Q-type), ganglionic acetylcholine receptor antibodies, muscle acetylcholine receptor antibodies, neuronal potassium channel antibodies, and striational antibodies.

Useful For: Evaluating patients who present with a subacute neurological disorder of undetermined etiology and have risk factors for lung cancer Reporting an end titer result from serum specimens

Interpretation: A positive value (at 1:240 dilution or higher) is consistent with neurological autoimmunity and justifies a thorough search for a lung cancer, particularly small-cell carcinoma. The cancers are usually limited in metastasis. An extrapulmonary primary small-cell carcinoma (eg, skin, breast, larynx, cervix, prostate) should be considered. Purkinje cell antibody type 2 is found in less than 2% of patients with uncomplicated small-cell lung carcinoma.

Reference Values:

Only orderable as a reflex. For more information see:
-PAVAL / Paraneoplastic, Autoantibody Evaluation, Serum
-DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
-ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
-MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
-MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-AIAES / Axonal Neuropathy, Autoimmune/Paraneoplastic Evaluation, Serum
-DYS2 / Dysautonomia, Autoimmune/Paraneoplastic Evaluation, Serum
-GID2 / Gastrointestinal Dysmotility, Autoimmune/Paraneoplastic Evaluation, Serum

<1:240

Neuron-restricted patterns of IgG staining that do not fulfill criteria for Purkinje cell cytoplasmic antibody type 2 may be reported as "unclassified antineuronal IgG." Complex patterns that include non-neuronal elements may be reported as "uninterpretable."

Clinical References: 1. Galanis E, Frytak S, Rowland KM, et al: Neuronal autoantibody titers in the course of small-cell lung carcinoma and platinum-associated neuropathy. Cancer Immunol Immunother. 1999 May-June;48(2-3):85-90 2. Vernino S, Lennon VA: New Purkinje cell antibody (PCA-2): marker of lung cancer-related neurological autoimmunity. Ann Neurol. 2000 Mar;47(3):297-305 3. McKeon A, Tracy JA, Pittock SJ, Parisi JE, Klein CJ, Lennon VA. Purkinje cell cytoplasmic autoantibody type 1 accompaniments: the cerebellum and beyond. Arch Neurol. 2011 Oct;68(10):1282-9. doi: 10.1001/archneurol.2011.128 4. Pittock SJ, Kryzer TJ, Lennon VA: Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. Ann Neurol. 2004 Nov;56(5):715-719

PC2TC 43447 Purkinje Cell Cytoplasmic Antibody Type 2 (PCA-2) Titer, Spinal Fluid

Clinical Information: Purkinje cell autoantibodies (PCA) are among the antineuronal antibodies (ANNA) recognized clinically as markers of a patient's immune response to specific cancers (paraneoplastic autoantibodies). In 1976, a PCA, defined by indirect immunofluorescence, was described by Dr. John Trotter and colleagues as a serological accompaniment of cerebellar ataxia related to Hodgkin lymphoma. That autoantibody is now known as anti-Tr or PCA-Tr. PCA-1 (or anti-Yo), first described in 1983, serves as a serological marker for a new or recurrent carcinoma of the ovary, other Mullerian tissue, or breast. PCA-1-positive patients are women in 99% of cases. They usually present with subacute cerebellar degeneration, but 10% have sensory or motor neuropathy. In 2000, the Mayo Clinic Neuroimmunology Laboratory described and named PCA-2, a new IgG marker of an immune response to small-cell lung carcinoma (SCLC) in patients presenting with a subacute paraneoplastic neurologic disorder. Other autoantibody markers of immune response to SCLC include ANNA-1, ANNA-2, ANNA-3, amphiphysin, collapsin response-mediator protein-5 (CRMP-5) IgG, antiglial/neuronal nuclear antibody type 1 (AGNA-1), neuronal calcium channel antibodies (N-type > P/Q-type), ganglionic acetylcholine receptor antibodies, muscle acetylcholine receptor antibodies, neuronal potassium channel antibodies, and striational antibodies.

Useful For: Evaluating patients who present with a subacute neurological disorder of undetermined etiology and have risk factors for lung cancer Reporting an end titer result from spinal fluid specimens

Interpretation: A positive value (at 1:2 dilution or higher) is consistent with neurological autoimmunity and justifies a thorough search for a lung cancer, particularly small-cell carcinoma. The cancers are usually limited in metastasis. An extrapulmonary primary small-cell carcinoma (eg, skin, breast, larynx, cervix, prostate) should be considered. Purkinje cell autoantibody type 2 is found in less than 2% of patients with uncomplicated small-cell lung carcinoma.

Reference Values:

Clinical References: 1. Galanis E, Frytak S, Rowland KM, et al: Neuronal autoantibody titers in the course of small-cell lung carcinoma and platinum-associated neuropathy. Cancer Immunol Immunother 1999 May-June;48(2-3):85-90 2. Vernino S, Lennon VA: New Purkinje cell antibody (PCA-2): marker of lung cancer-related neurological autoimmunity. Ann Neurol 2000 Mar;47(3):297-305 3. McKeon A, Tracy JA, Pittock SJ, Parisi JE, Klein CJ, Lennon VA. Purkinje cell cytoplasmic autoantibody type 1 accompaniments: the cerebellum and beyond. Arch Neurol. 2011 Oct;68(10):1282-9. doi: 10.1001/archneurol.2011.128 4. Hetzel DJ, Stanhope CR, O'Neill BP, Lennon VA: Gynecologic cancer in

patients with subacute cerebellar degeneration predicted by anti-Purkinje cell antibodies and limited in metastatic volume. Mayo Clin Proc. 1990 Dec;65(12):1558-15635 5. Horta ES, Lennon VA, Lachance DH, et al: Neural autoantibody clusters aid diagnosis of cancer. Clin Cancer Res. 2014 Jul;20(14):3862-3869

PCTTS 43439 Purkinje Cell Cytoplasmic Antibody Type Tr (PCA-Tr) Titer, Serum

Clinical Information: Purkinje cell autoantibodies are among the antineuronal autoantibodies that are recognized clinically as markers of a patient's immune response to specific cancers (paraneoplastic autoantibodies). The earliest description of a Purkinje cell cytoplasmic antibody (PCA) was reported by Trotter et al in 1976 as a serological accompaniment of paraneoplastic cerebellar ataxia in a patient with Hodgkin lymphoma.(1) IgG of that specificity was recently characterized more fully by Graus et al,(2) who confirmed the association with Hodgkin lymphoma and named the antibody "anti-Tr" in recognition of Dr. John L. Trotter's original report. To accord with a generic classification of neuronal nuclear and cytoplasmic autoantibodies,(3) the name PCA-Tr was introduced to distinguish this Purkinje cell cytoplasmic antibody from PCA-1 (a marker of ovarian or breast carcinoma) and PCA-2 (a marker of small-cell lung carcinoma),(4) which are also found in patients presenting with paraneoplastic neurological autoimmunity.

Useful For: Serological testing for Purkinje cell cytoplasmic antibody-Tr for patients with acquired cerebellar ataxia of undetermined etiology, particularly if the patient has a history of Hodgkin lymphoma Reporting an end titer result from serum specimens

Interpretation: A positive value (at 1:240 dilution or higher) is consistent with neurological autoimmunity and justifies a search for Hodgkin lymphoma. Purkinje cell cytoplasmic antibody type Tr has not yet been identified in any other context. Seropositive patients usually have Hodgkin lymphoma and present with subacute cerebellar ataxia.(1-3)

Reference Values:

Only orderable as a reflex. For more information see:
-PAVAL / Paraneoplastic Autoantibody Evaluation, Serum
-DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
-ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
-MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
-PCDES / Pediatric Autoimmune Encephalopathy/CNS Disorder Evaluation, Serum

<1:240
Neuron-restricted patterns of IgG staining that do not fulfill criteria for Purkinje cell cytoplasmic antibody type-Tr may be reported as "unclassified antineuronal IgG." Complex patterns that include nonneuronal elements may be reported as "uninterpretable."

Clinical References: 1. Trotter JL, Hendin BA, Osterland CK: Cerebellar degeneration with Hodgkin disease. An immunological study. Arch Neurol. 1976 Sep;33(9):660-661 2. Graus F, Gultekin SH, Ferrer I, et al: Localization of the neuronal antigen recognized by anti-Tr antibodies from patients with paraneoplastic cerebellar degeneration and Hodgkin's disease in the rat nervous system. Acta Neuropathologica. 1998 Jul;96(1):1-7 3. Vernino S, Lennon VA: New Purkinje cell antibody (PCA-2): marker of lung cancer-related neurological autoimmunity. Ann Neurol. 2000 Mar;47(3):297-305 4. Graus F, Vincent A, Pozo-Rosich P, et al: Anti-glial nuclear antibody: marker of lung cancer-related paraneoplastic neurological syndromes. J Neuroimmunol. 2005 Aug;165(1-2):166-171 5. Klein CJ: Autoimmune-mediated peripheral neuropathies and autoimmune pain. In: Pittock SJ, Vincent A, eds.

Autoimmune Neurology. Elsevier; 2016: 417-446. Aminoff MJ, Boller F, Swaab DF, eds. Handbook of Clinical Neurology; vol 133

PCTTC 43448 Purkinje Cell Cytoplasmic Antibody, Type Tr (PCA-Tr) Titer, Spinal Fluid

Clinical Information: Purkinje cell autoantibodies are among the antineuronal Purkinje cell autoantibodies are among the antineuronal autoantibodies that are recognized clinically as markers of a patient's immune response to specific cancers (paraneoplastic autoantibodies). The earliest description of a Purkinje cell cytoplasmic antibody (PCA) was reported by Trotter et al in 1976 as a serological accompaniment of paraneoplastic cerebellar ataxia in a patient with Hodgkin lymphoma.(1) IgG of that specificity was recently characterized more fully by Graus et al,(2) who confirmed the association with Hodgkin lymphoma and named the antibody "anti-Tr" in recognition of Dr. John L. Trotter's original report. To be consistent with a generic classification of neuronal nuclear and cytoplasmic autoantibodies,(3) we introduced the name PCA-Tr to distinguish this Purkinje cell cytoplasmic antibody from PCA-1 (a marker of ovarian or breast carcinoma) and PCA-2 (a marker of small-cell lung carcinoma),(4) which also are found in patients presenting with paraneoplastic neurological autoimmunity.

Useful For: Serological testing for Purkinje cell cytoplasmic antibody-Tr for patients with acquired cerebellar ataxia of undetermined etiology, particularly if the patient has a history of Hodgkin lymphoma Reporting an end titer result from spinal fluid specimens

Interpretation: A positive value (at 1:2 dilution or higher) is consistent with neurological autoimmunity and justifies a search for Hodgkin lymphoma. Purkinje cell cytoplasmic antibody-Tr (PCA-Tr) has not yet been identified in any other context. Seropositive patients usually have Hodgkin lymphoma and present with subacute cerebellar ataxia.(1-3)

Reference Values:

Only orderable as a reflex. For more information see:
-DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
-PCDEC / Pediatric Autoimmune Encephalopathy/CNS Disorder Evaluation, Spinal Fluid

<1:2
Neuron-restricted patterns of IgG staining that do not fulfill criteria for Purkinje cell cytoplasmic antibody type Tr may be reported as "unclassified antineuronal IgG." Complex patterns that include non-neuronal elements may be reported as "uninterpretable."

Clinical References: 1. Trotter JL, Hendin BA, Osterland CK: Cerebellar degeneration with Hodgkin disease. An immunological study. Arch Neurol. 1976 Sept;33(9):660-661 2. Graus F, Gultekin SH, Ferrer I, Reiriz J, Alberch J, Dalmau J: Localization of the neuronal antigen recognized by anti-Tr antibodies from patients with paraneoplastic cerebellar degeneration and Hodgkin's disease in the rat nervous system. Acta Neuropathologica. 1998 July;96(1):1-7 3. Vernino S, Lennon VA: New Purkinje cell antibody (PCA-2): marker of lung cancer-related neurological autoimmunity. Ann Neurol. 2000 Mar;47(3):297-305 4. Graus F, Vincent A, Pozo-Rosich P, et al: Anti-glial nuclear antibody: marker of lung cancer-related paraneoplastic neurological syndromes. J Neuroimmunol. 2005 Aug;165(1-2):166-171 5. Klein CJ: Autoimmune-mediated peripheral neuropathies and autoimmune pain. In: Pittock SJ, Vincent A, eds. Autoimmune Neurology. Elsevier; 2016:417-446. Aminoff MJ, Boller F, Swaab DF, eds. Handbook of Clinical Neurology; vol 133

FPYRE
57540

Pyrethrum IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

FPD5C
75891

Pyridoxal 5-phosphate (CSF)

Reference Values:
0 to <3 months: 30-80 nmol/L
3 months to <1 years: 23-65 nmol/L
1 year to <4 years: 15-51 nmol/L
4 years to adult: 10-37 nmol/L

PLP
42359

Pyridoxal 5-Phosphate, Plasma

Clinical Information: Vitamin B6 is a generic term that refers to the pyridine-based compounds pyridoxine, 4-pyridoxic acid (PA), pyridoxamine, pyridoxal, and their phosphorylated derivatives. Pyridoxal-5'-phosphate (PLP) is the biologically active form and serves as a cofactor for more than 140 different enzyme reactions, representing 4% of all known catalytic activity. Deficiencies can occur in people with mutations of pyridoxal kinase (PLK) or pyridoxine 5' phosphate oxidase (PNPOx), as well as in individuals who are pregnant, have kidney disease, are severely malnourished, or have malabsorption. Additionally, deficiencies have been observed with the usage of certain drugs such as isoniazid, penicillamine, benserazide, and carbidopa. Vitamin B6 deficiency is a potential cause of burning mouth syndrome and a possible potentiating factor for carpal tunnel and tarsal tunnel syndromes. Persons who present chronic, progressive nerve compression disorders may be deficient in vitamin B6 and should be evaluated. Vitamin B6 deficiency is associated with symptoms of scaling of the skin, severe gingivitis, irritability, weakness, depression, dizziness, peripheral neuropathy, and seizures. In the pediatric population, deficiencies have been characterized by diarrhea, anemia, and seizures. Conversely, exceptionally high levels of vitamin B6 can also have toxic effects resulting in sensory and motor neuropathies. Markedly elevated PLP in conjunction with low or normal levels of pyridoxic acid are observed in cases of hypophosphatasia, a disorder caused by loss-of-function mutations of the gene ALPL that encodes the tissue-nonspecific isoenzyme of alkaline phosphatase.

Useful For: Determining vitamin B6 status, including in persons who present with progressive nerve compression disorders, such as carpal tunnel and tarsal tunnel syndromes Determining the overall success of a vitamin B6 supplementation program Diagnosis and evaluation of hypophosphatasia

Interpretation: Levels for fasting individuals falling in the range of 3 to 30 mcg/L for pyridoxic acid (PA) and 5 to 50 mcg/L for pyridoxal 5-phosphate (PLP) are indicative of adequate nutrition. The following are interpretative guidelines based upon PLP and PA results: If PLP is >100 mcg/L and PA is < or =30 mcg/L: -The increased pyridoxal 5-phosphate is suggestive of hypophosphatasia. Consider analysis of serum alkaline phosphatase isoenzymes (ALKP / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine). If PLP is >100 mcg/L and PA is 31 to 100 mcg/L or PLP is 81 to 100 mcg/L and PA is < or=30 mcg/L: -The increased pyridoxal 5-phosphate is likely related to dietary supplementation; however, a mild expression of hypophosphatasia cannot be excluded. Consider analysis of serum alkaline phosphatase isoenzymes (ALKP / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary

phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine). If PLP is 51 to 80 mcg/L or PLP is 81 to 100 mcg/L and PA is >30 mcg/L; or PLP is >100 mcg/L and PA is >100 mcg/L: -The elevated PLP is likely due to dietary supplementation.

Reference Values:
5-50 mcg/L

Clinical References: 1.Whyte MP, Zhang F, Wenkert D, Mack KE, et al. Hypophosphatasia: Vitamin B6 status of affected children and adults. Bone. 2022;154:116204. doi:10.1016/j.bone.2021.116204 2. Vitamin B6-Fact Sheet for Health Professionals. US Department of Health and Human Services, National Institutes of Health. Office of Dietary Supplements. Updated June 16, 2023. Accessed February 5, 2025. Available at: https://ods.od.nih.gov/factsheets/VitaminB6-HealthProfessional/ 3. Sodi R, Taylor A. Vitamins and trace elements In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics. 8th ed. Elsevier; 2020:466-487 4. Morris MS, Picciano MF, Jacques PF, Selhub J. Plasma pyridoxal 5'-phosphate in the US population: the National Health and Nutrition Examination Survey, 2003-2004. Am J Clin Nutr. 2008;87(5):1446-54. doi:10.1093/ajcn/87.5.1446 5. Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Cholineexternal link disclaimer. National Academy Press; 1998

B6PA
42361

Pyridoxic Acid, Plasma

Clinical Information: Vitamin B6 is a complex of 6 vitamers: pyridoxal, pyridoxol, pyridoxamine, and their 5'-phosphate esters. Due to its role as a cofactor in many enzymatic reactions, pyridoxal 5-phosphate (PLP) has been determined to be the biologically active form of vitamin B6. Vitamin B6 deficiency is a potential cause of burning mouth syndrome and a possible potentiating factor for carpal tunnel and tarsal tunnel syndromes. Persons who present with chronic, progressive nerve compression disorders may be deficient in vitamin B6 and should be evaluated. Vitamin B6 deficiency is associated with symptoms of scaling of the skin, severe gingivitis, irritability, weakness, depression, dizziness, peripheral neuropathy, and seizures. In the pediatric population, deficiencies have been characterized by diarrhea, anemia, and seizures. Markedly elevated PLP in conjunction with low levels of pyridoxic acid are observed in cases of hypophosphatasia, a disorder characterized by low levels of alkaline phosphatase and a range of skeletal abnormalities.

Useful For: Determining the concentration of pyridoxic acid in the assessment of vitamin B6 status

Interpretation: Levels for fasting individuals falling in the range of 3 to 30 mcg/L for pyridoxic acid (PA) and 5 to 50 mcg/L for pyridoxal 5-phosphate (PLP) are indicative of adequate nutrition. PA results are not clinically significant by themselves and must be interpreted in conjugation with PLP concentrations. The following are interpretative guidelines based on PLP and PA results: If PLP is >100 mcg/L and PA is < or =30 mcg/L: -The increased PLP is suggestive of hypophosphatasia. Consider analysis of serum alkaline phosphatase isoenzymes (ALKI / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine). If PLP is >100 mcg/L and PA is 31 to 100 mcg/L or PLP is 81 to 100 mcg/L and PA is < or =30 mcg/L: -The increased PLP is likely related to dietary supplementation; however, a mild expression of hypophosphatasia cannot be excluded. Consider analysis of serum alkaline phosphatase isoenzymes (ALKI / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine). If PLP is 51 to 80 mcg/L or PLP is 81 to 100 mcg/L and PA is >30 mcg/L or PLP is >100 mcg/L and PA is >100 mcg/L: -The elevated PLP is likely due to dietary supplementation.

Reference Values:
Only orderable as part of a profile. For more information see B6PRO / Vitamin B6 Profile (Pyridoxal 5-Phosphate and Pyridoxic Acid), Plasma.

3-30 mcg/L

Clinical References: 1. Kimura M, Kanehira K, Yokoi K. Highly sensitive and simple liquid chromatographic determination in plasma of B6 vitamins, especially pyridoxal 5'-phosphate. J Chromatogr A. 1996;722(1-2):296-301. doi:10.1016/0021-9673(95)00354-1 2. Ball GFM: Vitamins: Their Role in the Human Body. Blackwell Publishing; 2004;310-325 3. Mackey AD, Davis SR, Gregory JF III: Vitamin B6. In: Shils ME, Shike M, Ross AC, et al. eds. Modern Nutrition in Health and Disease. 10th ed. Lippincott Williams and Wilkins; 2006:452-461 4. Roberts NB. Taylor A. Sodi R: Vitamins and trace elements. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:639-718

P5NT
80650

Pyrimidine 5' Nucleotidase, Blood

Clinical Information: Pyrimidine 5' nucleotidases (P5'Ns) are catabolic enzymes that regulate cellular nucleotide and nucleoside levels through the dephosphorylation of noncyclic nucleoside 5'-monophosphates. P5'N activity is much higher in reticulocytes than in aged red blood cells due to increased demand during erythroid maturation. Reticulocyte ribosomal RNA degradation results in pyrimidine nucleotide residues that require conversion to nucleosides to allow diffusion outside the cell. Disruption of this process results in intracellular pyrimidine nucleotide accumulation visible as coarse basophilic stippling. Several different 5'-nucleotidase enzymes have been identified with distinctive substrate specificity, cellular localization, and tissue distribution. Only P5'N type 1 is known to be associated with P5'N deficiency (also called uridine 5' monophosphate hydrolase deficiency), a cause of congenital nonspherocytic hemolytic anemia (OMIM 266120, autosomal recessive). The disorder manifests as mild/compensated to moderate hemolytic anemia with persistent reticulocytosis. Additional features include jaundice/neonatal hyperbilirubinemia, splenomegaly, and characteristic marked basophilic stippling on the peripheral blood smear. Coincident hemoglobin E may lead to a more severe hemolytic anemia. Pyrimidine 5' nucleotidase deficiency is caused by homozygous or compound heterozygous alterations in the NT5C3A gene, mapped to chromosome 7p14. Assaying for the presence of pyrimidine nucleotides serves as a surrogate marker for P5'N deficiency and is not specific for a diagnosis of hereditary P5'N deficiency. Enzyme function is magnesium ion-dependent and is inhibited by metal chelating reagents, such as EDTA. Activity is inhibited by heavy metal ions including lead, mercury, copper, nickel, and cadmium, and toxic levels can cause accumulation of intracellular pyrimidine nucleotides.

Useful For: Evaluation of marked basophilic stippling Evaluation of hemolytic anemia

Interpretation: A normal result indicates the absence of pyrimidine nucleotides and indicates normal pyrimidine 5' nucleotidase (P5'N) function. An abnormal result (abnormal spectral scan) indicates the presence of pyrimidine nucleotides and possible P5'N deficiency. Enzyme activity is inhibited by heavy metal ions, including lead, mercury, copper, nickel, and cadmium. Toxic levels can cause accumulation of intracellular pyrimidine nucleotides. If results are abnormal clinical correlation is recommended to exclude heavy metal poisoning.

Reference Values:
Normal

Clinical References: 1. Rees DC, Duley JA, Marinaki AM. Pyrimidine 5' nucleotidase deficiency. Br J Haematol. 2003;120(3):375-383 2. Zanella A, Bianchi P, Fermo E, Valentini G. Hereditary

pyrimidine 5'-nucleotidase deficiency: from genetics to clinical manifestations. Br J Haematol. 2006;133(2):113-123 3. Fairbanks VF, Klee GG. Biochemical aspects of hematology. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 3rd ed. WB Saunders; 1999:1642-1647 4. Gregg XT, Prchal JT. Red blood cell enzymopathies. In: Hoffman R, Benz, Jr EJ, et al, eds. Hematology : Basic Principles and Practice, 7th ed. Elsevier; 2018:616-625 5. Warang P, Colah R, Kedar P. Lead poisoning induced severe hemolytic anemia, basophilic stippling, mimicking erythrocyte pyrimidine 5'-nucleotidase deficiency in beta thalassemia minor. J Clin Toxicol. 2017;7(2):1000346. doi:10.4172/2161-0495.1000346

PK1
607459

Pyruvate Kinase Enzyme Activity, Blood

Clinical Information: Deficiencies of most of the enzymes of the Embden-Meyerhof (glycolytic) pathway, including pyruvate kinase (PK), have been reported. PK deficiency (OMIM 266200) is the erythrocyte enzyme deficiency most frequently found to be a cause of chronic nonspherocytic hemolytic anemia. It is an autosomal recessive disorder, and parents of affected patients are typically carriers. Some PK carrier states can exacerbate other red blood cell disorders (ie, coincident glucose 6-phosphate dehydrogenase deficiency or hemoglobin S trait). Clinically significant PK deficiency manifests in widely variable severity ranging from incidental compensated mild normocytic anemia to severe anemia. Neonatal jaundice is very common, and a significant subset of neonates have perinatal complications. Other symptoms include early gallstones and splenomegaly. Iron overload, even in the absence of frequent transfusions, is very common. Rare severe PK deficiency is associated with hydrops fetalis/fetal demise or unexplained noninfectious hepatic failure. Acquired PK deficiency can arise secondary to myeloid neoplasms.

Useful For: Evaluation of nonspherocytic hemolytic anemia Evaluation of neonatal anemia or jaundice Evaluation of unexplained noninfectious hepatic failure Evaluation of unexplained iron overload Evaluation of unusually severe hemoglobin S trait Evaluation of unusually severe glucose 6-phosphate dehydrogenase deficiency Investigating families with pyruvate kinase deficiency to determine inheritance pattern and for genetic counseling

Interpretation: Pyruvate kinase (PK) deficiency is the most easily masked of the red blood cell (RBC) enzyme disorders and can be difficult to classify without complete information, which may require comparison to other RBC enzyme activity levels or correlation with results of PKLR gene molecular testing (PKLRZ / PKLR Full Gene Analysis, Varies). Most hemolytic anemias due to PK deficiency are associated with activity levels less than 40% of mean normal. However, some patients with clinically significant hemolysis can have normal or only mildly decreased PK enzyme activity, which paradoxically may occur in individuals with the most severe symptoms. Isolated carriers (heterozygotes) may show mildly decreased activity and are typically hematologically normal, although the carrier state may exacerbate other RBC disorders such as glucose 6-phosphate dehydrogenase deficiency, RBC membrane disorders, or hemoglobinopathies. Some alterations in other genes (ie, KLF1) can be associated with decreased PK levels. Elevated PK concentrations can be found in those patients with younger erythrocyte population. This may be due to the patient being a newborn or young RBCs are being produced in response to the anemia (reticulocytosis). Rare PK deficient cases have been associated with minimally increased PK levels; however, comparison to other RBC enzyme activity would be critical in these cases for accurate interpretation.

Reference Values:
> or =12 months of age: 5.5-12.4 U/g Hb
Reference values have not been established for patients who are younger than 12 months.

Clinical References: 1. Grace RF, Bianchi P, van Beers EJ, et al. The clinical spectrum of pyruvate kinase deficiency: data from the Pyruvate Kinase Deficiency Natural History Study. Blood.

2018;131(20):2183-2192 2. Gallagher PG, Glader B: Diagnosis of pyruvate kinase deficiency. Pediatr Blood Cancer. 2016;63(5):771-772 3. Grace RF, Zanella A, Neufeld EJ, et al: Erythrocyte pyruvate kinase deficiency: 2015 status report. Am J Hematol. 2015;90(9):825-830 4. Zanella A, Fermo E, Bianchi P, Chiarelli LR, Valentini G: Pyruvate kinase deficiency: the genotype-phenotype association. Blood Rev. 2007;21(4):217-231

PKC
608418

Pyruvate Kinase Enzyme Activity, Blood

Clinical Information: Deficiencies of most of the enzymes of the Embden-Meyerhof (glycolytic) pathway, including pyruvate kinase (PK), have been reported. PK deficiency (OMIM 266200) is the erythrocyte enzyme deficiency most frequently found to be a cause of chronic nonspherocytic hemolytic anemia. It is an autosomal recessive disorder and parents of affected patients are typically carriers. Some PK carrier states can exacerbate other red blood cell disorders (ie, coincident glucose 6-phosphate dehydrogenase deficiency or hemoglobin S trait). Clinically significant PK deficiency manifests in widely variable severity ranging from incidental compensated mild normocytic anemia to severe anemia. Neonatal jaundice is very common, and a significant subset of neonates have perinatal complications. Other symptoms include early gallstones and splenomegaly. Iron overload, even in the absence of frequent transfusions, is very common. Rare severe PK deficiency is associated with hydrops fetalis/fetal demise or unexplained noninfectious hepatic failure. Acquired PK deficiency can arise secondary to myeloid neoplasms.

Useful For: Evaluation of nonspherocytic hemolytic anemia as a part of a profile Evaluation of neonatal anemia or jaundice Evaluation of unexplained noninfectious hepatic failure Evaluation of unexplained iron overload Evaluation of unusually severe hemoglobin S trait Evaluation of unusually severe glucose-6-phosphate dehydrogenase deficiency Investigating families with pyruvate kinase deficiency to determine inheritance pattern and for genetic counseling

Interpretation: Pyruvate kinase (PK) deficiency is the most easily masked of the red blood cell (RBC) enzyme disorders and can be difficult to classify without complete information, which may require comparison to other RBC enzyme activity levels and/or correlation with results of PKLR gene molecular testing (PKLRZ / PKLR Full Gene Analysis, Varies). Most hemolytic anemias due to PK deficiency are associated with activity levels less than 40% of mean normal. However, some patients with clinically significant hemolysis can have normal or only mildly decreased PK enzyme activity, which, paradoxically, may occur in individuals with the most severe symptoms. Isolated carriers (heterozygotes) may show mildly decreased activity and are typically hematologically normal, although the carrier state may exacerbate other RBC disorders such as glucose 6-phosphate dehydrogenase deficiency, RBC membrane disorders, or hemoglobinopathies. Some alterations in other genes (ie, KLF1) can be associated with decreased PK levels. Elevated PK concentrations can be found in those patients with younger erythrocyte population. This may be due to the patient being a newborn or young RBCs are being produced in response to the anemia (reticulocytosis). Rare PK deficient cases have been associated with minimally increased PK levels; however, comparison to other RBC enzyme activity would be critical in these cases for accurate interpretation.

Reference Values:
Only available as part of a profile. For more information see:
HAEV1 / Hemolytic Anemia Evaluation, Blood
EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation, Blood

> or =12 months of age: 5.5-12.4 U/g Hb
Reference values have not been established for patients who are younger than 12 months.

Clinical References: 1. Grace RF, Bianchi P, van Beers EJ, et al. The clinical spectrum of

pyruvate kinase deficiency: data from the Pyruvate Kinase Deficiency Natural History Study. Blood. 2018 ;131(20):2183-2192 2. Gallagher PG, Glader B. Diagnosis of pyruvate kinase deficiency. Pediatr Blood Cancer. 2016;63(5):771-772 3. Grace RF, Zanella A, Neufeld EJ, et al. Erythrocyte pyruvate kinase deficiency: 2015 status report. Am J Hematol. 2015;90(9):825-830 4. Zanella A, Fermo E, Bianchi P, Chiarelli LR, Valentini G. Pyruvate kinase deficiency: the genotype-phenotype association. Blood Rev. 2007;21(4):217-231

PYRC
83356

Pyruvate, Spinal Fluid

Clinical Information: Pyruvic acid, an intermediate metabolite, plays an important role in linking carbohydrate and amino acid metabolism to the tricarboxylic acid cycle, the fatty acid beta-oxidation pathway, and the mitochondrial respiratory chain complex. Though pyruvate is not diagnostic in itself, analysis with lactate has diagnostic value as many inborn errors of metabolism present with laboratory findings that include lactic acidosis and/or a high lactate:pyruvate (L:P) ratio. The L:P ratio is elevated in several, but not all, mitochondrial respiratory chain disorders. Mitochondrial disorders vary widely in presentation and age of onset. Many mitochondrial disorders have neurologic and myopathic features and may involve multiple organ systems. Determination of lactate, pyruvate, and the L:P ratio in cerebrospinal fluid is helpful in directing attention toward a possible mitochondrial disorder in cases with predominantly neurologic dysfunction and normal blood lactate levels. A low L:P ratio is observed in inherited disorders of pyruvate metabolism including pyruvate dehydrogenase complex (PDHC) deficiency. Clinical presentation of PDHC deficiency can range from fatal congenital lactic acidosis to relatively mild ataxia or neuropathy. The most common features in infants and children with PDHC deficiency are delayed development and hypotonia. Seizures and ataxia are also frequent features. Other manifestations can include congenital brain malformations, degenerative changes including Leigh disease, and facial dysmorphism.

Useful For: Investigating possible disorders of mitochondrial metabolism, when used in conjunction with cerebrospinal fluid lactate, collected at the same time, to determine the lactate-to-pyruvate (L:P) ratio Evaluating patients with neurologic dysfunction and normal blood L:P ratios

Interpretation: An elevated lactate-to-pyruvate (L:P) ratio may indicate inherited disorders of the respiratory chain complex, tricarboxylic acid cycle disorders and pyruvate carboxylase deficiency. Respiratory chain defects usually result in L:P ratios above 20. A low L:P ratio (disproportionately elevated pyruvic acid) may indicate an inherited disorder of pyruvate metabolism. Defects of the pyruvate dehydrogenase complex result in L:P ratios below 10. The L:P ratio is characteristically normal in other patients. An artifactually high ratio can be found in acutely ill patients.

Reference Values:
0.06-0.19 mmol/L

Clinical References: 1. Munnich A, Rotig A, Cormier-Daire V, Rustin P. Clinical presentation of Respiratory Chain Deficiency. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed January 14, 2025. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225086827 2. Robinson BH: Lactic acidemia. Disorders of pyruvate carboxylase and pyruvate dehydrogenase. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed January 14, 2025. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225087140 3. Shoffner JM. Oxidative phosphorylation diseases. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill. Accessed January 14, 2025. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225088339 4. Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: a

consensus statement from the Mitochondrial Medicine Society. Genet Med. 2015;17(9):689-701. doi:10.1038/gim.2014.177

PYR
8657

Pyruvic Acid, Blood

Clinical Information: Pyruvic acid, an intermediate metabolite, plays an important role in linking carbohydrate and amino acid metabolism to the tricarboxylic acid cycle, the fatty acid beta-oxidation pathway, and the mitochondrial respiratory chain complex. Though isolated elevated pyruvate is not diagnostic of any inborn error of metabolism, analysis with lactate may suggest an inborn error of metabolism as some present with lactic acidosis or a high lactate-to-pyruvate (L:P) ratio. The L:P ratio is elevated in several, but not all, mitochondrial respiratory chain disorders. Mitochondrial disorders vary widely in presentation and age of onset. Many mitochondrial disorders have neurologic and myopathic features and may involve multiple organ systems. Determination of lactate, pyruvate, and L:P ratio in cerebrospinal fluid is helpful in directing attention toward a possible mitochondrial disorder in cases with predominantly neurologic dysfunction and normal blood lactate levels, though further confirmatory testing will be required to establish a diagnosis. A low L:P ratio is observed in inherited disorders of pyruvate metabolism including pyruvate dehydrogenase complex (PDHC) deficiency. Clinical presentation of PDHC deficiency can range from fatal congenital lactic acidosis to relatively mild ataxia or neuropathy. The most common features in infants and children with PDHC deficiency are delayed development and hypotonia. Seizures and ataxia are also frequent features. Other manifestations can include congenital brain malformations, degenerative changes including Leigh disease, and facial dysmorphism.

Useful For: Screening for possible disorders of mitochondrial metabolism, when used in conjunction with blood lactate collected at the same time, to determine the lactate-to-pyruvate ratio

Interpretation: An elevated lactate-to-pyruvate (L:P) ratio may indicate inherited disorders of the respiratory chain complex, tricarboxylic acid cycle disorders and pyruvate carboxylase deficiency. Respiratory chain defects usually result in L:P ratios above 20. A low L:P ratio (disproportionately elevated pyruvic acid) may indicate an inherited disorder of pyruvate metabolism. Defects of the pyruvate dehydrogenase complex result in L:P ratios below 10. The L:P ratio is characteristically normal in other patients. An artifactually high ratio can be found if the patient is acutely ill. Cerebrospinal fluid (CSF) L:P ratio may assist in evaluation of patients with neurologic dysfunction and normal blood L:P ratios. Blood and CSF specimens should be collected at the same time.

Reference Values:
0.08-0.16 mmol/L

NIH Unit
0.7-1.4 mg/dL

Clinical References: 1. Munnich A, Rotig A, Cormier-Daire V, Rustin P. Clinical presentation of respiratory chain deficiency. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed January 14, 2025.Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225086827 2. Robinson BH. Lactic acidemia: Disorders of pyruvate carboxylase and pyruvate dehydrogenase. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed January 14, 2025. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225087140 3. Shoffner JM. Oxidative phosphorylation diseases. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019 Accessed

January 14, 2025.. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225088339 4. Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genet Med. 2015;17(9):689-701. doi:10.1038/gim.2014.177

QFEVR
616832

Q Fever Antibody Screen with Titer Reflex, Serum

Clinical Information: Q fever, a rickettsial infection caused by Coxiella burnetii, has been recognized as a widely distributed zoonosis with the potential for causing both sporadic and epidemic disease. The resistance of C burnetii to heat, chemical agents, and desiccation allows the agent to survive for extended periods outside the host. C burnetii is spread by the inhalation of infected material, largely from dried sheep and goat reproductive material; the organism is also shed in feces, milk, nasal discharge, placental tissue, and amniotic fluid from ruminant animals. The clinical spectrum of disease ranges from unapparent to fatal. Respiratory manifestations usually predominate; endocarditis and hepatitis can be complications. During the course of the infection, the outer membrane of the organism undergoes changes in its lipopolysaccharide structure, called phase variation. Differences in the host antibody response between phase I and phase II antigens can help classify infections as either acute or chronic: -In acute Q fever, the phase II antibody is generally higher than the phase I titer, often by 4-fold, even in early specimens. Although a rise in phase I as well as phase II titers may occur in later specimens, the phase II titer remains higher. -In chronic Q fever, the reverse situation is generally seen. Serum specimens collected late in the illness from chronic Q fever patients demonstrate significantly higher phase I titers, sometimes much greater than 4-fold. -In the case of chronic granulomatous hepatitis, IgG and IgM titers to phase I and phase II antigens are quite elevated, with phase II titers generally equal to or greater than phase I titers. -Titers seen in Q fever endocarditis are similar in magnitude, although the phase I titers are quite often higher than the phase II titers.

Useful For: Screening for exposure to Coxiella burnetii, the causative agent of Q fever This test should not be used as a screening procedure for the general population.

Interpretation: Negative: No antibodies to Q fever (Coxiella burnetii) detected. Repeat testing on a new sample collected in 2 to 3 weeks if acute Q fever is suspected. Reactive: Not diagnostic. Sample reflexed to the indirect immunofluorescence assay to determine Q fever (Coxiella burnetii) phase I and phase II IgM and IgG titers.

Reference Values:
Negative
Reference values apply to all ages

Clinical References: 1. Hartzell JD, Marrie TJ, Raoult D. Coxiella burnetii (Q fever). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2360-2367 2. Anderson A, Bijlmer H, Fournier PE, et al. Diagnosis and management of Q fever--United States, 2013: recommendations from CDC and the Q Fever Working Group [published correction appears in MMWR Recomm Rep. 2013 Sep 6;62(35):730]. MMWR Recomm Rep. 2013;62(RR-03):1-30

QFP
83149

Q Fever IgM and IgG, Titer, Serum

Clinical Information: Q fever, a rickettsial infection caused by Coxiella burnetii, has been recognized as a widely distributed zoonosis with the potential for causing both sporadic and epidemic disease. The resistance of C burnetii to heat, chemical agents, and desiccation allows the agent to survive for extended periods outside the host. C burnetii is spread by the inhalation of infected material, largely

from dried sheep and goat reproductive material; the organism is also shed in feces, milk, nasal discharge, placental tissue, and amniotic fluid from ruminant animals. The clinical spectrum of disease ranges from unapparent to fatal. Respiratory manifestations usually predominate; endocarditis and hepatitis can be complications. During the course of the infection, the outer membrane of the organism undergoes changes in its lipopolysaccharide structure, called phase variation. Differences in the host antibody response between phase I and phase II antigens can help classify infections as either acute or chronic: -In acute Q fever, the phase II antibody is generally higher than the phase I titer, often by 4-fold, even in early specimens. Although a rise in phase I as well as phase II titers may occur in later specimens, the phase II titer remains higher. -In chronic Q fever, the reverse situation is generally seen. Serum specimens collected late in the illness from chronic Q fever patients demonstrate significantly higher phase I titers, sometimes much greater than 4-fold. -In the case of chronic granulomatous hepatitis, IgG and IgM titers to phase I and phase II antigens are quite elevated, with phase II titers generally equal to or greater than phase I titers. -Titers seen in Q fever endocarditis are similar in magnitude, although the phase I titers are quite often higher than the phase II titers.

Useful For: Diagnosis of Coxiella burnetii, the causative agent of Q fever

Interpretation: A negative result argues against Coxiella burnetii infection. If early acute Q fever infection is suspected, collect a second specimen 2 to 3 weeks later and retest. A negative result following a reactive C burnetii enzyme immunoassay screen suggests a falsely reactive screen. In cases of suspected acute C burnetii infection, repeat testing in 2 to 3 weeks is recommended. Phase I antibody titers greater than or equal to phase II antibody titers are consistent with chronic infection or convalescent phase Q fever. Phase II antibody titers greater than or equal to phase I antibody titers are consistent with acute/active infection. In Q fever sera, it is common to see IgG titers of 1:128 or greater to both phase I and phase II antibody titers. IgG class antibody titers appear very early in the disease, reaching maximum phase II titers by week 8 and persisting at elevated titers for longer than a year. Phase I titers follow the same pattern, although at much lower levels, and may not be initially detected until convalescence. In Q fever sera, it is common to see IgM titers of 1:64 or greater. IgM class antibody titers appear very early in the disease, reaching maximum phase II titers by week 3 and declining to very low levels by week 14. Phase I titers follow the same pattern, although at much lower levels, and may not be initially detected until convalescence.

Reference Values:
Only orderable as a reflex. For more information see QFEVR / Q Fever Antibody Screen with Titer Reflex, Serum.

Q fever phase I antibody, IgG
<1:16

Q fever phase II antibody, IgG
<1:16

Q fever phase I antibody, IgM
<1:16

Q fever phase II antibody, IgM
<1:16

Reference values apply to all ages.

Clinical References: 1. Hartzell JD, Marrie TJ, Raoult D. Coxiella burnetii (Q fever). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2360-2367 2. Anderson A, Bijlmer H, Fournier PE, et al. Diagnosis and management of Q fever--United States, 2013: recommendations from CDC and the Q Fever Working

Group [published correction appears in MMWR Recomm Rep. 2013 Sep 6;62(35):730]. MMWR Recomm Rep. 2013;62(RR-03):1-30

QUAD1
113145

Quad Screen (Second Trimester) Maternal, Serum

Clinical Information: Maternal serum screening is used to identify pregnancies that may have an increased risk for certain birth defects, including neural tube defects (NTD), trisomy 21 (Down syndrome), and trisomy 18 (Edwards syndrome). The screen is performed by measuring analytes in maternal serum that are produced by the fetus and the placenta. The analyte values along with maternal demographic information such as age, weight, gestational age, diabetic status, and race are combined in a mathematical model to derive a risk estimate. A specific cutoff for each condition is used to classify the risk estimate as either screen-positive or screen-negative. A screen-positive result indicates that the value obtained exceeds the established cutoff. A positive screen does not provide a diagnosis but rather indicates that further evaluation should be considered. Analytes: Alpha-Fetoprotein: Alpha-fetoprotein (AFP) is a fetal protein that is initially produced in the fetal yolk sac and liver. A small amount is produced by the gastrointestinal tract. By the end of the first trimester, nearly all AFP is produced by the fetal liver. The concentration of AFP peaks in fetal serum between 10 to 13 weeks. Fetal AFP diffuses across the placental barrier into the maternal circulation. A small amount also is transported from the amniotic cavity. The AFP concentration in maternal serum rises throughout pregnancy, from a non-pregnancy level of 0.2 ng/mL to about 250 ng/mL at 32 weeks gestation. If the fetus has an open NTD, AFP is thought to leak directly into the amniotic fluid causing unexpectedly high concentrations of AFP. Subsequently, the AFP reaches the maternal circulation, thus producing elevated serum levels. Other fetal abnormalities such as omphalocele, gastroschisis, congenital kidney disease, esophageal atresia, and other fetal distress situations (eg, threatened abortion and fetal demise) also may result in maternal serum AFP elevations. Increased maternal serum AFP concentrations also may be seen in multiple pregnancies and in unaffected singleton pregnancies in which the gestational age has been underestimated. Lower maternal serum AFP concentrations have been associated with an increased risk for genetic conditions such as trisomy 21 and trisomy 18. Estriol: Estriol (E3), the principal circulatory estrogen hormone in the blood during pregnancy, is synthesized by the intact feto-placental unit. E3r exists in maternal blood as a mixture of the unconjugated form and a number of conjugates. The half-life of unconjugated estriol (uE3) in the maternal blood system is 20 to 30 minutes because the maternal liver quickly conjugates E3 to make it more water soluble for urinary excretion. E3 levels increase during the course of pregnancy. Decreased uE3 has been shown to be a marker for trisomy 21 and trisomy 18. Low levels of E3 also have been associated with pregnancy loss, Smith-Lemli-Opitz, and X-linked ichthyosis (placental sulfatase deficiency). Decreased second trimester uE3 has been shown to be a marker for trisomy-21 and trisomy-18 syndromes. uE3 is a part of multiple marker prenatal biochemical screening, together with alpha-fetoprotein, human chorionic gonadotropin, and inhibin-A measurements. Low levels of uE3 also have been associated with pregnancy loss, Smith-Lemli-Opitz syndrome (defect in cholesterol biosynthesis), X-linked ichthyosis and contiguous gene syndrome (placental sulfatase deficiency disorders), aromatase deficiency, and primary or secondary fetal adrenal insufficiency. Human Chorionic Gonadotropin: Human chorionic gonadotropin (hCG) is a glycoprotein consisting of 2 noncovalently bound subunits. The alpha subunit is identical to that of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyrotropin (TSH, previously thyroid-stimulating hormone), while the beta subunit has significant homology to the beta subunit of LH and limited similarity to the FSH and TSH beta subunits. The beta subunit determines the unique physiological, biochemical, and immunological properties of hCG. hCG is synthesized by placental cells, starting very early in pregnancy, and serves to maintain the corpus luteum, and hence, progesterone production, during the first trimester. Thereafter, the concentration of hCG begins to fall as the placenta begins to produce steroid hormones and the role of the corpus luteum in maintaining pregnancy diminishes. Increased total hCG levels are associated with trisomy 21, while decreased levels may be seen in trisomy 18. Elevations of hCG also can be seen in multiple pregnancies, unaffected singleton pregnancies in which the gestational age has been overestimated, triploidy, fetal loss, and hydrops fetalis. Inhibin A: Inhibins are a family of heterodimeric glycoproteins, primarily secreted by ovarian granulosa cells and testicular Sertoli cells, which consist of

disulfide-linked alpha and beta subunits. While the alpha subunits are identical in all inhibins, the beta subunits exist in 2 major forms, termed A and B, each of which can occur in different isoforms. Depending on whether an inhibin heterodimer contains a beta A or a beta B chain, they are designated as inhibin A or inhibin B, respectively. Together with the related activins, which are homodimers or heterodimers of beta A and B chains, the inhibins are involved in gonadal-pituitary feedback and in paracrine regulation of germ cell growth and maturation. During pregnancy, inhibins and activins are produced by the feto-placental unit in increasing quantities, mirroring fetal growth. Their physiological role during pregnancy is uncertain. They are secreted into the coelomic and amniotic fluid, but only inhibin A is found in appreciable quantities in the maternal circulation during the first and second trimesters. Maternal inhibin A levels are correlated with maternal hCG levels and are abnormal in the same conditions that are associated with abnormal hCG levels (eg, inhibin A levels are typically higher in trisomy 21 pregnancies). However, despite their similar behavior, measuring maternal serum inhibin A concentrations in addition to maternal serum hCG concentrations further improves the sensitivity and specificity of maternal multiple marker screening for trisomy 21.

Useful For: Prenatal screening for open neural tube defect (alpha-fetoprotein only), trisomy 21 (alpha-fetoprotein, human chorionic gonadotropin, estriol, and inhibin A) and trisomy 18 (alpha-fetoprotein, human chorionic gonadotropin, and estriol)

Interpretation: Neural Tube Defects A screen-negative result indicates that the calculated alpha-fetoprotein (AFP) multiple of the median (MoM) falls below the established cutoff of 2.50 MoM. A negative screen does not guarantee the absence of neural tube defects (NTD). A screen-positive result indicates that the calculated AFP MoM is 2.50 or greater and may indicate an increased risk for open NTD. The actual risk depends on the level of AFP and the individual's pretest risk of having a child with NTD based on family history, geographical location, maternal conditions such as diabetes and epilepsy, and use of folate prior to conception. A screen-positive result does not infer a definitive diagnosis of NTD but indicates that further evaluation should be considered. Approximately 80% of pregnancies affected with NTD have elevated AFP, MoM values greater than 2.5. Trisomy 21 (Down syndrome) and Trisomy 18 (Edwards syndrome): A screen-negative result indicates that the calculated screen risk is below the established cutoff of 1/270 for trisomy 21 and 1/100 for trisomy 18. A negative screen does not guarantee the absence of trisomy 21 or trisomy 18. When a trisomy 21 second-trimester risk cutoff of 1/270 is used for follow-up, the combination of maternal age, AFP, estriol, human chorionic gonadotropin, and inhibin A has an overall detection rate of approximately 77% to 81% with a false-positive rate of 6% to 7%. In practice, both the detection rate and false-positive rate increase with age. The detection rate ranges from 66% (early teens) to 99% (late 40s), with false-positive rates of between 3% and 62%, respectively. The detection rate for trisomy 18 is 60% to 80% using a second trimester cutoff of 1/100. Follow-up Upon receiving maternal serum screening results, all information used in the risk calculation should be reviewed for accuracy (maternal date of birth, gestational dating, etc). If any information is incorrect, the laboratory should be contacted for a recalculation of the estimated risks. Screen-negative results typically do not warrant further evaluation. Ultrasound is recommended to confirm dates for NTD or trisomy 21 screen-positive results. Many pregnancies affected with trisomy 18 are small for gestational age. Recalculations that lower the gestational age may decrease the detection rate for trisomy 18. If ultrasound yields new dates that differ by at least 7 days, a recalculation should be considered. If dates are confirmed, high-resolution ultrasound and amniocentesis (including amniotic fluid AFP and acetylcholinesterase measurements for NTD) are typically offered.

Reference Values:

Neural Tube Defect Risk Estimate:

An alpha-fetoprotein (AFP) multiple of the median (MoM) <2.5 is reported as screen negative.
AFP MoM > or =2.5 (singleton and twin pregnancies) are reported as screen positive.

Down Syndrome Risk Estimate:

Calculated screen risks <1/270 are reported as screen negative, risks > or =1/270 are reported as screen

positive.

Trisomy 18 Risk Estimate:
Calculated screen risks <1/100 are reported as screen negative, risks > or =1/100 are reported as screen positive.

An interpretive report will be provided.

Clinical References: 1. Wald NJ, Cuckle HS, Densem JW, Stone RB. Maternal serum unconjugated oestriol and human chorionic gonadotrophin levels in pregnancies with insulin-dependent diabetes: implications for screening for Down's syndrome. Br J Obstet Gynaecol. 1992;99(1):51-53 2. American College of Obstetricians and Gynecologists. Practice Bulletin No. 163: Screening for Fetal Aneuploidy. Obstet Gynecol. 2016;127(5):e123-137 3. Malone FD, Canick JA, Ball RH, et al. First-trimester or second-trimester screening, or both, for Down's syndrome. N Engl J Med. 2005;353(19):2001-2011 4. Wald NJ, Rodeck C, Hackshaw AK, et al. SURUSS in perspective. Semin Perinatol. 2005;29(4):225-235 5. Rudnicka AR, Wald NJ, Huttly W, Hackshaw AK. Influence of maternal smoking on the birth prevalence of Down syndrome and on second trimester screening performance. Prenat Diagn. 2002;22(10):893-897 6. Zhang J, Lambert-Messerlian G, Palomaki GE, Canick JA. Impact of smoking on maternal serum markers and prenatal screening in the first and second trimesters. Prenat Diagn. 2011;31(6):583-588 7. Yarbrough ML, Stout M, Gronowski AM. Pregnancy and its disorders. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1655-1696

QFT4
113563

QuantiFERON-TB Gold Plus, Blood

Clinical Information: Latent tuberculosis infection (LTBI) is a non-communicable, asymptomatic condition that persists for many years in individuals and may progress to active tuberculosis disease, particularly in patients who are immunosuppressed. The primary goal for diagnosis of LTBI is to initiate medical treatment in order to prevent progression to active disease. Historically, detection of LTBI has been done using the tuberculin skin test (TST). The TST has certain limitations, however, including subjective interpretation, limited sensitivity in immunosuppressed patients, and the possibility of false-positive results in individuals who have received the BCG vaccine or are infected with other mycobacteria. The QuantiFERON-TB Gold Plus (QFT-Plus) test is an interferon (IFN)-gamma release assay (IGRA) that assesses the cell-mediated immune response to 2 Mycobacterium tuberculosis complex antigens, ESAT-6 and CFP-10, by measuring IFN-gamma levels in plasma. These 2 proteins are absent from all BCG strains and from most nontuberculosis mycobacteria with the exception of Mycobacterium kansasii, Mycobacterium szulgai, and Mycobacterium marinum. Individuals infected with M tuberculosis complex agents, including M tuberculosis, Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti, Mycobacterium caprae, and Mycobacterium canetti, usually have lymphocytes in their blood that recognize these specific antigens, and this recognition leads to the generation and secretion of IFN-gamma. This cytokine is subsequently detected and quantified using an IFN-gamma enzyme-linked immunosorbent assay. In an M tuberculosis infection, CD4+ T cells play a critical role in immunological control through secretion of IFN-gamma. The prior version of the QFT-Plus assay, the QuantiFERON-TB Gold In-Tube (QFT-Gold) assay, only detected IFN-gamma secreted from CD4+ T cells. Evidence now supports a role for CD8+ T cells in host defense against M tuberculosis infection by likewise producing IFN-gamma, but also by stimulating macrophages to suppress the growth of M tuberculosis, to kill infected cells, and to directly lyse intracellular M tuberculosis bacteria. IFN-gamma-producing M tuberculosis specific CD8+ T cells have been detected in subjects with LTBI and in patients with active TB. ESAT-6 and CFP-10 specific CD8+ T cells have also been frequently described in patients with active tuberculosis (TB) versus patients with LTBI and have been detected in HIV-positive patients and children with TB disease. The QFT-Plus assay has 2 distinct TB antigen tubes: TB Antigen Tube 1 (TB1) and TB Antigen Tube 2 (TB2). Both tubes contain peptide antigens from ESAT-6 and CFP-10 for stimulation of a CD4+ T-cell IFN-gamma response. However, the TB2 tube also contains an

additional set of ESAT-6 and CFP-10 peptides specifically designed to stimulate a CD8+ T-cell response. For the most up-to-date information regarding use of IGRAs, refer to the most recent guidelines on the Diagnosis of Tuberculosis in Adults and Children from the American Thoracic Society, the Infectious Diseases Society of America, the Centers for Disease Control and Prevention.(1)

TBBS 9336 Quantitative Lymphocyte Subsets: T, B, and Natural Killer (NK) Cells, Blood

Clinical Information: Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer (NK) cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/mcL) and relative (%) quantitation for the main categories of T cells, B cells, and NK cells, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of one or more cell surface markers. The CD3 antigen is a pan-T-cell marker, and T cells can be further divided into 2 broad categories based on the expression of CD4 or CD8 coreceptors. B cells can be identified by expression of CD19 while NK cells are typically identified by the coexpression of CD16 and CD56. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon with no change between noon and afternoon. NK-cell counts, on the other hand, are constant throughout the day.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening(5) and during summer compared to winter.(6) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of T (CD3, CD4, CD8), B (CD19), and NK (CD16+CD56) lymphocytes have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T lymphocytes in patients infected with HIV is associated with increased infections and complications. The US Public Health Service has recommended that all patients who are HIV-positive be tested every 3 to 6 months for the level of CD4 T lymphocytes. Lymphocyte subset quantitation is also very useful in the evaluation of patients with primary immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, or any other relevant clinical condition where immunomodulatory treatment is used. It is also helpful as a preliminary screening assay for gross quantitative anomalies in any lymphocyte subset, whether related to malignancies or infection. The 2008 guidelines for diagnosis and treatment of Chronic Lymphocytic Leukemia (CLL) from the International Workshop on Chronic Lymphocytic Leukemia(7) recommends changing the diagnostic criteria for CLL from an absolute lymphocyte count greater than 5 x 10(9)/L to a circulating B-cell count greater than 5 x 10(9)/L(8,9) previously defined in the 1996 National Cancer Institute (NCI) guidelines for CLL. This flow cytometric assay enables accurate quantitation of circulating B cells using a single platform technology with absolute quantitation through the use of flow cytometry beads.

Useful For: Serial monitoring of CD4 T-cell count in patients who are HIV-positive Follow-up and diagnostic evaluation of primary immunodeficiencies, including severe combined immunodeficiency Immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of immune reconstitution post-

hematopoietic cell transplantation Early screening of gross quantitative anomalies in lymphocyte subsets in infection or malignancies Absolute quantitation of circulating B cells for diagnosis of patients with chronic lymphocytic leukemia as indicated in the 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines

Interpretation: HIV treatment guidelines from the US Department of Health and Human Services and the International Antiviral Society-USA Panel recommend antiviral treatment in all patients with HIV infection, regardless of CD4 T-cell count.(10,11) Additionally, antibiotic prophylaxis for Pneumocystis jiroveci infection is recommended for patients with CD4 count less than 200 cells/mcL. For other opportunistic infections, see the recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.(12)

Reference Values:

The appropriate age-related reference values will be provided on the report.

Clinical References: 1. Carmichael KF, Abayomi A. Analysis of diurnal variation of lymphocyte subsets in healthy subjects and its implication in HIV monitoring and treatment. 15th Intl Conference on AIDS, 2004, Abstract B11052 2. Dimitrov S, Benedict C, Heutling D, Westermann J, Born J, Lange T. Cortisol and epinephrine control opposing circadian rhythms in T-cell subsets. Blood. 2009;113(21):5134-5143 3. Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating antigen presenting cells regulated by sleep. Sleep. 2007;30(4):401-411 4. Kronfol Z, Nair M, Zhang Q, Hill EE, Brown MB. Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Psychosom Med. 1997;59(1):42-50 5. Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS. Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J AIDS. 1990;3(2):144-151 6. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994;34(6):512-516 7. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on chronic lymphocytic leukemia updating the National Cancer Institute Working Group 1996 guidelines. Blood. 2008;111(12):5446-5456 8. Hanson CA, Kurtin PJ, Dogan A. The proposed diagnostic criteria change for chronic lymphocytic leukemia: unintended consequences? Blood. 2009;113(25):6495-6496 9. Hillmen P, Cheson BD, Catovsky D, et al: Response: Letters regarding Blood. 2008;111:5446-5456 by Hanson et al and Mulligan et al. Blood. 2009 Jun;113(25):6497-6498. doi:10.1182/blood-2009-04-165324 10. Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services; Updated February 27, 2024. Accessed August 19, 2024. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf 11. Thompson MA, Horberg MA, Agwu AL, et al. Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2021;73(11):e3572-e3605. Erratum in: Clin Infect Dis. 2021 Dec 08 12. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Department of Health and Human Services; Updated February 17, 2022. Accessed August 19, 2024. Available at https://clinicalinfo.hiv.gov/en/guidelines

TBNK
800295

Quantitative Lymphocyte Subsets: T, B, and NK, Blood

Clinical Information: Normal immunity requires a balance between the activities of various lymphocyte subpopulations with different effector and regulatory functions. Different immune cells can

be characterized by unique surface membrane antigens described by a cluster of differentiation nomenclature (eg, CD3 is an antigen found on the surface of T lymphocytes). Abnormalities in the number and percent of T (CD3), T-helper (CD4), T-suppressor (CD8), B (CD19), and natural killer (CD16+CD56) lymphocytes have been described in a number of different diseases. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T lymphocytes in patients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all patients who are HIV-positive be tested every 3 to 6 months for the level of CD4 T lymphocytes. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day.(1) Circadian variations in circulating T-cell counts have been shown to negatively correlate with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening(5) and during summer compared to winter.(6) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Serial monitoring of CD4 T-cell count in HIV-positive patients Follow-up and diagnostic evaluation of primary immunodeficiencies, including severe combined immunodeficiency Immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of immune reconstitution post hematopoietic cell transplantation Early screening of gross quantitative anomalies in lymphocyte subsets in infection or malignancies Absolute quantitation of circulating B cells for diagnosis of chronic lymphocytic leukemia patients as indicated in the 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines

Interpretation: When the CD4 count falls below 500 cells/mcL, patients who are HIV-positive can be diagnosed with AIDS and can receive antiretroviral therapy. When the CD4 count falls below 200 cells/mcL, prophylaxis against Pneumocystis jiroveci pneumonia is recommended.

Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References: 1. Carmichael KF, Abayomi A: Analysis of diurnal variation of lymphocyte subsets in healthy subjects and its implication in HIV monitoring and treatment. 15th Intl Conference on AIDS. , Bangkok, Thailand, 2004, Abstract B11052 2. Dimitrov S, Benedict C, Heutling D, Westermann J, Born J, Lange T: Cortisol and epinephrine control opposing circadian rhythms in T-cell subsets. Blood. 2009 May 21;113(21):5134-5143 3. Dimitrov S, Lange T, Nohroudi K, Born J: Number and function of circulating antigen presenting cells regulated by sleep. Sleep. 2007 Apr;30(4):401-411 4. Kronfol Z, Nair M, Zhang Q, Hill EE, Brown MB: Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Psychosom Med. 1997 Jan-Feb;59(1):42-50 5. Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS: Sources of variability in repeated T-helper lymphocyte counts from human immunodeficiency virus type 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J Acquir Immune Defic Syndr. 1990;3(2):144-151 6. Paglieroni TG, Holland PV: Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994 Jun;34(6):512-516 7. Hallek M, Cheson BD, Catovsky D, et al: Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute Working Group 1996 guidelines. Blood. 2008 Jun 15;111(12):5446-5456 8. Hanson CA, Kurtin PJ, Dogan A: The proposed diagnostic criteria change for chronic lymphocytic leukemia: unintended consequences? Blood. 2009 Jun

18;113(25):6495-6496 9. Hillmen P, Cheson BD, Catovsky D, et al: Letter to Editor. Blood. 2009;113:6497-6498 10. National Institutes of Health. Guidelines for the use of antiretroviral agents adults and adolescents with HIV. Updated September 21, 2022. Accessed January 17, 2023. Available at https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new-guidelines 11. Thompson MA, Aberg JA, Hoy JF, et al: Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA. 2012 Jul 25;308(4):387-402

QPALM
82863

Queen Palm, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to queen palm Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FQUET 91727 Quetiapine (Seroquel)

Reference Values:
Units: ng/mL

Therapeutic and toxic ranges have not been established. Expected steady-state Quetiapine plasma levels in patients receiving recommended daily dosages: 100 - 1000 ng/mL.

QUIN 8302 Quinidine, Serum

Clinical Information: Quinidine is indicated for atrial fibrillation and flutter, and life-threatening ventricular arrhythmia. Optimal serum concentrations are in the range of 2.0 to 5.0 mcg/mL, with toxicity apparent at levels of 6.0 mcg/mL or higher. Symptoms of toxicity (cinchonism) include tinnitus, light-headedness, premature ventricular contractions, and atrioventricular block. Gastrointestinal distress is a frequent side effect that becomes more severe and is associated with nausea and vomiting at higher drug concentrations. The half-life of quinidine is 6 to 8 hours. Physiologic processes that generally reduce hepatic metabolism and renal clearance increase serum quinidine levels, while comedication with cytochrome p450 (CYP)-enzyme inducers enhances clearance and results in lower blood concentrations.

Useful For: Assessing and adjusting quinidine dosage for optimal therapeutic level Assessing quinidine toxicity

Interpretation: Optimal response to quinidine occurs when the serum level is between 2.0 to 5.0 mcg/mL.

Reference Values:
Therapeutic: 2.0-5.0 mcg/mL
Critical value: > or =6.0 mcg/mL

Clinical References: 1. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453.e9. 2. Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. McGraw-Hill; 2018

FQUIN 57922 Quinoa (Chenopodium quinoa) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.5 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

REPII
82782

Rabbit Epithelium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to rabbit epithelium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

RAMB
82860

Rabbit Meat, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to rabbit meat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

RSER
82544

Rabbit Serum Proteins, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an

allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to rabbit serum proteins Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

RUPR
82148

Rabbit Urine Proteins, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In

individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to rabbit urine proteins Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FRFIT
90330

Rabies Antibody Endpoint

Interpretation: Quantitative results. For those who want to know their exact titer between the reportable range. RFFIT stands for Rapid Fluorescent Foci Inhibition Test. It is a serum neutralization (inhibition) test, which means it measures the ability of rabies specific antibodies to neutralize rabies virus and prevent the virus from infecting cells. The antibodies are called rabies virus neutralizing antibodies (RVNA).

Reference Values:
Reportable range is 0.1 to 15.0 IU/mL

Less than 0.1 IU/mL: Below detection limit

In humans a results of 0.5 IU/mL or higher is considered an acceptable response to rabies vaccination according to the World Health Organization (WHO) guidelines; see WHO and Advisory Committee on Immunization Practices documents for additional guidance.

FRAD
57933

Radish (Raphanus sativus) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

RASE
82366

Rape Seed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to rape seed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal

2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

RWEED
82616

Rape Weed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to rape weed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive

4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BRTP
619957

Rapid Hereditary Breast Cancer Treatment Decision Panel, Varies

Clinical Information: Breast cancers occur in about 12% of the general population.(1) In some cases, breast cancer may be attributed to a hereditary cancer syndrome.(2-5) Evaluation of the genes on this panel may be useful for patients with breast cancer to determine surgical and management decision making. Rapid turnaround time testing allows for informative results to be returned to patients and providers prior to surgery or initiation of other treatment. Hereditary breast and ovarian cancer syndrome (HBOC), caused by disease-causing variants in the BRCA1 and BRCA2 genes, accounts for the majority of hereditary breast cancer.(2,4) HBOC is predominantly characterized by early-onset breast cancer and ovarian cancer. Individuals with HBOC are also at increased risks for prostate, pancreatic, and male breast cancers.(2,4) There are other genes known to increase risk for breast cancer that are included on this panel.(2) The risk for developing cancer associated with these syndromes varies.(2) Some individuals with a disease-causing variant in one of these genes develop multiple primary cancers or bilateral cancers.(2) The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with hereditary breast cancer syndromes.(2,3,6,7)

Useful For: Establishing a diagnosis of a hereditary breast cancer syndrome allowing for surgical and management decision making Determining therapeutic eligibility with poly (adenosine diphosphate-ribose) polymerase inhibitors based on certain gene alterations (eg, BRCA1, BRCA2) in selected tumor types Evaluating patients with breast cancer who have a personal history suggestive of a hereditary breast or gynecological cancer syndrome Identifying genetic variants associated with increased risk for breast cancer, allowing for predictive testing and appropriate screening of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Howlader N, Noone AM, Krapcho M. SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Updated April 2021. Accessed May 11, 2023. Available at https://seer.cancer.gov/csr/1975_2018/ 2. Daly MB, Pal T, Berry M, et al. NCCN Guidelines Insights: Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 2.2021. J Natl Compr Canc Netw. 2021;19(1):77-102 3. Gupta S, Provenzale D, Llor X, et al. NCCN Guidelines Insights: Genetic/familial high-risk assessment: colorectal, version 2.2019. J Natl Compr Canc Netw. 2019;17(9):1032-1041 4. Petrucelli N, Daley MB, Pal T. BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. In: Adams MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet].

University of Washington, Seattle; 1998. Updated September 21, 2023. Accessed September 12, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1247/ 5. Idos G, Valle L. Lynch syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated February 2, 2021. Accessed September 12, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1211/ 6. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007;57(2):75-89 7. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2019;69(3):184-210 8. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

MAL
9240

Rapid Malaria/Babesia Smear, Varies

Clinical Information: Malaria is a mosquito-transmitted disease caused by apicomplexan parasites in the genus Plasmodium. It is an important cause of morbidity and mortality worldwide, with the World Health Organization estimating 219 million cases and 435,000 malaria-related deaths in 2017. Malaria disproportionately affects individuals living in Africa (90% of cases), with individuals living in southeast Asia and the eastern Mediterranean regions next most affected. Malaria is also encountered outside of endemic regions, such as the United States, usually in returning travelers. Malaria is caused primarily by 4 species of the protozoa Plasmodium: Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale. A fifth Plasmodium species, Plasmodium knowlesi, is a simian parasite that may be an important source of human infection in some regions of Southeast Asia. Differentiating P falciparum and P knowlesi from other species is important since both can cause life-threatening infections. In addition, P falciparum is typically resistant to many commonly used antimalarial agents such as chloroquine. Babesiosis is an emergent zoonosis caused by an intraerythrocytic protozoan in the genus Babesia. Babesia microti is responsible for the vast majority of human cases in the United States, with "hot spots" of disease along the Northeast Coast (eg, Martha's Vineyard, Long Island, and Nantucket) and Midwest states, although the distribution of disease is spreading. In addition, a small number of cases of Babesia duncani and Babesia duncani-like human infection (WA and CA strains) have been reported along Pacific Coast states from Washington to northern California, and Babesia divergens/B divergens-like strains have been isolated from humans in Missouri (MO-1 strain), Kentucky, and Washington. At this time, only Babesia microti is a nationally notifiable disease. Babesia microti shares a tick vector with Borrelia burgdorferi and Anaplasma phagocytophilum, the causative agents of Lyme disease and human granulocytic anaplasmosis, respectively. Recent studies suggest that exposure to B microti is quite common in areas endemic for Lyme disease and anaplasmosis, so it is prudent to consider testing for all 3 diseases concurrently. Less commonly, babesiosis may be acquired through blood transfusion, and therefore the US Food and Drug Administration approved testing for this parasite in donor units in 2018. Most patients with babesiosis have a mild illness or are asymptomatic, but some develop a severe illness that may result in death. Patient symptoms may include fever, chills, extreme fatigue, and severe anemia. The most severe cases occur in asplenic individuals and those over 50 years of age. Rare cases of chronic parasitemia, usually in patients who are immunocompromised, have been described. Microscopy of Giemsa-stained thick and thin blood films is the standard laboratory method for diagnosis and differentiation of Plasmodium and Babesia species. Under optimal conditions, the sensitivity of the thick film microscopy is estimated to be 10 to 30 parasites per microliter of blood. This test can also detect trypanosomes that cause Chagas disease (Trypanosoma cruzi) and African sleeping sickness (T brucei) as well as some species of filariae. If filarial infection is suspected, FIL / Filaria, Blood is recommended since it is more sensitive than the traditional blood smear examination. Examination of the thin film allows for calculation of malaria percent parasitemia, which can be used to predict prognosis and monitor response to treatment for patients with malaria and babesiosis. The percentage of parasitemia represents the percentage of infected red blood cells. This is calculated from representative microscopic fields on the

thin blood film. Malarial gametocytes are not included in the calculation since they are not infectious to humans and are not killed by most antimalarial drugs.

Useful For: Rapid and accurate detection and species identification of Plasmodium Detection of Babesia, trypanosomes, and some species of microfilariae

Interpretation: A positive smear indicates infection with the identified species of Plasmodium or with Babesia. Species identification can indicate the appropriate antimalarial therapy.

Reference Values:
Negative

If positive, organism identified and percent parasitemia calculated, if applicable.

Clinical References: Mathison BA, Pritt BS. Update on malaria diagnostics and test utilization. J Clin Microbiol. 2017;55(7):2009-2017

RPRT1
616863

Rapid Plasma Reagin (RPR) Screen with Reflex to Titer, Serum

Clinical Information: Syphilis is caused by infection with the spirochete Treponema pallidum subspecies pallidum. The infection is systemic, and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial nontreponemal screening test, such as the rapid plasma reagin (RPR) or the VDRL tests. Because these tests measure the host's immune response to nontreponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorption (FTA-ABS) or microhemagglutination (MHA-TP) assay. Although the FTA-ABS and MHA-TP assays are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. As an alternative to the traditional syphilis screening algorithm, many laboratories utilize the reverse syphilis screening algorithm. This algorithm starts with an automated treponemal assay to detect antibodies specific to T pallidum. If this screening assay is positive, the sample is reflexed for testing by RPR, which, if positive, is reported with a titer and is indicative of active or recent syphilis infection. If the RPR is negative, the sample is reflexed to a second treponemal assay, such as the T pallidum particle agglutination (TP-PA) assay. If the TP-PA is positive, this would indicate previously treated or late-stage syphilis infection. Alternatively, if the TP-PA is negative, the initial positive screen is interpreted as a false positive result. Patients with primary or secondary syphilis are typically tested by RPR to monitor response to treatment. Typically, RPR titers decrease following successful treatment, but this may occur over a period of months to years. Additionally, testing of maternal and neonate serum, collected concurrently, by RPR can be used as an aid to diagnose congenital syphilis.

Useful For: Determining the current disease status Monitoring response to therapy for syphilis Aid to diagnose congenital syphilis This test cannot be used for testing spinal fluid specimens. This test is not intended for medical-legal use.

Interpretation: Negative: Nontreponemal antibodies not detected. Positive: Specimen reflexed to determine rapid plasma reagin titer.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Centers for Disease Control and Prevention (CDC). Discordant results from reverse sequence syphilis screening-five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011;60(5):133-137 2. Radolf JD, Tramont EC, Salazar JC. Syphilis (Treponema pallidum). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2865-2892 3. Binnicker MJ, Jespersen DJ, Rollins LO. Direct comparison of the traditional and reverse syphilis screening algorithms in a population with a low prevalence of syphilis. J Clin Microbiol. 2012;50(1):148-150

RPRT3 616970 Rapid Plasma Reagin (RPR) with Reflex to Treponema pallidum Particle Agglutination, Serum

Clinical Information: Syphilis is caused by infection with the spirochete Treponema pallidum subspecies pallidum. The infection is systemic, and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial nontreponemal screening test, such as the rapid plasma reagin (RPR) or the VDRL tests. Because these tests measure the host's immune response to nontreponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorption (FTA-ABS) or microhemagglutination (MHA-TP) assay. Although the FTA-ABS and MHA-TP assays are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. As an alternative to the traditional syphilis screening algorithm, many laboratories utilize the reverse syphilis screening algorithm. This algorithm starts with an automated treponemal assay to detect antibodies specific to T pallidum. If this screening assay is positive, the sample is reflexed for testing by RPR, which, if positive, is reported with a titer and is indicative of active or recent syphilis infection. If the RPR is negative, the sample is reflexed to a second treponemal assay, such as the T pallidum particle agglutination (TP-PA) assay. If the TP-PA is positive, this would indicate previously treated or late-stage syphilis infection. Alternatively, if the TP-PA is negative, the initial positive screen is interpreted as a false positive result. Patients with primary or secondary syphilis are typically tested by RPR to their monitor response to treatment. Typically, RPR titers decrease following successful treatment, but this may occur over a period of months to years. Additionally, testing of maternal and neonate serum, collected concurrently, by RPR can be used as an aid to diagnose congenital syphilis.

Useful For: Diagnosing syphilis

Interpretation: Negative: Non-treponemal antibodies not detected. Testing on a new specimen collected in 2 to 3 weeks is recommended if acute infection is suspected. Sample reflexed for detection of Treponema pallidum specific antibodies by the T pallidum particle agglutination assay. Positive: Specimen reflexed to determine rapid plasma reagin titer.

Reference Values:
Negative

Reference values apply to all ages.

Clinical References: 1. Tuddenham S, Katz SS, Ghanem KG. Syphilis Laboratory Guidelines: Performance characteristics of nontreponemal antibody tests. Clin Infect Dis. 2020;71(Suppl 1):S21-S42. doi:10.1093/cid/ciaa306 2. Park IU, Tran A, Pereira L, Fakile Y. Sensitivity and specificity of treponemal-specific tests for the diagnosis of syphilis. Clin Infect Dis. 2020;71(Suppl 1):S13-S20. doi:10.1093/cid/ciaa349 3. Theel ES, Katz SS, Pillay A. Molecular and direct detection tests for Treponema pallidum subspecies pallidum: A review of the literature, 1964-2017. Clin Infect Dis.

2020;71(Suppl 1):S4-S12. doi:10.1093/cid/ciaa176 4. Ortiz DA, Shukla MR, Loeffelholz MJ. The traditional or reverse algorithm for diagnosis of syphilis: Pros and cons. Clin Infect Dis. 2020;71(Suppl 1):S43-S51. doi:10.1093/cid/ciaa307

RRPRS
616866

Rapid Plasma Reagin Screen with Reflex to Titer, Serum

Clinical Information: Syphilis is caused by infection with the spirochete Treponema pallidum subspecies pallidum. The infection is systemic, and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial nontreponemal screening test, such as the rapid plasma reagin (RPR) or the VDRL tests. Because these tests measure the host's immune response to nontreponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorption (FTA-ABS) or microhemagglutination (MHA-TP) assay. Although the FTA-ABS and MHA-TP assays are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. As an alternative to the traditional syphilis screening algorithm, many laboratories utilize the reverse syphilis screening algorithm. This algorithm starts with an automated treponemal assay to detect antibodies specific to T pallidum. If this screening assay is positive, the sample is reflexed for testing by RPR, which, if positive, is reported with a titer and is indicative of active or recent syphilis infection. If the RPR is negative, the sample is reflexed to a second treponemal assay, such as the T pallidum particle agglutination (TP-PA) assay. If the TP-PA is positive, this would indicate previously treated or late-stage syphilis infection. Alternatively, if the TP-PA is negative, the initial positive screen is interpreted as a false-positive result. Syphilis screening at Mayo Clinic is performed using the reverse algorithm, which first tests sera for T pallidum specific IgG antibodies using an automated enzyme immunoassay. A positive treponemal test suggests infection with T pallidum but does not distinguish between recent, past, treated, or untreated infections. This is because treponemal tests may remain reactive for life, even following adequate therapy. Therefore, the results of a nontreponemal assay, such as RPR, are needed to provide information on a patient's disease state and history of therapy.(Table) In some patients, the results of the treponemal screening test and RPR may be discordant (eg, syphilis IgG positive and RPR negative). To discriminate between a falsely reactive screening result and past syphilis, a second treponemal-specific antibody test is recommended using a method that is different from the initial screen test (eg, TP-PA). In the setting of a positive syphilis IgG screening result and a negative RPR, a positive TP-PA result is consistent with either 1) past, successfully treated syphilis, 2) early syphilis with undetectable RPR, or 3) late/latent syphilis in patients who do not have a history of treatment for syphilis. Further historical evaluation is necessary to distinguish between these scenarios.(Table) In the setting of a positive syphilis IgG screening result and a negative RPR, a negative TP-PA result is most consistent with a falsely reactive syphilis IgG screen.(Table) If syphilis remains clinically suspected, a second specimen should be submitted for testing. Table. Interpretation and follow-up of reverse screening results: Test and result Patient history Syphilis IgG antibody by EIA RPR TP-PA Interpretation Follow-up Unknown history of syphilis Nonreactive NA NA No serologic evidence of syphilis None, unless clinically indicated (eg, early/acute/ primary syphilis) Unknown history of syphilis Reactive Reactive NA Untreated or recently treated syphilis See Centers for Disease Control and Prevention treatment guidelines Unknown history of syphilis Reactive Nonreactive Nonreactive Probable false-positive screening test No follow-up testing, unless clinically indicated (eg, acute/ primary syphilis) Unknown history of syphilis Reactive Nonreactive Reactive Possible syphilis (eg, early or latent) or previously treated syphilis Historical and clinical evaluation required Unknown history of syphilis Equivocal NA NA NA Unknown history of syphilis Known history of syphilis Reactive Nonreactive Reactive or NA Past, successfully treated syphilis None EIA-enzyme immunoassay NA-not applicable RPR-rapid plasma reagin TP-PA-T pallidum particle agglutination

Useful For: Aid for the diagnosis of infection with Treponema pallidum Rapid plasma reagin testing following a positive treponemal antibody test This test is not useful as a screening or confirmatory test for

blood donor specimens.

Interpretation: Negative: Treponema pallidum-particle agglutination has been ordered to distinguish between infection with T pallidum (syphilis) versus a falsely reactive treponemal antibody result. Positive: Specimen reflexed to determine rapid plasma reagin titer value.

Reference Values:

Only orderable as a reflex. For more information see SYPH1 / Syphilis IgG with Reflex, Enzyme Immunoassay, Serum.

Negative
Reference values apply to all ages

Clinical References: 1. Centers for Disease Control and Prevention (CDC). Discordant results from reverse sequence syphilis screening-five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011;60(5):133-137 2. Radolf JD, Tramont EC, Salazar JC. Syphilis (Treponema pallidum). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2865-2892 3. Binnicker MJ, Jespersen DJ, Rollins LO. Direct comparison of the traditional and reverse syphilis screening algorithms in a population with a low prevalence of syphilis. J Clin Microbiol. 2012;50(1):148-150. doi:10.1128/JCM.05636-11

RPRS
603261

Rapid Plasma Reagin Screen with Reflex, Serum

Clinical Information: Syphilis is a disease caused by infection with the spirochete Treponema pallidum. The infection is systemic, and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial non-treponemal screening test, such as the rapid plasma reagin (RPR) or VDRL tests. Because these tests measure the host's antibody response to non-treponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorbed (FTA-ABS) or microhemagglutination assay (MHA-TP). Although the FTA-ABS and MHA-TP are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. As an alternative to the traditional syphilis screening algorithm as described above, many laboratories utilize the reverse syphilis screening algorithm. This algorithm starts with an automated treponemal assay, such as an enzyme immunoassay and multiplex flow immunoassay (MFI), to detect antibodies specific to T pallidum. If the screening assay is positive, the sample is reflexed to a RPR assay, which, if positive, is reported with a titer and is indicative of active or recent syphilis infection. If the RPR is negative, the sample is reflexed to a second treponemal assay, such as the T pallidum particle agglutination (TP-PA) assay. If the TP-PA is positive, this would indicate previously treated or late stage syphilis infection. Alternatively, if the TP-PA is negative, the initial positive screen is interpreted as a false positive result. Syphilis screening at Mayo Clinic is performed by using the reverse algorithm, which first tests sera for T pallidum specific IgG/IgM antibodies using an automated MFI. A positive treponemal test suggests infection with T pallidum, but does not distinguish between recent or past, or treated and untreated infection. This is because treponemal tests may remain reactive for life, even following adequate therapy. Therefore, the results of a non-treponemal assay, such as RPR, are needed to provide information on a patient's disease state and history of therapy.(Table 1) In some patients, the results of the treponemal screening test and RPR may be discordant (eg, syphilis IgG/IgM positive and RPR negative). To discriminate between a falsely reactive screening result and past syphilis, a second treponemal-specific antibody test is recommended using a method that is different from the initial screen test (eg, -TP-PA). In the setting of a positive syphilis IgG/IgM screening

result and a negative RPR, a positive TP-PA result is consistent with either 1) past, successfully treated syphilis, 2) early syphilis with undetectable RPR titers, or 3) late/latent syphilis in patients who do not have a history of treatment for syphilis. Further historical evaluation is necessary to distinguish between these scenarios.(Table 1) In the setting of a positive syphilis IgG/IgM screening result and a negative RPR, a negative TP-PA result is most consistent with a falsely reactive syphilis IgG/IgM screen.(Table 1) If syphilis remains clinically suspected, a second specimen should be submitted for testing. Table 1. Interpretation and follow-up of reverse screening results: Test and result Patient history Syphilis total antibody by MFI RPR TP-PA Interpretation Follow-up Unknown history of syphilis Nonreactive NA NA No serologic evidence of syphilis None, unless clinically indicated (eg, early/acute/ primary syphilis) Unknown history of syphilis Reactive Reactive NA Untreated or recently treated syphilis See CDC treatment guidelines Unknown history of syphilis Reactive Nonreactive Nonreactive Probable false-positive screening test No follow-up testing, unless clinically indicated (eg, acute/ primary syphilis) Unknown history of syphilis Reactive Nonreactive Reactive Possible syphilis (eg, early or latent) or previously treated syphilis Historical and clinical evaluation required Unknown history of syphilis Equivocal NA NA NA Unknown history of syphilis Known history of syphilis Reactive Nonreactive Reactive or NA Past, successfully treated syphilis None MFI - multiplex flow immunoassay NA - not applicable RPR - rapid plasma reagin TP-PA - Treponema pallidum particle agglutination

Useful For: Aiding in the diagnosis of recent or past Treponema pallidum infection Rapid plasma reagin screening when T pallidum antibody screen is positive This test is not useful as a screening or confirmatory test for blood donor specimens.

Interpretation: Nonreactive: Treponema pallidum-particle agglutination (TP-PA) has been ordered to distinguish between infection with T pallidum (syphilis) versus a falsely reactive treponemal antibody result Reactive: Specimen reflexed to determine rapid plasma reagin (RPR) titer value

Reference Values:
Only available as a reflex test. For more information see SYPHT / Syphilis Total Antibody with Reflex, Serum.

Nonreactive

Clinical References: 1. Centers for Disease Control and Prevention (CDC). Discordant results from reverse sequence syphilis screening-five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011;60(5):133-137 2. Radolf JD, Tramont EC, Salazar JC: Syphilis (Treponema pallidum). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2865-2892 3. Binnicker MJ, Jespersen DJ, Rollins LO: Direct comparison of the traditional and reverse syphilis screening algorithms in a population with a low prevalence of syphilis. J Clin Microbiol. 2012 Jan;50(1):148-150. doi: 10.1128/JCM.05636-11

RPRT2
616865

Rapid Plasma Reagin Titer, Serum

Clinical Information: Syphilis is caused by infection with the spirochete Treponema pallidum subspecies pallidum. The infection is systemic, and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial nontreponemal screening test, such as the rapid plasma reagin (RPR) or the VDRL tests. Because these tests measure the host's immune response to nontreponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorption (FTA-ABS) or microhemagglutination (MHA-TP) assay. Although the FTA-ABS and MHA-TP assays are technically simple to perform, they are labor intensive and require subjective interpretation by testing

personnel. As an alternative to the traditional syphilis screening algorithm, many laboratories utilize the reverse syphilis screening algorithm. This algorithm starts with an automated treponemal assay to detect antibodies specific to T pallidum. If this screening assay is positive, the sample is reflexed for testing by RPR, which, if positive, is reported with a titer and is indicative of active or recent syphilis infection. If the RPR is negative, the sample is reflexed to a second treponemal assay, such as the T pallidum particle agglutination (TP-PA) assay. If the TP-PA is positive, this would indicate previously treated or late-stage syphilis infection. Alternatively, if the TP-PA is negative, the initial positive screen is interpreted as a false positive result. Patients with primary or secondary syphilis are typically tested by RPR to monitor response to treatment. Typically, RPR titers decrease following successful treatment, but this may occur over a period of months to years. Additionally, testing of maternal and neonate serum, collected concurrently, by RPR can be used as an aid to diagnose congenital syphilis.

Useful For: Determining the current disease status Monitoring response to therapy for syphilis This test cannot be used for testing spinal fluid specimens.

Interpretation: Negative: No rapid plasma reagin (RPR) detected. Initial reactive RPR screen was likely a false-reactive result. Repeat testing if clinically indicated on a new specimen. Positive: Patients being monitored for response to therapy; a 4-fold or greater decrease in RPR titers between pre- and post-treatment samples indicates response to therapy. Patients evaluated for congenital syphilis: a 4-fold or higher RPR difference between neonate and maternal RPR titers suggests congenital syphilis.

Reference Values:
Only orderable as a reflex. For more information see RPRT1 / Rapid Plasma Reagin (RPR) Screen with Reflex to Titer, Serum.

Negative
Reference values apply to all ages.

Clinical References: 1. Centers for Disease Control and Prevention (CDC): Discordant results from reverse sequence syphilis screening-five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011;60(5):133-137 2. Radolf JD, Tramont EC, Salazar JC. Syphilis (Treponema pallidum). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2865-2892 3. Binnicker MJ, Jespersen DJ, Rollins LO. Direct comparison of the traditional and reverse syphilis screening algorithms in a population with a low prevalence of syphilis. J Clin Microbiol. 2012;50(1):148-150

RPDEI
620377

Rapidly Progressive Dementia Evaluation Interpretation, Spinal Fluid

Clinical Information: Primary rapid progressive dementia (RPD) occurs in human prion diseases, rapidly progressive types of other neurodegenerative dementias (Lewy Body dementia, Alzheimer disease), autoimmune central nervous system (CNS) disorders and other conditions that involved rapid neuronal damage. Based on data from tertiary medical centers, when there is high clinical suspicion of Creutzfeldt-Jakob disease (CJD), a majority will be proven to be CJD upon autopsy. However, in those where CJD has been ruled out either by additional diagnostic testing or autopsy, the most common differential diagnoses include rapidly progressive Alzheimer disease or autoimmune CNS disease. Distinguishing these diseases is often challenging, and the use of cerebrospinal fluid (CSF) biomarker testing is an important tool in establishing the correct diagnosis. CJD is a rare and fatal neurodegenerative disorder that predominantly affects the brain and is caused by misfolded prion proteins (PrP[Sc]). CJD accounts for more than 90% of human prion diseases. Initial symptom onset is heterogenous but commonly includes rapidly progressive dementia, cerebellar ataxia, and myoclonus. The timeline of symptom progression and the pattern of symptom evolution can be divergent across

patients and CJD subtypes, making an accurate diagnosis based on clinical presentation alone challenging. The inclusion of biomarkers with high diagnostic accuracy has improved the differentiation of CJD and related prion diseases from treatable neurological conditions with overlapping phenotypes. The real-time quaking-induced conversion (RT-QuIC) assay in CSF has been established to have strong clinical utility for early and accurate diagnosis of CJD through numerous independent studies. Furthermore, the robustness and reproducibility of the RT-QuIC assay for CJD across laboratories has been demonstrated through international ring trials. The clinical sensitivity and specificity of second-generation RT-QuIC assays in CSF have been consistently reported to be greater than or equal to 92% and greater than or equal to 99%, respectively. Despite the high diagnostic accuracy of the assay, RT-QuIC results should be interpreted in the appropriate clinical context along with other clinical and paraclinical findings. A definitive diagnosis of sporadic prion disease can be established only through neuropathological assessment of brain tissue. Unexpectedly negative RT-QuIC test results should prompt careful consideration of the differential diagnosis. If there is high suspicion of prion disease, repeat RT-QuIC testing may be warranted. A small subset of cases initially negative by RT-QuIC may become positive as the disease progresses. However, RT-QuIC may be persistently negative in a small proportion of patients with definite prion disease. False-negative RT-QuIC results are most often encountered in cases of genetic prion disease (eg, fatal familial insomnia and Gerstmann-Straussler-Scheinker disease) and in atypical sporadic prion disease subtypes (eg, MM2 cortical subtype) that have slower indolent disease progression. Other CSF biomarkers have been utilized to support the diagnosis of CJD, including 14-3-3, total Tau measurement, and the ratio of total Tau (t-Tau) to phosphorylated Tau at threonine 181. Recent studies have indicated that the Tau ratio (t-Tau to pT181-Tau or vice versa) has a very high diagnostic accuracy, which exceeds that provided by t-Tau or 14-3-3 enzyme-linked immunosorbent assays (ELISA). In a cohort of probable/definite CJD cases and controls tested utilizing the Roche Total-Tau and p-Tau (threonine 181) Elecsys assays, the optimized cut-off value for total Tau (>393 ng/L) had a clinical sensitivity and specificity of 92.3% and 88.3% for CJD, respectively; and the optimized cut-off value for the t-Tau to p-Tau ratio (>18) has a clinical sensitivity and specificity of 97.4% and 95.9% for CJD, respectively. Importantly, t-Tau or t-Tau to p-Tau ratios utilize assay-dependent cut-off values, and cut-off values from one assay are not transferable to different assay platforms. Alzheimer disease (AD) is the most common cause of dementia. The pathologic changes observed in the brain of individuals with AD dementia are the presence of plaques composed of beta-amyloid (Abeta) peptides and intracellular neurofibrillary tangles containing hyperphosphorylated Tau (tubulin-associated unit) proteins. Accumulation of Abeta is one target for AD therapeutics. Accumulation of Abeta can be measured by amyloid positron emission tomography (PET) imaging or by measurement of Abeta42 peptides and certain phosphorylated Tau (such as p-Tau181) proteins in CSF. In particular, the use of the p-Tau181/Abeta42 ratio has been shown to be an excellent surrogate marker of amyloid plaque burden. Abeta42 is approximately 4-kDa protein of 42 amino acids that is formed following proteolytic cleavage of a transmembrane protein known as amyloid precursor protein. Due to its hydrophobic nature, Abeta42 has the propensity to form aggregates and oligomers. Oligomers form fibrils that accumulate into amyloid plaques. These pathological changes in Abeta42 are reflected by the decrease in the CSF concentrations of Abeta42 and/or by the increase in the brain uptake of specific tracers during amyloid-PET. Tau is present as six isoforms in human brain tissue. These isoforms are generated by alternative splicing of the pre-messenger RNA. The t-Tau assay measures all these isoforms. The most common post-translational modification of Tau proteins is phosphorylation. During neurodegeneration, abnormal phosphorylation leads to the formation of intracellular neurofibrillary tangles composed of the Tau protein that has undergone hyperphosphorylation and developed aggregates of hyperphosphorylated Tau proteins called p-Tau. Pathological changes associated with AD are reflected by an increase in the CSF concentrations of t-Tau and p-Tau. Increases in CSF t-Tau concentrations reflect the intensity of the neuronal and axonal damage and degeneration and are associated with a faster progression from mild cognitive impairment (MCI) to AD. Increases in CSF p-Tau concentrations are also associated with a faster progression from MCI to AD with more rapid cognitive decline in patients with AD and in mild AD dementia cases. The p-Tau assay used in this evaluation detects p-Tau at threonine 181.

Useful For: Interpretation of the Rapidly Progressive Dementia Evaluation

Interpretation: An interpretive report will be provided when no abnormal results are detected. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis and recommendations for patient management resources.

Reference Values:

Only orderable as part of a profile. For more information see RPDE / Rapidly Progressive Dementia Evaluation, Spinal Fluid.

An interpretive report will be provided.

Clinical References: 1. Hermann P, Appleby B, Brandel JP, et al. Biomarkers and diagnostic guidelines for sporadic Creutzfeldt-Jakob disease. Lancet Neurol. 2021;20(3):235-246 2. Orru CD, Groveman BR, Hughson AG, et al. RT-QuIC assays for prion disease detection and diagnostics. Methods Mol Biol. 2017;1658:185-203 3. Rhoads DD, Wrona A, Foutz A, et al. Diagnosis of prion diseases by RT-QuIC results in improved surveillance. Neurology. 2020;95(8):e1017-e1026 4. Hamlin C, Puoti G, Berri S, et al. A comparison of tau and 14-3-3 protein in the diagnosis of Creutzfeldt-Jakob disease.Neurology.2012;79(6):547-552 5. Shir D, Lazar EB, Graff-Radford J, et al. Analysis of clinical features, diagnostic tests, and biomarkers in patients with suspected Creutzfeldt-Jakob disease, 2014-2021. JAMA Netw Open. 2022;5(8):e2225098 6. Skillback T, Rosen C, Asztely F, Mattsson N, Blennow K, Zetterberg H. Diagnostic performance of cerebrospinal fluid total tau and phosphorylated tau in Creutzfeldt-Jakob disease: results from the Swedish Mortality Registry. JAMA Neurol. 2014;71(4):476-483 7. Hermann P, Haller P, Goebel S, et al. Total and phosphorylated cerebrospinal fluid Tau in the differential diagnosis of sporadic Creutzfeldt-Jakob disease and rapidly progressive Alzheimer's disease. Viruses. 2022;14(2):276 8. van Harten AC, Wiste HJ, Weigand SD, et al. Detection of Alzheimer's disease amyloid beta 1-42, p-tau, and t-tau assays. Alzheimers Dement. 2022;18(4):635-644. doi:10.1002/alz.12406 9. Campbell MR, Ashrafzadeh-Kian S, Petersen RC, et al. P-tau/AB42 and AB42/40 ratios in CSF are equally predictive of amyloid PET status. Alzheimers Dement (Amst). 2021;13(1):e12190. doi:10.1002/dad2.12190 10. Blennow K, Stomrud E, Zetterberg H, et al. Second-generation Elecsys cerebrospinal fluid immunoassays aid diagnosis of early Alzheimer's disease. Clin Chem Lab Med. 2022;61(2):234-244. doi:10.1515/cclm-2022-0516 11. Jack CR Jr, Bennett DA, Blennow K, et al: NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535-562

RPDE
620376

Rapidly Progressive Dementia Evaluation, Spinal Fluid

Clinical Information: Primary rapid progressive dementia (RPD) occurs in human prion diseases, rapidly progressive types of other neurodegenerative dementias (Lewy Body dementia, Alzheimer disease), autoimmune central nervous system (CNS) disorders and other conditions that involved rapid neuronal damage. Based on data from tertiary medical centers, when there is high clinical suspicion of Creutzfeldt-Jakob disease (CJD), a majority will be proven to be CJD upon autopsy. However, in those where CJD has been ruled out either by additional diagnostic testing or autopsy, the most common differential diagnoses include rapidly progressive Alzheimer disease or autoimmune CNS disease. Distinguishing these diseases is often challenging, and the use of cerebrospinal fluid (CSF) biomarker testing is an important tool in establishing the correct diagnosis. CJD is a rare and fatal neurodegenerative disorder that predominantly affects the brain and is caused by misfolded prion proteins (PrP[Sc]). CJD accounts for more than 90% of human prion diseases. Initial symptom onset is heterogenous but commonly includes rapidly progressive dementia, cerebellar ataxia, and myoclonus. The timeline of symptom progression and the pattern of symptom evolution can be divergent across patients and CJD subtypes, making an accurate diagnosis based on clinical presentation alone challenging. The inclusion of biomarkers with high diagnostic accuracy has improved the differentiation of CJD and related prion diseases from treatable neurological conditions with overlapping phenotypes. The real-time quaking-induced conversion (RT-QuIC) assay in CSF has been established to have strong

clinical utility for early and accurate diagnosis of CJD through numerous independent studies. Furthermore, the robustness and reproducibility of the RT-QuIC assay for CJD across laboratories has been demonstrated through international ring trials. The clinical sensitivity and specificity of second-generation RT-QuIC assays in CSF have been consistently reported to be greater than or equal to 92% and greater than or equal to 99%, respectively. Despite the high diagnostic accuracy of the assay, RT-QuIC results should be interpreted in the appropriate clinical context along with other clinical and paraclinical findings. A definitive diagnosis of sporadic prion disease can be established only through neuropathological assessment of brain tissue. Unexpectedly negative RT-QuIC test results should prompt careful consideration of the differential diagnosis. If there is high suspicion of prion disease, repeat RT-QuIC testing may be warranted. A small subset of cases initially negative by RT-QuIC may become positive as the disease progresses. However, RT-QuIC may be persistently negative in a small proportion of patients with definite prion disease. False-negative RT-QuIC results are most often encountered in cases of genetic prion disease (eg, fatal familial insomnia and Gerstmann-Straussler-Scheinker disease) and in atypical sporadic prion disease subtypes (eg, MM2 cortical subtype) that have slower indolent disease progression. Other CSF biomarkers have been utilized to support the diagnosis of CJD, including 14-3-3, total Tau measurement, and the ratio of total Tau (t-Tau) to phosphorylated Tau at threonine 181. Recent studies have indicated that the Tau ratio (t-Tau to pT181-Tau or vice versa) has a very high diagnostic accuracy, which exceeds that provided by t-Tau or 14-3-3 enzyme-linked immunosorbent assays (ELISA). In a cohort of probable/definite CJD cases and controls tested utilizing the Roche Total-Tau and p-Tau (threonine 181) Elecsys assays, the optimized cut-off value for total Tau (>393 ng/L) had a clinical sensitivity and specificity of 92.3% and 88.3% for CJD, respectively; and the optimized cut-off value for the t-Tau to p-Tau ratio (>18) has a clinical sensitivity and specificity of 97.4% and 95.9% for CJD, respectively. Importantly, t-Tau or t-Tau to p-Tau ratios utilize assay-dependent cut-off values, and cut-off values from one assay are not transferable to different assay platforms. Alzheimer disease (AD) is the most common cause of dementia. The pathologic changes observed in the brain of individuals with AD dementia are the presence of plaques composed of beta-amyloid (Abeta) peptides and intracellular neurofibrillary tangles containing hyperphosphorylated Tau (tubulin-associated unit) proteins. Accumulation of Abeta is one target for AD therapeutics. Accumulation of Abeta can be measured by amyloid positron emission tomography (PET) imaging or by measurement of Abeta42 peptides and certain phosphorylated Tau (such as p-Tau181) proteins in CSF. In particular, the use of the p-Tau181/Abeta42 ratio has been shown to be an excellent surrogate marker of amyloid plaque burden. Abeta42 is approximately 4-kDa protein of 42 amino acids that is formed following proteolytic cleavage of a transmembrane protein known as amyloid precursor protein. Due to its hydrophobic nature, Abeta42 has the propensity to form aggregates and oligomers. Oligomers form fibrils that accumulate into amyloid plaques. These pathological changes in Abeta42 are reflected by the decrease in the CSF concentrations of Abeta42 and/or by the increase in the brain uptake of specific tracers during amyloid-PET. Tau is present as six isoforms in human brain tissue. These isoforms are generated by alternative splicing of the pre-messenger RNA. The t-Tau assay measures all these isoforms. The most common post-translational modification of Tau proteins is phosphorylation. During neurodegeneration, abnormal phosphorylation leads to the formation of intracellular neurofibrillary tangles composed of the Tau protein that has undergone hyperphosphorylation and developed aggregates of hyperphosphorylated Tau proteins called p-Tau. Pathological changes associated with AD are reflected by an increase in the CSF concentrations of t-Tau and p-Tau. Increases in CSF t-Tau concentrations reflect the intensity of the neuronal and axonal damage and degeneration and are associated with a faster progression from mild cognitive impairment (MCI) to AD. Increases in CSF p-Tau concentrations are also associated with a faster progression from MCI to AD with more rapid cognitive decline in patients with AD and in mild AD dementia cases. The p-Tau assay used in this evaluation detects p-Tau at threonine 181.

Useful For: Evaluation of individuals presenting with rapidly progressive dementia of uncertain disease etiology and a differential diagnosis of Creutzfeldt-Jakob disease and rapidly progressive Alzheimer disease

Interpretation: An interpretive report will be provided when no abnormal results are detected. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and

of their significance, a correlation to available clinical information, elements of differential diagnosis and recommendations for patient management resources.

Reference Values:

RT-QuIC PRION, CSF:
Negative

t-TAU/p-TAU:
< or =18

p-TAU/ABETA 42:
< or =0.028

BETA-AMYLOID (1-42) (Abeta42):
>834 pg/mL

TOTAL TAU:
< or =238 pg/mL (Alzheimer disease)
< or =393 pg/mL (Creutzfeldt-Jakob disease)

PHOSPHORYLATED TAU 181:
< or =21.6 pg/mL

Clinical References: 1. Hermann P, Appleby B, Brandel JP, et al. Biomarkers and diagnostic guidelines for sporadic Creutzfeldt-Jakob disease. Lancet Neurol. 2021;20(3):235-246 2. Rhoads DD, Wrona A, Foutz A, et al. Diagnosis of prion diseases by RT-QuIC results in improved surveillance. Neurology. 2020;95(8):e1017-e1026 3. Hamlin C, Puoti G, Berri S, et al. A comparison of tau and 14-3-3 protein in the diagnosis of Creutzfeldt-Jakob disease. Neurology. 2012;79(6):547-552 4. Shir D, Lazar EB, Graff-Radford J, et al. Analysis of clinical features, diagnostic tests, and biomarkers in patients with suspected Creutzfeldt-Jakob disease, 2014-2021. JAMA Netw Open. 2022;5(8):e2225098 5. Skillback T, Rosen C, Asztely F, Mattsson N, Blennow K, Zetterberg H. Diagnostic performance of cerebrospinal fluid total tau and phosphorylated tau in Creutzfeldt-Jakob disease: results from the Swedish Mortality Registry. JAMA Neurol. 2014;71(4):476-483 6. Hermann P, Haller P, Goebel S, et al. Total and phosphorylated cerebrospinal fluid Tau in the differential diagnosis of sporadic Creutzfeldt-Jakob disease and rapidly progressive Alzheimer's disease. Viruses. 2022;14(2):276 7. van Harten AC, Wiste HJ, Weigand SD, et al. Detection of Alzheimer's disease amyloid beta 1-42, p-tau, and t-tau assays. Alzheimers Dement. 2022;18(4):635-644. doi:10.1002/alz.12406 8. Campbell MR, Ashrafzadeh-Kian S, Petersen RC, et al. P-tau/AB42 and AB42/40 ratios in CSF are equally predictive of amyloid PET status. Alzheimers Dement (Amst). 2021;13(1):e12190. doi:10.1002/dad2.12190 9. Blennow K, Stomrud E, Zetterberg H, et al. Second-generation Elecsys cerebrospinal fluid immunoassays aid diagnosis of early Alzheimer's disease. Clin Chem Lab Med. 2022;61(2):234-244. doi:10.1515/cclm-2022-0516 10. Jack CR Jr, Bennett DA, Blennow K, et al: NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535-562

RSBV
621403

Rare Subepithelial Autoimmune Blistering Disease Variants, Serum

Clinical Information: Laminin 332 (LM332) pemphigoid is a rare subepithelial autoimmune blistering disease that can affect the conjunctival, esophageal, oral, and genital mucosa and skin. With LM332 pemphigoid, there is a risk of blindness and esophageal stricture, among other serious complications. In addition, approximately 20% to 30% of patients with LM332 pemphigoid have an

underlying malignancy driving their mucocutaneous disease. Therefore, it is generally accepted that patients found to have circulating LM332 antibodies should be screened for an occult malignancy. P200 pemphigoid, a rare subepithelial autoimmune blistering disease affecting the skin, shares some clinical characteristics with psoriasis, a much more common inflammatory dermatosis of the skin. However, identification of circulating p200 autoantibodies predicts the development of blisters and portends a worse clinical therapeutic response. Collagen VII autoantibodies are pathogenic in two rare subepithelial autoimmune blistering diseases: epidermolysis bullosa acquisita (EBA) and bullous systemic lupus erythematosus (BSLE). A diagnosis of EBA is confirmed upon identification of circulating autoantibodies to collagen VII and predicts a refractory treatment course. In addition, patients with EBA have a high rate of associated inflammatory bowel disease (IBD), so identification of collagen VII autoantibodies may prompt clinicians to increase surveillance for IBD. In the appropriate clinical context, circulating autoantibodies to collagen VII may support a diagnosis of BSLE. Accurate identification of BSLE is important, as most patients with this condition have severe manifestations of lupus in other organs, such as lupus nephritis. While our immunodermatology laboratory offers another test to detect collagen VII autoantibodies (COL7 / Anti-Collagen type VII, IgG antibodies, Serum), collagen VII is a large protein, rendering autoantibodies against this target immunologically heterogeneous.

Useful For: Aiding in the diagnosis of rare subepithelial autoimmune blistering diseases, including anti-laminin 332 pemphigoid, anti-p200 pemphigoid, epidermolysis bullosa acquisita, and systemic bullous lupus erythematosus

Interpretation: This test panel is comprised of cell-based assays to detect antibodies directed against laminin-332, p200, or collagen VII. This panel's intended in vitro use is as an aid in the diagnosis of rare subepithelial autoimmune blistering diseases, including anti-laminin 332 pemphigoid, anti-p200 pemphigoid, epidermolysis bullosa acquisita, and systemic bullous lupus erythematosus. A positive test result for laminin-332 antibodies may correlate with a diagnosis of laminin-332 pemphigoid in the appropriate clinical setting. Laminin-332 pemphigoid is associated with a higher rate of associated malignancy and ocular mucosal disease than conventional pemphigoid. A positive test result for p200 antibodies may correlate with a diagnosis of p200 pemphigoid in the appropriate clinical setting. P200 pemphigoid can be associated with a more recalcitrant disease course than conventional pemphigoid and may be associated with psoriasis. A positive test result for collagen VII antibodies may correlate with a diagnosis of epidermolysis bullosa acquisita (EBA) or bullous systemic lupus erythematosus (BSLE) in the appropriate clinical setting. EBA can be associated with inflammatory bowel disease and a more recalcitrant disease course in some patients. BSLE is usually associated with systemic lupus erythematosus. Recommend correlation with clinical presentation, histopathologic findings from standard biopsy, direct immunofluorescence from a perilesional biopsy (CIB / Cutaneous Direct Immunofluorescence Assay, Varies), indirect immunofluorescence with IgG (CIFS / Cutaneous Immunofluorescence Antibodies, IgG, Serum), and other testing as clinically indicated.

Reference Values:
Normal patients: Negative

Clinical References: 1. Goletz S, Probst C, Komorowski L, et al. A sensitive and specific assay for the serological diagnosis of antilaminin 332 mucous membrane pemphigoid. Br J Dermatol. 2019;180(1):149-156 2. Amber KT, Bloom R, Hertl M. A systematic review with pooled analysis of clinical presentation and immunodiagnostic testing in mucous membrane pemphigoid: association of anti-laminin-332 IgG with oropharyngeal involvement and the usefulness of ELISA. J Eur Acad Dermatol Venereol. 2016;30(1):72-77. doi:10.1111/jdv.13397 3. Ahmed AR, Kalesinskas M, Kooper-Johnson S. Paraneoplastic autoimmune Laminin-332 syndrome (PALS): Anti-Laminin-332 mucous membrane pemphigoid as a prototype. Autoimmun Rev. 2023;22(10):103444. doi:10.1016/j.autrev.2023.103444 4. Seta V, Aucouturier F, Bonnefoy J, et al. Comparison of 3 type VII collagen (C7) assays for serologic diagnosis of epidermolysis bullosa acquisita (EBA). J Am Acad Dermatol. 2016;74(6):1166-1172. doi:10.1016/j.jaad.2016.01.005 5. Kridin K, Kneiber D, Kowalski EH, Valdebran M, Amber KT. Epidermolysis bullosa acquisita: A comprehensive review. Autoimmun Rev. 2019 Aug;18(8):786-795.

doi: 10.1016/j.autrev.2019.06.007 6. Holtsche MM Goletz S, von Georg A, et al. Serologic characterization of anti-p200 pemphigoid: Epitope spreading as a common phenomenon. J Am Acad Dermatol. 2021;84(4):1155-1157 7. Lau I, Goletz S, Holtsche MM, et al. Anti-p200 pemphigoid is the most common pemphigoid disease with serum antibodies against the dermal side by indirect immunofluorescence microscopy on human salt-split skin. J Am Acad Dermatol. 2019;81(5):1195-1197

FRASP
57665

Raspberry IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

RASP
86305

Raspberry, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to raspberry Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

RAT
82725

Rat Epithelium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to rat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

RTSP
82793

Rat Serum Protein, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to rat serum protein Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

RTUP
82794

Rat Urine Protein, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to rat urine protein Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

RAVMP
618645

Ravulizumab Monitoring Panel, Serum

Clinical Information: Ravulizumab (Ultomiris, Alexion Pharmaceuticals) is a humanized hybrid monoclonal antibody (IgG2/IgG4) that blocks complement C5 cleavage, thereby preventing the activation of the proinflammatory effects of C5a and the cytolytic effects of the membrane attack complex (MAC) formed by C5b-C9. The dosing regimen for ravulizumab is weight-based, and after a loading dose schedule, the maintenance therapy requires administration intravenously every 8 weeks. Therapy efficacy may be monitored by measuring efficiency of complement blockade. Ravulizumab will affect complement function assays that rely on the formation of the MAC to generate cell lysis. Validation studies performed by Mayo Clinic show that the alternative pathway (AH50) enzyme-linked immunosorbent assay is the most helpful of the complement tests to monitor efficacy of the complement blockage by ravulizumab. Ravulizumab serum concentrations greater than 200 mcg/mL inhibited the AH50 activity completely, and undetectable activity was measured at all subsequent tested concentrations up to 1000 mcg/mL.(1) Some patients whose serum concentrations persist above therapeutic targets with complete complement blockade could benefit from dose deescalation or prolonged infusion intervals. Therapeutic drug monitoring of ravulizumab could result in cost-savings and improved quality of life if target therapeutic concentrations can be achieved with complete complement system blockage at less frequent dosing intervals.

Useful For: Monitoring of complement blockage by ravulizumab Assessing the response to ravulizumab therapy Assessing the need for dose escalation Evaluating the potential for dose deescalation or discontinuation of therapy in remission states Monitoring patients who need to be above a certain ravulizumab concentration in order to improve the odds of a clinical response for therapy optimization

Interpretation: Target trough therapeutic concentrations (immediately before next infusion) of ravulizumab are expected to be above 175 mcg/mL for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Pharmacodynamic studies of complement blockage may also be recommended for patients undergoing therapy. For the complement blockage monitoring of ravulizumab: -When ravulizumab is present in serum at concentrations around 50 mcg/mL, the results range from 20% to 29% of normal. -When ravulizumab concentrations are around 100 mcg/mL, the results range from below 10% to 13% of normal. -When ravulizumab concentrations are greater than

200 mcg/mL, the results are below the limit of quantitation of the assay (<10% of normal).

Reference Values:
RAVULIZUMAB COMPLEMENT BLOCKAGE:
> or =46% normal

RAVULIZUMAB:
Lower limit of quantitation =5.0 mcg/mL
>175 mcg/mL: Therapeutic concentration for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome

Clinical References: 1. Willrich MAV, Ladwig PM, Martinez MA, et al. Monitoring ravulizumab effect on complement assays. J Immunol Methods. 2021;490:112944. doi:10.1016/j.jim.2020.112944 2. Go RS, Winters JL, Leung N, et al. Thrombotic microangiopathy care pathway: A consensus statement for the Mayo Clinic Complement Alternative Pathway-Thrombotic Microangiopathy (CAP-TMA) Disease-Oriented Group. Mayo Clin Proc. 2016;91(9):1189-1211 doi:10.1016/j.mayocp.2016.05.015 3. Ardissino G, Tel F, Sgarbanti M, et al. Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome: an update. Pediatr Nephrol. 2018;33(3):457-461 4. Volokhina EB, van de Kar NC, Bergseth G, et al. Sensitive, reliable and easy-performed laboratory monitoring of eculizumab therapy in atypical hemolytic uremic syndrome. Clin Immunol. 2015;160(2):237-243 5. Cataland S, Ariceta G, Chen P, et al. Discordance between free C5 and CH50 complement assays in measuring complement C5 inhibition in patients with aHUS treated with ravulizumab. Blood. 2019;134(Supplement_1):1099 6. Ladwig PM, Barnidge DR, Willrich MA. Quantification of the IgG2/4 kappa monoclonal therapeutic eculizumab from serum using isotype specific affinity purification and microflow LC-ESI-Q-TOF Mass Spectrometry. J Am Soc Mass Spectrom. 2017;28(5):811-817. doi: 10.1007/s13361-016-1566-y 7. Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019;133(6):540-549. doi:10.1182/blood-2018-09-876805 8. Stern RM, Connell NT: Ravulizumab. a novel C5 inhibitor for the treatment of paroxysmal nocturnal hemoglobinuria. Ther Adv Hematol. 2019;10:2040620719874728. doi:10.1177/2040620719874728 9. Alexion Pharmaceuticals. BLA 761108-S1 Multi-disciplinary review and evaluation: Ultomiris (ravulizumab-cwvz). FDA; April 2, 2019. Accessed August 7, 2023. Available at www.fda.gov/media/135113/download 10. Vu, T, Meisel, A, Mantegazza, R, et al. Terminal complement inhibitor ravulizumab in generalized myasthenia gravis. N Engl J Med Evid. 2022;1(5):1-12. doi:10.1056/EVIDoa2100066 11. Sridharan M, Go RS, Willrich MAV. Clinical utility and potential cost savings of pharmacologic monitoring of eculizumab for complement-mediated thrombotic microangiopathy. Mayo Clin Proc Innov Qual Outcomes. 2022;6(5):458-464. doi:10.1016/j.mayocpiqo.2022.03.005

RAVU
609420

Ravulizumab, Serum

Clinical Information: Ravulizumab (Ultomiris) is a humanized monoclonal IgG2/4 kappa antibody therapeutic directed against the complement component 5 (C5). By association with C5, ravulizumab inhibits the terminal complement pathway through simultaneous blockade of the generation of the potent prothrombotic and proinflammatory molecule, C5a, and the formation of membrane attack complex initiator, C5b. Since ravulizumab demonstrated noninferiority to eculizumab in clinical trials for both paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (aHUS), there is likelihood of patients being moved from eculizumab to ravulizumab therapy. Ravulizumab is a longer-acting hybrid IgG2/IgG4 therapeutic monoclonal antibody (145 kDa). Its sequence is very similar to eculizumab (148 kDa), except for a 4 amino acid difference in the heavy chain of the molecule. Eculizumab binds to C5 in the intravascular space and, after the resulting eculizumab-C5 complex is taken up by endothelial cells, it is degraded in the endosomes. In order to increase its half-life, two changes were made to ravulizumab: 2 amino acids substituted in the constant region give ravulizumab more affinity for the Brambell receptor (FcRn), which recycles IgG instead of degrading it. The other 2

amino acid changes are in the variable region of the heavy chain, changing the affinity of the Fab fraction for C5, making it possible for C5 to be released from ravulizumab before it is recycled, so that C5 is left alone inside the endosome to be degraded. Eculizumab is administered as a standard (non-weight based) dose for approved conditions. Ravulizumab's key improvements over eculizumab include a longer half-life, leading to intravenous infusions every 8 weeks instead of every 2 weeks, along with a weight-based dosing schedule that further personalizes therapy regimens. Some patients who persist with serum concentrations above therapeutic targets with complete complement blockade could benefit from dose deescalation or prolonged infusion intervals and visit the clinic for infusions less frequently than the US Food and Drug Administration-label recommendation. Therapeutic drug monitoring of ravulizumab could result in cost-savings and improved quality of life if target therapeutic concentrations can be achieved with complete complement system blockage at less frequent dosing intervals. Ravulizumab trough therapeutic concentration is greater than 175 mcg/mL Complement blockage studies can aid in determining that a therapeutic concentration of the drug has blocked the complement function and subsequent production of sC5b-9. The recommended test for complement blockage evaluation in ravulizumab therapy is the alternative pathway function assay; see AH50 / Alternative Complement Pathway, Functional, Serum. A panel with both ravulizumab concentration and alternative pathway function is available; see RAVMP / Ravulizumab Monitoring Panel, Serum.

Useful For: Assessing the response to ravulizumab therapy Assessing the need for dose escalation Evaluating the potential for dose deescalation or discontinuation of therapy in remission states Monitoring patients who need to be above a certain ravulizumab concentration in order to improve the odds of a clinical response for therapy optimization This test is not useful as the sole basis for a diagnosis or treatment decisions

Interpretation: Target trough therapeutic concentrations (immediately before next infusion) of ravulizumab are expected to be above 175 mcg/mL for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Pharmacodynamic studies of complement blockage may also be recommended for patients undergoing therapy.

Reference Values:
Lower limit of quantitation=5.0 mcg/mL

>175 mcg/mL-Therapeutic concentration for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome

Clinical References: 1. Willrich MA, Murray DL, Barnidge DR, Ladwig PM, Snyder MR. Quantitation of infliximab using clonotypic peptides and selective reaction monitoring by LC-MS/MS. Int Immunopharmacol. 2015;28(1):513-520. doi:10.1016/j.intimp.2015.07.007 2. Ladwig PM, Barnidge DR, Willrich MA. Quantification of the IgG2/4 kappa monoclonal therapeutic eculizumab from serum using isotype specific affinity purification and microflow LC-ESI-Q-TOF Mass Spectrometry. J Am Soc Mass Spectrom. 2017;28(5):811-817. doi:10.1007/s13361-016-1566-y 3. Ladwig PM, Barnidge DR, Willrich MA. Mass spectrometry approaches for identification and quantitation of therapeutic monoclonal antibodies in the clinical laboratory. Clin Vaccine Immunol. 2017;24(5):e00545-16. doi:10.1128/CVI.00545-16 4. Sridharan M, Willrich MA, Go R. Personalized dosing of eculizumab using C5 functional activity and eculizumab level in complement-mediated thrombotic microangiopathy: A safe and cost-saving approach. Presented at XXVIII Congress of the International Society on Thrombosis and Haemostasis; July 12-14, 2020; Virtual ISTH 2020 5. Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019;133(6):540-549. doi:10.1182/blood-2018-09-876805 6. Stern RM, Connell NT. Ravulizumab: a novel C5 inhibitor for the treatment of paroxysmal nocturnal hemoglobinuria. Ther Adv Hematol. 2019;10:2040620719874728. doi:10.1177/2040620719874728 7. Alexion Pharmaceuticals. BLA 761108-S1 Multi-disciplinary review and evaluation: Ultomiris (ravulizumab-cwvz). FDA; April 2, 2019. Accessed January 27, 2025. Available at www.fda.gov/media/135113/download 8. Ladwig PM,

Barnidge DR, Willrich MA. Quantification of the IgG2/4 kappa monoclonal therapeutic eculizumab from serum using isotype specific affinity purification and microflow LC-ESI-Q-TOF mass spectrometry. J Am Soc Mass Spectrom. 2017;28(5):811-817 9. Peffault de Latour R, Fremeaux-Bacchi V, Porcher R, et al. Assessing complement blockade in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab. Blood. 2015;125(5):775-783 10. Noris M, Galbusera M, Gastoldi S, et al. Dynamics of complement activation in aHUS and how to monitor eculizumab therapy. Blood. 2014;124(11):1715-1726 11. Zuber J, Le Quintrec M, Krid S, et al. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation. Am J Transplant. 2012;12(12):3337-3354 12. Zimmerhackl LB, Hofer J, Cortina G, et al. Prophylactic eculizumab after renal transplantation in atypical hemolytic-uremic syndrome. N Engl J Med. 2010;362(18):1746-1748 13. Nester C, Stewart Z, Myers D, et al. Pre-emptive eculizumab and plasmapheresis for renal transplant in atypical hemolytic uremic syndrome. Clin J Am Soc Nephrol. 2011;6(6):1488-1494 14. Krid S, Roumenina LT, Beury D, et al. Renal transplantation under prophylactic eculizumab in atypical hemolytic uremic syndrome with CFH/CFHR1 hybrid protein. Am J Transplant. 2012;12(7):1938-1944 15. Weitz M, Amon O, Bassler D, Koenigsrainer A, Nadalin S. Prophylactic eculizumab prior to kidney transplantation for atypical hemolytic uremic syndrome. Pediatr Nephrol. 2011;26(8):1325-1329 16. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med. 2013;368(23):2169-2181 17. Reis ES, Mastellos DC, Yancopoulou D, Risitano AM, Ricklin D, Lambris JD. Applying complement therapeutics to rare diseases. Clin Immunol. 2015;161(2):225-240 18. Rother RP, Rollins SA, Mojcik CF, Brodsky RA, Bell L. Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria [published correction appears in Nat Biotechnol. 2007 Dec;25(12):1488]. Nat Biotechnol. 2007;25(11):1256-1264 19. Thomas TC, Rollins SA, Rother RP, et al. Inhibition of complement activity by humanized anti-C5 antibody and single-chain Fv. Mol Immunol. 1996;33(17-18):1389-1401

NGSFX 65718 Reanalysis of Acute Myeloid Leukemia 4- or 11- Gene Panels, Additional Genes

Clinical Information:

Useful For: Comprehensive reanalysis of a larger set of genes/gene regions when a more targeted gene panel was previously performed in this laboratory Evaluation of known or suspected hematologic neoplasms, specifically of myeloid origin (eg, acute myeloid leukemia, myelodysplastic syndrome, myeloproliferative neoplasm, myelodysplastic/myeloproliferative neoplasm, unexplained cytopenias) at the time of diagnosis or possibly disease relapse, to help determine diagnostic classification and provide prognostic or therapeutic information for helping guide clinical management Determine the presence of new clinically important gene mutation changes at relapse

Interpretation: Detailed variant assessment and interpretive comments will be provided for all reportable genetic alterations. If this test is ordered in the setting of erythrocytosis and suspicion of polycythemia vera, interpretation requires correlation with a concurrent or recent prior bone marrow evaluation.

Reference Values:

Only orderable as a reflex. For more information see:
-NGAMT / MayoComplete Acute Myeloid Leukemia, Therapeutic Gene Mutation Panel (FLT3, IDH1, IDH2, TP53), Next-Generation Sequencing, Varies
-NGAML / MayoComplete Acute Myeloid Leukemia, 11-Gene Panel, Varies

Clinical References: 1. National Comprehensive Cancer Network (NCCN). NCCN Guidelines: Acute Myeloid Leukemia. NCCN; Version 3.2024. Accessed November 27, 2024. Available at www.nccn.org/guidelines/guidelines-detail?category=1&id=1411 2. National Comprehensive Cancer

Network (NCCN): NCCN Guidelines: Myeloproliferative Neoplasms. NCCN; Version 2.2024. Accessed November 27, 2024. Available at www.nccn.org/guidelines/guidelines-detail?category=1&id=1477 3. National Comprehensive Cancer Network (NCCN): NCCN Guidelines: Myelodysplastic Syndromes. NCCN; Version 1.2025. Accessed November 27, 2024. Available at www.nccn.org/guidelines/guidelines-detail?category=1&id=1446 4. He R, Chiou J, Chiou A, et al. Molecular markers demonstrate diagnostic and prognostic value in the evaluation of myelodysplastic syndromes in cytopenia patients. Blood Cancer J. 2022;12(1):12. doi:10.1038/s41408-022-00612-w 5. Malcovati L, Galli A, Travaglino E, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. Blood. 2017;129(25):3371-3378. doi:10.1182/blood-2017-01-763425 6. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med. 2018;378(25):2386-2398. doi:10.1056/NEJMoa1716984 7. Stein EM, DiNardo CD, Fathi AT, et al. Molecular remission and response patterns in patients with mutant-IDH2 acute myeloid leukemia treated with enasidenib. Blood. 2019;133(7):676-687. doi:10.1182/blood-2018-08-869008 8. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447. doi:10.1182/blood-2016-08-733196 9. Smith CC. The growing landscape of FLT3 inhibition in AML. Hematology Am Soc Hematol Educ Program. 2019;2019(1):539-547. doi:10.1182/hematology.2019000058 10. Kennedy JA, Ebert BL. Clinical implications of genetic mutations in myelodysplastic syndrome. J Clin Oncol. 2017;35(9):968-974. doi:10.1200/JCO.2016.71.0806 11. Daver N, Schlenk RF, Russell NH, Levis MJ. Targeting FLT3 mutations in AML: review of current knowledge and evidence. Leukemia. 2019;33(2):299-312. doi:10.1038/s41375-018-0357-9 12. Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of hematopoietic and lymphoid tissues. IARC Press; 2017

NCYB
618977

Recessive Congenital Methemoglobinemia, CYB5 and CYB5 Reductase Genetic Analysis, Next-Generation Sequencing, Varies

Clinical Information: Methemoglobin forms when the hemoglobin (Hb) molecule contains iron in the ferric (Fe3[+]) form, which cannot carry oxygen. Methemoglobin is converted back to the functional ferrous state (Fe2[+]) by the enzyme cytochrome b5 reductase (methemoglobin reductase). Methemoglobinemia can be hereditary or acquired and is present when methemoglobin levels exceed the normal range. Acquired methemoglobinemia results after toxic exposure to nitrates and nitrites/nitrates (fertilizer, nitric oxide), topical anesthetics ("caines"), dapsone, naphthalene (moth balls/toilet deodorant cakes), and industrial use of aromatic compounds (aniline dyes). Congenital methemoglobinemias are rare and are characterized by lifelong cyanosis. They are due either to an intrinsic structural disorders of hemoglobin, called M-Hbs (autosomal dominant inheritance)(1,2); or a deficiency of cytochrome b5 reductase (methemoglobin reductase) in erythrocytes (autosomal recessive inheritance). The hemoglobin genes, HBA1/HBA2 and HBB, are not assessed in this assay. Recessive congenital methemoglobinemia results from genetic variants in either CYB5R3 or CYB5A and is described as type I, type II, or methemoglobinemia and ambiguous genitalia (previously type IV).(1-4) Methemoglobinemia type I results from alterations to CYB5R3 with clinical impact exclusive to the red blood cells (erythrocytes) and typically presents as asymptomatic, well tolerated cyanosis. Methemoglobinemia type II also results from alterations to CYB5R3; however, it is due to alterations that lower activity or expression of the enzyme in all tissues. Methemoglobin type II is a more severe condition associated with cyanosis, neurological impairment, and altered lipid metabolism. Methemoglobinemia and ambiguous genitalia (previously type IV) is a very rare autosomal recessive condition caused by deleterious alterations of the CYB5A gene that produce an isolated 17,20-lyase deficiency. In addition to mild to severe methemoglobinemia, individuals with this condition have been reported to have male under-masculinization/ambiguous genitalia and absent/disturbed pubertal development.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of recessive congenital methemoglobinemia Genotype confirmation of borderline cytochrome b5 reductase (methemoglobin reductase: METR) enzyme activity levels Identifying variants within the CYB5 and CYB5 reductase genes (CYB5A, CYB5R3) allowing for further genetic counseling

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. OMIM: 250800 Methemoglobinemia due to deficiency of methemoglobin reductase. Updated May 20, 2019. Accessed May 19, 2023. Available at www.omim.org/entry/250800?search=250800&highlight=250800 2. OMIM: 250790 Methemoglobinemia and ambiguous genitalia. Updated May 18, 2018. Accessed May 19, 2023. Available at www.omim.org/entry/250790?search=250790&highlight=250790 3. Iolascon A, Bianchi P, Andolfo I, et al. Recommendations for diagnosis and treatment of methemoglobinemia. Am J Hematol. 2021;96(12):1666-1678. doi: 10.1002/ajh.26340 4. Percy MJ, Lappin TR. Recessive congenital methaemoglobinaemia: cytochrome b(5) reductase deficiency. Br J Haematol. 2008;141(3):298-308. doi:10.1111/j.1365-2141.2008.07017.x 5. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

RCVBS
610009

Recoverin-IgG Antibody, Immunoblot, Serum

Clinical Information: Patients with recoverin autoimmunity present with insidious onset vision change, often night-vision loss, floaters, and constricted vision, that can rapidly progress to blindness. On ophthalmologic examination, there are features of non-inflammatory retinopathy; retinal and optic nerve head pallor/atrophy, constricted visual fields and flat electroretinogram (ERG), but without anterior chamber disease, which is encountered with CRMP-5 paraneoplastic ophthalmitis. Small cell (pulmonary or extrapulmonary) or neuroendocrine carcinoma should be sought. Trials of immunotherapy could be attempted to improve vision, though generally this is not successful.

Useful For: Evaluating patients with suspected paraneoplastic retinopathy accompanying small cell carcinoma

Interpretation: Seropositivity is consistent with a diagnosis of paraneoplastic retinopathy. Small cell carcinoma (pulmonary or extrapulmonary) and neuroendocrine carcinoma should be considered.

Reference Values:
Negative

Clinical References: 1. McKeon A, Lopez A, Lachance D, et al: Recoverin antibody: Ophthalmologic and oncologic significance. Neurology. 2016;86:(16 Supplement)

EEEV1
607493

Red Blood Cell (RBC) Enzyme Evaluation, Blood

Clinical Information: Erythrocyte (red blood cell) enzyme deficiencies are inherited causes of hemolytic anemia. Some are very common, such as glucose 6-phosphate dehydrogenase (G6PD) deficiency, and others are very rare, found in only a few families around the world. Most are autosomal in inheritance, but some are sex-linked and located on the X chromosome. Most enzyme deficiencies result in chronic nonspherocytic hemolytic anemia of variable severity; however, some, such as G6PD, can be hematologically normal with episodic acute hemolysis due to a trigger event such as medications, toxins, or some foods. The red blood cell (RBC) enzymopathies do not typically show recurrent pathognomonic changes on the peripheral blood smear other than generic features of hemolytic anemia, although some such as pyruvate kinase deficiency can have echinocytes and pyrimidine 5' nucleotidase (P5NT) deficiency is associated with basophilic stippling. RBC enzyme activity levels are best evaluated as a panel as reticulocytosis can mask some deficient states and comparison to the background enzyme activity is useful. This is a consultative evaluation of red cell enzyme activity as a potential cause of early red cell destruction.

Useful For: Identifying defects of red blood cell enzyme metabolism Evaluating patients with Coombs-negative hemolytic anemia

Interpretation: A hematopathologist expert in these disorders evaluates the case, and an interpretive report is issued.

Reference Values:
Definitive results and an interpretive report will be provided.

Clinical References: 1. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia - pathophysiology, clinical aspects, and laboratory diagnosis. Int J Lab Hematol. 2014;36(3):388-397 2. Beutler E. Glucose-6-phosphate dehydrogenase deficiency and other enzyme abnormalities. In: Beutler E, Lichtmann MA, Coller BS, Kipps TJ, eds. Hematology. 5th ed. McGraw-Hill Book Company; 1995:564-581

EEEVI
608087

Red Blood Cell (RBC) Enzyme Interpretation

Clinical Information: Erythrocyte enzyme deficiencies are inherited causes of hemolytic anemia. Some are very common, such as glucose 6-phosphate dehydrogenase (G6PD) deficiency, and others are very rare, found in only a few families around the world. Most are autosomal in inheritance, but some are sex-linked and located on the X chromosome. Most enzyme deficiencies result in chronic nonspherocytic hemolytic anemia of variable severity; however, some, such as G6PD, can be hematologically normal with episodic acute hemolysis due to a trigger event such as medications, toxins, or some foods. The red blood cell (RBC) enzymopathies do not typically show recurrent pathognomonic changes on the peripheral blood smear other than generic features of hemolytic anemia, although some such as pyruvate kinase deficiency can have echinocytes and pyrimidine 5' nucleotidase (P5NT) deficiency is associated with basophilic stippling. RBC enzyme activity levels are best evaluated as a panel as reticulocytosis can mask some deficient states and comparison to the background enzyme activity is useful. This is a consultative evaluation of red cell enzyme activity as a potential cause of early red cell destruction.

Useful For: Interpretation of results for the red blood cell enzyme evaluation Identifying defects of red cell enzyme metabolism Evaluating patients with Coombs-negative hemolytic anemia

Interpretation: A hematopathologist expert in these disorders evaluates the case and an interpretive report is issued.

Reference Values:

Only orderable as part of a profile. For more information see EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation, Blood.

Definitive results and an interpretive report will be provided.

Clinical References: 1. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia - pathophysiology, clinical aspects, and laboratory diagnosis. Int J Lab Hematol. 2014;36(3):388-397 2. Beutler E. Glucose-6-phosphate dehydrogenase deficiency and other enzyme abnormalities. In: Beutler E, Lichtmann MA, Coller BS, Kipps TJ, eds. Hematology. 5th ed. McGraw-Hill Book Company; 1995:564-581

NENZ
619047

Red Blood Cell Enzyme Disorders Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Next-generation sequencing is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene variants can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. Mature erythrocytes are dependent upon glycolysis for energy production and the hexose monophosphate shunt for oxidation-reduction stability. Hereditary deficiencies in red blood cell (RBC) enzymes within these pathways cause nonspherocytic hemolytic anemia with variable clinical presentations, therapeutic considerations, and inheritance patterns.(1-3) Most of these deficiencies cause chronic hemolysis with little to no pathognomonic morphologic changes in the peripheral blood smear, making correlation with enzyme activity critical for diagnosis. Some are associated with acute episodic anemia triggered by medications, food, or viral illness. Variable additional symptoms may be present for some deficiency types, including myopathy, neuropathy, and developmental delay. Because a subset of clinically significant RBC enzyme disorders can have indeterminate to normal enzyme activity (masking in the presence of increased reticulocytes), the protein (enzymatic activity) studies are more sensitive when performed as a panel of RBC enzymes, which allows comparison of multiple enzyme activities. This genetic panel can aid in the interpretation of equivocal protein findings and genetically confirm an enzyme deficiency, especially if the patient has been recently transfused with red blood cells. Additionally, there are genes interrogated on this panel for which an enzyme test is not clinically available for correlation.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an underlying red blood cell enzymopathy Identifying variants within genes associated with phenotypic severity, allowing for predictive testing and further genetic counseling

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Orkin SH, Nathan DG, Ginsburg D, et al, eds. Nathan and Oski's Hematology of Infancy and Childhood. 7th ed. Saunders Elsevier; 2009:360-364 2. Iolascon A, Andolfo I, Barcellini W, et al. Recommendations for splenectomy in hereditary hemolytic anemias. Haematologica. 2017;102(8):1304-1313. doi:10.3324/haematol.2016.161166 3. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia - pathophysiology, clinical aspects, and laboratory diagnosis. Int J Lab Hematol. 2014;36(3):388-397 4. Zanella A, Fermo E, Bianchi P, Chiarelli LR, Valentini G. Pyruvate kinase deficiency: the genotype-phenotype association. Blood Rev. 2007;21(4):217-231. doi:10.1016/j.blre.2007.01.001 5. Richards S, Aziz N, Bale S, et al.

ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

NMEM
619061

Red Blood Cell Membrane Disorders Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Next-generation sequencing is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene variants can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. This panel aids in the diagnosis and genetic counseling of individuals with red blood cell (RBC) membrane disorders, including hereditary spherocytosis, hereditary elliptocytosis, hereditary pyropoikilocytosis, Southeast Asian ovalocytosis, hereditary stomatocytosis (both overhydrated and dehydrated/hereditary xerocytosis subtypes), and cryohydrocytosis.(1-5) The functional red cell membrane is composed of a cholesterol and phospholipid bilayer anchored by integral proteins to an elastic cytoskeletal network. These interactions form the shape, deformability, and proper ion balance of the cell. Abnormalities in these moieties result in RBC membrane disorders. Hereditary spherocytosis is a common membrane disorder that can be present in all ethnic groups. It is usually associated with visible spherocytes on the peripheral blood smear and can be associated with variable clinical features of hemolysis ranging from mild to severe. Paradoxically, erythrocytosis can occur after splenectomy. Hereditary elliptocytosis (HE) is another fairly common and clinically variable disorder that can range from normal RBC indices, in the large majority of cases, to a minor subset of patients with moderate to severe anemia. Common hereditary elliptocytosis is characterized by the presence of elliptocytes on the peripheral blood smear and the absence of anemia. Variants associated with HE have been reported in widely variable ethnicities with greater prevalence in populations overlapping the malaria belt. Hereditary pyropoikilocytosis is now best classified as a severe form of hereditary elliptocytosis. It is uncommon and presents in early childhood as a severe hemolytic anemia. These disorders are associated with marked poikilocytosis on the peripheral blood smear.(1,2) Hereditary stomatocytosis is an RBC membrane permeability disorder that can manifest as the more common dehydrated hereditary stomatocytosis (DHSt), also known as hereditary xerocytosis (HX), and the rarer overhydrated hereditary stomatocytosis (OHSt) subtypes. These disorders are important to confirm or exclude as splenectomy has been associated with an increased risk for serious venous thrombosis and thromboembolism events and is contraindicated in published guidelines.(5) DHSt/HX manifests variably as mild to compensated anemia to some cases with increased hemoglobin levels. Some patients are asymptomatic, others show hemolysis after even nontraumatic exercise sessions. Others display perinatal edema and susceptibility to iron overload. DHSt/HX is associated with pseudohyperkalemia, increased MCHC (mean corpuscular hemoglobin concentration), and decreased osmotic fragility due to relative dehydration of the red blood cell. OHSt is similarly associated with anemia of variably severity but is associated with increased osmotic fragility due to a relatively overhydrated steady state.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of a red blood cell (RBC) membrane disorder Second-tier testing for patients in whom previous targeted gene variant analyses were negative for a specific RBC membrane disorder Establishing a diagnosis of a hereditary RBC membrane disorder, allowing for appropriate management and surveillance of disease features based on the gene involved, especially if splenectomy is a consideration(5) Identifying variants within genes associated with phenotypic severity, allowing for predictive testing and further genetic counseling

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Gallagher PG. Abnormalities of the erythrocyte membrane. Pediatr Clin North Am. 2013;60(6):1349-1362. doi:10.1016/j.pcl.2013.09.001 2. Barcellini W, Bianchi P, Fermo E, et al. Hereditary red cell membrane defects: diagnostic and clinical aspects. Blood Transfus. 2011;9(3):274-277. doi:10.2450/2011.0086-10 3. Zarychanski R, Schulz VP, Houston BL, et al. Mutations in the mechanotransduction protein PIEZO1 are associated with hereditary xerocytosis. Blood. 2012;120(9):1908-1915. doi:10.1182/blood-2012-04-422253 4. Andolfo I, Russo R, Gambale A, Iolascon A. Hereditary stomatocytosis: an underdiagnosed condition. Am J Hematol. 2018;93(1):107-121. doi:10.1002/ajh.24929 5. Iolascon A, Andolfo I, Barcellini W, et al. Recommendations regarding splenectomy in hereditary hemolytic anemias. Haematologica. 2017;102(8):1304-1313. doi:10.3324/haematol.2016.161166 6. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

RBCME
64897

Red Blood Cell Membrane Evaluation, Blood

Clinical Information: The functional red cell membrane is composed of a cholesterol and phospholipid bilayer anchored by integral proteins to an elastic cytoskeletal network. These interactions form the shape, deformability, and proper ion balance of the cell. Abnormalities in these moieties result in red cell membrane disorders. Hereditary spherocytosis (HS) is a common membrane disorder, which can be present in many ethnic groups. Its prevalence has been estimated at approximately 1 in 3000 persons of Northern European ancestry. It is usually associated with visible spherocytes on the peripheral blood smear and can be associated with variable clinical features of hemolysis ranging from completely compensated to mild to severe. Hereditary elliptocytosis (HE) is another fairly common and clinically variable disorder that can range from normal red blood cell indices in the large majority of cases to rare patients with moderate to severe anemia. Common hereditary elliptocytosis is characterized by the presence of elliptocytes on the peripheral blood smear. Genetic variants associated with HE have been reported in widely variable ethnicities, with greater prevalence in populations overlapping the malaria belt. Hereditary pyropoikilocytosis is best classified as a severe form of hereditary elliptocytosis. It is uncommon and presents in early childhood as a severe hemolytic anemia. These disorders are associated with marked poikilocytosis on the peripheral blood smear.(1,2) Red cell membrane disorders can result from abnormalities involving several red cell membrane proteins, such as band 3, alpha and beta spectrin, protein 4.1, protein 4.2, glycophorin C, and ankyrin. Most often, red cell membrane disorders are diagnosed in childhood, adolescence, or early adult life. The diagnosis of HS is usually made by a combination of patient and family history, laboratory evidence of hemolysis, and review of a peripheral blood smear. The osmotic fragility (OF) test is usually markedly abnormal in HS cases. However, factors such as age, iron status, and medications can affect the OF test. OF is nonspecific and can be increased in acquired disorders, such as autoimmune hemolytic anemia. Coombs testing should be negative prior to ordering this test. The addition of eosin-5-maleimide (EMA) binding (band 3) flow cytometry to this profile increases specificity if a typical moderately decreased pattern is present. Hereditary pyropoikilocytosis can have normal or only mildly increased OF results and often displays a very dim and sometimes dual peak pattern with EMA-binding testing. Common hereditary elliptocytosis cases are not discriminated from normal patients in either OF and EMA binding testing, and this profile does not add confirmatory information for HE.

Useful For: Investigation of suspected red cell membrane disorders, such as hereditary spherocytosis or hereditary pyropoikilocytosis This test is not useful for hereditary elliptocytosis.

Interpretation: An interpretive report will be provided.

Reference Values:
> or =12 months:
0.50 g/dL NaCl (unincubated): 3-53% hemolysis
0.60 g/dL NaCl (incubated): 14-74% hemolysis
0.65 g/dL NaCl (incubated): 4-40% hemolysis
0.75 g/dL NaCl (incubated): 1-11% hemolysis
NaCl = sodium chloride
An interpretive report will be provided.

Reference values have not been established for patients who are younger than 12 months of age.

Clinical References: 1. King MJ, Garcon L, Hoyer JD, et al: International Council for Standardization in Haematology. ICSH guidelines for the laboratory diagnosis of nonimmune hereditary red cell membrane disorders. Int J Lab Hematol. 2015 Jun;37(3):304-325 2. Lux SE, IV: Anatomy of the red cell membrane skeleton: unanswered questions. Blood. 2016 Jan 14;127(2):187-199 doi: 10.1182/blood-2014-12-512772 3. Gallagher PG: Abnormalities of the erythrocyte membrane. Pediatr Clin North Am. 2013 Dec;60(6):1349-1362 4. Bianchi P, Fermo E, Vercellati C, et al: Diagnostic power of laboratory tests for hereditary spherocytosis: a comparison study in 150 patients grouped according to molecular and clinical characteristics. Haematologica. 2012 Apr;97(4):516-523

FRSE
57939

Red Snapper (Lutjanus spp) IgE

Interpretation:

Reference Values:
<0.35 kU/L

SORR
82737

Red Sorrel, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to red sorrel Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be

responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

REDT
82901

Red Top, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to red top Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
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5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

UREDF
607696

Reducing Substance, Feces

Clinical Information: Fecal reducing substances (carbohydrates) aids in determining the underlying cause of diarrhea. Elevations in fecal reducing substances help distinguish between osmotic diarrhea caused by abnormal excretion of various sugars as opposed to diarrhea caused by viruses and parasites. Increased reducing substances in stool are consistent with, but not diagnostic of, primary or secondary disaccharidase deficiency (primarily lactase deficiency) or intestinal monosaccharide malabsorption. Similar intestinal absorption deficiencies are associated with short bowel syndrome and necrotizing enterocolitis.

Useful For: Assisting in the differentiation between osmotic and nonosmotic diarrhea Screening test for: -Diarrhea from disaccharidase deficiencies, (eg, lactase deficiency) -Monosaccharide malabsorption

RBCS
36440

Relative B-Cell Subset Analysis Percentage, Blood

Clinical Information: The adaptive immune response includes both cell-mediated (mediated by T cells and natural killer cells) and humoral immunity (mediated by B cells). After antigen recognition and maturation in secondary lymphoid organs, some antigen-specific B cells terminally differentiate into antibody-secreting plasma cells or become memory B cells. Memory B cells are of 3 subsets: marginal zone B cells (MZ or non-switched memory), class-switched memory B cells, and IgM-only memory B cells. Decreased B-cell numbers, B-cell function, or both, result in immune deficiency states and increased susceptibility to infections. These decreases may be either primary (genetic) or secondary. Secondary causes include medications, malignancies, infections, and autoimmune disorders. Common variable immunodeficiency (CVID), a disorder of B-cell function, is the most prevalent primary immunodeficiency with a prevalence of 1:25,000 to 1:50,000.(1) CVID has a bimodal presentation with a subset of patients presenting in early childhood and a second set presenting between 15 and 40 years, or occasionally even later. Various genetic defects have been associated with CVID, including variants in the ICOS, CD19, BAFF-R, and TACI genes.; TACI variants account for 8% to 15% of CVID cases.

CVID is characterized by hypogammaglobulinemia usually involving most or all immunoglobulin classes (IgG, IgA, IgM, and IgE), impaired functional antibody responses, and recurrent sinopulmonary infections.(1,2) B-cell numbers may be normal or decreased. A minority of patients with CVID (5%-10%) have very low B-cell counts (<1% of peripheral blood leukocytes), while another subset (5%-10%) exhibit noncaseating, sarcoid-like granulomas in different organs and also tend to develop a progressive T-cell deficiency.(1) Of all patients with CVID, 25% to 30% have increased numbers of CD8 T cells and a reduced CD4:CD8 ratio (<1). Studies have shown the clinical relevance of classifying patients with CVID by assessing B-cell subsets, since changes in different B-cell subsets are associated with specific clinical phenotypes or presentations.(3,4) The B-cell phenotyping assay can be used in the diagnosis of hyper-IgM syndromes, which are characterized by increased or normal levels of IgM with low IgG and/or IgA.(5) Patients with hyper-IgM syndromes can have 1 of 5 known genetic defects in the CD40L, CD40, AID (activation-induced cytidine deaminase), UNG (uracil DNA glycosylase), and NEMO (NF-kappa B essential modulator) genes.(5) Variants in CD40L and NEMO are inherited in an X-linked fashion, while variants in the other 3 genes are inherited in an autosomal recessive fashion. Patients with hyper-IgM syndromes have a defect in isotype class-switching, which leads to a decrease in class-switched memory B cells, with or without an increase in non-switched memory B cells and IgM-only memory B cells. In addition to its utility in the diagnosis of the above-described primary immunodeficiencies, B-cell phenotyping may be used to assess reconstitution of B-cell subsets after hematopoietic stem cell or bone marrow transplant. This test is also used to monitor B-cell-depleting therapies, such as Rituxan (rituximab) and Zevalin (ibritumomab tiuxetan).

Useful For: Screening for humoral or combined immunodeficiencies, including common variable immunodeficiency, hyper IgM syndrome, among others, where B-cell subset distribution information is desired Assessing B-cell subset reconstitution after hematopoietic cell or bone marrow transplant Assessing B-cell subset reconstitution following recovery of B cells after B-cell-depleting immunotherapy This test is not indicated for the evaluation of lymphoproliferative disorders (eg, leukemia, lymphoma, multiple myeloma). This test should not be used to monitor B-cell counts to assess B-cell depletion in patients on B-cell-depleting therapies.

Interpretation: The assay provides semiquantitative information on the various B-cell subsets. Each specimen is evaluated for B-cell subsets with respect to the total number of CD19+ B cells present in the peripheral blood mononuclear cell population, compared to the reference range. In order to verify that there are no CD19-related defects, CD20 is used as an additional pan-B-cell marker (expressed as percentage of CD45+ lymphocytes). The B-cell panel assesses the following B-cell subsets: CD19+=B cells expressing CD19 as a percent of total lymphocytes CD19+ CD27+=total memory B cells CD19+ CD27+ IgD+ IgM+=marginal zone or non-switched memory B cells CD19+ CD27+ IgD- IgM+=IgM-only memory B cells CD19+ CD27+ IgD- IgM-=class-switched memory B cells CD19+ IgM+=IgM B cells CD19+ CD38+ IgM+=transitional B cells CD19+ CD38+ IgM-=plasmablasts CD19+ CD21-=CD21-negative B cells CD19+ CD21+=CD21-positive B cells CD19+ CD20+=B cells coexpressing both CD19 and CD20 as a percent of total lymphocytes

Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References: 1. Warnatz K, Denz A, Drager R, et al. Severe deficiency of switched memory B cells (CD27+ IgM- IgD-) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. Blood. 2002;99(5):1544-1551 2. Brouet JC, Chedeville A, Fermand JP, Royer B. Study of the B cell memory compartment in common variable immunodeficiency. Eur J Immunol. 2000;30(9):2516-2520 3. Wehr C, Kivioja T, Schmitt C, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood. 2008;111(1):77-85 4. Alachkar H, Taubenheim N, Haeney MR, Durandy A, Arkwright PD. Memory switched B-cell percentage and not serum immunoglobulin concentration is associated with clinical complications in children and adults with specific antibody deficiency and common variable immunodeficiency. Clin Immunol. 2006;120(3):310-318 5. Lee WI, Torgerson TR, Schumacher MJ, Yel L, Zhu Q, Ochs HD. Molecular

analysis of a large cohort of patients with hyper immunoglobulin M (hyper IgM) syndrome. Blood. 2005;105(5):1881-1890 6. Ramirez NJ, Posadas-Cantera S, Caballero-Oteyza A, Camacho-Ordonez N, Grimbacher B. There is no gene for CVID - novel monogenetic causes for primary antibody deficiency. Curr Opin Immunol. 202172:176-185. doi:10.1016/j.coi.2021.05.010 7. Kumanovics A, Sadighi Akha AA. Flow cytometry for B-cell subset analysis in immunodeficiencies. J Immunol Methods. 2022;509:113327. doi:10.1016/j.jim.2022.113327 8. Sadighi Akha AA, Csomos K, Ujhazi B, Walter JE, Kumanovics A. Evolving approach to clinical cytometry for immunodeficiencies and other immune disorders. Clin Lab Med. 2023;43(3):467-483. doi:10.1016/j.cll.2023.05.002

TFEBF
64973

Renal Cell Carcinoma, 6p21.1 (TFEB) Rearrangement, FISH, Tissue

Clinical Information: The TFEB gene may be altered in some patients with renal cell carcinoma (RCC). Identification of rearrangement of the TFEB gene region by FISH analysis can aid in the diagnosis of RCC.

Useful For: Identifying TFEB gene rearrangements in patients with renal cell carcinoma (RCC)

Interpretation: A positive result with the TFEB probe is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result of TFEB suggests promotor substitution caused by structural alterations of the TFEB gene region at 6p21.1. A negative result suggests no structural alterations of the locus.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Argani P, Yonescu R, Morsberger L, et al: Molecular confirmation of t(6:11)(p21;q12) renal cell carcinoma in archival paraffin-embedded material using a break-apart TFEB FISH assay expands its clinicopathologic spectrum. Am J Surg Pathol 2012 Oct;36(10):1516-1526 2. Argani P, Cheville J, Ladanyi M: MiT family translocation renal cell carcinomas. In WHO Classifications of Tumours of Urinary System and Male Genital Organs. Fourth edition. Edited by H Moch, PA Humphrey, TM Ulbright, VE Reuter VE. Lyon, France, IARC Press, 2016, 33-34

RFAMA
113634

Renal Function Panel, Serum

Clinical Information: This panel could be ordered when a patient has risk factors for kidney dysfunction such as high blood pressure (hypertension), diabetes, cardiovascular disease, obesity, elevated cholesterol, or a family history of kidney disease. This panel may also be ordered when someone has signs and symptoms of kidney disease, though early kidney disease often does not cause any noticeable symptoms. It may be initially detected through routine blood or urine testing.

Useful For: Aiding in diagnosis and management of conditions affecting kidney function General health screening Screening patients at risk of developing kidney disease Management of patients with known kidney disease

Interpretation: Panel results are not diagnostic but rather indicate that there may be a problem with the kidneys and that further testing is required to make a diagnosis and determine the cause. Results of the panel are usually considered together, rather than separately. Individual test results can be abnormal due to causes other than kidney disease but taken together with risks and signs and symptoms, they may give an indication of whether kidney disease is present.

Reference Values:

SODIUM
<1 year: Not established
> or =1 year: 135-145 mmol/L

POTASSIUM
<1 year: Not established
> or =1 year: 3.6-5.2 mmol/L

CHLORIDE
<1 year: Not established
1-17 years: 102-112 mmol/L
> or =18 years: 98-107 mmol/L

BICARBONATE
Males
<1 year: Not established
1-2 years: 17-25 mmol/L
3 years: 18-26 mmol/L
4-5 years: 19-27 mmol/L
6-7 years: 20-28 mmol/L
8-17 years: 21-29 mmol/L
> or =18 years: 22-29 mmol/L

Females
<1 year: Not established
1-3 years: 18-25 mmol/L
4-5 years: 19-26 mmol/L
6-7 years: 20-27 mmol/L
8-9 years: 21-28 mmol/L
> or =10 years: 22-29 mmol/L

ANION GAP
<7 years: Not established
> or =7 years: 7-15

BLOOD UREA NITROGEN (BUN)
Males
<12 months: Not established
1-17 years: 7-20 mg/dL
> or =18 years: 8-24 mg/dL

Females
<12 months: Not established
1-17 years: 7-20 mg/dL
> or =18 years: 6-21 mg/dL

CREATININE
Males
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL

Females
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL

ESTIMATED GLOMERULAR FILTRATION RATE (eGFR)

>= 18 years old: > or =60 mL/min/BSA (body surface area)
Estimated GFR calculated using the 2021 CKD-EPI creatinine equation.
Note: eGFR results will not be calculated for patients younger than 18 years old.

CALCIUM
<1 year: 8.7-11.0 mg/dL
1-17 years: 9.3-10.6 mg/dL
18-59 years: 8.6-10.0 mg/dL
60-90 years: 8.8-10.2 mg/dL
>90 years: 8.2-9.6 mg/dL

GLUCOSE
0-11 months: Not established
> or =1 year: 70-140 mg/dL

Total Protein
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients who are younger than 12 months of age.

ALBUMIN
> or =12 months: 3.5-5.0 g/dL
Reference values have not been established for patients who are younger than 12 months of age.

PHOSPHORUS
Males
1-4 years: 4.3-5.4 mg/dL
5-13 years: 3.7-5.4 mg/dL
14-15 years: 3.5-5.3 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL
Reference values have not been established for patients that are younger than 12 months of age.

Females
1-7 years: 4.3-5.4 mg/dL
8-13 years: 4.0-5.2 mg/dL
14-15 years: 3.5-4.9 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL
Reference values have not been established for patients that are younger than 12 months of age.

Clinical References:

RPCWT Renal Pathology Consultation, Wet Tissue
70591

Clinical Information: The Mayo Renal Pathology service is staffed by board-certified pathologists who have a special interest in non-neoplastic diseases of the kidney. Kidney biopsy has proven to be of value in the clinical evaluation and management of patients with kidney disease, including acute and chronic renal insufficiency, nephrotic syndrome, nephritic syndrome, proteinuria, and hematuria, and in the overall management of kidney transplant recipients. Optimal interpretation of a kidney biopsy requires integration of clinical and laboratory results with light microscopic, immunofluorescent histology, and electron microscopy findings.

Useful For: Evaluating and managing patients with kidney disease Following the progression of known kidney disease or response to therapy Determining the cause of dysfunction in the transplanted kidney (allograft)

Interpretation: A verbal report is provided to nephrologists for Mayo Clinic Laboratories cases. Digital images for electron microscopy and immunofluorescent stains may be downloaded as needed using the digital imaging link provided in the final report. In most cases, electron microscopy results are reported as an addendum, and a final report including these findings is issued.

Reference Values:
Results of the consultation are reported in a formal pathology report, which may include a description of ancillary test results (if applicable) and an interpretive comment.

Clinical References: 1. Chang A, Gibson IW, Cohen AH, et al. A position paper on standardizing the nonneoplastic kidney biopsy report. Clin J Am Soc Nephrol. 2012;7:1365-1368 2. Jennette JC, D'Agati VD, Olson JL, Silva FG, eds. Heptinstall's Pathology of the Kidney. 7th ed. Lippincott Williams and Wilkins; 2014

RFCWT 620415 Renal Pathology Tissue Consultation, Wet Tissue

Clinical Information: The Mayo Renal Pathology service is staffed by board-certified pathologists who have a special interest in non-neoplastic diseases of the kidney. Kidney biopsy has proven to be of value in the clinical evaluation and management of patients with kidney disease, including acute and chronic renal insufficiency, nephrotic syndrome, nephritic syndrome, proteinuria, and hematuria, and in the overall management of kidney transplant recipients. Optimal interpretation of a kidney biopsy requires integration of clinical and laboratory results with light microscopic, immunofluorescent histology, and electron microscopy findings.

Useful For: Evaluating and managing patients with kidney disease Following the progression of known kidney disease or response to therapy Determining the cause of dysfunction in the transplanted kidney (allograft)

Interpretation: Both a verbal report and a faxed report are provided to nephrologists for Mayo Clinic Laboratories cases. Representative electron microscopy images and significant positive immunofluorescent stain findings can be provided on a CD upon request. In most cases, the electron microscopy results are reported as an addendum, and a final report is issued including these findings. This final report is again faxed to the submitting nephrologist and mailed to the submitting pathology laboratory, along with a representative set of the light microscopy slides. Digital images for electron microscopy and immunofluorescent stains may be downloaded as needed using the digital imaging link provided in the final report.

Reference Values:
Results of the consultation are reported in a formal pathology report, which may include a description of ancillary test results (if applicable) and an interpretive comment.

Clinical References: 1. Chang A, Gibson IW, Cohen AH, et al. A position paper on standardizing the nonneoplastic kidney biopsy report. Clin J Am Soc Nephrol. 2012; 7(8):1365-1368. doi:10.2215/CJN.02300312 2. Jennette JC, D'Agati VD, Olson JL, Silva FG, eds. Heptinstall's Pathology of the Kidney. 7th ed. Lippincott Williams and Wilkins; 2014

PRA
8060

Renin Activity, Plasma

Clinical Information: The renal juxtaglomerular apparatus generates renin, an enzyme that converts angiotensinogen to angiotensin I. The inactive angiotensin I is enzymatically converted to the active octapeptide angiotensin II, a potent vasopressor responsible for hypertension of renal origin. Angiotensin II also stimulates the zona glomerulosa of the adrenal cortex to release aldosterone. Renin secretion by the kidney is stimulated by a fall in glomerular blood pressure, by decreased sodium concentration at the macula densa at the distal tubule, or by stimulation of sympathetic outflow to the kidney, such as in renal vascular diseases.

Useful For: Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome) This test is not useful for determination of plasma renin concentration.

Interpretation: A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL/h, is a positive screening test result, a finding that warrants further testing. A SA:PRA ratio greater than or equal to 20 and SA of greater than or equal to 15 ng/dL indicates probable primary aldosteronism. Kidney disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Kidney venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected:normal) above 1.5. For more information see Renin-Aldosterone Studies.

Reference Values:

0-2 years: 4.6 ng/mL/h (mean)* Range: 1.4-7.8 ng/mL/h
3-5 years: 2.5 ng/mL/h (mean)* Range: 1.5-3.5 ng/mL/h
6-8 years: 1.4 ng/mL/h (mean)* Range: 0.8-2.0 ng/mL/h
9-11 years: 1.9 ng/mL/h (mean)* Range: 0.9-2.9 ng/mL/h
12-17 years: 1.8 ng/mL/h (mean)* Range: 1.2-2.4 ng/mL/h
Mean data not standardized as to time of day or diet. Infants were supine, children sitting.
*Stalker HP, Holland NH, Kotchen JM, Kotchen TA. Plasma renin activity in healthy children. J Pediatr. 1976;89(2):256-258

Na-depleted, upright (peripheral vein specimen)
18-39 years: 10.8 ng/mL/h (mean)
2.9-24.0 ng/mL/h (range)
> or =40 years: 5.9 ng/mL/h (mean)
2.9-10.8 ng/mL/h (range)

Na-replete, upright (peripheral vein specimen)
18-39 years: 1.9 ng/mL/h (mean)
< or =0.6-4.3 ng/mL/hour (range)
> or =40 years: 1.0 ng/mL/h (mean)
< or =0.6-3.0 ng/mL/h (range)

Clinical References: 1. Young WF Jr. Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev. 1999;7(4):207-214 2. Young WF Jr. Pheochromocytoma and primary aldosteronism: diagnostic approaches. Endocrinol Metab Clin North Am. 1997;26(4):801-827.

doi:10.1016/s0889-8529(05)70283-8 3. Baudrand R, Vaidya A. The low-renin hypertension phenotype: genetics and the role of the mineralocorticoid receptor. Int J Mol Sci. 2018;19(2):546. doi:10.3390/ijms19020546

RTSCJ 622836 Reptilase Time, Plasma

Clinical Information: Prolonged clotting times may be associated with a wide variety of coagulation abnormalities including: -Deficiency or functional abnormality (congenital or acquired) of any of the coagulation proteins -Deficiency or functional abnormality of platelets -Specific factor inhibitors -Acute disseminated intravascular coagulation -Exogenous anticoagulants (eg, heparin, warfarin) The prothrombin time (PT) and activated partial thromboplastin time (aPTT) are first-order tests for coagulation abnormalities and are prolonged in many bleeding disorders. A battery of coagulation tests is often required to determine the cause of prolonged clotting times. The thrombin time (TT) test is used to identify the cause of prolonged aPTT or dilute Russell's viper venom time (DRVVT). Reptilase time (RT) test is used to evaluate a prolonged TT. Reptilase is a thrombin-like enzyme isolated from the venom of Bothrops atrox. Thrombin splits small fibrinopeptides A and B from fibrinogen molecules, producing fibrin monomer, which polymerizes to form a clot. Reptilase, however, splits off fibrinopeptide A but not B, which results in fibrin polymerization. In contrast to thrombin and the TT test which are inhibited by heparin, the RT is normal in the presence of heparin. Similar to the TT test, the RT is prolonged in the presence of hypofibrinogenemia and dysfibrinogenemia.

Useful For: Evaluation of a prolonged thrombin time (TT) Confirm or exclude the presence of heparin in the specimen or specimen type Evaluating hypofibrinogenemia or dysfibrinogenemia in conjunction with the TT and fibrinogen assay

Interpretation: As seen in the following table, reptilase time can help distinguish among the various causes of a prolonged thrombin time (TT). Table. Thrombin time Reptilase time Causes Remarks Prolonged Prolonged Hypo- or afibrinogenemia Ascertain by determination of fibrinogen Prolonged Prolonged Dysfibrinogenemia Ascertain by specific assay Prolonged Normal Heparin or inhibitor of thrombin Differentiate by human TT and/or heparin assays Prolonged Prolonged Fibrin(ogen) split products (FSP) Ascertain by FSP or D-dimer assay

Reference Values:
14.0-23.9 seconds

Clinical References: Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. Humana Press; 2017

RTSC 602185 Reptilase Time, Plasma

Clinical Information: Prolonged clotting times may be associated with a wide variety of coagulation abnormalities including: -Deficiency or functional abnormality (congenital or acquired) of any of the coagulation proteins -Deficiency or functional abnormality of platelets -Specific factor inhibitors -Acute disseminated intravascular coagulation -Exogenous anticoagulants (eg, heparin, warfarin) The prothrombin time (PT) and activated partial thromboplastin time (APTT) are first-order tests for coagulation abnormalities and are prolonged in many bleeding disorders. A battery of coagulation tests is often required to determine the cause of prolonged clotting times. The thrombin time (TT) test is used to identify the cause of prolonged APTT or dilute Russell viper venom time (DRVVT). Reptilase time (RT) test is used to evaluate a prolonged TT. Reptilase is a thrombin-like enzyme isolated from the venom of Bothrops atrox. Thrombin splits small fibrinopeptides A and B from fibrinogen molecules, producing fibrin monomer, which polymerizes to form a clot. Reptilase, however, splits off fibrinopeptide A but not

B, which results in fibrin polymerization. In contrast to thrombin and the TT test which are inhibited by heparin, the RT is normal in the presence of heparin. Similar to the TT test, the RT is prolonged in the presence of hypofibrinogenemia and dysfibrinogenemia.

Useful For: Evaluation of a prolonged thrombin time (TT): It is mainly used to confirm or exclude the presence of heparin in the specimen or specimen type Evaluating hypofibrinogenemia or dysfibrinogenemia in conjunction with the TT and fibrinogen assay

Interpretation: As seen in the following table, reptilase time can help distinguish among the various causes of a prolonged thrombin time (TT). Thrombin Time Reptilase Time Causes Remarks Prolonged Prolonged Hypo- or afibrinogenemia Ascertain by determination of fibrinogen Prolonged Prolonged Dysfibrinogenemia Ascertain by specific assay Prolonged Normal Heparin or inhibitor of thrombin Differentiate by human TT and/or heparin assays Prolonged Prolonged Fibrin(ogen) split products (FSP) Ascertain by FSP or D-dimer assay

Reference Values:
14.0-23.9 seconds

Clinical References: Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. 1st ed. Humana Press; 2017

RP
609409

Respiratory Panel, PCR, Nasopharyngeal

Clinical Information: Respiratory infections are common and generally cause self-limited illnesses in healthy, immunocompetent hosts. Viruses account for a significant percentage of respiratory diseases, but bacteria can be associated with respiratory infections. Although respiratory illnesses are frequently mild, viruses may cause significant morbidity and mortality in immunocompromised hosts (eg, transplant recipients, patients with underlying malignancies). Influenza viruses (types A and B) and respiratory syncytial virus (RSV) are 2 common causes of viral respiratory illness, with peak incidence in the winter and spring months in the Northern hemisphere. Both viruses can cause a clinically indistinguishable syndrome characterized by fever, cough, headache, and general malaise. RSV is a leading cause of respiratory illness in young children. Early diagnosis of influenza and RSV is important so necessary infection control precautions can be taken if the patient is hospitalized, and antiviral therapy can be considered if the patient is hospitalized or considered at high-risk for severe disease.(1) Human metapneumovirus is also a cause of respiratory illness in both children and adults. Human rhinovirus and coronavirus serotypes HKU1, NL63, 229E, and OC43 are the causative agents of the common cold, with symptoms including runny nose, sore throat, and malaise. Infections with rhinovirus and coronaviruses are extremely common, due to the large number of serotypes of these viruses. Most infections are mild and self-limiting; however, immunocompromised individuals may suffer more severe illnesses, including lower respiratory tract disease. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus that causes COVID-19. Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract illness. Symptoms can range from mild (eg, the common cold) to severe (eg, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19 disease, the symptoms may be nonspecific and resemble other common respiratory infections, such as influenza. Parainfluenza viruses and adenovirus are also common causes of viral infection, especially in young children. Parainfluenza viruses are most common during the spring, summer, and fall months, with symptoms including fever, runny nose, and cough. However, parainfluenza viruses may also cause more severe lower respiratory disease, such as croup or pneumonia. Adenoviruses may infect a range of organ systems, with sequelae ranging from cold-like symptoms (sore throat) to pneumonia, conjunctivitis (pink eye), or diarrhea. Similar to the viruses described above, parainfluenza viruses and adenoviruses generally cause mild, self-limited infections

but may cause severe disease in immunosuppressed patients. Respiratory infections may also be caused by bacterial pathogens, including Bordetella pertussis, Bordetella parapertussis, Chlamydia pneumoniae, and Mycoplasma pneumoniae. B pertussis is the causative agent of pertussis, or whooping cough, a disease characterized by a prolonged cough that may be associated with an inspiratory whoop and post-tussive vomiting. B parapertussis causes a similar, but generally less severe, illness. M pneumoniae is a cause of upper respiratory infection, pharyngitis, tracheobronchitis, and pneumonia. C pneumoniae is a rare cause of pneumonia.

Useful For: Rapid detection of respiratory infections caused by the following: -Adenovirus -Coronavirus serotypes HKU1, NL63, 229E, OC43 - SARS-CoV-2, the causative agent of COVID-19 -Human metapneumovirus -Human rhinovirus/enterovirus -Influenza A subtypes H1, H1-2009, H3, influenza A undifferentiated subtypes (including subtype H5N1) -Influenza B -Parainfluenza virus serotypes 1-4 -Respiratory syncytial virus (RSV) -Bordetella pertussis -Bordetella parapertussis -Chlamydia pneumoniae -Mycoplasma pneumoniae This test is not recommended as a test of cure.

Interpretation: Results are intended to aid in the diagnosis of illness and are meant to be used in conjunction with other clinical and epidemiological findings. A negative result should not rule out infection in patients with a high pretest probability for a respiratory infection. The assay does not test for all potentially infectious agents of respiratory disease. Specimens collected too early or too late in the clinical course may not yield the organism causing disease. Negative results should be considered in the context of a patient's clinical course and treatment history, if applicable. For patients who are immunocompromised and have a negative FilmArray respiratory panel test from a nasopharyngeal sample but a high suspicion for infection, there may be additional value in testing a bronchoalveolar lavage specimen (RPB / Respiratory Panel, PCR, Varies). Positive results do not distinguish between a viable or replicating organism and the presence of a nonviable organism or nucleic acid, nor do they exclude the potential for coinfection by organisms not included in the panel. Nucleic acid may persist in some patients for days to weeks, even following appropriate therapy. Detection of 1 or more organisms included in this test suggests that the virus or bacteria is present in the clinical sample; however, the test does not distinguish between organisms that are causing disease and those that are present but not associated with a clinical illness. Coinfections (eg, detection of multiple viruses or bacteria or viruses and bacteria) may be observed with this test. In these situations, the clinical history and presentation should be reviewed thoroughly to determine the clinical significance of multiple pathogens in the same specimen.

Reference Values:
Undetected (for all targets)

Clinical References: 1. Lee N, Lui GC, Wong KT, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. Clin Infect Dis. 2013:57(8):1069-1077. doi:10.1093/cid/cit471 2. Miliander C, Espy M, Binnicker MJ. Evaluation of the BioFire FilmArray for the detection of respiratory viruses in clinical samples. Clinical Virology Symposium Annual Meeting. Daytona, Florida; April 2013 3. Ramanan P, Bryson AL, Binnicker MJ, Pritt BS, Patel R. Syndromic panel-based testing in clinical microbiology. Clin Microbiol Rev. 2017;31(1):e00024-17. doi:10.1128/CMR.00024-17

RPB
616389

Respiratory Panel, PCR, Varies

Clinical Information: Respiratory infections are common and generally cause self-limited illnesses in healthy, immunocompetent hosts. Viruses account for a significant percentage of respiratory diseases, but bacteria can be associated with respiratory infections. Although respiratory illnesses are frequently mild, viruses may cause significant morbidity and mortality in individuals who are immunocompromised (eg, transplant recipients, patients with underlying malignancies). Influenza viruses (types A and B) and respiratory syncytial virus (RSV) are 2 common causes of viral respiratory illness, with peak incidence in

the winter and spring months in the Northern Hemisphere. Both viruses can cause a clinically indistinguishable syndrome characterized by fever, cough, headache, and general malaise. RSV is a leading cause of respiratory illness in young children. Early diagnosis of influenza and RSV is important so necessary infection control precautions can be taken if the patient is hospitalized, and antiviral therapy can be considered if the patient is hospitalized or considered at high-risk for severe disease.(1) Human metapneumovirus is also a cause of respiratory illness in both children and adults. Human rhinovirus and coronavirus serotypes HKU1, NL63, 229E, and OC43 are the causative agents of the common cold, with symptoms including runny nose, sore throat, and malaise. Infections with rhinovirus and coronaviruses are extremely common due to the large number of serotypes of these viruses. Most infections are mild and self-limiting; however, individuals who are immunocompromised may suffer more severe illnesses, including lower respiratory tract disease. SARS-CoV-2 virus is an RNA virus that causes COVID-19. Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract illness. Symptoms can range from mild (eg, the common cold) to severe (eg, pneumonia) in both healthy individuals and patients who are immunocompromised. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19 disease, the symptoms may be nonspecific and resemble other common respiratory infections, such as influenza. Parainfluenza viruses and adenovirus are also common causes of viral infection, especially in young children. Parainfluenza viruses are most common during the spring, summer, and fall months, with symptoms including fever, runny nose, and cough. However, parainfluenza viruses may also cause more severe lower respiratory disease, such as croup or pneumonia. Adenoviruses may infect a range of organ systems, with sequelae ranging from cold-like symptoms (sore throat) to pneumonia, conjunctivitis (pink eye), or diarrhea. Similar to the viruses described above, parainfluenza viruses and adenoviruses generally cause mild, self-limited infections but may cause severe disease in patients who are immunosuppressed. Respiratory infections may also be caused by bacterial pathogens, including Bordetella pertussis, Bordetella parapertussis, Chlamydia pneumoniae, and Mycoplasma pneumoniae. B pertussis is the causative agent of pertussis, or whooping cough, a disease characterized by prolonged cough that may be associated with an inspiratory whoop and post-tussive vomiting. B parapertussis causes a similar, but generally less severe, illness. M pneumoniae is a cause of upper respiratory infection, pharyngitis, tracheobronchitis, and pneumonia. C pneumoniae is a rare cause of pneumonia.

Useful For: Rapid detection of respiratory infections caused by the following: -Adenovirus -Coronavirus serotypes HKU1, NL63, 229E, OC43 -SARS-CoV-2 -Human metapneumovirus -Human rhinovirus/enterovirus -Influenza A subtypes H1, H1-2009, H3, influenza A undifferentiated subtypes (including subtype H5N1) -Influenza B -Parainfluenza virus serotypes 1-4 -Respiratory syncytial virus (RSV) -Bordetella pertussis -Bordetella parapertussis -Chlamydia pneumoniae -Mycoplasma pneumoniae This test is not recommended as a test of cure.

Interpretation: Results are intended to aid in the diagnosis of illness and are meant to be used in conjunction with other clinical and epidemiological findings. A negative result should not rule out infection in patients with a high pretest probability for a respiratory infection. The assay does not test for all potential infectious agents of respiratory disease. Specimens collected too early or too late in the clinical course may not yield the organism causing disease. Negative results should be considered in the context of a patient's clinical course and treatment history, if applicable. Positive results do not distinguish between a viable or replicating organism and the presence of a nonviable organism or nucleic acid, nor do they exclude the potential for coinfection by organisms not included in the panel. Nucleic acid may persist in some patients for days to weeks, even following appropriate therapy. Detection of 1 or more organisms included in this test suggests that the virus or bacteria is present in the clinical sample; however, the test does not distinguish between organisms that are causing disease and those that are present but not associated with a clinical illness. Coinfections (eg, detection of multiple viruses or bacteria or viruses and bacteria) may be observed with this test. In these situations, the clinical history and presentation should be reviewed thoroughly to determine the clinical significance of multiple pathogens in the same specimen.

Reference Values:
Undetected (for all targets)

Clinical References: 1. Lee N, Lui GC, Wong KT, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. Clin Infect Dis. 2013;57(8):1069-1077 2. Miliander C, Espy M, Binnicker MJ. Evaluation of the BioFire FilmArray for the detection of respiratory viruses in clinical samples. Clinical Virology Symposium Annual Meeting. Daytona, Florida; April 2013 3. Ramanan P, Bryson AL, Binnicker MJ, Pritt BS, Patel R. Syndromic panel-based testing in clinical microbiology. Clin Microbiol Rev. 2017;31(1):e00024-17. doi:10.1128/CMR.00024-17

RPR1 62046 Respiratory Profile, Region 1, North Atlantic (CT, MA, ME, NJ, NH, NY, PA, RI, VT), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI -bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the North Atlantic region including Connecticut, Maryland, Maine, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	
9-12 years	< or =696	
13-15 years	< or =629	
16 and 17 years	< or =537	
18 years and older	< or =214	

Clinical References:

RPR10
62056

Respiratory Profile, Region 10, Southwestern Grasslands (OK, TX), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various

other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Southwestern Grasslands region, including Oklahoma and Texas Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	
9-12 years	< or =696	
13-15 years	< or =629	
16 and 17 years	< or =537	

18 years and older	< or =214

Clinical References:

RPR11
62057

Respiratory Profile, Region 11, Rocky Mountain (AZ [Mt]; CO; ID [Mt]; NM, UT [Mt]; WY), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Rocky Mountain region including Arizona, Colorado, Idaho, New Mexico, Utah, and Wyoming Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	
9-12 years	< or =696	
13-15 years	< or =629	
16 and 17 years	< or =537	
18 years and older	< or =214	

Clinical References:

RPR12
62058

Respiratory Profile, Region 12, Arid Southwest (Southern AZ Desert, Southern CA Desert), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary

immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the arid Southwest region, including the southern Arizona desert and the southern California desert Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	
9-12 years	< or =696	
13-15 years	< or =629	
16 and 17 years	< or =537	

18 years and older	< or =214

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol 2008 Mar;100(3 Suppl 3):S1-148

RPR13
62059

Respiratory Profile, Region 13, Southern Coastal California, Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Southern Coastal California region Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	
9-12 years	< or =696	
13-15 years	< or =629	
16 and 17 years	< or =537	
18 years and older	< or =214	

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: An updated practice parameter. Ann Allergy Asthma Immunol. 2008 Mar;100(3 Suppl 3):S1-148

RPR14
62060

Respiratory Profile, Region 14, Central California, Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes)

and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in Central California Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	
9-12 years	< or =696	
13-15 years	< or =629	

16 and 17 years	< or =537
18 years and older	< or =214

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: An updated practice parameter. Ann Allergy Asthma Immunol. 2008 Mar;100(3 Suppl 3):S1-148

RPR15
62061

Respiratory Profile, Region 15, Intermountain West (Southern ID, NV), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Intermountain West region including southern Idaho and Nevada Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	
9-12 years	< or =696	
13-15 years	< or =629	
16 and 17 years	< or =537	
18 years and older	< or =214	

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol 2008 Mar;100(3 Suppl 3):S1-148

RPR16
62062

Respiratory Profile, Region 16, Inland Northwest (OR, Central and Eastern WA), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low

concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the inland Northwest region, including Oregon and central and east Washington Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	

9-12 years	< or =696
13-15 years	< or =629
16 and 17 years	< or =537
18 years and older	< or =214

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol. 2008 Mar;100(3 Suppl 3):S1-148

RPR17
62063

Respiratory Profile, Region 17, Pacific Northwest (Northwestern CA, Western OR, WA), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Pacific Northwest including the region of Northwestern California, Western Oregon and Washington Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may

be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	
9-12 years	< or =696	
13-15 years	< or =629	
16 and 17 years	< or =537	
18 years and older	< or =214	

Clinical References: 1. H Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: An updated practice parameter. Ann Allergy Asthma Immunol. 2008 Mar;100(3 Suppl 3):S1-148

RPR18
62064

Respiratory Profile, Region 18, Alaska, Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because

of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in Alaska Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	

9-12 years	< or =696
13-15 years	< or =629
16 and 17 years	< or =537
18 years and older	< or =214

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: An updated practice parameter. Ann Allergy Asthma Immunol. 2008 Mar;100(3 Suppl 3):S1-148

RPR19
62065

Respiratory Profile, Region 19, Puerto Rico, Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in Puerto Rico Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	
9-12 years	< or =696	
13-15 years	< or =629	
16 and 17 years	< or =537	
18 years and older	< or =214	

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol. 2008 Mar;100(3 Suppl 3):S1-148

RPR2
62047

Respiratory Profile, Region 2, Mid-Atlantic (DC, DE, MD, NC, VA), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low

concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Mid-Atlantic region including the District of Columbia, Delaware, Maryland, North Carolina, and Virginia Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	

7 and 8 years	< or =403
9-12 years	< or =696
13-15 years	< or =629
16 and 17 years	< or =537
18 years and older	< or =214

Clinical References: 1. Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: An updated practice parameter. Ann Allergy Asthma Immunol. 2008 Mar;100(3 Suppl 3):S1-148

RPR3
62048

Respiratory Profile, Region 3, South Atlantic (GA, N.FA, SC), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the South Atlantic region, including Georgia, Northern Florida, and South Carolina Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and

malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	
9-12 years	< or =696	
13-15 years	< or =629	
16 and 17 years	< or =537	
18 years and older	< or =214	

Clinical References: 1. Homburger HA, Hamilton RG: Chapter 55: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol. 2008 Mar;100(3 Suppl 3):S1-148

RPR4
62049

Respiratory Profile, Region 4, Sub-tropic Florida (Florida S. of Orlando), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically

helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in sub-tropic Florida, which is south of Orlando Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	

3 years	< or =199
4-6 years	< or =307
7 and 8 years	< or =403
9-12 years	< or =696
13-15 years	< or =629
16 and 17 years	< or =537
18 years and older	< or =214

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol 2008 Mar;100(3 Suppl 3):S1-148

RPR5
62050

Respiratory Profile, Region 5, Ohio Valley (IN, KY, OH, TN, WV), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Ohio Valley region including Indiana, Kentucky, Ohio, Tennessee, and West Virginia Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	
9-12 years	< or =696	
13-15 years	< or =629	
16 and 17 years	< or =537	
18 years and older	< or =214	

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, ed. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: An updated practice parameter. Ann Allergy Asthma Immunol 2008 Mar;100(3 Suppl 3):S1-148

RPR6
62051

Respiratory Profile, Region 6, South Central (AL, AR, LA, MS), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low

concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the South Central region including Alabama, Arkansas, Louisiana and Mississippi Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	

6-11 months	< or =34
1 and 2 years	< or =97
3 years	< or =199
4-6 years	< or =307
7 and 8 years	< or =403
9-12 years	< or =696
13-15 years	< or =629
16 and 17 years	< or =537
18 years and older	< or =214

Clinical References:

RPR7
62052

Respiratory Profile, Region 7, Northern Midwest (MI, MN, WI), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Northern Midwest region including Michigan, Minnesota, and Wisconsin Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	
9-12 years	< or =696	
13-15 years	< or =629	
16 and 17 years	< or =537	
18 years and older	< or =214	

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol 2008 Mar;100(3 Suppl 3):S1-148

RPR8
62053

Respiratory Profile, Region 8, Central Midwest (IA, IL, MO), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very

low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Central Midwest region including Iowa, Illinois, and Missouri Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	

6-11 months	< or =34
1 and 2 years	< or =97
3 years	< or =199
4-6 years	< or =307
7 and 8 years	< or =403
9-12 years	< or =696
13-15 years	< or =629
16 and 17 years	< or =537
18 years and older	< or =214

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol 2008 Mar;100(3 Suppl 3):S1-148

RPR9
62054

Respiratory Profile, Region 9, Great Plains (KS, ND, NE, SD), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer and is present in the circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminths. The function of IgE is distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mites, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Great Plains region including Kansas, North Dakota, Nebraska, and South Dakota Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or

anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

Specific IgE: Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive
Reference values apply to all ages. Total IgE: Age	Reference interval (in kU/L)	
0-5 months	< or =13	
6-11 months	< or =34	
1 and 2 years	< or =97	
3 years	< or =199	
4-6 years	< or =307	
7 and 8 years	< or =403	
9-12 years	< or =696	
13-15 years	< or =629	
16 and 17 years	< or =537	
18 years and older	< or =214	

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070 2. Bernstein IL, Li JT, Bernstein DI, et al: Allergy diagnostic testing: an updated practice parameter. Annals Allergy Asthma and Immunol 2008; 100:S1-S148

RSVAB
601948

Respiratory Syncytial Virus (RSV) In Situ Hybridization, Technical Component Only

Clinical Information: Respiratory syncytial virus (RSV) causes a wheezing illness that especially affects young children. The virus infects alveolar pneumocytes and induces fusion of multiple cells, creating a "syncytial" multinucleated cell. This RSV probe sequence was designed to identify subgroups RSV-A and RSV-B. It has been verified to not cross react with the following viruses in formalin-fixed, paraffin-embedded tissue: adenovirus, BK virus, cytomegalovirus, Epstein-Barr virus, hepatitis C virus, human herpes virus, type 8, human papillomavirus types 6, 11, 16, E6/E7, Helicobacter pylori, herpes simplex virus types 1 and 2, JC virus, parvovirus, toxoplasma, and varicella-zoster viruses.

Useful For: Aids in the identification of respiratory syncytial viral infection

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Hall CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med. 2001;344(25):1917-1928 2. Essaidi-Laziosi M, Lyon M, Mamin A, Fernandes Rocha M, Kaiser L, Tapparel C. A new real-time RT-qPCR assay for the detection, subtyping and quantification of human respiratory syncytial viruses positive- and negative-sense RNAs. J Virol Methods. 2016;235:9-14 3. User manual: RNAscope 2.5 VS Assay for Ventana DISCOVER ULTRA System BROWN, Document Number 322200-USM_ULT 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FRSVQ
75669

Respiratory Syncytial Virus (RSV) RNA, Qualitative Real-Time PCR

Clinical Information: This test is used to determine the presence of respiratory synctial virus (RSV) in a patient's specimen. Organisms may be detected by PCR prior to diagnosis by immunological methods. PCR provides more rapid results than other methods, including culture.

Reference Values:
Not Detected

RETB
616856

Reticulocyte Profile, Blood

Clinical Information: Reticulocytes are immature erythrocytes (red blood cells: RBC) that have been released into the peripheral blood from the bone marrow after extrusion of their nucleus. The reticulocyte contains residual polyribosomes used in the formation of hemoglobin in the developing erythrocyte. Iron deficiency suppresses hemoglobin synthesis.(1) Iron indices that rely on measurement of mature RBC may not accurately reflect acute iron status due to their long (approximately 120 days) lifespan. Reticulocytes are differentiated from erythroblasts (RBC containing a nucleus made in the bone marrow) after hemoglobin synthesis is complete and enucleation (extrusion of the nucleus). The reticulocyte is released from the bone marrow into peripheral circulation to complete maturation through loss of its reticulum (RNA and protein visible with staining) over the course of 1 to 2 days becoming mature RBC. Ultimately, hemoglobin content in reticulocytes is more reflective of real-time hemoglobin synthesis, provided there is not an underlying hematopoietic disorder preventing the production of reticulocytes. Reticulocyte hemoglobin may be particularly useful to evaluate iron deficiency in patients with chronic kidney disease who are on hemodialysis and receiving erythropoietin

or other erythropoiesis-stimulating agents, as they are prone to chronic inflammatory states that complicate traditional iron evaluations. Studies report reticulocyte hemoglobin concentrations below 29 to 32 pg in this population have areas under the receiver-operating curve (ROC area) of 0.74-0.95 for diagnosing iron deficiency compared to low serum ferritin (ROC area range: 0.53 to 0.63) or transferrin saturation (ROC area range: 0.56 to 0.76).(2) Iron deficiency in childhood is common yet critical to recognize early and treat. Guidelines recommend using hemoglobin in combination with either ferritin and C-reactive protein or reticulocyte hemoglobin. The advantage of using reticulocyte hemoglobin is its lower cost and does not require additional blood volume to be collected when combined with complete blood cell count testing. Reticulocyte hemoglobin is also used to evaluate response to treatment for iron deficiency, which is one of the earliest markers of response to oral iron treatment (48 hour) in children with severe iron deficiency anemia. Measurement within 7 days from the start of oral iron is predictive of reaching reference value of hemoglobin at day 30 (3) and has been used to improve iron sufficiency rates in neonatal intensive care unit populations.(4) Other patient populations that may benefit from reticulocyte hemoglobin measurement include those with anemia of chronic disease, postpartum, and blood donors.(2) The reticulocyte is released from the bone marrow into peripheral circulation to complete maturation through loss of its reticulum (RNA and protein measured via fluorescence) over the course of 1 to 2 days becoming mature RBC. The immature reticulocyte fraction measures reticulocyte maturity through quantitation of fluorescence intensity. The most intense signal corresponds to the most immature reticulocytes containing the greatest amount of reticulin. When present in highest proportion of total reticulocytes can be the earliest indicator of beginning erythropoiesis.

Useful For: Assessing erythropoietic bone marrow activity in anemia and other hematologic conditions Assessment of acute iron deficiency Monitoring early response to iron therapy or erythropoiesis-stimulating agents Early monitoring of therapy for nutritional anemias (eg, megaloblastic, iron deficiency) where immature reticulocyte fraction precedes reticulocyte count increase by several days Monitoring therapeutic efficacy of erythropoietin treatment Monitoring early engraftment after bone marrow transplantation

Interpretation: Reticulocyte Quantitation: The reticulocyte count is a measure of the number of red blood cells delivered by the bone marrow. It is elevated with active erythropoiesis such as regeneration and is decreased in hypoplastic or deficiency conditions such as vitamin B12 deficiency. Reticulocyte Hemoglobin: Decreased values are suggestive of acute iron deficiency. Increasing values following treatment with iron or erythropoiesis-stimulating agents suggest early response to therapy. Immature Reticulocyte Fraction: Immature reticulocyte fraction (IRF) is interpreted in conjunction with the reticulocyte count. It provides similar information as the traditional reticulocyte production index, which was a value calculated from the reticulocyte percentage and hematocrit. An increase in both total reticulocytes and IRF is associated with erythropoiesis in conditions, such as acquired hemolytic anemias, or the loss of blood.(5) A decrease in both IRF and absolute reticulocyte count is associated with reduced marrow production.(5) An increased IRF associated with reduced or normal reticulocyte count is associated with acute infections, myelodysplastic syndromes, or dyserythropoietic anemias.(5)

Reference Values:

% RETICULOCYTES
1-3 days: 3.47-5.40%
4 days-4 weeks: 1.06-2.37%
5 weeks-7 weeks: 2.12-3.47%
8 weeks-5 months: 1.55-2.70%
6 months-23 months: 0.99-1.82%
24 months-5 years: 0.82-1.45%
6-11 years: 0.98-1.94%
12-17 years: 0.90-1.49%
Adults: 0.60-2.71%

ABSOLUTE RETICULOCYTES

1-3 days: 147.5-216.4 x 10(9)/L
4 days-4 weeks: 51.3-110.4 x 10(9)/L
5 weeks-7 weeks: 51.8-77.9 x 10(9)/L
8 weeks-5 months: 48.2-88.2 x 10(9)/L
6 months-23 months: 43.5-111.1 x 10(9)/L
24 months-5 years: 36.4-68.0 x 10(9)/L
6-11 years: 42.4-70.2 x 10(9)/L
12-17 years: 41.6-65.1 x 10(9)/L
Adults: 30.4-110.9 x 10(9)/L

IMMATURE RETICULOCYTE FRACTION (IRF)
1-3 days: 30.5-35.1%
4 days-4 weeks: 14.5-24.6%
5 weeks-2 months: 19.1-28.9%
3-5 months: 13.4-23.3%
6 months-<2 years: 11.4-25.8%
2-<6 years: 8.4-21.7%
6-<12 years: 8.9-24.1%
12-<18 years: 9.0-18.7%
> or = 18 years:
Female:3.0-15.9%
Male: 2.3-13.4%

RETICULOCYTE HEMOGLOBIN
Males:
1 day-5 months: 27.6-38.7 pg
6 months-<2 years: 28.7-35.7 pg
2-<6 years: 27.7-37.8 pg
6-<12 years: 32.4-37.6 pg
12-<18 years: 30.0-37.6 pg
Adults: 30.0-37.6 pg

Females:
1 day-5 months: 29.2-37.5 pg
6 months-<2 years: 30.1-35.7 pg
2-<6 years: 29.3-37.3 pg
6-<12 years: 30.4-39.7 pg
12-<18 years: 30.0-37.6 pg
Adults: 30.0-37.6 pg

RED BLOOD CELL COUNT (RBC)
Males:
0-14 days: 4.10-5.55 x 10(12)/L
15 days-4 weeks: 3.16-4.63 x 10(12)/L
5 weeks-7 weeks: 3.02-4.22 x 10(12)/L
8 weeks-5 months: 3.43-4.80 x 10(12)/L
6 months-23 months: 4.03-5.07 x 10(12)/L
24 months-35 months: 3.89-4.97 x 10(12)/L
3-5 years: 4.00-5.10 x 10(12)/L
6-10 years: 4.10-5.20 x 10(12)/L
11-14 years: 4.20-5.30 x 10(12)/L
15-17 years: 4.30-5.70 x 10(12)/L
Adults: 4.35-5.65 x 10(12)/L

Females:
0-14 days: 4.12-5.74 x 10(12)/L
15 days-4 weeks: 3.32-4.80 x 10(12)/L
5 weeks-7 weeks: 2.93-3.87 x 10(12)/L
8 weeks-5 months: 3.45-4.75 x 10(12)/L
6 months-23 months: 3.97-5.01 x 10(12)/L
24 months-35 months: 3.84-4.92 x 10(12)/L
3-5 years: 4.00-5.10 x 10(12)/L
6-10 years: 4.10-5.20 x 10(12)/L
11-14 years: 4.10-5.10 x 10(12)/L
15-17 years: 3.80-5.00 x 10(12)/L
Adults: 3.92-5.13 x 10(12)/L

Clinical References: 1. Chabot-Richards DS, Zhang QY, George TI. Automated hematology. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics; 6th ed. 2018:1734-1734 2. Ogawa C, Tsuchiya K, Maeda Kl. Reticulocyte hemoglobin content. Clinica Chimica Acta. 2020;504:138-145 3. Parodi E, Romano F, Ramenghi U. How we use reticulocyte parameters in workup and management of pediatric hematologic diseases. Front Pediatr. 2020;8:588617 4. Morton SU, Yuen JC, Feldman HA, et al. Screening with reticulocyte hemoglobin increased iron sufficiency among NICU patients. Pediatr Qual Saf. 2020;5(2):e258. doi:10.1097/pq9.0000000000000258 5. Buttarello M. Laboratory diagnosis of anemia: are the old and new red cell parameters useful in classification and treatment, how? Int Jn Lab Hematol. 2016;38 Suppl 1:123-132 6. Saboor M. Discrimination of iron deficiency, alpha and beta thalassemia on the basis of red cell distribution width and reticulocyte indices. Clin Lab. 2021;67(6):10.7754 7. Morkis IV, Farias M, Scotti L. Determination of reference ranges for immature platelet and reticulocyte fractions and reticulocyte hemoglobin equivalent. Rev Bras Hematol Hemoter. 2016;3 8(4):310-313 8. Soldin J, Brugnara C, Wong EC. Pediatric Reference Intervals. 5th ed. AACC Press; 2005

RB1
604028

Retinoblastoma Protein (Rb) Immunostain, Tech Only

Clinical Information: Retinoblastoma (Rb) is a phosphoprotein that is expressed in most normal cells and acts as a tumor suppressor by providing a cell cycle checkpoint between G1 and S phases. Loss of nuclear expression of Rb is useful in the identification of neuroendocrine carcinomas and small cell carcinomas. Loss of Rb can also be helpful to differentiate spindle cell lipomas from myofibroblastomas and cellular angiofibromas from other genital stromal lesions.

Useful For: Aids in the identification of high-grade neuroendocrine carcinomas and small cell carcinomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

FRBP
75570

Retinol Binding Protein

Reference Values:

1.5 - 6.7 mg/dL

RB24
609449

Retinol-Binding Protein, 24 Hour, Urine

Clinical Information: Retinol-binding protein is a low-molecular-weight protein of 21 kDa that transports retinol (vitamin A alcohol) from the liver to peripheral tissues.(1) Retinol-binding protein is most often found bound to transthyretin, but a small, unbound fraction (<10%) passes freely through glomerular membranes and is reabsorbed by renal proximal tubules cells where it is catabolized. Due to extensive tubular reabsorption, under normal conditions very little of the filtered retinol-binding protein appears in the final excreted urine. Therefore, an increase in the urinary excretion of retinol-binding protein indicates proximal tubule injury and/or impaired proximal tubular function.(1) Measurement of retinol-binding protein in urine is, therefore, a useful aid in the monitoring and/or diagnosis of kidney disease. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated retinol-binding protein excretion. Measurement of urinary excretion of alpha-1-microglobulin, another low-molecular-weight protein, is an alternative to the measurement of retinol-binding protein. To date, there are no convincing studies to indicate that one test has better clinical utility than the other. Urinary excretion of retinol-binding protein can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of retinol-binding protein is divided by the urinary creatinine concentration. This corrected value adjusts retinol-binding protein for variabilities in urine concentration.

Useful For: Assessing renal tubular injury or dysfunction Screening for other tubular abnormalities Detecting chronic asymptomatic renal tubular dysfunction.(2)

Interpretation: Retinol-binding protein above the reference values may be indicative of a proximal tubular dysfunction.

Reference Values:
Retinol-Binding Protein:
> or =18 years of age: <273 mcg/24 hour
Reference values have not been established for patients who are less than 18 years.

Creatinine:
Males > or =18: 930-2955 mg/24 hours
Females > or =18: 603-1783 mg/24 hours
Reference values have not been established for patients who are less than 18 years.

Clinical References: 1. Kirsztajn GM, Nishida SK, Silva MS, et al. Urinary retinol-binding protein as a prognostic marker in glomerulopathies. Nephron. 2002;90(4):424-431 2. Norden AG, Scheinman SJ, Deschodt-Lanckman MM, et al. Tubular proteinuria defined by a study of Dent's (CLCN5 mutation) and other tubular diseases. Kidney Int. 2000;57(1):240-249 3. Lamb EJ, Jones GJD. Kidney function tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:470-517

RBR
610010

Retinol-Binding Protein, Random, Urine

Clinical Information: Retinol-binding protein is a low-molecular-weight protein of 21 kDa that transports retinol (vitamin A alcohol) from the liver to peripheral tissues.(1) Retinol-binding protein is

most often found bound to transthyretin, but a small, unbound fraction (<10%) passes freely through glomerular membranes and is reabsorbed by renal proximal tubules cells where it is catabolized. Due to extensive tubular reabsorption, under normal conditions very little of the filtered retinol-binding protein appears in the final excreted urine. Therefore, an increase in the urinary excretion of retinol-binding protein indicates proximal tubule injury and/or impaired proximal tubular function.(1) Measurement of retinol-binding protein in urine is, therefore, a useful aid in the monitoring and/or diagnosis of kidney disease. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated retinol-binding protein excretion. Measurement of urinary excretion of alpha-1-microglobulin, another low-molecular-weight protein, is an alternative to the measurement of retinol-binding protein. To date, there are no convincing studies to indicate that one test has better clinical utility than the other. Urinary excretion of retinol-binding protein can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of retinol-binding protein is divided by the urinary creatinine concentration. This corrected value adjusts retinol-binding protein for variabilities in urine concentration.

Useful For: Assessing renal tubular injury or dysfunction using random urine collections Screening for other tubular abnormalities Detecting chronic asymptomatic renal tubular dysfunction.(2)

Interpretation: Retinol-binding protein values above the reference values may be indicative of a proximal tubular dysfunction.

Reference Values:
> or =18 years: <190 mcg/g creatinine
Reference values have not been established for patients that are less than 18 years.

Clinical References: 1. Kirsztajn GM, Nishida SK, Silva MS, Ajzen H, Moura LA, Bereira AB. Urinary retinol-binding protein as a prognostic marker in glomerulopathies. Nephron. 2002;90(4):424-431. doi:10.1159/000054730 2. Norden AG, Scheinman SJ, Deschodt-Lanckman MM, et al. Tubular proteinuria defined by a study of Dent's (CLCN5 mutation) and other tubular diseases. Kidney Int. 2000;57(1):240-249. doi:10.1046/j.1523-1755.2000.00847.x 3. Lamb EJ, Jones GJD. Kidney function tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:470-517

RAPAN
616785

Rheumatoid Arthritis Panel, Serum

Clinical Information: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by interactions between the environment, specific genetic risk factors, and the human immune system. It affects about 0.6% of the United States population with a global prevalence of 0.24%.(1) Clinically, RA is typified by progressive damage of synovial joints, inflammation, production of diverse autoantibodies, and variable extra-articular manifestations.(2-4) To facilitate early diagnosis, the American College of Rheumatology/European League Against Rheumatism 2010 RA classification criteria recommend testing for rheumatoid factors (RF) and anticitrullinated protein antibodies (ACPA).(2) RF are autoantibodies directed against the Fc portion of immunoglobulin, while ACPA are directed against peptides and proteins containing citrulline, a modified form of the amino acid arginine.(5,6) Rheumatoid factor is a heterogeneous group of autoantibodies and can be found in other inflammatory rheumatic and nonrheumatic conditions with increased prevalence in healthy individuals 60 years and older. More than 75% of patients with RA have an IgM antibody to RF. The titer of RF correlates poorly with disease activity, but those patients with high titers tend to have more severe disease and, thus, a poorer prognosis than seronegative patients. Compared to early serologic tests for RA, including RF, several studies have demonstrated that ACPA have much improved specificity for

RA.(4,5,7) A systemic review and meta-analysis of 33 studies, including patients with RA and healthy or disease controls, demonstrated the sensitivity of anti-mutated citrullinated vimentin, anticyclic citrullinated peptide, and RF of 71%, 71%, 77%, with the specificity of 89%, 95%, 73%, and the area under the curve of the summary receiver operating characteristic of 89%, 95%, 82%, respectively.(7) Based on these studies, there exist a subset of patients with RA who are negative for RF and ACPA IgG (seronegative) who must be diagnosed clinically or with use of emerging diagnostic tests.(4,6,8) In addition to the use of RF and ACPA IgG to diagnose RA, RF and ACPA isotype antibodies and other serologic biomarkers have been used to predict if, and when, an individual who has inflammatory arthritis (IA) may develop future clinically apparent IA and assess genetic and environmental risks.(3,4,8,9) Furthermore, patients with RA may be categorized based on the phase of disease (early versus established), presence or absence of antibodies (seropositive versus seronegative), clinical manifestations (joint erosion, interstitial lung disease, or cardiovascular), or specific risks (genes, sex, or smoking).(2-4) Delayed diagnosis of RA is associated with joint erosion, destruction or deformities, poor response to treatment with ultimate increase in morbidity, and mortality.(3,4) Although late RA prognosis may be linked to adverse consequences, early diagnosis has been reported to improve outcomes; notably reduced joint destruction or deformity, delayed radiologic progression, and decreased functional disability.(3,4,10) For more information see Connective Tissue Disease Cascade.

Useful For: Evaluating patients suspected of having rheumatoid arthritis (RA) Differentiating RA from other inflammatory arthritis or connective tissue diseases Diagnosis and stratification of rheumatoid arthritis

Interpretation: Cyclic Citrullinated Peptide Antibodies: A positive result for cyclic citrullinated peptide (CCP) antibodies may be suggestive of rheumatoid arthritis (RA) if compatible clinical features of disease are present. Significantly elevated levels of CCP antibodies may be useful to identify RA patients with erosive joint disease. A Mayo Clinic prospective clinical evaluation of the CCP antibody test showed a diagnostic sensitivity for RA of 78% with fewer than 5% false-positive results in healthy controls (see Cautions). Rheumatoid Factor: Positive results may be suggestive of RA if compatible clinical features of disease are present.

Reference Values:

Cyclic Citrullinated Peptide Antibodies, IgG
<20.0 U (negative)
20.0-39.9 U (weak positive)
40.0-59.9 U (positive)
> or =60.0 U (strong positive)
Reference values apply to all ages.

Rheumatoid Factor
<15 IU/mL

Clinical References: 1. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1316-1322 2. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-2581 3. Burgers LE, Raza K, van der Helm-van Mil AH. Window of opportunity in rheumatoid arthritis - definitions and supporting evidence: from old to new perspectives. RMD Open. 2019;5(1):e000870 4. Deane KD, Holers VM. Rheumatoid arthritis pathogenesis, prediction, and prevention: An emerging paradigm shift. Arthritis Rheumatol. 2021;73(2):181-193 5. Schellekens GA, Visser H, de Jong BA, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum. 2000;43(1):155-163 6. Derksen VFAM, Huizinga TWJ, van der Woude D. The role of autoantibodies in the pathophysiology of rheumatoid arthritis. Semin Immunopathol. 2017;39(4):437-446 7. Zhu JN, Nie LY, Lu XY, Wu HX. Meta-analysis: compared with anti-CCP and rheumatoid factor, could anti-MCV be the next biomarker

in the rheumatoid arthritis classification criteria? Clin Chem Lab Med. 2019;57(11):1668-1679 8. Verheul MK, Bohringer S, van Delft MAM, et al. Triple positivity for anti-citrullinated protein autoantibodies, rheumatoid factor, and anti-carbamylated protein antibodies conferring high specificity for rheumatoid arthritis: Implications for very early identification of at-risk individuals. Arthritis Rheumatol. 2018;70(11):1721-1731 9. Hedstrom AK, Ronnelid J, Klareskog L, Alfredsson L. Complex relationships of smoking, HLA-DRB1 genes, and serologic profiles in patients with early rheumatoid arthritis: Update from a Swedish population-based case-control study. Arthritis Rheumatol. 2019;71(9):1504-1511 10. Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. Ann Rheum Dis. 2002;61(4):290-297 11. Cush JJ. Rheumatoid arthritis: Early diagnosis and treatment. Rheum Dis Clin North Am. 2022;48(2):537-547

RFPN
621421

Rheumatoid Factor Panel, Serum

Clinical Information: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by interactions between the environment, specific genetic risk factors, and the human immune system. It affects about 0.6% of the United States population with a global prevalence of 0.24%.(1) Clinically, RA is typified by progressive damage of synovial joints, inflammation, production of diverse autoantibodies, and variable extra-articular manifestations.(1,2) To facilitate early diagnosis, the American College of Rheumatology/European League Against Rheumatism 2010 RA classification criteria recommend testing for rheumatoid factors (RF) and anti-citrullinated protein antibodies (ACPA).(2) RF are autoantibodies directed against the Fc portion of immunoglobulin, while ACPA are directed against peptides and proteins containing citrulline, a modified form of the amino acid arginine.(3,4) In addition to the defined interpretations for anti-cyclic citrullinate peptide (CCP) and RF antibodies, the classification criteria also endorse the combination of specific clinical features and inflammatory markers for RA diagnosis. The clinical symptoms in the early phase of RA may be nonspecific with some patients demonstrating relatively low levels of antibodies to RF or anti-CCP antibodies, which may not fulfill the diagnostic criteria for disease. In addition, some patients with clinical features of RA may test negative for criteria antibodies, a phenomenon referred to as seronegative or ACPA-negative. While alternative diagnoses may be implicated in at-risk RA patients, determination of autoantibody isotypes for RF and other RA-associated autoantibodies have been reported to improve diagnostic accuracy and/or provide prognostic clues.(5-8) Thus, determination of multiple analytes of diverse antibody isotypes in patients seropositive for RA may be useful in risk stratification for joint erosive disease and other clinical manifestations such as cardiovascular or lung involvements.(5,7,8) In routine clinical laboratory evaluation for RA, RF antibodies are generally detected and quantified using IgM RF or total (isotype-nonspecific) RF immunoassays and CCP IgG antibodies with a variety of solid-phase immunoassays, such the enzyme linked immunosorbent assay, chemiluminescence immunoassay (CIA), fluorescent enzyme immunoassay (FEIA), multiplexed immunoassay using manual or automated platforms.(5,6,9,10) With respect to RF antibody measurements, it has been established that separate determination of RF IgA and RF IgM antibodies is important in RA evaluation, as severe joint erosive disease is seen more in patients with significantly elevated IgA RF than in those who are IgA RF negative.(5,8,9) However, IgA RF is generally less sensitive than IgM RF for RA, and double positivity for IgM RF and IgA RF has a higher specificity for RA than either IgM RF or IgA RF.(9) Both tests should be offered in a panel, which is not intended to replace RF tests that detect IgA, IgG and IgM autoantibodies. The relevance of IgG RF in addition to IgA or IgM RF is of limited clinical value and not available for testing on the CIA or FEIA platforms due to this clinical limitation.

Useful For: Evaluating patients at-risk of rheumatoid arthritis (RA) or features of inflammatory arthritis Differentiating the antibody isotype profile in patients positive for rheumatoid factor (RF) Aid in the risk stratification of RF-seropositive patients with RA

Interpretation: The presence of rheumatoid factor (RF) IgM or IgA at abnormal levels in association with anti-citrullinated peptide/protein antibodies has high specificity for a diagnosis of rheumatoid

arthritis (RA). However, the presence of RF isotypes in any combination may be found in a variety of conditions, including Sjogren syndrome and hepatitis infections.

Reference Values:

RHEUMATOID FACTOR, IgA
Negative: <20 CU
Positive: > or =20 CU
Reference values apply to all ages.

RHEUMATOID FACTOR, IgM
Negative: <5.0 IU/mL
Positive: > or =5.0 IU/mL
Reference values apply to all ages.

Clinical References: 1. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1316-1322 2. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-2581 3. Schellekens GA, Visser H, de Jong BA, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum. 2000;43(1):155-163 4. Derksen VFAM, Huizinga TWJ, van der Woude D. The role of autoantibodies in the pathophysiology of rheumatoid arthritis. Semin Immunopathol. 2017;39(4):437-446 5. Sieghart D, Platzer A, Studenic P, et al. Determination of autoantibody isotypes increases the sensitivity of serodiagnostics in rheumatoid arthritis. Front Immunol. 2018;9:876 6. Brink M, Hansson M, Mathsson-Alm L, et al. Rheumatoid factor isotypes in relation to antibodies against citrullinated peptides and carbamylated proteins before the onset of rheumatoid arthritis. Arthritis Res Ther. 2016;18:43 7. Kelmenson LB, Wagner BD, McNair BK, et al. Timing of Elevations of Autoantibody Isotypes Prior to Diagnosis of Rheumatoid Arthritis. Arthritis Rheumatol. 2020;72(2):251-261 8. Oka S, Higuchi T, Furukawa H, et al. Serum rheumatoid factor IgA, anti-citrullinated peptide antibodies with secretory components, and anti-carbamylated protein antibodies associate with interstitial lung disease in rheumatoid arthritis. BMC Musculoskelet Disord. 2022;23(1):46 9. Van Hoovels L, Vander Cruyssen B, Sieghart D, et al. IgA rheumatoid factor in rheumatoid arthritis. Clin Chem Lab Med. 2022;60(10):1617-1626 10. Van Hoovels L, Vander Cruyssen B, Sieghart D, et al. Multicentre study to improve clinical interpretation of rheumatoid factor and anti-citrullinated protein/peptide antibodies test results. RMD Open. 2022;8(1):e002099

RHUT
603415

Rheumatoid Factor, Serum

Clinical Information: Rheumatoid factors (RF) are a heterogeneous group of autoantibodies associated with the diagnosis of rheumatoid arthritis (RA) but can also be found in other inflammatory rheumatic and nonrheumatic conditions. They can also be detected in some healthy individuals aged 60 years and older. Despite being nonspecific, the detection of RF or anti-citrullinated protein (anti-CCP) antibody is part of the 2010 diagnosis criterion of the American College of Rheumatology for classification of RA. More than 75% of patients with RA have an IgM antibody to IgG. The titer of RF correlates poorly with disease activity, but those patients with high titers tend to have more severe disease and, thus, a poorer prognosis than seronegative patients. A meta-analysis compared the sensitivity and specificity of IgM RF versus anti-CCP antibody. For IgM RF, the sensitivity was 69% (CI, 65%-73%) and specificity was 85% (CI, 82%-88%). For comparison, the sensitivity for anti-CCP antibody was 67% (95% CI, 62%-72%) and 95% (CI, 94%-97%).(1) Both anti-CCP and RF are useful in the diagnosis of RA, and the use of both tests has been shown to increase diagnostic sensitivity.(2)

Useful For: Diagnosis and prognosis of rheumatoid arthritis

Interpretation: Positive results are consistent with, but not specific for, rheumatoid arthritis.

Reference Values:
<15 IU/mL

Clinical References: 1. Nishimura K, Sugiyama D, Kogata Y, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med. 2007;146(11):797-808 2. Chang PY, Yang CT, Cheng CH, Yu KH. Diagnostic performance of anti-cyclic citrullinated peptide and rheumatoid factor in patients with rheumatoid arthritis. Int J Rheum Dis. 2016;19(9):880-886 3. Aletaha D, Neogi T, Silman AJ, Funovits J. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-2581 4. Smolen JS, Alethaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;388:2023-2038 5. Roberts-Thomson PJ, McEvoy R, Langhans T, Bradley J. Routine quantification of rheumatoid factor by rate nephelometry. Ann Rheum Dis. 1985;44:379-383

RHNI
82856

Rhizopus nigricans, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Rhizopus nigricans Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive

3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FRDG
57959

Rhodotorula IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

FRUB
57920

Rhubarb (Rheum rhaponticum) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

VITB2
42363

Riboflavin (Vitamin B2), Plasma

Clinical Information: There are 3 principal vitamin B2-active flavins found in nature: riboflavin, riboflavin 5-phosphate (flavin mononucleotide: FMN), and riboflavin-5'-adenosyl-diphosphate (flavin adenosine dinucleotide: FAD). In biological tissues, FMN and FAD serve as prosthetic groups for a large variety of flavoproteins, which are hydrogen carriers in oxidation-reduction processes. Dietary deficiency of riboflavin (ariboflavinosis) is characterized by sore throat, cheilosis (lesions on the lips), angular stomatitis (lesions on the angles of the mouth), glossitis (fissured and magenta-colored tongue), corneal vascularization, dyssebacia (red, scaly, greasy patches on the nose, eyelids, scrotum, and labia), and normocytic, normochromic anemia. Severe riboflavin deficiency may affect the conversion of vitamin B6 to its coenzyme, as well as conversion of tryptophan to niacin. There is also evidence that more subtle riboflavin deficiency might have negative health consequences. Finally, in addition to dietary deficiency, there are rare inborn errors of metabolism, primarily involving loss of function of riboflavin transporters, which result in functional vitamin B2 deficiency. Many of these latter cases present with neurodegenerative features. Riboflavin has a low level of toxicity and no case of riboflavin toxicity in humans has been reported. The limited absorptivity of riboflavin and its ready excretion in the urine normally preclude a health problem due to increased intake of riboflavin.

Useful For: Evaluation of individuals who present the signs of ariboflavinosis

Interpretation: Low concentrations in the blood plasma are indicative of nutritional deficiency. Concentrations below 1 mcg/L are considered significantly diminished. Marginally low levels probably represent nutritional deficiency that should be corrected.

Reference Values:
1-19 mcg/L

Clinical References:

RIB
87837

Ribosome P Antibodies, IgG, Serum

Clinical Information:

Useful For: As an adjunct in the diagnostic evaluation of patients with systemic lupus erythematosus (SLE) May be useful in the phenotypic stratification of SLE patients at risk for neuropsychiatric SLE, lupus nephritis and/or hepatitis

Interpretation: As an adjunct in the diagnostic evaluation of patients with systemic lupus erythematosus (SLE) May be useful in the phenotypic stratification of SLE patients at risk for neuropsychiatric SLE, lupus nephritis and/or hepatitis

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References:

FRICE
57633

Rice IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

RICE
82709

Rice, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical

manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to rice Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FRIFA
75628

Rifampin Level (PKRIF)

Interpretation: The target range for mycobacterial infections is 8 to 24 mcg/mL 2 hours after oral dose or 2 hours after the end of intravenous infusion. Samples drawn later than 2 hours after the dose will often display concentrations below the stated range. Rifampin generally should be given as a single daily dose. If the patient is receiving 2 small daily doses, consider combining the doses and rechecking the concentration. Rifampin absorption may be reduced by food. Take on an empty stomach if possible. Rifampin does not have clear concentration-related toxicity and most patients tolerate concentrations above the stated range without difficulty. Hepatic dysfunction may produce elevated rifampin concentrations. Rifampin concentrations greater than 50% above the range may warrant a dose reduction of 150 to 300 mg. If the time of the dose and the blood draw were not accurately recorded, accurate interpretation of the concentration is not possible.

Reference Values:
mcg/mL

RISAP
621813

Risankizumab Quantitation with Antibodies, Serum

Clinical Information: Risankizumab (Skyrizi, AbbVie) is a humanized IgG1 kappa therapeutic monoclonal antibody approved for the treatment of moderate to severe plaque psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn disease.(1,2) Risankizumab targets interleukin 23A (IL-23p19), binding with high affinity to the p19 subunit and inhibiting further action.(3) Therapeutic drug monitoring (TDM) has become standard-of-care for biologic therapies used in inflammatory bowel disease (IBD). In this context, TDM requires both quantitation of the therapeutic monoclonal antibody and assessment for the presence of anti-drug antibodies. Accurate interpretation of drug quantitation requires knowledge regarding patient diagnosis, drug dosage, and treatment schedule. Patients with plaque psoriasis or psoriatic arthritis are treated with 150 mg subcutaneously at weeks 0, 4, and every 12 weeks thereafter. The steady state maximum concentration (Cmax) and trough concentration (Ctrough) are estimated to be 12 mcg/mL and 2 mcg/mL, respectively. Patients with Crohn disease are treated with 600 mg intravenously at weeks 0, 4, and 8, followed by 180 mg or 360 mg subcutaneously at week 12 and every 8 weeks thereafter. During induction weeks 8 through 12, the median Cmax is estimated to be 156 mcg/mL, and the Ctrough is estimated to be 38.8 mcg/mL, according to the drug package insert. Steady state is achieved at 28 weeks after starting treatment in the dosing regimen for Crohn disease. Median Cmax and Ctrough concentrations measured during weeks 40 through 48 of maintenance phase (or weeks 52-60 from start of treatment) are estimated to be 14.0 mcg/mL and 4.1 mcg/mL, respectively, for 180 mg dose or 28.0 mcg/mL and 8.1 mcg/mL, respectively, for 360 mg dose.(4) The other important aspect of TDM for therapeutic monoclonal antibodies is detection of anti-drug antibodies. Similar to other therapeutic antibodies, risankizumab is immunogenic. Development of antibodies to risankizumab (ATRs) may increase drug clearance in treated patients and/or neutralize the drug effect, thereby potentially contributing to loss-of-response. Clinical trials have shown ATRs occur at rates of about 24% for plaque psoriasis, 12% for psoriatic arthritis, and 3.4% for Crohn disease. In the context of limited initial response or loss-of-response over time to risankizumab, measurement of circulating drug concentrations and assessment for ATRs can help to guide patient management. For example, patients with low risankizumab trough concentrations in the absence of ATRs might benefit from dose escalation in an attempt to increase the circulating amount of the drug. In contrast, for patients with low drug concentrations and a detectable ATR, transition to a new drug therapy may be indicated.

Useful For: Evaluation of patients with limited primary (initial) response to or secondary loss of response to risankizumab

Interpretation: The optimal therapeutic serum concentration of risankizumab associated with favorable outcomes in Crohn disease is not known at this time. The current recommendation is to use the lowest dosing regimen that maintains response. According to the package insert, concentrations of risankizumab at steady state ranged from 4.1 mcg/mL (trough) to 14 mcg/mL (peak) at 180 mg dosing and 8.1 mcg/mL (trough) to 28 mcg/mL (peak) at 360 mg dosing. Steady state is achieved 28 weeks after initiation of therapy for the dosing regimen in Crohn disease. The presence of detectable anti-risankizumab antibodies may be associated with increased risankizumab clearance and lower circulating concentrations of risankizumab in serum. Low trough concentrations of risankizumab may be correlated with loss of response to the drug.

Reference Values:
RISANKIZUMAB QUANTITATION:
Risankizumab lower limit of quantitation =1.0 mcg/mL

RISANKIZUMAB ANTIBODIES:

Antibodies to risankizumab: <20.0 ng/mL

Clinical References: 1. Feagan BG, Panes J, Ferrante M, et al. Risankizumab in patients with moderate to severe Crohn's disease: an open-label extension study. Lancet Gastroenterol Hepatol. 2018;3(10):671-680 2. Ferrante M, Panaccione R, Baert F, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. Lancet. 2022;399(10340):2031-2046 3. Pang Y, D'Cunha R, Winzenborg I, Veldman G, Pivorunas V, Wallace K. Risankizumab: Mechanism of action, clinical and translational science. Clin Transl Sci. 2024;17(1):e13706 4. Skyrizi. Package insert. AbbVie, Inc.; Revised March 2024. Accessed June 3, 2024. Available at www.rxabbvie.com/pdf/skyrizi_pi.pdf

RISA
621304

Risankizumab, Serum

Clinical Information: Risankizumab (Skyrizi, AbbVie) is a humanized IgG1 kappa therapeutic monoclonal antibody used to treat moderate to severe plaque psoriasis, ulcerative colitis, and Crohn disease. Risankizumab targets interleukin 23A (IL-23p19) binding with high affinity to the p19 subunit and inhibiting further action. Therapeutic drug monitoring (TDM) has become standard of care in the gastroenterology practice for biologic therapies used in inflammatory bowel disease (IBD), Crohn disease, and ulcerative colitis. TDM is routinely used to assess loss of response to therapy and proactively manage patients taking tissue necrosis factor (TNF) inhibitors (eg, infliximab and adalimumab), alpha-4-beta7 integrins (vedolizumab), or IL12/23 blockers (ustekinumab). With the approval of risankizumab for IBD, TDM is expected to play an important role in managing loss of response to therapy and guide decision making for use of monotherapy or combination therapy. Risankizumab is currently US Food and Drug Administration-approved for plaque psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn disease. Patients with plaque psoriasis or psoriatic arthritis are treated with 150 mg subcutaneously at weeks 0, 4, and every 12 weeks thereafter. The steady state maximum concentration (Cmax) and trough concentration (Ctrough) are estimated to be 12 and 2 mcg/mL, respectively. Patients with Crohn disease are treated with 600 mg intravenously at weeks 0, 4, and 8, followed by 180 mg or 360 mg subcutaneously at week 12 and every 8 weeks thereafter. During induction weeks 8 through 12, the median Cmax is estimated to be 156 mcg/mL and the Ctrough is estimated to be 38.8 mcg/mL, according to the drug package insert. Steady state is achieved at 28 weeks after starting treatment in the dosing regimen for Crohn disease. Median Cmax and Ctrough concentrations measured during weeks 40 through 48 of maintenance phase (or weeks 52-60 from start of treatment) are estimated to be 14.0 mcg/mL and 4.1 mcg/mL, respectively, for 180 mg dose or 28.0 mcg/mL and 8.1 mcg/mL, respectively, for 360 mg dose. Risankizumab is immunogenic, like other therapeutic monoclonal antibodies. Clinical trials have shown antibodies-to-risankizumab occur at rates of about 24% for plaque psoriasis, 12% for psoriatic arthritis, and 3.4% for Crohn disease.

Useful For: Assessing the response to risankizumab therapy Assessing the need for dose escalation Evaluating potential changes or discontinuation of therapy Monitoring patients who need to be above a certain risankizumab concentration to improve the odds of a clinical response for therapy optimization

Interpretation: The optimal therapeutic concentration of risankizumab associated with favorable outcomes in inflammatory bowel disease is not known at this time. In Crohn disease, the recommendation is to use the lowest concentration that maintains response. According to the package insert, concentrations of risankizumab at steady state ranged from 4.1 mcg/mL (trough) to 14 mcg/mL (peak) at 180 mg dosing and 8.1 mcg/mL (trough) to 28 mcg/mL (peak) at 360 mg dosing. Steady state is achieved 28 weeks after initiation of therapy for the dosing regimen in Crohn disease. Other therapeutic thresholds vary according to the disease, treatment regimen, and response or lack of response to therapy.

Reference Values:
Lower limit of quantitation=1.0 mcg/mL

Clinical References: 1. Ladwig PM, Barnidge DR, Willrich MA. Quantification of the IgG2/4 kappa monoclonal therapeutic eculizumab from serum using isotype specific affinity purification and microflow LC-ESI-Q-TOF mass spectrometry. J Am Soc Mass Spectrom. 2017;28(5):811-817 2. Willrich MA, Murray DL, Barnidge DR, et al. Quantitation of infliximab using clonotypic peptides and selective reaction monitoring by LC-MS/MS. Int Immunopharmacol. 2015;28(1):513-520 3. Ladwig PM, Barnidge DR, Willrich MA. Mass spectrometry approaches for identification and quantitation of therapeutic monoclonal antibodies in the clinical laboratory. Clin Vaccine Immunol. 2017;24(5):e00545-16 4. Feagan, B. G., J. Panes, M. Ferrante, et al. Risankizumab in patients with moderate to severe Crohn's disease: an open-label extension study. Lancet Gastroenterol Hepatol. 2018;3(10):671-680 5. Ferrante, M., R. Panaccione, F. Baert, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. Lancet. 2022;399(10340):2031-2046 6. Skyrizi. Package insert. AbbVie, Inc.; Revised June 2024. Accessed October 4, 2024. Available at www.rxabbvie.com/pdf/skyrizi_pi.pdf

ROMA2 Risk Score, if Postmenopausal, Serum
46917

Clinical Information: Women with ovarian cancer symptoms and adnexal masses present primarily to gynecologists, primary care physicians, or general surgeons. Triage guidelines from the American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncologists recommend referral of women with a pelvic mass at high risk for ovarian cancer to gynecologic oncologists. Specialized treatment improves patient outcomes resulting in fewer complications and better survival rates when compared to patients treated by surgeons less familiar with the management of ovarian cancer. The risk of ovarian malignancy algorithm (ROMA) incorporates cancer antigen 125 (CA125), human epididymal protein 4 (HE4), and menopausal status to assign women that present with an adnexal mass into a high-risk or low-risk group for finding an ovarian malignancy. ROMA is indicated for women who meet the following criteria: older than age 18, presenting with an adnexal mass for which surgery is planned, and who have not yet been referred to an oncologist. ROMA must be interpreted in conjunction with clinical and radiological assessment.

Useful For: Calculating risk assessment for finding an ovarian malignancy during surgery in postmenopausal women who present with an adnexal mass

Interpretation: In postmenopausal women, a risk of ovarian malignancy algorithm (ROMA) value of 2.99 or greater indicates a high risk of finding epithelial ovarian cancer, whereas a ROMA value less than 2.99 indicates a low risk of finding epithelial ovarian cancer at surgery. The use of these cutpoints provides a 75% specificity and sensitivity of 84% in patients with stage I-IV epithelial ovarian cancer.

Reference Values:
Only orderable as part of a profile. For more information see ROMA / Ovarian Malignancy Risk Algorithm.

Clinical References: 1. Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. J Ovarian Res. 2019;12(1):28. doi:10.1186/s13048-019-0503-7 2. Moore RG, Jabre-Raughley M, Brown AK, et al. Comparison of a novel multiple marker assay vs the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. Am J Obstet Gynecol. 2010;203(3):228.e1-6 3. Karlsen MA, Sandhu N, Hogdall C, et al. Evaluation of HE4, CA125, risk of ovarian malignancy algorithm (ROMA) and risk of malignancy index (RMI) as diagnostic tools of epithelial ovarian cancer in

patients with a pelvic mass. Gynecol Oncol. 2012;127(2):379-383

ROMA1 Risk Score, if Premenopausal, Serum
46916

Clinical Information: Women with ovarian cancer symptoms and adnexal masses present primarily to gynecologists, primary care physicians, or general surgeons. Triage guidelines from the American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncologists recommend referral of women with a pelvic mass at high risk for ovarian cancer to gynecologic oncologists. Specialized treatment improves patient outcomes resulting in fewer complications and better survival rates when compared to patients treated by surgeons less familiar with the management of ovarian cancer. The risk of ovarian malignancy algorithm (ROMA) incorporates cancer antigen 125 (CA125), human epididymal protein 4 (HE4), and menopausal status to assign women that present with an adnexal mass into a high-risk or low-risk group for finding an ovarian malignancy. ROMA is indicated for women who meet the following criteria: older than age 18, presenting with an adnexal mass for which surgery is planned, and who have not yet been referred to an oncologist. ROMA must be interpreted in conjunction with clinical and radiological assessment

Useful For: Calculating risk assessment for finding an ovarian malignancy during surgery in premenopausal women who present with an adnexal mass

Interpretation: In premenopausal women, a risk of ovarian malignancy algorithm (ROMA) value of 1.14 or greater indicates a high risk of finding epithelial ovarian cancer, whereas a ROMA value less than 1.14 indicates a low risk of finding epithelial ovarian cancer at surgery. The use of these cutpoints provides a 75% specificity and sensitivity of 84% in patients with stage I-IV epithelial ovarian cancer.

Reference Values:
Only orderable as part of a profile. For more information see ROMA / Ovarian Malignancy Risk Algorithm.

Premenopausal:<1.14 (low risk)

Clinical References: 1. Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. J Ovarian Res. 2019;12(1):28. doi:10.1186/s13048-019-0503-7 2. Moore RG, Jabre-Raughley M, Brown AK, et al. Comparison of a novel multiple marker assay vs the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. Am J Obstet Gynecol. 2010;203(3):228.e1-6 3. Karlsen MA, Sandhu N, Hogdall C, et al. Evaluation of HE4, CA125, risk of ovarian malignancy algorithm (ROMA) and risk of malignancy index (RMI) as diagnostic tools of epithelial ovarian cancer in patients with a pelvic mass. Gynecol Oncol. 2012;127(2):379-383

FRISP Risperidone (Risperdal) and 9-Hydroxyrisperidone
91105

Reference Values:
Units: ng/mL

Expected steady state concentrations of risperidone and 9-hydroxyrisperidone (combined total) in patients receiving recommended daily dosages: 10 - 120 ng/mL.

RIVAR Rivaroxaban, Anti-Xa, Plasma
65847

Clinical Information: Rivaroxaban, an oral anticoagulant that directly inhibits factor Xa, has been approved by the US Food and Drug Administration for prophylaxis of thrombosis in atrial fibrillation and surgical patients and treatment of venous thromboembolism (VTE). Unlike warfarin, it does not require routine therapeutic monitoring. However, in selected clinical situations, measurement of drug level would be useful (eg, kidney insufficiency, assessment of compliance, periprocedural measurement of drug concentration, suspected overdose, advanced age, and extremes of body weight). Table. Plasma Concentrations of Rivaroxaban in Patient Populations Studied(1) Patient population/clinical setting Rivaroxaban dose C-min (ng/mL)* trough plasma concentration (predose) C-max (ng/mL)** peak plasma concentration (postdose) VTE prevention after total hip replacement surgery 10 mg once daily 9 (1-38) 125 (91-196) DVT treatment (continued treatment) 20 mg once daily 26 (6-87) 270 (189-419) Stroke prevention in patients with non-valvular AF (CR-CL > or =50 mL/min) 20 mg once daily 44 (12-137) 249 (184-343) Stroke prevention in patients with non-valvular AF (CR-CL 30-49 mL/min) 15 mg once daily 57 (18-136) 229 (178-313) Secondary prevention in patients with acute coronary syndrome 2.5 mg twice daily 17 (6-37) 46 (28-70) Median (5th-95th percentile) *Defined as samples collected 20-28 hours after dosing **Defined as samples collected 2-4 hours after dosing Abbreviations not previously defined: Atrial fibrillation (AF) Creatinine clearance (CR-CL) Deep vein thrombosis (DVT)

Useful For: Measuring rivaroxaban concentration in selected clinical situations (eg, kidney insufficiency, assessment of compliance, periprocedural measurement of drug concentration, suspected overdose, advanced age, and extremes of body weight)

Interpretation: The lower limit of detection of this assay is 4 ng/mL. Therapeutic reference ranges have not been established. See Clinical Information section for peak and trough drug concentrations observed from clinical trials.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clinical Pharmacokinetics. 2014;53(1):1-16 doi:10.1007/s40262-013-0100-7 2. Xarelto (rivaroxaban) Summary of Product Characteristics. Package insert. Bayer Pharma AG; 2013. Available at www.ema.europa.eu/en/documents/product-information/xarelto-epar-product-information_en.pdf 3. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499-2510 4. EINSTEIN-PE Investigators, Buller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287-1297 5. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-891 6. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373:2413-2424 7. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost. 2016;14(6):1308-1313

RNAP
83397

RNA Polymerase III Antibodies, IgG, Serum

Clinical Information: Systemic sclerosis (SSc) is a multisystem autoimmune connective tissue disease characterized by vascular dysfunction, fibrotic changes in the skin and internal organs, as well as an autoimmune response manifested by production of diverse antibodies.(1,2) While the clinical manifestations and severity of SSc are highly variable, two main subsets are widely recognized. These include the limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) subtypes of which the diffuse form has the worse prognosis and survival rates.(2) Immunologically, SSc is characterized by the presence of several disease-specific and mutually exclusive autoantibodies considered helpful in the diagnosis, stratification, and prognosis of disease.(1-3) Of the described autoantibodies, the 2013

American College of Rheumatology/European League against Rheumatism classification criteria for SSc recommends testing for centromere, topoisomerase I (topo I or Scl 70), and RNA polymerase III autoantibodies.(3) Antibodies to Scl 70 and RNA polymerase III are generally associated with dcSSc while those to centromere typically correlate with the lcSSc form of disease.(1-3) The human nuclei consist of three RNA polymerases, RNA polymerase I, II and III.(4) Of these, antibodies targeting RNA polymerases I and III are always present together and are most common in patients with SSc. The RPC155 immunodominant epitope has been identified in autoantibodies associated with anti-RNA polymerase I/III in patients with SSc and is widely used in solid-phase immunoassays for the detection and quantification of anti-RNA polymerase III antibodies in clinical laboratories.(5) The prevalence of anti-RNA polymerase III antibodies in patients with SSc is variable with a pooled prevalence of 11% and ranges from 0% to 41% in different studies.(4) This variability may be due to environmental and genetic factors as well as lack of harmonization of immunoassays for the detection of antibodies.(4,6) Positivity for anti-RNA polymerase III antibody is generally mutually exclusive of other SSc-specific antibodies such as centromere and Scl 70.(1-3) In addition, SSc patients who test positive for anti-RNA polymerase III antibodies have increased risk for the diffuse cutaneous involvement, hypertensive kidney disease, and poor prognosis.(1,2)

Useful For: Evaluating patients suspected of having systemic sclerosis as part of systemic sclerosis criteria antibody tests Providing diagnostic and prognostic information in patients with systemic sclerosis

Interpretation: A positive result for RNA polymerase III antibody may support a diagnosis of systemic sclerosis (SSc) in the appropriate clinical context. Anti-RNA polymerase III autoantibody in patients with SSc is associated with the diffuse cutaneous form of disease and an increased risk of sclerodermal renal crisis. A negative result indicates no detectable IgG antibodies to RNA polymerase III and does not rule out a diagnosis of SSc. The RNA polymerase III IgG enzyme-linked immunosorbent assay tests only for the RP155 dominant epitope, other epitopes in the antigenic complex are absent and cannot be detected.(6) The overall pooled prevalence of anti-RNA polymerase III antibody is reported to be 11%, 95% CI: 8 to 14, range of 0% to 41% in published studies.(4)

Reference Values:
<20.0 U (negative)
20.0-39.9 U (weak positive)
40.0-80.0 U (moderate positive)
>80.0 U (strong positive)

Clinical References: 1. Stochmal A, Czuwara J, Trojanowska M, Rudnicka L. Antinuclear antibodies in systemic sclerosis: An update. Clin Rev Allergy Immunol. 2020;58(1):40-51 2. Nihtyanova SI, Sari A, Harvey JC, et al. Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. Arthritis Rheumatol. 2020;72(3):465-476 3. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. Arthritis Rheum. 2013;65(11):2737-2747. doi:10.1002/art.38098 4.Sobanski V, Dauchet L, Lefevre G, et al. Prevalence of anti-RNA polymerase III antibodies in systemic sclerosis: New data from a French cohort and a systematic review and meta-analysis. Arthritis Rheumatol. 2014;66(2):407-417. doi:10.1002/art.38219 5. Kuwana M, Kimura K, Kawakami Y. Identification of an immunodominant epitope on RNA polymerase III recognized by systemic sclerosis sera: application to enzyme-linked immunosorbent assay. Arthritis Rheum. 2002;46(10):2742-2747 6. Damoiseaux J, Potjewijd J, Smeets RL, Bonroy C. Autoantibodies in the disease criteria for systemic sclerosis: The need for specification for optimal application. J Transl Autoimmun. 2022;5:100141. doi:10.1016/j.jtauto.202 7. Burbelo PD, Gordon SM, Waldman M, et al. Autoantibodies are present before the clinical diagnosis of systemic sclerosis. PLoS One. 2019;14(3);e0214202

RNP
81357

RNP Antibodies, IgG, Serum

Clinical Information: Antibodies to U1 ribonucleoprotein particle (U1-RNP) are central to the diagnosis of mixed connective tissue disease and are also associated with other antinuclear antibody (ANA)-associated connective tissue diseases (CTDs) such as systemic lupus erythematosus, systemic sclerosis, undifferentiated CTD, and CTD overlap syndromes.(1-5) Immunologic characterization studies suggest that anti-U1RNP antibodies are directed toward both discontinuous and linear epitopes that are either contained in the protein sequence or are post-translationally modified. These antibodies mainly target the RNP68 or RNP70, RNPA (33 kD), and occasionally RNPC (22 kD) proteins.(4-9) Originally described by Mattioli et al (3) by immunodiffusion assay using calf thymus extract, current solid-phase immunoassays now use diverse analytes (purified or recombinant proteins, synthetic peptides of dominant epitopes) of the 3 main proteins (RNP68 or RNP70, RNPA, and RNPC) either singly or in any of the various combinations.(4-10) Because of the use of these different antigens and combinations thereof, the nomenclature, reporting, and interpretation of anti-U1RNP antibodies remain obscure.(10) In the absence of standardized nomenclature for anti-U1-RNP antibody assays, familiarity of the analytes in specific assays and use of Hep-2 substrate by indirect immunofluorescence assay for ANA are required for appropriate interpretation. In addition, low level anti-U1-RNP antibodies in the absence of ANA have a low predictive value for ANA-CTD. The U1-RNP antibody test offered by Mayo Clinic detects antibodies to both RNP68 and RNPA proteins. Combined response is more sensitive and less specific than assays to the Sm (Smith)/RNP.(10) For more information see Connective Tissue Disease Cascade.

Useful For: Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive Testing for ribonucleoprotein particle antibodies is not useful in patients without demonstrable antinuclear antibodies.

Interpretation: A positive result for anti-ribonucleoprotein particle 68/A (RNP68/A) antibodies in association with positivity of antinuclear antibodies may be consistent with a diagnosis of connective tissue disease.

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References:

ROPAN
615248

Ro52 and Ro60 Antibodies, IgG, Serum

Clinical Information:

Useful For: Evaluating patients at risk for connective tissue disease with or without interstitial lung disease Differentiation of antibodies to Ro52 and Ro60 in patients known to be positive for anti-SS-A (Ro) antibodies

Interpretation: The presence of antibodies to both SS-A 52 (Ro52) or SSA 60 (Ro60) is highly suggestive of a diagnosis of Sjogren syndrome (SS), with positivity for Ro60 alone more likely to be associated with systemic lupus erythematosus (SLE). Antibodies to Ro52 may be present in patients with idiopathic inflammatory myopathy (IIM), systemic sclerosis (SSc) or overlap connective tissue disease (CTD). In CTD, antibodies to Ro52 alone, or in association with other specific autoantibodies may be associated with interstitial lung diseases. Negative results for antibodies to Ro52 and Ro60 does not exclude the possibility of any CTD, including SS, SLE, SSc, and IIM.

Reference Values:
Ro52 ANTIBODY, IgG
<20 CU (negative)
> or =20 CU (positive)
Reference values apply to all ages

Ro60 ANTIBODY, IgG
<20 CU (negative)
> or =20 CU (positive)
Reference values apply to all ages

Clinical References:

RO52
615246

Ro52 Antibody, IgG, Serum

Clinical Information:

Useful For: Evaluating patients at risk for connective tissue disease with or without interstitial lung disease Differentiating single vs double positivity for Ro52 and Ro60 antibodies in combination with anti-Ro60

Interpretation: Results from this testing should be interpreted in the context of clinical findings and other laboratory testing. Tests cannot be exclusively relied upon to establish a diagnosis for any connective tissue disease or related disorder, including systemic lupus erythematosus, Sjogren's syndrome (SS), systemic sclerosis, or idiopathic inflammatory myopathy. When assessed by standard SS-A (Ro) solid-phase immunoassays, such as enzyme immunoassays using combined antigens, some antibodies specific for either SSA 52 (Ro52) or SSA 60 (Ro60) may not be detected due to masking of target epitopes. In addition, multiplex bead assays with Ro52 or Ro60 antigens may simply be reported as SS-A/Ro positive without differentiation of the specific positive antibody.

Reference Values:
<20 CU (negative)
> or =20 CU (positive)
Reference values apply to all ages

Clinical References:

RO60
615247

Ro60 Antibody, IgG, Serum

Clinical Information:

Useful For: Evaluating patients at risk for connective tissue disease with or without interstitial lung disease Differentiating single vs double positivity for Ro52 and Ro60 antibodies in combination with anti-Ro60

Interpretation: The presence of antibodies to both SSA 52 (Ro52) or SSA 60 (Ro60) is highly suggestive of a diagnosis of Sjogren syndrome (SS), with positivity for Ro60 alone more likely to be associated with systemic lupus erythematosus (SLE). Antibodies to Ro52 may be present in patients with idiopathic inflammatory myopathy (IIM), systemic sclerosis (SSc), or overlap connective tissue disease (CTD). In CTD, antibodies to Ro52 alone or in association with other specific autoantibodies

may be associated with interstitial lung diseases. Negative results for antibodies to Ro52 and Ro60 does not exclude the possibility of any connective tissue disease, including SS, SLE, SSc, and IIM.

Reference Values:

<20 CU (negative)
> or =20 CU (positive)
Reference values apply to all ages

Clinical References: 1. Schulte-Pelkum J, Fritzler M, Mahler M. Latest update on the Ro/SS-A autoantibody system. Autoimmun Rev. 2009;8(7):632-637 2. Defendenti C, Atzeni F, Spina MF, et al. Clinical and laboratory aspects of Ro/SSA-52 autoantibodies. Autoimmun Rev. 2010;10(3):150-154 3. Fayyaz A, Kurien BT, Scofield H. Autoantibodies in Sjogren's syndrome. Rheum Dis Clin North Am. 2016;42(3):419-434 4. Armagan B, Robinson SA, Bazoberry A, et al. Antibodies to both ro52 and ro60 for identifying Sjogren's syndrome patients best suited for clinical trials of disease-modifying therapies. Arthritis Care Res (Hoboken). 2022;74(9):1559-1565 5. Robbins A, Hentzien M, Toquet S, et al. Diagnostic utility of separate anti-Ro60 and anti-Ro52/TRIM21 antibody detection in autoimmune diseases. Front Immunol. 2019;10:444 6. Lee AYS, Reed JH, Gordon TP. Anti-Ro60 and anti-Ro52/TRIM21: Two distinct autoantibodies in systemic autoimmune diseases. J Autoimmun. 2021;124:102724. 7. Chan EKL. Anti-Ro52 autoantibody is common in systemic autoimmune rheumatic diseases and correlating with worse outcome when associated with interstitial lung disease in systemic sclerosis and autoimmune myositis. Clin Rev Allergy Immunol. 2022;63(2):178-193 8. Gkoutzourelas A, Liaskos C, Mytilinaiou MG, et al. Anti-Ro60 seropositivity determines anti-ro52 epitope mapping in patients with systemic sclerosis. Front Immunol. 2018;9:2835 9. Deroo L, Achten H, De Boeck K, et al. The value of separate detection of anti-Ro52, anti-Ro60 and anti-SSB/La reactivities in relation to diagnosis and phenotypes in primary Sjogren's syndrome. Clin Exp Rheumatol. 2022;40(12):2310-1317 10. Zampeli E, Mavrommati M, Moutsopoulos HM, Skopouli FN. Anti-Ro52 and/or anti-Ro60 immune reactivity: autoantibody and disease associations. Clin Exp Rheumatol. 2020;38 Suppl 126(4):134-141

ROMA
62661

ROMA Score (Ovarian Malignancy Risk Algorithm), Serum

Clinical Information: Women with ovarian cancer symptoms and adnexal masses present primarily to gynecologists, primary care physicians, or general surgeons. Triage guidelines from the American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncologists recommend referral of women with a pelvic mass at high risk for ovarian cancer to gynecologic oncologists. Specialized treatment improves patient outcomes resulting in fewer complications and better survival rates when compared to patients treated by surgeons less familiar with the management of ovarian cancer. The risk of ovarian malignancy algorithm (ROMA) incorporates cancer antigen 125 (CA125), human epididymal protein 4 (HE4), and menopausal status to assign women that present with an adnexal mass into a high-risk or low-risk group for finding an ovarian malignancy. ROMA is indicated for women who meet the following criteria: older than age 18, presenting with an adnexal mass for which surgery is planned, and who have not yet been referred to an oncologist. ROMA must be interpreted in conjunction with clinical and radiological assessment.

Useful For: Risk assessment for finding an ovarian malignancy during surgery in women who present with an adnexal mass The test is not intended as a screening or stand-alone diagnostic assay for ovarian cancer.

Interpretation: In premenopausal women, a risk of ovarian malignancy algorithm (ROMA) value of 1.14 or greater indicates a high risk of finding epithelial ovarian cancer, whereas a ROMA value less than 1.14 indicates a low risk of finding epithelial ovarian cancer at surgery. In postmenopausal women, a ROMA value of 2.99 or greater indicates a high risk of finding epithelial ovarian cancer, whereas a ROMA value less than 2.99 indicates a low risk of finding epithelial ovarian cancer at surgery. The use of

these cut-points provides a 75% specificity and sensitivity of 84% in patients with stage I-IV epithelial ovarian cancer.

Reference Values:
Males: Not applicable

Females:
HUMAN EPIDIDYMIS PROTEIN 4< or =140 pmol/L

CANCER ANTIGEN 125 <46 U/mL

ROMA SCORE
Premenopausal: <1.14 (low risk)
Postmenopausal: <2.99 (low risk)

Clinical References: 1. Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. J Ovarian Res. 2019;12(1):28. doi:10.1186/s13048-019-0503-7. PMID: 30917847; PMCID: PMC6436208 2. Moore RG, Jabre-Raughley M, Brown AK, et al. Comparison of a novel multiple marker assay vs the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. Am J Obstet Gynecol. 2010;203(3):228.e1-6 3. Karlsen MA, Sandhu N, Hogdall C, et al. Evaluation of HE4, CA125, risk of ovarian malignancy algorithm (ROMA) and risk of malignancy index (RMI) as diagnostic tools of epithelial ovarian cancer in patients with a pelvic mass. Gynecol Oncol. 2012;127(2):379-383

FROPI
57171

Ropivacaine, Serum/Plasma

Reference Values:
Reporting limit determined each analysis.

Following epidural administration 10 mg/hr, 20 mg/hr and 30 mg/hr, mean plasma concentration of 0.39, 0.88, 1.19 mcg/mL at 21 hours respectively.
Bolus I.V. administration 84 mg/70 kg and 131 mg/70 kg, peak plasma concentrations of 1.1 and 1.7 mcg/mL at 2 minutes respectively.

ROTA
8886

Rotavirus Antigen, Feces

Clinical Information: Rotavirus is a major cause of nonbacterial gastroenteritis, especially in infants and very young children (6 months-2 years of age) who have not received the rotavirus vaccine. Infection may be entirely asymptomatic or produce a spectrum of disease ranging from mild gastroenteritis to severe diarrhea and vomiting with dehydration. Infection usually begins acutely and lasts for 4 to 8 days. In temperate climates, rotaviral infections are seasonal; they peak in frequency during the winter months and are uncommon during the summer. Rotaviral gastroenteritis is, therefore, sometimes called "winter vomiting disease." Infection is more likely to be symptomatic in preterm infants, immunosuppressed patients, and elderly individuals, especially those living in nursing homes or other confined quarters. In other children and adults, rotavirus infections are usually subclinical and may be associated with asymptomatic shedding of rotavirus in the feces. Rapid and accurate detection of rotavirus antigens in fecal specimens may lead to better patient management, particularly in hospitalized or institutionalized patients.

Useful For: Investigation of patients with diarrhea, particularly infants, the elderly, and

immunocompromised patients Investigation of nosocomial diarrhea

Interpretation: Peak viral counts are reported to occur on days 3 to 5 after onset of symptoms. The virus is eliminated from the infected individual within a few days following acute infection. Specimens collected 8 days or more after onset of symptoms may not contain enough rotavirus antigen to produce a positive reaction. A prolonged carrier state has been recognized with rotavirus infection. The rate of positive test results may vary due to age, weather, seasonal factors, geographic location, and the general health environment for the group under study. Information on other diagnostic tests that may be of value in evaluating patients with diarrhea can be found in Laboratory Testing for Infectious Causes of Diarrhea.

Reference Values:
Negative

Clinical References: Centers for Disease Control and Prevention: Rotavirus. Updated March 26, 2021. Accessed August 28,2023. Available at www.cdc.gov/rotavirus/index.html

MARS
82701

Rough Marsh Elder, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to rough marsh elder Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal

2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

RRRP
82723

Rough Pigweed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to rough pigweed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive

4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

RBPG
34938

Rubella Antibodies, IgG, Serum

Clinical Information: Rubella (German or 3-day measles) is a member of the Togavirus family, and humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets, and the incubation period following exposure can range from 12 to 23 days.(1) Infection is generally mild, self-limited, and characterized by a maculopapular rash beginning on the face and spreading to the trunk and extremities, as well as fever, malaise, and lymphadenopathy.(2) Primary in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of gestation. Congenital rubella syndrome is often associated with hearing loss and cardiovascular and ocular defects.(3) The United States 2-dose measles, mumps, rubella vaccination program, which calls for vaccination of all children, leads to seroconversion in 95% of children following the first dose.(1) A total of 4 cases of rubella were reported to the Centers for Disease Control and Prevention in 2011 without any cases of congenital rubella syndrome.(4) Due to the success of the national vaccination program, rubella is no longer considered endemic in the United States (www.cdc.gov/rubella). However, immunity may wane with age as approximately 80% to 90% of adults will show serologic evidence of immunity to rubella.

Useful For: Determining immune status to the rubella virus

Interpretation: The reported antibody index (AI) value is for reference only. This is a qualitative test and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cutoff for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. Positive: AI value of 1.0 or higher -The presence of detectable IgG-class antibodies indicates immunity to the rubella virus through prior immunization or exposure. Individuals testing positive are considered immune to rubella infection. Equivocal: AI value 0.8-0.9 Submit an additional sample for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: AI value of 0.7 or lower The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the rubella virus.

Reference Values:
Vaccinated: Positive (> or =1.0 AI)
Unvaccinated: Negative (< or =0.7 AI)
Reference values apply to all ages.

Clinical References: 1. AAP Committee on Infectious Diseases: Rubella. In: Pickering LK, Baker CJ, Kimberlin DW, eds. Red Book. 2012 Report of the Committee on 1. AAP Committee on Infectious Diseases: Rubella. In: Pickering LK, Baker CJ, Kimberlin DW, eds. Red Book. 2012 Report of the Committee on Infectious Diseases. 29th ed. American Academy of Pediatrics; 2012 2. Best JM: Rubella. Semin Fetal Neonatal Med. 2007;12(3):182. doi:10.1016/j.siny.2007.01.017 3. Duszak RS: Congenital rubella syndrome-major review. Optometry. 2009;80(1):36. doi:10.1016/j.optm.2008.03.006 4. Notifiable

ROC
5194

Rubeola (Measles) Antibodies, IgG and IgM, Spinal Fluid

Clinical Information: Measles is a serious and highly contagious disease that can be a leading cause of death where nutrition and sanitation are limited. Onset begins with cough, fever, and lymphadenopathy approximately 2 weeks after exposure. Diagnosis is usually made when the rash appears. Koplik spots may be seen earlier on the buccal mucosa. Complications of measles may develop in children who appear to have normal immune functions. Persistent infection of the central nervous system with measles virus is recognized to cause the disease subacute sclerosing panencephalitis (SSPE). SSPE is a rare, late complication of measles with an incidence of approximately 1 per 100,000 cases. SSPE is a progressive, usually fatal disease that occurs most often in children between the ages of 5 and 14 years. The onset is insidious and progressive. The incubation period from acute measles to onset of neurological symptoms varies from several months to many years. One of the most useful diagnostic tests involves the measurement of measles-specific antibodies in the cerebrospinal fluid (CSF) of patients with SSPE. Levels of antibody are significantly elevated in the CSF of SSPE patients compared to those without the disease.

Useful For: Diagnosing central nervous system rubeola (measles) virus infection and/or subacute sclerosing panencephalitis

Interpretation: Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection. Patients with subacute sclerosing panencephalitis have serum antibody titers that are 10 to 100 times higher than those seen in late convalescent-phase sera. More importantly, there is pronounced local production of oligoclonal measles virus antibodies in the central nervous system.

Reference Values:
IgG: <1:5
IgM: <1:10
Reference values apply to all ages.

Clinical References: 1. Gascon GG. Subacute sclerosing panencephalitis. Semin Pediatr Neurol. 1996;3(4):260-269 2. Gershon AA. Measles virus (Rubeola). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2110-2116

RUFI
63030

Rufinamide, Serum

Clinical Information: Rufinamide is a new antiepileptic drug approved by the Food and Drug Administration as an add-on treatment for seizures associated with Lennox-Gastaut syndrome in children aged 4 years and older, and for the treatment of focal seizures in adults and adolescents. Its mechanism of action is not completely understood, but it is believed to work by prolonging the inactive state of sodium channels, therefore limiting excessive firing of sodium-dependent action potentials. The commonly observed side effects are headache, dizziness, fatigue, somnolence, and nausea.

Useful For: Monitoring serum rufinamide concentrations, assessing compliance, and adjusting dosage in patients receiving other drugs that interact pharmacokinetically with rufinamide (ie, drugs that

induce liver CYP3A4 enzymes) and may be helpful in those who are receiving hemodialysis

Interpretation: The reference interval is broad and represents the concentrations observed to be associated with the greatest drug efficacy without side effects or toxicity.

Reference Values:
5.0-30.0 mcg/mL

Clinical References: 1. Krasowski MD: Antiepileptic drugs. Therapeutic drug monitoring of the new generation drugs. Clinical Laboratory News. 2013 Jun;39(6):8-10 2. Aneja S, Sharma S. Newer anti-epileptic drugs. Indian Pediatr. 2013;50(11):1033-40. doi:10.1007/s13312-013-0284-9 3. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-02):9-62. doi:10.1055/s-0043-116492

T821Q
615905

RUNX1-RUNX1T1 Translocation (8;21), Minimal Residual Disease Monitoring, Quantitative, Varies

Clinical Information: RUNX1-RUNX1T1 minimal residual disease (MRD) monitoring in patients with acute myeloid leukemia (AML) with translocation t(8;21)(q22;q22) is useful for evaluating disease response after therapy and identifying individuals with increased risk of relapse. Quantitative real-time reverse transcription polymerase chain reaction testing in neoplasms with known clonal genetic markers can achieve highly sensitive detection of neoplastic cells in blood or bone marrow samples. It is one of the most mature technologies available for this purpose. In this assay, translocation of chromosome 8q22 to 21q22 resulting in fusion of two genes RUNX1 and RUNX1T1 will be evaluated. Quantitative results will provide physicians with an accurate and precise measurement of disease burden to guide patient intervention decisions. This assay can be used for post-therapy MRD monitoring as well as detection of RUNX1-RUNX1T1 fusion in AML patients at the time of diagnosis.

Useful For: Detection of RUNX1-RUNX1T1 gene fusion in acute myeloid leukemia patients at the time of diagnosis Minimal residual disease monitoring during the clinical and therapeutic course of these patients

Interpretation: The assay is reported in the form of a normalized ratio of RUNX1-RUNX1T1 fusion transcript to the control gene ABL1 expressed as a percentage, which is an estimate of the level of RUNX1-RUNX1T1 fusion RNA present in the specimen, expressed in relation to the level of RNA from an internal control gene (ABL1). The normalized ratio has no units but is directly related to the level of RUNX1-RUNX1T1 detected (ie, larger numbers indicate higher relative levels of RUNX1-RUNX1T1 and smaller numbers indicate lower levels). A relative expression value minimizes variability in the RNA levels and cell numbers measured in separate specimens tested at different times. The precision of the quantitative assay is excellent, but interassay variability can occur such that result changes should not be considered significant if 2 single measurements differ by less than 0.5 log. More critical results, such as a change in the status of positivity or 1 log or greater increase between 2 positive samples should be repeated on a separate specimen with appropriate time interval to verify the result.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Corbacioglu A, Scholl C, Schlenk RF, et al: Prognostic impact of minimal residual disease in RUNX1-RUNX1T1-positive acute myeloid leukemia. J Clin Oncol. 2010 Aug 10;28(23):3724-3729. doi: 10.1200/JCO.2010.28.6468 2. Dohner H, Estey E, Grimwade D, et al:

Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017 Jan 26;129(4):424-447. doi: 10.1182/blood-2016-08-733196 3. Tallman MS, Wang ES, Altman JK, et al: Acute Myeloid Leukemia, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019 Jun 1;17(6):721-749. doi: 10.6004/jnccn.2019.0028 4. Schuurhuis GJ, Heuser M, Freeman S, et al: Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2018 Mar 22;131(12):1275-1291. doi: 10.1182/blood-2017-09-801498 5. Jourdan E, Boissel N, Chevret S, et al: Prospective evaluation of gene mutations and minimal residual disease in patients with core binding factor acute myeloid leukemia. Blood. 2013 Mar 21;121(12):2213-2223. doi: 10.1182/blood-2012-10-462879 6. Lane S, Saal R, Mollee P, et al: A >or=1 log rise in RQ-PCR transcript levels defines molecular relapse in core binding factor acute myeloid leukemia and predicts subsequent morphologic relapse. Leuk Lymphoma. 2008 Mar;49(3):517-523. doi: 10.1080/10428190701817266 7. Yin JA, O'Brien MA, Hills RK, et al: Minimal residual disease monitoring by quantitative RT-PCR in core binding factor AML allows risk stratification and predicts relapse: results of the United Kingdom MRC AML-15 trial. Blood. 2012 Oct 4;120(14):2826-2835. doi: 10.1182/blood-2012-06-435669

RUSS
82681

Russian Thistle, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to russian thistle Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal

2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FRFYG
57579

Rye Food IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

RYEG
82908

Rye Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to rye grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the

concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

RYE
82689

Rye, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to rye Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

2SC
610031

S-(2-Succinyl)-Cysteine (2SC) Immunostain, Technical Component Only

Clinical Information: A subset of aggressive renal tumors have pathogenic alterations of fumarate hydratase (FH) that do not result in the loss of FH expression. Typically FH alterations are associated with aberrantly high levels of S-(2-succino)-cysteine (2SC) expression observed in the nucleus. FH and 2SC immunohistochemistry assays may be used in combination to identify these pathogenic conditions. This is useful in the diagnosis of renal cell carcinomas, and cutaneous and uterine leiomyomas that occur secondary to somatic or germline (hereditary leiomyomatosis and renal cell cancer) alterations of the FH gene.

Useful For: Identification of high levels of aberrant S-(2-succino)-cysteine (2SC), secondary to pathogenic alterations of the fumarate hydratase (FH) gene

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Gupta S, Swanson AA, Chen YB, et al. Incidence of succinate dehydrogenase and fumarate hydratase-deficient renal cell carcinoma based on immunohistochemical screening with SDHA/SDHB and FH/2SC. Hum Pathol. 2019;91:114-122. doi:10.1016/j.humpath.2019.07.004 2. Andrici J, Gill AJ, Hornick JL. Next generation immunohistochemistry: Emerging substitutes to genetic testing? Semin Diagn Pathol. 2018;35(3):161-169. doi:10.1053/j.semdp.2017.05.004 3. Muller M, Guillaud-Bataille M, Salleron J, et al. Pattern multiplicity and fumarate hydratase (FH)/S-(2-succino)-cysteine (2SC) staining but not eosinophilic nucleoli with perinucleolar halos differentiate hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinomas from kidney tumors without FH gene alteration. Mod Pathol.

2018;31(6):974-983. doi:10.1038/s41379-018-0017-7 4. Buelow B, Cohen J, Nagymanyoki Z, et al. Immunohistochemistry for 2-succinocystine (2SC) and fumarate hydratase (FH) in cutaneous leiomyomas may aid in identification of patients with HLRCC (hereditary leiomyomatosis and renal cell carcinoma syndrome). Am J Surg Pathol. 2016;40(7):982-988. doi:10.1097/PAS.0000000000000626 5. Trpkov K, Hes O, Agaimy A, et al. Fumarate hydratase-deficient renal cell carcinoma is strongly correlated with fumarate hydratase mutation and hereditary leiomyomatosis and renal cell carcinoma syndrome. Am J Surg Pathol. 2016;40(7):865-875. doi:10.1097/PAS.0000000000000617 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

S100
70547

S-100 Immunostain, Technical Component Only

Clinical Information: S100 protein expression is seen in cartilaginous tumors, myoepithelial tumors, Schwann cells and neural tumors, Langerhans cell proliferations, benign and malignant melanocytes, clear cell sarcoma, and some carcinomas (particularly of the breast). S100 staining occurs both in the nucleus and cytoplasm.

Useful For: Aids in the identification of various neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Blessing K, Sanders DS, Grant JJ. Comparison of immunohistochemical staining of the novel antibody melan-A with S100 protein and HMB-45 in malignant melanoma and melanoma variants. Histopathology. 1998;32(2):139-146. doi:10.1046/j.1365-2559.1998.00312.x 2. Clarkson KS, Sturdgess IC, Molyneux AJ. The usefulness of tyrosinase in the immunohistochemical assessment of melanocytic lesions: a comparison of the novel T311 antibody (anti-tyrosinase) with S-100, HMB45, and A103 (anti-melan-A). J Clin Pathol. 2001;54(3):196-200 3. Matsunou H, Shimoda T, Kakimoto S, Yamashita H, Ishikawa E, Mukai M. Histopathologic and immunohistochemical study of malignant tumors of peripheral nerve sheath (malignant schwannoma). Cancer. 1985;56(9):2269-2279 4. Orchard GE. Comparison of immunohistochemical labelling of melanocyte differentiation antibodies melan-A, tyrosinase and HMB 45 with NKIC3 and S100 protein in the evaluation of benign naevi and malignant melanoma. Histochem J. 2000;32(8):475-481. doi:10.1023/a:1004192232357 5. Al-Ismaeel Q, Neal CP, Al-Mahmoodi H, et al. ZEB1 and IL-6/11-STAT3 signalling cooperate to define invasive potential of pancreatic cancer cells via differential regulation of the expression of S100 proteins. Br J Cancer. 2019;121(1):65-75. doi:10.1038/s41416-019-0483-9 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

F100B
57349

S-100B Protein, Serum

Reference Values:

Age	Reference Interval
19 years and older:	0 - 96 ng/L
3 years to 19 years:	less than or equal to 160 ng/L
25 months to 3 years	less than or equal to 170 ng/L
10 months to 25 months:	less than or equal to 230 ng/L
5 months to 10 months:	less than or equal to 350 ng/mL
0 days to 5 months:	less than or equal to 510 ng/mL

SSCTU
607001

S-Sulfocysteine Panel, Urine

Clinical Information: Urine S-sulfocysteine is elevated in 2 disorders with similar clinical phenotypes, molybdenum cofactor deficiency (MoCD) and isolated sulfite oxidase deficiency. Molybdenum is an important trace element that is biosynthesized into an important cofactor, which is essential for the proper functioning of the enzymes, xanthine oxidase, sulfite oxidase, and aldehyde oxidase in addition to nitrogenases and nitrate reductase. Four genes are important in mediating the biosynthetic pathway to create molybdenum cofactor, MOCS1, MOCS2, MOCS3, and GPHN (gephyrin). The 3 clinical types of MoCD are autosomal recessive diseases resulting from 2 disease-causing variants in the respective causative gene. MoCDs result in a progressive neurodegenerative disease that manifests with seizures and brain abnormalities in the first weeks to months of life. The most common type of MoCD is MoCD A, caused by variants in MOCS1 and resulting in neonatal or infantile onset seizures and postnatal encephalopathy with rapidly progressive neurodegeneration. Infants with MoCD B (MOCS2 or MOCS3), and C (GPHN) have all been reported but are rare. Infants with MoCD have increased S-sulfocysteine and hypoxanthine and decreased uric acid concentrations in urine. The treatment for MoCD A only is cyclic pyranopterin monophosphate infusion and is most effective when initiated early. Isolated sulfite oxidase deficiency (ISOD) is an autosomal recessive disorder caused by deficiency of the enzyme sulfite oxidase, which results in progressive neurodegenerative disease in most cases. ISOD is the result of disease-causing variants in the SUOX gene. ISOD is a spectrum of disease ranging from severe, early onset disease that appears in the first days of life with seizures, feeding issues, and neurologic issues causing abnormal muscle tone, to mild, later onset disease manifesting after 6 months of age with developmental delay or regression, movement issues, which can be episodic, and ectopia lentis in some cases. Infants with ISOD have increased S-sulfocysteine and normal hypoxanthine concentrations in urine. Treatment is largely symptomatic, with medication for seizures and movement/neurologic issues. Unfortunately, no treatment for the underlying metabolic defect is currently available. Prevalence is unknown, but ISOD is likely underdiagnosed. Hereditary xanthinuria results in kidney stones and, less commonly, muscle pain and cramping caused by accumulation of xanthine that forms crystals in the kidneys and muscle tissue. There are 2 types of hereditary xanthinuria: type I caused by deficiency of xanthine dehydrogenase resulting from disease-causing variants in the XDH gene, and type II caused by deficiency of molybdenum cofactor sulfurase resulting from variants in the MOCOS gene. Individuals with xanthinuria have increased xanthine and decreased uric acid concentrations in urine. The incidence of both types of hereditary xanthinuria is about 1 in 69,000 individuals.

Useful For: Diagnosis of molybdenum cofactor deficiency, isolated sulfite oxidase deficiency, and hereditary xanthinuria Monitoring patients with molybdenum cofactor deficiency or isolated sulfite

oxidase deficiency who are on treatment

Interpretation: Abnormal concentrations of measurable compounds will be reported along with an interpretation. The interpretation of an abnormal metabolite pattern includes an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnosis, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis), name, and phone number of contacts who may provide these studies, and a phone number of the laboratory directors in case the referring physician has additional questions.

Reference Values:

	0-3 years	4-6 years	7-12 years	13-18 years
Hypoxanthine	< or =65	< or =30	< or =30	< or =30
Xanthine	< or =54	< or =21	< or =35	< or =15
Uric Acid	350-2500	200-2000	200-1400	150-700
S-Sulfocysteine	< or =11	< or =5	< or =5	< or =5

Clinical References: 1. Melcher K, Mountford WK, Hoffmann GF, Ries M. Ultra-orphan diseases: a quantitative analysis of the natural history of molybdenum cofactor deficiency. Gen Med. 2015;17(12):965-970 2. Claerhout H, Witters P, Regal L, et al. Isolated sulfite oxidase deficiency. J Inherit Metab Dis. 2018;41(1):101-108 3. Misko AL, Liang Y, Kohl JB, Eichler F. Delineating the phenotypic spectrum of sulfite oxidase and molybdenum cofactor deficiency. Neurol Genet. 2020;6(4):e486

SCERA
610002

Saccharomyces cerevisiae Antibody, IgA, Serum

Clinical Information: Inflammatory bowel disease (IBD) refers to 2 diseases, ulcerative colitis (UC) and Crohn disease (CD, regional enteritis), both of which result from chronic inflammation in the gastrointestinal (GI) tract.(1) CD is characterized by chronic diarrhea, abdominal pain, and fatigue.(2) In comparison, UC frequently presents with bloody diarrhea that is of an urgent nature.(3) Inflammation in UC most frequently affects the rectum and proximal colon, and presents with continue mucosal involvement. In CD, inflammation can affect almost any area of the GI tract and is usually evidenced as patchy, transmural lesions. Diagnosis of IBD is primarily based on clinical evaluation, endoscopy with biopsy, and imaging studies.(4) Because CD and UC are characterized by GI inflammation, fecal calprotectin can be used to differentiate IBD from noninflammatory conditions such as irritable bowel syndrome (IBS). Fecal calprotectin is useful in excluding IBD as a diagnosis and avoiding unnecessary endoscopic or imaging procedures. CD and UC are associated with the presence of various antimicrobial and autoantibodies.(5) Patients with UC often have measurable antineutrophil cytoplasmic antibodies (ANCA), which react with as yet uncharacterized target antigens in human neutrophils; in contrast, patients with CD often have measurable IgA and/or IgG antibodies, which react with cell wall mannan of Saccharomyces cerevisiae. Despite these associations, current guidelines indicate that testing for these antibodies is not sufficiently sensitive for use in the diagnosis of IBD.(2,3) Rather, these antibodies should be limited to distinguishing between CD and UC in cases where the specific diagnosis is unclear based on pathologic and imaging studies.

Useful For: Measuring IgA anti-Saccharomyces cerevisiae antibodies as a part of a profile to aid in distinguishing between ulcerative colitis and Crohn disease in patients for whom the specific diagnosis

is unclear based on endoscopic, pathologic, and imaging evaluations This test is not useful for determining the extent of disease in patients with inflammatory bowel disease or determining the response to disease-specific therapy including surgical resection of diseased intestine

Interpretation: The presence of antineutrophil cytoplasmic antibodies (ANCA) in the absence of IgA and IgG anti-Saccharomyces cerevisiae antibodies (ASCA) is consistent with the diagnosis of ulcerative colitis; the presence of IgA and IgG ASCA in the absence of ANCA is consistent with Crohn disease.

Reference Values:
Negative: <20.0 RU/mL
Positive: > or =20.0 RU/mL
Reference values apply to all ages.

Clinical References: 1. Rose NR, Mackay IR, eds: Inflammatory bowel diseases. In: The Autoimmune Diseases: Elsevier; 2008 2. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE: ACG Clinical Guideline: Management of Crohn's disease in adults. Am J Gastroenterol. 2018 Apr;113(4):481-517 3. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD: ACG Clinical Guideline: Ulcerative colitis in adults. Am J Gastroenterol. 2019 Mar;114(3):384-413 4. Clark C, Turner J: Diagnostic modalities for inflammatory bowel disease: Serologic markers and endoscopy. Surg Clin North Am. 2015 Dec;95(6):1123-1141 5. Zhou G, Song Y, Yang W, et al: ASCA, ANCA, ALCA and many more: Are they useful in the diagnosis of inflammatory bowel disease? Dig Dis. 2016;34(1-2):90-97. doi: 10.1159/000442934

SCERG
610003

Saccharomyces cerevisiae Antibody, IgG, Serum

Clinical Information: Inflammatory bowel disease (IBD) refers to 2 diseases, ulcerative colitis (UC) and Crohn disease (CD, regional enteritis), both of which result from chronic inflammation in the gastrointestinal (GI) tract.(1) CD is characterized by chronic diarrhea, abdominal pain, and fatigue.(2) In comparison, UC frequently presents with bloody diarrhea that is of an urgent nature.(3) Inflammation in UC most frequently affects the rectum and proximal colon, and presents with continue mucosal involvement. In CD, inflammation can affect almost any area of the GI tract, and is usually evidenced as patchy, transmural lesions. Diagnosis of IBD is primarily based on clinical evaluation, endoscopy with biopsy, and imaging studies.(4) Because CD and UC are characterized by GI inflammation, fecal calprotectin can be used to differentiate IBD from non-inflammatory conditions such as irritable bowel syndrome (IBS). Fecal calprotectin is useful in excluding IBD as a diagnosis and avoiding unnecessary endoscopic or imaging procedures. CD and UC are associated with the presence of various anti-microbial and autoantibodies.(5) Patients with UC often have measurable antineutrophil cytoplasmic antibodies (ANCA), which react with as yet uncharacterized target antigens in human neutrophils; in contrast, patients with CD often have measurable IgA and/or IgG antibodies which react with cell wall mannan of Saccharomyces cerevisiae. Despite these associations, current guidelines indicate that testing for these antibodies is not sufficiently sensitive for use in the diagnosis of IBD.(2,3) Rather, these antibodies should be limited to distinguishing between CD and UC in cases where the specific diagnosis is unclear based on pathologic and imaging studies.

Useful For: Measuring IgG anti-Saccharomyces cerevisiae antibodies as a part of a profile to aid in distinguishing between ulcerative colitis and Crohn disease in patients for whom the specific diagnosis is unclear based on endoscopic, pathologic, and imaging evaluations This test is not useful for determining the extent of disease in patients with inflammatory bowel disease or determining the response to disease-specific therapy including surgical resection of diseased intestine

Interpretation: The presence of antineutrophil cytoplasmic antibodies (ANCA) in the absence of IgA and IgG anti-Saccharomyces cerevisiae antibodies (ASCA) is consistent with the diagnosis of ulcerative

colitis; the presence of IgA and IgG ASCA in the absence of ANCA is consistent with Crohn disease.

Reference Values:
Negative: <20.0 RU/mL
Positive: > or =20.0 RU/mL
Reference values apply to all ages.

Clinical References: 1. Rose NR, Mackay IR, eds: Inflammatory bowel diseases. In: The Autoimmune Diseases: Elsevier; 2008 2. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE: ACG Clinical Guideline: Management of Crohn's disease in adults. Am J Gastroenterol. 2018 Apr;113(4):481-517 3. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD: ACG Clinical Guideline: Ulcerative colitis in adults. Am J Gastroenterol. 2019 Mar;114(3):384-413 4. Clark C, Turner J: Diagnostic modalities for inflammatory bowel disease: Serologic markers and endoscopy. Surg Clin North Am. 2015 Dec;95(6):1123-1141 5. Zhou G, Song Y, Yang W, et al: ASCA, ANCA, ALCA and many more: Are they useful in the diagnosis of inflammatory bowel disease? Dig Dis. 2016;34(1-2):90-97. doi: 10.1159/000442934

FSFLE
57541

Safflower (Carthamus tinctorius) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

FSAG
57957

Sage (Artemisia spp.) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

SALCA
37061

Salicylate, Serum

Clinical Information: Therapeutic salicylates include, among others, salicylic acid, sodium salicylate, methyl salicylate (oil of wintergreen), and acetylsalicylic acid (aspirin). Aspirin is an analgesic, antipyretic, anti-inflammatory drug contained in a large number of preparations. Aspirin is rapidly hydrolyzed by hepatic and blood esterases to the pharmacologically active intermediate, salicylic acid, which has a dose-dependent serum half-life ranging from 3 to 20 hours. Stimulation of the respiratory center in the central nervous system and uncoupling of oxidative phosphorylation are direct effects of salicylate that lead to many of the toxic symptoms observed in overdose situations. Symptoms of salicylate toxicity can include nausea, vomiting, tinnitus, headache, hyperpnea, confusion, hyperthermia, slurred speech, and convulsions. Acid-base disturbances such as compensated respiratory alkalosis (mild toxicity) and metabolic acidosis with increased anion gap (severe toxicity) are commonplace.

Useful For: Quantitative determination of toxic levels of salicylate This test is not useful for assessing low-dose aspirin therapy.

Interpretation: Therapeutic concentrations for antipyretic/analgesic are 3.0 to 10.0 mg/dL, while concentrations between 1.5 and 30 mg/dL are for anti-inflammatory effect and treatment of rheumatic fever. Toxic concentrations are 50.0 mg/dL or higher.

Reference Values:
Therapeutic: <30.0 mg/dL
Critical value: > or =50.0 mg/dL

Clinical References: 1. Flower RJ, Moncada S, Vane JR. Analgesic-antipyretics and anti-inflammatory agents: drugs employed in the treatment of gout. In The Pharmacological Basis of Therapeutics. 1980:688-698 2. Adeli K, Higgins V, Bohn MK. Reference Information for the Clinical Laboratory. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:1390-1470

SALL4
71534

SALL4 Immunostain, Technical Component Only

Clinical Information: SALL4 (sal-like protein 4) is a zinc-finger transcriptional factor. It is required for the maintenance of embryonic stem cell pluripotency by regulating OCT4 transcription. Staining for SALL4 is useful in distinguishing germ cell tumors from carcinomas, lymphomas, and melanomas.

Useful For: Aids in the identification of germ cell tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Miettinen M, Wang Z, McCue PA, et al. SALL4 expression in germ cell and non-germ cell tumors: a systematic immunohistochemical study of 3215 cases. Am J Surg Pathol. 2014;38(3):410-420 2. Cao D, Li J, Guo CC, Allan RW, Humphrey PA. SALL4 is a novel diagnostic marker for testicular germ cell tumors. Am J Surg Pathol. 2009;33(7):1065-1077 3. Cao D, Humphrey PA, Allan RW. SALL4 is a novel sensitive and specific marker for metastatic germ cell tumors, with particular utility in detection of metastatic yolk sac tumors. Cancer. 2009;115(12):2640-2651. doi:10.1002/cncr.24308 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FSALG
57631

Salmon IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

SALM
82754

Salmon, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to salmon Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SALMC
606220

Salmonella Culture, Feces

Clinical Information: Diarrhea may be caused by a number of agents, including bacteria, viruses, parasites, and chemicals; these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the healthcare provider determine the appropriate testing to be performed. Salmonella species cause disease in 2 broad categories-gastroenteritis, and typhoid (or paratyphoid) fever (eg, Salmonella enterica subspecies enterica serovar Typhi, Salmonella enterica subspecies enterica serovar Paratyphi A, Salmonella enterica subspecies enterica serovar Paratyphi B [tartrate negative], and Salmonella enterica subspecies enterica serovar Paratyphi C). In the United States, gastroenteritis is most common clinical presentation.

Useful For: Determining whether Salmonella species may be the cause of diarrhea Reflexive testing for Salmonella species from nucleic acid amplification test-positive feces This test is generally not useful for patients hospitalized more than 3 days because the yield from specimens from these patients is very low, as is the likelihood of identifying a pathogen that has not been detected previously.

Interpretation: The growth of Salmonella species identifies a potential cause of diarrhea.

Reference Values:
No growth of Salmonella species.

Clinical References: 1. Pillai DR, Griener T: Culture for Campylobacter and related organisms. In: Leber AL, Church DL, eds. Clinical Microbiology Procedures Handbook. 4th ed. ASM Press; 2016:Section 3.8.2 2. DuPont HL. Persistent diarrhea: A clinical review. JAMA. 2016;315(24):2712-2723. doi:10.1001/jama.2016.7833 3.Heymann DL: Salmonellosis. In: Control of Communicable Diseases Manual. 21st ed. APHA Press; 2022 4. Johnson LR, Gould LH, Dunn JR, et al. Salmonella infections associated with international travel: A Foodborne Diseases Active Surveillance Network (FoodNet) study. Foodborne Pathog Dis. 2011;8(9):1031-1037

HEXBZ
608026

Sandhoff Disease, HEXB Gene, Full Gene Analysis, Varies

Clinical Information: Sandhoff disease is an autosomal recessive lysosomal storage disorder resulting from deficiencies of hexosaminidase A and hexosaminidase B isoenzymes caused by autosomal recessive disease-causing variants in HEXB. These isoenzymes are dimers, which differ in their subunit composition. Hexosaminidase A is a heterodimer comprised of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer consisting of 2 beta subunits (beta-beta). HEXB gene alterations impact the levels of both hexosaminidase A and hexosaminidase B enzymes and result in defective lysosomal degradation and excessive accumulation of GM2 ganglioside. This causes the clinical symptomology observed in Sandhoff disease. Variability is observed with respect to age of onset and clinical symptoms. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by 1 year of age. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past age 5 years. The juvenile or subacute form of Sandhoff disease often presents between 2 and 10 years of age with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively worsen, and death typically occurs 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Sandhoff disease. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria (loss of speech), and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are

observed in some patients. Significant clinical variability exists both between and within families. Hexosaminidase A and total enzyme activity testing in serum (NAGS / Hexosaminidase A and Total Hexosaminidase, Serum) or leukocytes (NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes) is the recommended first-tier test for individuals with suspected Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with high percent hexosaminidase A in serum and leukocytes. However, not all individuals with this pattern are true carriers of Sandhoff disease, and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies.

Useful For: Follow up for abnormal biochemical results suggestive of Sandhoff disease Establishing a molecular diagnosis for patients with Sandhoff disease Identifying variants within genes known to be associated with Sandhoff disease, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Gravel RA, Kaback MM, Proia RL, Sandhoff K, Suzuki K, Suzuki K. The GM2 Gangliosidoses. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed March 8, 2024. Available at http://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225547784 3. Delnooz CCS, Lefeber DJ, Langemeijer SMC, et al. New cases of adult-onset Sandhoff disease with a cerebellar or lower motor neuron phenotype. J Neurol Neurosurg Psychiatry. 2010;81(9):968-972 4. Scarpelli M, Tomelleri G, Bertolasi L, Salviati A. Natural history of motor neuron disease in adult onset GM2-gangliosidosis: A case report with 25 years of follow-up. Mol Genet Metab Rep. 2014;1:269-272

SARCP
606427

Sarcoma Targeted Gene Fusion/Rearrangement Panel, Next-Generation Sequencing, Tumor

Clinical Information: Molecular analysis of biomarkers is increasingly being utilized in oncology practices to support and guide patient diagnosis, prognosis, and therapeutic management. Chromosomal translocations, interstitial deletions, and inversions that lead to gene fusions are common in various sarcomas, such as Ewing sarcoma and rhabdomyosarcoma. This next-generation sequencing assay is used to detect specific gene fusions to assist in the diagnosis of sarcomas. See Method Description for details regarding the targeted gene regions identified by this test.

Useful For: Diagnosing specific soft tissue and bone tumors (sarcoma) based on the observed gene fusions (eg, PAX3/FOXO1 gene fusion observed in alveolar rhabdomyosarcoma, EWSR1-FLI1 gene fusion for Ewing sarcoma, SS18-SSX1/2 gene fusion for synovial sarcoma)

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Jia Y, Xie Z, Li H. Intergenically spliced chimeric RNAs in cancer. Trends Cancer. 2016;2(9):475-484. doi:10.1016/j.trecan.2016.07.006 2. Jo VY, Fletcher CD. WHO classification of soft tissue tumours: an update based on the 2013 (fourth) edition. Pathology. 2014;46(2):95-104. doi:10.1097/PAT.0000000000000050 3. Fletcher CD. The evolving classification of soft tissue tumours - an update based on the new 2013 WHO classification. Histopathology. 2014;64(1):2-11. doi:10.1111/his.12267 4. Quesada J, Amato R. The molecular biology of soft-tissue sarcomas and current trends in therapy. Sarcoma. 2012;2012(3):849456. doi:10.1155/2012/849456 5. Podnar J, Deiderick H, Huerta G, Hunicke-Smith S. Next-generation sequencing RNA-seq library construction. Curr Protoc Mol Biol. 2014;106:4.21.1-4.21.19 6. Mertens F, Tayebwa J. Evolving techniques for gene fusion detection in soft tissue tumours. Histopathology. 2014;64(1):151-162. doi:10.1111/his.12272 7. AI-Zaid T, Wang WL, Somaiah N, Lazar AJ. Molecular profiling of sarcomas: new vistas for precision medicine. Virchows Arch. 2017;471(2):243-255 8. Gao Q, Liang WW, Foltz SM, et al. Driver fusions and their implications in the development and treatment of human cancers. Cell Rep. 2018;23(1):227-238. doi:10.1016/j.celrep.2018.03.050 9. Lam SW, Cleton-Jansen AM, Cleven AHG, et al. Molecular analysis of gene fusions in bone and soft tissue tumors by anchored multiplex PCR-based targeted next-generation sequencing. J Mol Diagn. 2018 Sep;20(5):653-663. doi:10.1016/j.jmoldx.2018.05.007 10. Roy A, Kumar V, Zorman B, et al. Recurrent internal tandem duplications of BCOR in clear cell sarcoma of the kidney. Nat Commun. 2015;6:8891. doi:10.1038/ncomms9891 11. Marino-Enriquez A, Lauria A, Przybyl J, et al. BCOR Internal tandem duplication in high-grade uterine sarcomas. Am J Surg Pathol. 2018;42(3):335-341. doi:10.1097/PAS.0000000000000993

SARD
82818

Sardine (Pilchard), IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to sardine (pilchard) Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SATB2
607600

SATB2 Immunostain, Technical Component Only

Clinical Information: Special AT-rich sequence binding protein 2 (SATB2) is a transcription factor that regulates gene expression through chromatin remodeling. SATB2, when used in combination with the marker Keratin 20, may identify more than 95% of colorectal carcinoma. It may also be used to differentiate rectal neuroendocrine tumors from other neuroendocrine tumors of the gastrointestinal tract.

Useful For: Identification of colorectal carcinoma and rectal neuroendocrine tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Berg KB, Schaeffer DF. SATB2 as an immunohistochemical marker for colorectal adenocarcinoma, A concise review of benefits and pitfalls. Arch Pathol Lab Med. 2017;141(10):1428-1433 2. Davis JL, Horvai AE. Special AT-rich sequence-binding protein 2 (SATB2) expression is sensitive but may not be specific for osteosarcoma as compared with other high-grade primary bone sarcomas. Histopathology. 2016;69(1):84-90 3. Dragomir A, de Wit M, Johansson C, et al. The role of SATB2 as a diagnostic marker for tumors of colorectal origin. Am J Clin Pathol. 2014;141(5):630-638 4. Magnusson K, de Wit M, Brennan DJ, et al. SATB2 in combination with cytokeratin 20 identifies over 95% of all colorectal carcinoma. Am J Surg Pathol. 2011;35(7):937-948 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

C5B9
616921

SC5b-9 Level Terminal Complement Complex, Plasma

Clinical Information: The complement system membrane attack complex (MAC) is formed by the

C5b fragment along with C6, C7, C8 and several C9 molecules. This complex is recognized by multiple names, including MAC, terminal complement complex and C5b-9. Laboratory tests measure the amount of soluble C5b-9 (sC5b-9) complex. The formation of C5b-9 and sC5b-9 is a consequence of activation of the complement system by either the classical, lectin, or alternative pathways. Therefore, measurement of the sC5b-9 complex can be used as a surrogate marker of terminal complement activation via all complement pathways. Elevated concentrations of C5b-9 are associated with the development of transplant-associated thrombotic microangiopathy (TA-TMA), a complication of hematopoietic stem cell transplant.(1-3) Patients with higher sC5b-9 concentrations at baseline may require the use of higher doses of eculizumab to treat TA-TMA,(4) especially in children. Because of this association, measurement of sC5b-9 before transplant as part of a diagnostic evaluation and then repeat measurements during therapy have been proposed as tools to follow-up patients.(5) Importantly, while the elevation of sC5b-9 has shown very high sensitivity for TA-TMA, it has shown only a modest specificity, ranging from 40% to 50%, and the increased sC5b-9 may be found in other transplant complications as well as several other conditions where complement activation may occur: immune-complex disease, infection, atypical hemolytic uremic syndrome, C3 glomerulopathies, etc. A panel of complement tests, such as AHUSD / Atypical Hemolytic Uremic Syndrome Complement Panel, Serum and Plasma, may provide additional information on the extent of the complement activation, along with the information of which pathway is most dysregulated.

Useful For: Detecting increased complement activation

Interpretation: Elevated concentrations of soluble C5b-9 suggest recent or ongoing activation of the complement system, while normal and low concentrations suggest that the complement system has not been excessively activated. A panel of complement tests may be clinically indicated to further identify the extent of the complement activation, along with the information of which pathway is most dysregulated.

Reference Values:
< or =250 ng/mL

Clinical References: 1. Qi J, Wang J, Chen J, Su J, et al. Plasma levels of complement activation fragments C3b and sC5b-9 significantly increased in patients with thrombotic microangiopathy after allogeneic stem cell transplantation. Ann Hematol. 2017;96(11):1849-1855 2. Horvath O, Kallay K, Csuka D, et al. Early increase in complement terminal pathway activation marker sC5b-9 Is predictive for the development of thrombotic microangiopathy after stem cell transplantation. Biol Blood Marrow Transplant. 2018;24(5):989-996 3. Mezo B, Horvath O, Sinkovits G, Veszeli N, Krivan G, Prohaszka Z. Validation of early increase in complement activation marker sC5b-9 as a predictive biomarker for the development of thrombotic microangiopathy after stem cell transplantation. Front Med (Lausanne). 2020;7:569291 4. Jodele S, Dandoy CE, Lane A, et al. Complement blockade for TA-TMA: lessons learned from a large pediatric cohort treated with eculizumab. Blood. 2020;135(13):1049-1057 5. Young JA, Pallas CR, Knovich MA. Transplant-associated thrombotic microangiopathy: theoretical considerations and a practical approach to an unrefined diagnosis. Bone Marrow Transplant. 2021;56(8):1805-1817

SCLE
82716

Scale, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical

manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to scale Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SCALS
82259

Scallop, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to

inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to scallop Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SHUR
60451

Schistosoma Exam, Random, Urine

Clinical Information: Schistosomiasis is an infection caused by several species of trematodes (flukes) in the genus Schistosoma. The adult worms of Schistosoma haematobium inhabit the venus plexus of the bladder and produce eggs that are typically passed in the urine. Peak egg excretion occurs between noon and 3 p.m. Identification of characteristic eggs in urine is diagnostic for infection with this organism.

Useful For: Aiding in the diagnosis of schistosomiasis infections involving the urinary tract

Interpretation: A positive result indicates the presence of Schistosoma species ova in urine. A negative result does not rule out the presence of Schistosoma species since ova may be present at levels below the detection limits of this assay, or infection may not involve the urinary tract.

Reference Values:
Negative
If positive, organism identified

Clinical References: 1. Ash L, Orihel T: Atlas of Human Parasitology. 5th ed. American Society of Clinical Pathologists (ASCP) Press; 2007 2. Global Health, Division of Parasitic Diseases: Parasites-Schistosomiasis. Centers for Disease Control and Prevention. Reviewed Apri 11, 2018. Accessed August 28, 2023. Available at: www.cdc.gov/parasites/schistosomiasis/index.html 3. World Health Organization (WHO): Schistosomiasis (Bilharzia). WHO. Accessed August 28, 2023. Available at: www.who.int/health-topics/schistosomiasis#tab=tab_1

BILHA
65019

Schistosoma species Antibody, IgG, Serum

Clinical Information: Schistosoma species (class Trematoda) are flukes, characterized by their flat, leaf-like morphology as adults and use of gastropod mollusks (eg, snails) as an intermediate host. The schistosomes are also referred to as the "blood flukes" of which there are 5 species known to infect humans: Schistosoma mansoni, Schistosoma japonicum, Schistosoma haematobium, Schistosoma mekongi, and Schistosoma intercalatum. Among these S mansoni, S japonicum and S haematobium are most common. These species have a defined geographic distribution, with S mansoni occurring throughout sub-Saharan Africa, the Middle East, and islands in the Caribbean; S haematobium found in much of the African continent and the Middle East; and S japonicum localized to China, Indonesia, and the Philippines. Humans are definitive hosts for all Schistosoma species except for S japonicum, and infection begins with skin penetration of cercariae in contaminated water sources. The cercariae shed their bifurcated tails, becoming schistosomulae and migrate through the vascular system to the lungs, heart, and the portal venous system in the liver. There they mature to adults, pair off and migrate to the mesenteric venules of the bowel and rectum (S mansoni, S japonicum) or venus plexus of the bladder (S haematobium). Females will shed eggs, which are moved progressively towards the lumen of the intestine (S mansoni, S japonicum) and bladder (S haematobium) and are eliminated in the feces or urine, respectively. These eggs will hatch under ideal conditions, releasing miracidia, which penetrate specific snail (mollusk) intermediate hosts and develop into cercariae, continuing the life cycle. While many infections are asymptomatic, acute schistosomiasis (Katayama fever), due to S mansoni or S japonicum, may occur weeks after initial infection. Symptoms include fever, cough, abdominal pain, diarrhea, hepatosplenomegaly, and eosinophilia. Central nervous system infection is uncommon; however, cerebral granulomatous disease may be caused by migration of Schistosoma eggs into the brain or spinal cord. Cystitis and ureteritis with hematuria are associated with S haematobium infection and can progress to bladder cancer. Diagnosis of schistosomiasis can be made by detection of eggs in fecal or urine samples as appropriate for each species. Antibody detection can be useful for patients who reside in nonendemic areas but have recently traveled to regions where Schistosoma species are found and in whom eggs cannot be identified in fecal or urine examinations.

Useful For: Detection of antibodies to Schistosoma species

Interpretation: Negative: No IgG antibodies to Schistosoma species detected. Equivocal: Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive: IgG antibody to Schistosoma species detected. Differentiation between Schistosoma species is not possible by this assay. Serologic cross-reactivity may occur in individuals with other helminth infections, including Echinococcus or Taenia species.

Reference Values:
Negative

Clinical References: 1. Weerakoon KG, Gobert GN, Cai P, McManus DP. Advances in the

SCL70
80178

Scl-70 Antibodies, IgG, Serum

diagnosis of human schistosomiasis. Clin Microbiol Rev. 2015;28(4):939-967 2. McManus DP, Dunne DW, Sacko M, Utzinger J, Vennervald BJ, Zhou XN. Schistosomiasis. Nat Rev Dis Primers. 2018;4(1):13

Clinical Information: Scl 70 (DNA topoisomerase 1) is an enzyme localized in both the cytoplasm and the nucleoli of the interphase cell that is an autoantibody target in patients with systemic sclerosis (SSc).(1,2) SSc is a complex autoimmune rheumatic disease of unknown etiology, characterized by widespread vasculopathy, fibrosis of the skin and internal organs, and immunologic derangements, including the production of diverse autoantibodies.(3-5) Antibody to Scl 70 is considered specific for SSc (also referred to as scleroderma) and together with anti-centromere and anti-RNA polymerase III autoantibodies is recommended for the diagnostic classification for disease by the American College of rheumatology/European League Against Rheumatism collaborative initiative.(3) Antibody to Scl 70 is typically associated with diffuse cutaneous SSc (dcSSc), a clinical subset of SSc which is characterized by disease severity including musculoskeletal and cardiac involvement, interstitial lung disease and poor survival outcomes.(4,5) In addition, Scl 70 antibody are more commonly found in African American patients with dcSSc compared to their Caucasian counterpart.(6,7) In general, the presence of Scl 70 antibody is associated with a positive antinuclear antibody (ANA) when tested with the HEp-2 substrate using the indirect immunofluorescence assay (IFA).(1,2) ANA positivity with HEp-2 substrate IFA referred to as Scl-70 pattern is a composite of five cellular regions: nucleus, nucleolus and cytoplasm in interphase cells; nucleolar organizing region and chromosomes in mitotic cells.(2) Antibodies to Scl 70 were traditionally tested in clinical laboratories using immunodiffusion (ID), however, with increasing demands, methods for the detection and quantification of these autoantibodies have evolved to include diverse types of solid-phase immunoassays (SPAs) such as the line immunoblot, enzyme-linked immunosorbent assay, multiplex bead immunoassay, chemiluminescence immunoassay, and fluorescence enzyme immunoassay.(6-10) These SPAs have been reported to be less specific than the ID, especially in distinguishing SSc patients from those with other rheumatic diseases, though performance characteristics of individual assays may vary.(6-8). In a recent report, it was noted that discrepancy between anti-Scl-70 antibody assays can have relevant implications for clinical care and trial enrichment strategies for SSc patients with interstitial lung disease.(9) Data from routine clinical practice do suggest that at diagnosis, positive results for Scl 70 antibody using SPAs must be interpreted in the appropriate clinical context taking into consideration the presence of a positive ANA test using the HEp-2 substrate by IFA, and/or the level of anti-Scl 70 antibody level.(6-8, 10) Low levels of anti-Scl 70 antibodies have been reported in non-SSc patients including those with SLE.(6, 8, 10) In SLE patients, it remains to be determined if this points to a unique subset of individuals or the phenomenon is due to cross-reactivity with dsDNA antibody.(10) Based on this observation, testing for dsDNA antibody may provide additional diagnostic clues, especially in the absence of the ID assay.(10) For more information see Connective Tissue Disease Cascade.

Useful For: Evaluating patients with clinical features of systemic sclerosis and in the differential evaluation of individuals at-risk for connective tissue disease with Hep-2 substrate antinuclear antibody positive result, preferably using antinuclear antibodies Testing for Scl70 antibodies is not useful who test negative for antinuclear antibody using Hep-2 substrate by IFA.

Interpretation: A positive test result for Scl 70 antibodies may be consistent with a diagnosis of systemic sclerosis in the appropriate clinical context.

Reference Values:

<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References:

FSCPR
75625

Scleroderma Comprehensive Profile

Clinical Information: Anti-U1 RNP Abs can be found in 2-14% of limited SSC and 5% of diffuse SSc. They are associated with isolated pulmonary arterial hypertension, arthritis and esophageal dysfunction. Anti-Th/To Abs are present in 2-6% of patients with limited SSc and are rarely found in diffuse SSc. They have specificity and are associated with isolated pulmonary arterial HTN, pulmonary fibrosis and renal crisis. Anti-U3 RNP (Fibrillarin) Abs are highly specific for diffuse SSc with a sensitivity of 4-10%. They are associated with isolated arterial hypertension, myositis, renal and cardiac manifestations of SSc. Anti-PM/SCL Abs are found in 25% of Scleroderma/myositis overlap, 10% of idiopathic inflammatory myopathy and 2% of Scleroderma cutaneous changes and ILD. Anti-RNA Polymerase III Abs are useful in the diagnosis of SSc and for the identification of patients at risk for developing renal crisis, progressive skin thickening and cancer. The prevalence of IgG RNAP III antibodies is 20-35% in diffuse SSC and 9% in limited SSc.

Reference Values:

Anti-Nuclear Ab by IFA, Anti-U3 RNP(Fibrillarin), Anti-Th/To Ab:
Reference Range: Negative

Anti-Centromere Ab:
Reference Range: <1:40

Anti-SCL-70 Ab:
Reference Range: <20

Anti-RNA Polymerase III, Anti-U1RNP Ab, and Anti-PM/Scl-100 Ab:
Reference Range: <20
Negative: <20 units
Weak Positive: 20-39 units
Moderate Positive: 40-80 units
Strong Positive: >80 units

FSCN4
75263

SCN4A (Myotonia) DNA Sequencing Test

Reference Values:

A final report will be attached in MayoAccess.

SDHMP
619712

SDH Genes Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information: Disease-causing alterations of the succinate dehydrogenase complex genes (including SDHA, SDHB, SDHC, and SDHD) have been implicated in multiple tumor types, including pheochromocytoma/paraganglioma, renal cell carcinoma, gastrointestinal stromal tumors, and pituitary adenoma. Germline alterations of the SDH genes have been associated with hereditary pheochromocytoma/paraganglioma syndromes. The 5th edition of the World Health Organization classification of tumors recognizes succinate dehydrogenase-deficient renal cell carcinoma as a molecularly defined entity.(1) This assay, performed using formalin-fixed paraffin-embedded tissue or cytology material, is therefore helpful in documenting an underlying pathogenic alteration of the SDH genes and is diagnostically significant. Note that this assay does not distinguish between germline and somatic alterations or identify epigenetic alterations of interest (such as SDHC promoter hypermethylation).

Useful For: Identifying specific mutations within the SDHA, SDHB, SDHC, and SDHD genes to assist in tumor diagnosis/classification, including pheochromocytoma/paraganglioma, renal cell carcinoma, and pituitary adenoma

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board, eds. Urinary and male genital tumors. 5th ed. World Health Organization; 2022. WHO Classification of Tumours. Vol 8 2. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 3. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 4. Trpkov K, Hes O, Williamson SR, et al. New developments in existing WHO entities and evolving molecular concepts: The Genitourinary Pathology Society (GUPS) update on renal neoplasia. Mod Pathol. 2021;34(7):1392-1424 5. Fuchs TL, Maclean F, Turchini J, et al. Expanding the clinicopathological spectrum of succinate dehydrogenase-deficient renal cell carcinoma with a focus on variant morphologies: a study of 62 new tumors in 59 patients. Mod Pathol. 2022;35(6):836-849 6. Gupta S, Swanson AA, Chen YB, et al. Incidence of succinate dehydrogenase and fumarate hydratase-deficient renal cell carcinoma based on immunohistochemical screening with SDHA/SDHB and FH/2SC. Hum Pathol. 2019;91:114-122 7. Carlo MI, Hakimi AA, Stewart GD, et al. Familial kidney cancer: Implications of new syndromes and molecular insights. Eur Urol. 2019;76(6):754-764 8. Gupta S, Erickson LA. Back to biochemistry: Evaluation for and prognostic significance of SDH mutations in paragangliomas and pheochromocytomas. Surg Pathol Clin. 2023;16(1):119-129

SDHB
70550

SDHB Immunostain, Technical Component Only

Clinical Information: Succinate dehydrogenase B (SDHB) protein is an integral part of the complex II oxidation/reduction pathway. Its function is to transfer electrons from succinate to coenzyme Q. De novo and inheritable mutations in this gene result in paragangliomas and pheochromocytomas. SDHB can be used to differentiate between type 1 (SDHB +) and type 2 (SDHB -) gastrointestinal stromal tumors (GIST). SDHB-deficient GIST do not respond to imatinib. The cellular localization for SDHB is cytoplasmic and staining is granular (localized to mitochondria). Endothelial cells often stain positive for SDHB and can be used as an internal control when testing GIST tumors.

Useful For: Aids in the identification of succinate dehydrogenase B-deficient tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Gill AJ, Benn DE, Chou A, et al. Immunohistochemistry for SDHB triages genetic testing of SDHB, SDHC, and SDHD in paraganglioma-pheochromocytoma syndromes. Hum Pathol. 2010;41(6):805-814 2. Zhang L, Smyrk TC, Young WF Jr, et al. Gastric stromal tumors in Carney triad are different clinically, pathologically, and behaviorally from sporadic gastric gastrointestinal stromal tumors: findings in 104 cases. Am J Surg Pathol. 2010;34(1):53-64 3. van Nederveen FH, Gaal J, Favier J, et al. An immunohistochemical procedure to detect patients with paraganglioma and

phaeochromocytoma with germline SDHB, SDHC, or SDHD gene mutations: a retrospective and prospective analysis. Lancet Oncol. 2009;10(8):764-771 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

SEAFP
31770

Seafood Allergen Profile, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years of age due to food sensitivity (milk, egg, soy, and wheat proteins), followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mites, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to seafood Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070

SEAS
31766

Seasonal Inhalants Allergen Profile, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years of age due to food sensitivity (milk, egg, soy, and wheat proteins), followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mites, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to seasonal inhalants Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070

SECOS
8243

Secobarbital, Serum

Clinical Information: Secobarbital is a short-acting barbiturate with hypnotic properties used as a preanesthetic agent and in the short-term treatment of insomnia.(1,2) Secobarbital is administered orally. The duration of its hypnotic effect is about 3 to 4 hours. The drug distributes throughout the body, with a

volume of distribution of 1.6 to 1.9 L/kg, and about 46% to 70% of a dose is bound to plasma proteins. Metabolism takes place in the liver primarily via hepatic microsomal enzymes. The half-life of secobarbital is about 15 to 40 hours (mean: 28 hours).(2,3)

Useful For: Monitoring secobarbital therapy

Interpretation: Secobarbital concentrations above 5 mcg/mL have been associated with toxicity.

Reference Values:
Therapeutic concentration: 1.0-2.0 mcg/mL
Toxic concentration: >5.0 mcg/mL

Clinical References: 1. Langman LJ, Bechtel LK, Holstege CP. Chapter 43: Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:454-454.e484 2. Baselt RC. Disposition of Toxic Drugs and Chemical in Man. 12th ed. Biomedical Publications; 2020. 3. Milone MC, Shaw LM. Chapter 42: Therapeutic Drugs and Their Management. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453 4. Mihic SJ, Mayfield J. Hypnotics and Sedatives. In: Brunton LL, Knollmann BC, eds. In: Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 14th ed. McGraw-Hill Education; 2023

FSHPU
58038

Sedative Hypnotic Panel, Urine

Reference Values:
The following threshold concentrations are used for this analysis.

Drug	Screening Threshold	Confirmation Threshold
Ethyl Alcohol	0.020 gm/dL	0.020 gm/dL
Barbiturates	300 ng/mL	100 ng/mL
Benzodiazepines	100 ng/mL	75 ng/mL
Flunitrazepam	100 ng/mL	300 ng/mL

Ketamine: Negative
Screening threshold: 100 ng/mL

Gamma-Hydroxybutyric Acid (GHB): Negative
Screening threshold: 5.0 ug/mL

SEWB
65600

Selenium, Blood

Clinical Information: Selenium is a naturally occurring, solid substance that is widely but unevenly distributed in the earth's crust. Selenium and its compounds are used in some photographic devices, gun bluing, plastics, paints, antidandruff shampoos, vitamin and mineral supplements, fungicides, and certain types of glass. Selenium is also used to prepare drugs and as a nutritional feed supplement for poultry and livestock. It is an essential element for humans and animals. People are exposed to low levels of selenium daily through food, water, and air. Plasma and serum typically contain approximately 75% of the selenium measured in whole blood. Selenium whole blood concentrations can be used to assess tissue stores.

Useful For: Assessment of tissue stores of selenium

Interpretation: Ultimately, any metal ion concentration value needs to be interpreted in relation to the overall clinical scenario including symptoms, physical findings, and other diagnostic results when determining further actions.

Reference Values:
0-17 years: Not established
> or =18 years: 150-241 ng/mL

Clinical References: 1. US Department of Health and Human Services. Toxicological profile for selenium. HHS: Agency for Toxic Substances and Disease Registry; 2003. Accessed December 3, 2024. Available at www.atsdr.cdc.gov/toxprofiles/tp92.pdf 2. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

SES
9765

Selenium, Serum

Clinical Information: Selenium is an essential element; it is a cofactor required to maintain activity of glutathione peroxidase (GSH-Px), an enzyme that catalyzes the degradation of organic hydroperoxides. The absence of selenium correlates with loss of GSH-Px activity and is associated with damage to cell membranes due to accumulation of free radicals. The normal daily dietary intake of selenium is 0.01 to 0.04 parts per million (ppm), which is similar to the typical content of soil (0.05 ppm) and sea water (0.09 ppm). Selenium is found in many over-the-counter vitamin preparations because its antioxidant activity is thought to be anticarcinogenic. There is no supporting evidence that selenium suppresses cancer. In humans, cardiac muscle is the most susceptible to selenium deficiency. With cell membrane damage, normal cells are replaced by fibroblasts. This condition is known as cardiomyopathy and is characterized by an enlarged heart whose muscle is largely replaced by fibrous tissue. In the United States, selenium deficiency is related to use of total parenteral nutrition. This therapy is administered to patients with no functional bowel, such as after surgical removal of the small and large intestine because of cancer or because of acute inflammatory bowel disease such as Crohn disease. Selenium supplementation to raise the serum concentration to above 70 mcg/L is the usual treatment. Serum monitoring done on a semiannual basis checks the adequacy of supplementation. Selenium toxicity has been observed in animals when daily intake exceeds 4 ppm. Teratogenic effects are frequently noted in the offspring of animals living in regions where soil content is high in selenium such as south-central South Dakota and northern-coastal regions of California. Selenium toxicity in humans is not known to be a significant problem except in acute overdose cases. Selenium is not classified as a human teratogen.

Useful For: Monitoring selenium replacement therapy

Interpretation: Selenium accumulates in biological tissue. The normal concentration in adult human serum is 110 to 165 mcg/L. Optimal selenium concentration is age dependent (see Reference Values); children require less circulating selenium than adults. In the state of selenium deficiency associated with loss of glutathione peroxidase activity, the serum concentration is usually below 40 mcg/L.

Reference Values:
0-2 months: 45-90 mcg/L
3-6 months: 50-120 mcg/L
7-9 months: 60-120 mcg/L
10-12 months: 70-130 mcg/L
13 months-17 years: 70-150 mcg/L
> or =18 years: 110-165 mcg/L

Clinical References: 1. Muntau AC, Streiter M, Kappler M, et al. Age-related reference values for

serum selenium concentrations in infants and children. Clin Chem. 2002;48(3):555-560 2. Gonzalez S, Huerta JM, Fernandez S, Patterson EM, Lasheras C. Food intake and serum selenium concentration in elderly people. Ann Nutr Metab. 2006;50(2):126-131 3. Skelton JA, Havens PL, Werlin SL. Nutrient deficiencies in tube-fed children. Clin Pediatr. 2006;45(1):37-41 4. Gosney MA, Hammond MF, Shenkin A, Allsup S. Effect of micronutrient supplementation on mood in nursing home residents. Gerontology. 2008;54(5):292-299 5. Burri J, Haldimann M, Dudler V. Selenium status of the Swiss population: assessment and change over a decade. J Trace Elem Med Biol. 2008;22(2):112-119 6. Ayling RM, Crook M. Nutrition: Laboratory and clinical aspects. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:457-501

SEMA3 617055 Semaphorin 3B (SEMA3B) Immunostain, Technical Component Only

Clinical Information: Primary membranous nephropathy (MN) is an autoimmune disease of the kidney where antibodies target an antigen in the glomerular basement membrane resulting in kidney damage or failure. In up to 75% of primary membranous nephropathy cases PLA2R (phospholipase A2 receptor) and THSD7A (thrombospondin type-1 domain-containing 7A) are the target antigens. SEMA3B (semaphorin 3B)-associated MN is a very rare disease that accounts for only 1% to 3% of all MN specimens. SEMA3B-associated MN is observed mostly in pediatric patients and young adults.

Useful For: Aiding in the diagnosis of semaphorin 3B-associated membranous nephropathy

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Sethi S, Debiec H, Madden B, et al: Semaphorin 3B-associated membranous nephropathy is a distinct type of disease predominantly present in pediatric patients. Kidney Int. 2020 Nov;98(5):1253-1264 2. Sethi S: Membranous nephropathy: a single disease or a pattern of injury resulting from different diseases. Clin Kidney J. 2021 Mar 26;14(10):2166-2169 3. Sethi S: New 'antigens' in membranous nephropathy. J Am Soc Nephrol. 2021 Feb;32(2):268-278

SEMB 60556 Semen Analysis with Strict Morphology, Semen

Clinical Information: Infertility affects 1 out of 6 couples of child-bearing age. Approximately 40% of infertility has a female-factor cause and 40% a male-factor cause. The remaining 20% of infertility is due to a combination of male- and female-factor disorders or is unexplained. Semen is composed of spermatozoa suspended in seminal fluid (plasma). The function of the seminal fluid is to provide nutrition and volume for conveying the spermatozoa to the endocervical mucus. Male infertility can be affected by a number of causes. Chief among these is a decrease in the number of viable sperm. Other causes include sperm with abnormal morphology and abnormalities of the seminal fluid. One of the more successful treatments for male and female infertility is in vitro fertilization (IVF). Male partners are tested with the strict criteria sperm morphology test prior to IVF to assist in the diagnosis of male-factor defects. Abnormalities in sperm morphology are related to defects in sperm transport, sperm capacitation, the acrosome reaction, binding and penetration of the zona pellucida, and fusion with the oocyte vitelline membrane. All steps are essential to normal fertility. Strict criteria sperm morphology

testing also greatly assists with selecting the most cost-effective in vitro sperm processing and insemination treatment for the couple's IVF cycle. Sperm with severe head abnormalities are unlikely to bind to the zona pellucida. These patients may require intracytoplasmic sperm injection in association with their IVF cycle to ensure optimal levels of fertilization are achieved. This, in turn, provides the patient with the best chance of pregnancy. Multiple semen analyses are usually conducted over the course of the spermatogenic cycle (approximately 70 days).

Useful For: Determining male fertility status Selecting the most cost-effective therapy for treating male-factor infertility Quantifying the number of germinal and white blood cells per milliliter of semen

Interpretation: Semen specimens can vary widely in the same man from specimen to specimen. Semen parameters falling outside of the normal ranges do not preclude fertility for that individual. Multiple samples may need to be analyzed prior to establishing patient’s fertility status. Sperm are categorized according to strict criteria based on measurements of head and tail sizes and shapes. Sperm with abnormalities in head/tail size/shape may not be capable of completing critical steps in sperm transport and fertilization.

Reference Values:

SEMEN ANALYSIS
Appearance: normal
Volume: > or =1.5 mL
pH: > or =7.2
Motile/mL: > or =6.0 x 10(6)
Sperm/mL: > or =15.0 x 10(6)
Motility: > or =40%
Grade: > or =2.5
Note: Multiple laboratory studies have indicated that semen parameters for motility and grade on average retain 80% of original parameters when our shipping method is used for transport. Using these averages, samples with 32% to 39% motility and grade of 2 may be in the normal range if testing was performed shortly after collection. Therefore, these borderline patients may need to collect another sample at a local fertility center to verify fertility status.
Motile/ejaculate: > or =9.0 x 10(6)
Viscosity: > or =3.0
Agglutination: > or =3.0
Supravital: > or =58% live
Fructose: positive
Note: Fructose testing cannot be performed on semen analysis specimens shipped through Mayo Clinic Laboratories. If patient is azoospermic, refer to FROS2 / Fructose, Qualitative, Semen. Submit separate specimen to rule-out ejaculatory duct blockage. Positive result indicates no blockage.

STRICT MORPHOLOGY
Normal forms: > or =4.0% normal oval sperm heads
Germ cells: <4 x 10(6) (normal)
> or =4 x 10(6)/mL (elevated germinal cells in semen are of unknown clinical significance)
White blood cell count:
<1 x 10(6) (normal)
> or =1 x 10(6)/mL (elevated white blood cells in semen are of questionable clinical significance)

Clinical References: 1. WHO laboratory manual for the examination of human semen and processing. 5th ed. World Health Organization; 2010 2. WHO laboratory manual for the examination and processing of human semen. 6th ed. World Health Organization; 2021

FER
81641

Semen Analysis, Semen

Clinical Information: Semen is composed of spermatozoa suspended in seminal fluid (plasma). The function of the seminal fluid is to provide nutrition and volume for conveying the spermatozoa to the endocervical mucus. Male infertility can be affected by a number of causes. Chief among these is a decrease in the number of viable sperm. Other causes include sperm with abnormal morphology and abnormalities of the seminal fluid.

Useful For: Determining male fertility status

Interpretation: Semen specimens can vary widely in the same man from specimen to specimen. Semen parameters falling outside of the normal ranges do not preclude fertility for that individual. Multiple samples may need to be analyzed prior to establishing patient's fertility status.

Reference Values:
Appearance: Normal
Volume: > or =1.5 mL
pH: > or =7.2
Motile/mL: > or =6.0 x 10(6)
Sperm/mL: > or =15.0 x 10(6)
Motility: > or =40%
Grade: > or =2.5

Note: Multiple laboratory studies have indicated that semen parameters for motility and grade, on average, retain 80% of original parameters when our shipping method is used for transport. Using these averages, samples with 32% to 39% motility and grade of 2 may be in the normal range if testing was performed shortly after collection. Therefore, these borderline patients may need to collect another sample at a local fertility center to verify fertility status.

Motile/ejaculate: > or =9.0 x 10(6)
Viscosity: > or =3.0
Agglutination: > or =3.0
Supravital: > or =58% live
Fructose: Positive

Note: Fructose testing cannot be performed on semen analysis specimens shipped through Mayo Clinic Laboratories.

Submit separate specimen to rule out ejaculatory duct blockage. Positive result indicates no blockage.

Clinical References: 1. Cooper TG, Aitken J, Auger J, et al, eds. WHO laboratory manual for the examination and processing of human semen. 5th ed. WHO Press; 2010 2. Bjorndahl L, Apolikhin O, Baldi E, et al, eds. WHO laboratory manual for the examination and processing of human semen. 6th ed. World Health Organization; 2021

SMFL
82858

Seminal Fluid, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend

upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to seminal fluid Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SP5CS
615869

Septin-5 Antibody, Cell Binding Assay, Serum

Clinical Information: Septin-5 IgG is a biomarker of a rapidly progressive, but treatable, form of autoimmune cerebellar ataxia. Patients present with subacute onset of cerebellar ataxia with prominent eye movement symptoms (oscillopsia or vertigo). Improvement may occur after immunotherapy.

Useful For: Detecting septin-5 IgG by cell-binding assay using serum specimens

Interpretation: Seropositivity for septin antibodies by indirect immunofluorescence is consistent with

a diagnosis of autoimmune disease of the central nervous system. Cell-binding assay (CBA) testing for septin-5 IgG is required to confirm the diagnosis. Seropositivity for septin-5 IgG by CBA confirms a diagnosis of autoimmune disease of the central nervous system.

Reference Values:
Only orderable as a reflex. For more information see MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum.

Negative

Clinical References: 1. Honorat JA, Lopez-Chiriboga AS, Kryzer TJ, et al: Autoimmune septin-5 cerebellar ataxia. Neurol Neuroimmunol Neuroinflamm. 2018 Jul 9;5(5):e474 2. Honorat JA, Miske R, Scharf M, et al: 416. Neuronal septin autoimmunity: Differentiated serological profiles and clinical findings. Ann Neurol. 2020 Oct;88(Suppl 25):S55. Abstract

SP5CC
615868

Septin-5 Antibody, Cell-Binding Assay, Spinal Fluid

Clinical Information: Septin-5 IgG is a biomarker of a rapidly progressive, but treatable, form of autoimmune cerebellar ataxia. Patients present with subacute onset of cerebellar ataxia with prominent eye movement symptoms (oscillopsia or vertigo). Improvement may occur after immunotherapy.

Useful For: Detecting septin-5 IgG by cell-binding assay using cerebrospinal fluid specimens

Interpretation: Seropositivity for septin antibodies by indirect immunofluorescence (IFA) is consistent with a diagnosis of autoimmune disease of the central nervous system. Cell-binding assay (CBA) testing for septin-5 IgG is required to confirm the diagnosis. Seropositivity for septin-5 IgG by CBA confirms a diagnosis of autoimmune disease of the central nervous system.

Reference Values:
Only orderable as a reflex. For more information see MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid.

Negative

Clinical References: 1. Honorat JA, Lopez-Chiriboga AS, Kryzer TJ, et al: Autoimmune septin-5 cerebellar ataxia. Neurol Neuroimmunol Neuroinflamm. 2018 Jul 9;5(5):e474 2. Honorat JA, Miske R, Scharf M, et al: 416. Neuronal septin autoimmunity: Differentiated serological profiles and clinical findings. Ann Neurol. 2020 Oct;88(Suppl 25):S55. Abstract

SP5TS
616113

Septin-5 Antibody, Tissue Immunofluorescence Titer, Serum

Clinical Information: Septin-5 IgG is a biomarker of a rapidly progressive, but treatable, form of autoimmune cerebellar ataxia. Patients present with subacute onset of cerebellar ataxia with prominent eye movement symptoms (oscillopsia or vertigo). Improvement may occur after immunotherapy.

Useful For: Detecting septin-5 IgG in serum specimens Reporting an end titer result from serum specimens

Interpretation: Seropositivity for septin antibodies by indirect immunofluorescence is consistent with a diagnosis of autoimmune disease of the central nervous system. Cell-binding assay testing for

septin-5 IgG is required to confirm the diagnosis.

Reference Values:
Only orderable as a reflex. For more information see MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum.

<1:240

Clinical References: 1. Honorat JA, Lopez-Chiriboga AS, Kryzer TJ, et al: Autoimmune septin-5 cerebellar ataxia. Neurol Neuroimmunol Neuroinflamm. 2018 Jul 9;5(5):e474 2. Honorat JA, Miske R, Scharf M, et al: 416. Neuronal septin autoimmunity: Differentiated serological profiles and clinical findings. Ann Neurol. 2020 Oct;88(Suppl 25):S55. Abstract

SP5TC
616114

Septin-5 Antibody, Tissue Immunofluorescence, Spinal Fluid

Clinical Information: Septin-5 IgG is a biomarker of a rapidly progressive, but treatable, form of autoimmune cerebellar ataxia. Patients present with subacute onset of cerebellar ataxia with prominent eye movement symptoms (oscillopsia or vertigo). Improvement may occur after immunotherapy.

Useful For: Detecting septin-5 IgG in spinal fluid (CSF) specimens Reporting an end titer result from CSF specimens

Interpretation: Seropositivity for septin antibodies by indirect immunofluorescence is consistent with a diagnosis of autoimmune disease of the central nervous system. Cell-binding assay testing for septin-5 IgG is required to confirm the diagnosis.

Reference Values:
Only orderable as a reflex. For more information see MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid.

<1:2

Clinical References: 1. Honorat JA, Lopez-Chiriboga AS, Kryzer TJ, et al: Autoimmune septin-5 cerebellar ataxia. Neurol Neuroimmunol Neuroinflamm. 2018 Jul 9;5(5):e474 2. Honorat JA, Miske R, Scharf M, et al: 416. Neuronal septin autoimmunity: Differentiated serological profiles and clinical findings. Ann Neurol. 2020 Oct; 88(Suppl 25):S55. Abstract

SP7CS
615873

Septin-7 Antibody, Cell-Binding Assay, Serum

Clinical Information: Neurological phenotypes for septin-7 IgG positive patients include encephalopathy, myelopathy, encephalomyelopathy, painful myelopolyradiculopathy, and episodic ataxia. Psychiatric symptoms are also common with encephalopathic symptoms. Septin-7 IgG is also associated with cancer. Positive response to immunotherapy.

Useful For: Detecting septin-7 IgG by cell-binding assay using serum specimens

Interpretation: Seropositivity for septin antibodies by immunofluorescence is consistent with a diagnosis of autoimmune disease of the central nervous system. Cell-binding assay (CBA) testing for septin-7 IgG is required to confirm the diagnosis. Seropositivity for septin-7 IgG by CBA confirms a diagnosis of autoimmune disease of the central nervous system. A paraneoplastic cause should be

considered in patients with septin-7 IgG.

Reference Values:
Only orderable as a reflex. For more information see:
-ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
-MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum

Negative

Clinical References: Honorat JA, Miske R, Scharf M, et al: 416. Neuronal septin autoimmunity: Differentiated serological profiles and clinical findings. Ann Neurol. 2020 Oct;88(Suppl 25):S55. Abstract

SP7CC
615872

Septin-7 Antibody, Cell-Binding Assay, Spinal Fluid

Clinical Information: Neurological phenotypes for septin-7 IgG positive patients include encephalopathy, myelopathy, encephalomyelopathy, painful myelopolyradiculopathy, and episodic ataxia. Psychiatric symptoms are also common with encephalopathic symptoms. Septin-7 IgG is also associated with cancer. Positive response to immunotherapy.

Useful For: Detecting septin-7 IgG by cell-binding assay using cerebrospinal fluid specimens

Interpretation: Seropositivity for septin antibodies by indirect immunofluorescence assay is consistent with a diagnosis of autoimmune disease of the central nervous system. Cell-binding assay (CBA) testing for septin-7 IgG is required to confirm the diagnosis. Seropositivity for Septin-7 IgG by CBA confirms a diagnosis of autoimmune disease of the central nervous system. A paraneoplastic cause should be considered in patients with septin-7-IgG.

Reference Values:
Only orderable as a reflex. For more information see:
-ENC2 / Encephalopathy, Autoimmune /Paraneoplastic Evaluation, Spinal Fluid
-MDC2 / Movement Disorder, Autoimmune /Paraneoplastic Evaluation, Spinal Fluid
-MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

Negative

Clinical References: Honorat JA, Miske R, Scharf M, et al: 416. Neuronal septin autoimmunity: Differentiated serological profiles and clinical findings. Ann Neurol. 2020 Oct;88(Suppl 25):S55. Abstract

SP7TS
616115

Septin-7 Antibody, Tissue Immunofluorescence Titer, Serum

Clinical Information: Neurological phenotypes for septin-7 IgG positive patients include encephalopathy, myelopathy, encephalomyelopathy, painful myelopolyradiculopathy, and episodic ataxia. Psychiatric symptoms are also common with encephalopathic symptoms. Septin-7 IgG is also associated with cancer. Positive response to immunotherapy.

Useful For: Detecting septin-7 IgG in serum specimens Reporting an end titer result from serum specimens

Interpretation: Seropositivity for septin antibodies by indirect immunofluorescence assay is consistent with a diagnosis of autoimmune disease of the central nervous system. Cell-binding assay testing for septin-7 IgG is required to confirm the diagnosis.

Reference Values:

Only orderable as a reflex. For more information see:
-ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
-MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
-MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum

<1:240

Clinical References: Honorat JA, Miske R, Scharf M, et al: 416. Neuronal septin autoimmunity: Differentiated serological profiles and clinical findings. Ann Neurol. 2020 Oct;88(Suppl 25):S55. Abstract

SP7TC
616116

Septin-7 Antibody, Tissue Immunofluorescence Titer, Spinal Fluid

Clinical Information: Neurological phenotypes for septin-7 IgG positive patients include encephalopathy, myelopathy, encephalomyelopathy, painful myelopolyradiculopathy, and episodic ataxia. Psychiatric symptoms are also common with encephalopathic symptoms. Septin-7 IgG is also associated with cancer and positive response to immunotherapy.

Useful For: Detecting septin-7 IgG in cerebrospinal fluid (CSF) specimens Reporting an end titer result from CSF specimens

Interpretation: Seropositivity for septin antibodies by immunofluorescence is consistent with a diagnosis of autoimmune disease of the central nervous system. Cell-binding assay testing for septin-7 IgG is required to confirm the diagnosis.

Reference Values:

Only orderable as a reflex. For more information see:
-ENC2 / Encephalopathy, Autoimmune /Paraneoplastic Evaluation, Spinal Fluid
-MDC2 / Movement Disorder, Autoimmune /Paraneoplastic Evaluation, Spinal Fluid
-MAC1 / Autoimmune Myelopathy /Paraneoplastic Evaluation, Spinal Fluid

<1:2

Clinical References: Honorat JA, Miske R, Scharf M, et al: 416. Neuronal septin autoimmunity: Differentiated serological profiles and clinical findings. Ann Neurol. 2020 Oct;88(Suppl 25):S55. Abstract

SEP9Z
617714

SEPTIN9 Gene, Full Gene Analysis, Varies

Clinical Information: Hereditary neuralgic amyotrophy (HNA) is an autosomal dominant disorder characterized by periods of severe pain involving the brachial plexus followed by muscle atrophy and weakness. These recurrent episodes can also be accompanied by decreased sensation and paresthesias. Individuals with this disease are generally symptom-free between pain attacks, though many patients experience lingering effects with repeated attacks. The pain episodes are frequently triggered by physical,

emotional, or immunological stress. Less commonly, affected individuals can exhibit non-neurological features including short stature, skin folds, hypotelorism, and cleft palate. Variants in the SEPTIN9 gene cause the clinical manifestations of HNA. SEPTIN9 is currently the only known gene associated with HNA, although approximately 15% of HNA families do not show linkage to this gene.

Useful For: Establishing a molecular diagnosis for patients with hereditary neuralgic amyotrophy
Identifying variants within SEPTIN9 known to be associated with hereditary neuralgic amyotrophy, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Klein CJ, Duan X, Shy ME. Inherited neuropathies: clinical overview and update. Muscle Nerve. 2013;48(4):604-622

FSERO 75621 SeroNeg RAdx3 Profile

Clinical Information: SeroNeg RAdx3 is a diagnostic and prognostic panel for Rheumatoid Arthritis designed to complement traditional RF and Anti-CCP testing. This profile, consisting of 14-3-3 eta protein, Anti -CEP-1 Ab and Anti-Sa Ab, enhances the diagnosis of established or early RA (in individuals seronegative for RF and Anti-CCP Ab) and also helps predict disease severity. Decrease in 14-3-3eta and/or Anti-Sa Ab with treatment is associated with less radiographic progression. The presence of Anti-CEP1 and Anti-CCP Antibodies suggests the imminent progression of pre-clinical RA into clinical RA

Reference Values:

SRAU 616216 Serotonin Release Assay, Unfractionated Heparin, Mass Spectrometry, Serum

Clinical Information: There are established and emerging disorders that are collectively termed thrombocytopenia and thrombosis syndromes. The most commonly recognized is heparin-induced thrombocytopenia (HIT); additional newer associations include adenovirus vector-based SARS-CoV-2 vaccine-induced thrombocytopenia and HIT-like syndromes that occur in the absence of exposure to heparin (currently termed spontaneous or autoimmune HIT). In this situation, the heparin platelet-factor 4 (PF4) IgG antibody typically develops after surgery or infection. Heparin-induced thrombocytopenia is a serious immune-mediated syndrome, (ie, type II HIT or immune HIT), which occurs in 1% to 5% of patients treated with unfractionated heparin and at a lower frequency in patients treated with low-molecular weight heparin. The 4Ts score is a validated scoring system to estimate the pretest clinical probability of HIT. Scores are assigned to the degree and timing of onset of thrombocytopenia, and the presence or absence of thrombosis (arterial or venous), in the absence of other potential explanations for the thrombocytopenia. In HIT, typical onset of thrombocytopenia is between days 5 and 10 of heparin

therapy, but thrombocytopenia can arise earlier (<5 days after heparin exposure, ie, rapid onset of HIT) or later (>4 weeks after heparin exposure, ie, delayed onset of HIT). The platelet count typically decreases by 40% to 50% from baseline or the postoperative peak (in surgical patients), even though the absolute count may remain normal and the thrombocytopenia resolves within 7 to 14 days of cessation of heparin therapy (unless there is another coexisting cause of thrombocytopenia). Development or progression of (venous or arterial) thrombosis is termed heparin-induced thrombocytopenia with thrombosis syndrome and can occur in 30% to 50% of patients, rarely even following discontinuation of heparin therapy. Other Syndromes of Thrombocytopenia and Thrombosis: There are an increasing number of reports of patients who develop thrombocytopenia and thrombosis after surgery, particularly after orthopedic surgery and after selected infections. The clinical course and laboratory characteristics of this group of patients are similar to the classical HIT occurring with heparin exposure except perhaps development of high-titer antibodies against heparin/PF4 complexes. An emerging recognition is the development of thrombocytopenia and thrombosis occurring 3 to 4 weeks after adenovirus vector SARS-CoV-2 exposure. The clinical course is also similar to immune HIT. Laboratory Characteristics of HIT: Heparin-induced thrombocytopenia is caused, in at least 90% of cases, by antibodies to antigen complexes of heparinoid (heparin or similar glycosaminoglycans) and PF4. PF4 is a platelet-specific heparin-binding (neutralizing) protein that is abundant in platelet alpha granules from which it is secreted following platelet stimulation. A reservoir of PF4 normally accumulates on vascular endothelium. Following heparin administration, immunogenic complexes of PF4 and heparin can provide an antigenic stimulus for antibody development in some patients. Antibodies bound to platelets that display complexes of PF4/heparin antigen can activate platelets via interaction of the Fc immunoglobulin tail of the IgG antibody with platelet Fc gamma IIa receptors, leading to perpetuation of the pathologic process that can cause platelet-rich thrombi in the microcirculation in some cases. Functional assays for HIT antibody detection rely on antibody-mediated heparin-dependent platelet activation. The endpoint of platelet activation may be platelet aggregation or platelet secretion of serotonin or adenosine triphosphate using patient serum or plasma supplemented with heparin and platelets from carefully normal selected donors. The sensitivity of functional assays for HIT ranges from 50% to 60% for heparin-dependent platelet aggregation assays to 70% to 80% for serotonin release assays. The specificity of positive functional tests for HIT diagnosis is believed to be high (> or =90%). However, because of their complexity, functional tests for detecting HIT antibodies are not widely available.

Useful For: Detecting heparin-dependent platelet activating antibodies implicated in the pathogenesis of heparin-induced thrombocytopenia

Interpretation: In a negative serotonin release assay (SRA), patient serum induced serotonin release of below 20% from normal donor platelets in presence of low concentration of unfractionated heparin (UFH) (0.1U/mL) regardless of the serotonin release with high concentration of UFH (100 U/mL). In a positive SRA, patient serum induced serotonin release of 20% or more from normal donor platelets in presence of low concentration of UFH (0.1U/mL). This release is inhibited in presence of high concentration of UFH (100 U/mL) and falls below 20%. In an indeterminate SRA, patient serum induced serotonin release of 20% or more from normal donor platelets in presence of low concentration of UFH (0.1U/mL) and high concentration of UFH (100 U/mL). Indeterminate results can occur due to non-heparin dependent antibodies (eg, human leukocyte antigen antibodies). Occasionally some indeterminate results may show greater than 50% inhibition of serotonin release from normal donor platelets in presence of high concentration of UFH (100 U/mL) compared to low concentration of UFH (0.1U/mL), which is suggestive for heparin-induced thrombocytopenia in the right clinical context. Table. Results and Interpretation Low heparin release % High heparin release % Interpretation <20% <20% Negative <20% > or =20% Negative > or =20% <20% Positive

Reference Values:

Low Heparin Serotonin Release: <20%
High Heparin Serotonin Release: <20%
Serotonin Release Assay Result: Negative

Clinical References: 1. Warkentin TE, Arnold DM, Nazi I, Kelton JG. The platelet serotonin-release assay. Am J Hemtol. 2015;90(6):564-572. doi:10.1002/ajh.24006 2. Minet V, Dogne JM, Mullier F. Functional assays in the diagnosis of heparin-induced thrombocytopenia: a review. Molecules. 2017;22(4):617. doi:10.3390/molecules22040617 3. Sono-Koree NK, Crist RA, Frank EL, Rodgers GM, Smock KJ. A high-performance liquid chromatography method for the serotonin release assay is equivalent to the radioactive method. Int. J Lab Hematol. 2016;38(1):72-80. doi:10.1111/ijlh.12442

SERU
87834

Serotonin, 24 Hour, Urine

Clinical Information:

Useful For: Diagnosis of a small subgroup of carcinoid tumors that produce predominately 5-hydroxytryptophan (5-HTP) but very little serotonin and chromogranin A Follow-up for patients with known or treated carcinoid tumors that produce predominately 5-HTP but very little serotonin and chromogranin A

Interpretation: It is usually impossible to diagnose asymptomatic, small carcinoid tumors by measurement of serum or urine serotonin, urine 5 hydroxyindoleacetic acid (5-HIAA), or serum chromogranin A. By contrast, 1 or more of these markers are elevated in most patients with more advanced and symptomatic tumors, usually to levels several times the upper limit of the reference interval. In patients with advanced and symptomatic tumors the following patterns of tumor marker elevations are observed: -Serum or whole blood serotonin is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors, because foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and, therefore, may produce little, if any, serotonin. -Urine 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. -Serum chromogranin A measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though serotonin and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with symptomatic foregut and midgut tumors. -Urine serotonin is in most circumstances the least likely marker to be elevated. The exception is tumors (usually foregut tumors) that produce predominately 5-HTP, rather than serotonin, and also secrete little, if any, chromogranin A. In this case, circulating chromogranin A, circulating serotonin levels, and urine 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to serotonin, leading to high urine serotonin levels. Urine serotonin measurements are not commonly employed in carcinoid tumor follow-up. The exceptions are patients with tumors that almost exclusively secrete 5-HTP, as summarized above. In these individuals, urine serotonin is the tumor marker of choice to monitor disease progression. In all other patients, disease progression is monitored best using urinary 5-HIAA and serum chromogranin A measurements. These markers are usually proportional to the patient's tumor burden over a wide range of tumor extent and tumor secretory activity.

Reference Values:
< or =210 mcg/24 h
Reference values apply to all ages.

Clinical References:

SERWB
84373

Serotonin, Blood

Clinical Information:

Useful For: In conjunction with, or as an alternative to, first-order tests in the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing (5-hydroxyindoleacetic acid or serum chromogranin A measurements are first-line tests) Second-order test in the follow-up of patients with known or treated carcinoid tumors using whole blood specimens

Interpretation: Metastasizing midgut carcinoid tumors usually produce blood or serum serotonin (5-hydroxytryptamine) concentrations greater than 1000 ng/mL. However, elevations above 400 ng/mL are suggestive of carcinoid tumors as the cause of carcinoid syndrome-like symptoms. Lesser increases may be nonspecific or drug-related (see Cautions). Only a minority of patients with carcinoid tumors will have elevated serotonin levels. It is usually impossible to diagnose small carcinoid tumors (>95% of cases) without any symptoms suggestive of carcinoid syndrome by measurement of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), or chromogranin A. In patients with more advanced tumors, circulating serotonin is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors. Foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and, therefore, may produce little if any serotonin. Urinary 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. Serum chromogranin A measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though serotonin and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with foregut and midgut tumors. Therefore, to achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, serotonin in serum/blood, 5-HIAA in urine, and serum chromogranin A should all be measured. In most cases, if none of these 3 analytes is elevated, carcinoids can be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests, such as urinary serotonin measurement, will be required. An example would be a non-chromogranin-secreting foregut tumor that only produces 5-HTP, rather than serotonin. In this case, circulating chromogranin, serotonin levels, and urinary 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to serotonin, leading to high urinary serotonin levels. Disease progression can be monitored in patients with serotonin-producing carcinoid tumors by measurement of serotonin in blood. However, at levels above approximately 5000 ng/mL, the serotonin storage capacity of platelets becomes limiting, and there is no longer a linear relationship between tumor burden and blood serotonin levels. Urinary 5-HIAA and serum chromogranin A continue to increase in proportion to the tumor burden to much higher serotonin production levels and are, therefore, better suited for follow-up in patients with extensive disease.

Reference Values:
< or =330 ng/mL

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Kema IP, Schellings AM, Meibotg G, Hoppenbrouwers CJ, Muskiet FA. Influence of a serotonin- and dopamine-rich diet on platelet serotonin content and urinary excretion of biogenic amines and their metabolites. Clin Chem. 1992;38(9):1730-1736 2. Kema IP, de Vries EG, Muskiet FA. Clinical chemistry of serotonin and metabolites. J Chromatogr B Biomed Sci Appl. 2000;747:33-48 3. Meijer W, Kema I, Volmer M, et al. Discriminating capacity of indole markers in the diagnosis of carcinoid tumors. Clin Chem. 2000;46(10):1588-1596 4. Eisenhofer G, Grebe S, Cheung NKV. Monamine-producing tumors. In: Rifai N, Horvath AR, Wittwer C, eds Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2017: chap 63 5. Brand T, Anderson GM. The measurement of platelet-poor plasma serotonin: a systematic review of prior reports and recommendations for improved analysis. Clin Chem. 2011;57(10):1376-1386 6. Liu EH, Solorzano CC, Katznelson L, Vinik AI, Wong R, Randolph G. AACE/ACE disease state clinical review: diagnosis and management of midgut carcinoids. Endocr Prac. 2015;21(5):534-545 7. Ganim RB, Norton JA. Recent advances in carcinoid pathogenesis, diagnosis and management. Surg Oncol. 2000;9(4):173-179 8. Carling RS, Degg TS, Allen KR, Bax ND, Barth JH. Evaluation of whole blood serotonin and plasma and urine

5-hydroxyindole acetic acid in diagnosis of carcinoid disease. Ann Clin Biochem. 2002;39(Pt 6):577-582 9. Stiefel R, Lehmann K, Winder T, Siebenhuner AR. What have we learnt from the past - would treatment decisions for GEP-NET patients differ between 2012 to 2016 by the new recommendations in 2022?. BMC Cancer. 2023;23(1):148. Published 2023 Feb 13. doi:10.1186/s12885-023-10567-1

SER
84395

Serotonin, Serum

Clinical Information:

Useful For: In conjunction with, or as an alternative to, first-order tests in the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing (5-hydroxyindoleacetic acid or serum chromogranin A measurements are first-line tests) Second-order test in the follow-up of patients with known or treated carcinoid tumors

Interpretation: Metastasizing midgut carcinoid tumors usually produce blood or serum serotonin (5-hydroxytryptamine) concentrations greater than 1000 ng/mL. However, elevations above 400 ng/mL are suggestive of carcinoid tumors as the cause of carcinoid syndrome-like symptoms. Lesser increases may be nonspecific or drug-related (see Cautions). Only a minority of patients with carcinoid tumors will have elevated serotonin levels. It is usually impossible to diagnose small carcinoid tumors (>95% of cases) without any symptoms suggestive of carcinoid syndrome by measurement of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), or chromogranin A. In patients with more advanced tumors, circulating serotonin is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors. Foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and, therefore, may produce little if any serotonin. Urinary 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. Serum chromogranin A measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though serotonin and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with foregut and midgut tumors. Therefore, to achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, serotonin in serum/blood, 5-HIAA in urine, and serum chromogranin A should all be measured. In most cases, if none of these 3 analytes is elevated, carcinoids can be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests, such as urinary serotonin measurement will be required. An example would be a non-chromogranin-secreting foregut tumor that only produces 5-HTP, rather than serotonin. In this case, circulating chromogranin, serotonin levels, and urinary 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to serotonin, leading to high urinary serotonin levels. Disease progression can be monitored in patients with serotonin-producing carcinoid tumors by measurement of serotonin in blood. However, at levels above approximately 5000 ng/mL, the serotonin storage capacity of platelets becomes limiting, and there is no longer a linear relationship between tumor burden and blood serotonin levels. Urinary 5-HIAA and serum chromogranin A continue to increase in proportion to the tumor burden to much higher serotonin production levels and are, therefore, better suited for follow-up in patients with extensive disease.

Reference Values:
< or =230 ng/mL

Clinical References:

SERPZ
63128

SERPINA1 Gene, Full Gene Analysis, Varies

Clinical Information:

Useful For: Identification of causative mutations when a deficient serum level of alpha-1-antitrypsin is not explained by routine testing, such as proteotyping, genotyping, or isoelectric focusing phenotyping. Determining the specific allelic variant (full gene analysis) for prognosis and genetic counseling

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424 2. Stoller JK, Aboussouan LS: Alpha-1-antitrypsin deficiency. Lancet 2005;365:2225-2236 3. McElvaney NG, Stoller JK, Buist AS, et al: Baseline characteristics of enrollees in the National Heart, Lung and Blood Institute Registry of alpha 1-antitrypsin deficiency. Alpha 1-Antitrypsin Deficiency Registry Study Group. Chest 1997;111:394-403 4. Snyder MR, Katzmann JA, Butz ML, et al: Diagnosis of alpha-1-antitrypsin deficiency: an algorithm of quantification, genotyping, and phenotyping. Clin Chem 2006;52:2236-2242 5. Graham RP, Dina MA, Howe SC, et al: SERPINA1 full-gene sequencing identifies rare mutations not detected in targeted mutation analysis. J Mol Diag 2015;17:689-694

FSERT
91345

Sertraline (Zoloft) and Desmethylsertraline

Reference Values:
Sertraline:
Reference Range: 30 - 200 ng/mL
Report Limit 10 ng/mL

Desmethylsertraline: ng/mL
No reference range provided

The stated reference range is the range of observed steady-state concentrations in individuals receiving therapeutic dosage regimens of sertraline. This is not a defined therapeutic range.
Report Limit 10 ng/mL

FSESG
57682

Sesame Seed IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

SESA
82728

Sesame Seed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to sesame seed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SESPF
621157

Sesame Seed, IgE, with Reflex to Sesame Seed Component, IgE, Serum

Clinical Information: De novo IgE sensitization to Sesamum indicum (sesame) seed and related products, such as sesame seed oil, can occur in both children and adults. In the United States, 0.21% of children and 0.24% of adults have reported convincing sesame allergy, but this varies around world. While sesame allergy is the ninth most common childhood food allergy in the United States, it is the third most common food allergy in Israel, with a prevalence of 0.93% in children. The allergy commonly lasts for life, with only 20% to 30% of children gaining tolerance to sesame seed. The median age onset for sesame allergy is 1 year. The use of whole sesame seed and its derivatives in food and health products is growing worldwide. Sesame seed contains many components capable of eliciting an allergic response. A prospective multicenter European investigation suggests that sesame seed can cause allergic reactions that are more severe compared to other common seeds and nuts. In one study (n=16), 56% of patients developed urticaria while 38% presented with anaphylaxis after exposure to sesame seed. However, rhinitis and asthma have also been reported. Ses i 1 is the major allergenic component of sesame. 2S albumins, like Ses i 1, are extremely stable proteins, able to withstand temperatures up to 100 degrees C, acidic conditions, and pepsin digestion. Consequently, immunological exposure to these proteins is thought to occur directly in the gut, resulting in sensitization or an allergic response. Seven sesame seed components are registered by the joint World Health Organization/International Union of Immunological Societies Allergen Nomenclature Subcommittee including Ses i 1 and Ses i 2 (2S albumin proteins), Ses i 3 (7S vicilin-like globulin), Ses i 4 and Ses i 5 (oleosins), and Ses i 6 and Ses i 7 (11S globulins). Ses i 1 is the major allergenic component of sesame. Of all sesame protein components, serum IgE antibodies against Ses i 1 are the most useful for diagnosis of sesame allergy. Measurement of IgE against Ses i 1 for the diagnosis of sesame allergy was shown to have a sensitivity and specificity of 86.1% and 85.7%, respectively, using a cutoff of 3.96 kUa/L. Comparatively, measure of IgE against sesame extract (cutoff of 7.97 kUa/L) had a similar sensitivity of 83.3%, but a much lower specificity of 48.2% due to known cross-reactivity with peanut and tree nuts/seeds. In the same study, it was shown that 92% of symptomatic patients were sensitized to Ses i 1, while only 32% of nonsymptomatic patients were sensitized. Despite minor homology between 2S albumins, crossreactivity with other 2S albumin proteins still exists, such as those found in sesame seed, hazelnuts, peanuts, English walnuts, Brazil nuts, cashews, pistachios, poppyseed, or rapeseed. For example, Ses i 1 and Ses i 2 are related the peanut allergens Ara h 2, 6, and 7. Sesame seed allergy can coexist with peanut and tree nut allergies, and co-sensitization with these allergens, alongside kiwi and rye, have been reported. There is varying prevalence of sesame seed and tree nut/peanut related allergy coexistence. Sesame seed allergy coexists with 15% to 54% of self-reported peanut allergies, 8% to 14.8% of tree nut allergies, and 50% to 54% of patients who have both tree nut and peanut allergies.

Useful For: Evaluating patients with suspected sesame seed allergy

Interpretation: If the total serum IgE antibody against sesame seed is detectable (> or =0.10 IgE kUa/L), it is possible the patient has been sensitized to the components of sesame seed or other potential substances with cross activity. An additional test utilizing Ses i 1, a specific allergenic sesame seed component IgE antibody, will be performed to further confirm sensitization to sesame seed. If the total serum IgE antibody against sesame seed is negative (<0.10 IgE kUa/L), the patient lacks detectable sensitization to sesame seed components. A report will be provided without additional testing performed. An oral food challenge may be helpful in the diagnosis of sesame seed allergy.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive

3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Dalal I, Goldberg M, Katz Y. Sesame seed food allergy. Curr Allergy Asthma Rep. 2012;12(4):339-345 2. Warren CM, Chadha AS, Sicherer SH, et al. Prevalence and severity of sesame allergy in the United States. JAMA network open. 2019;2(8):e199144-e199144 3. Sokol K, Rasooly M, Dempsey C, et al. Prevalence and diagnosis of sesame allergy in children with IgE-mediated food allergy. Pediatr Allergy Immunol. 2020;31(2):214-218 4. Adatia A, Clarke AE, Yanishevsky Y, Ben-Shoshan M. Sesame allergy: current perspectives. J Asthma Allergy. 2017;10:141-151. 5. Cohen A, Goldberg M, Levy B, Leshno M, Katz Y. Sesame food allergy and sensitization in children: the natural history and long-term follow-up. Pediatr Allergy Immunol. 2007;18(3):217-223 6. Gupta RS, Lau CH, Sita EE, Smith B, Greenhawt M. Factors associated with reported food allergy tolerance among US children. Ann Allergy Asthma Immunol. 2013;111(3):194-198 7. Ziegler JB, Aalberse RC. Sesame: an increasingly popular word and common food allergen. J Allergy Clin Immunol: Pract. 2020;8(5):1689-1691 8. U.S. Food and Drug Administration. Allergic to Sesame? Food Labels Now Must List Sesame as an Allergen. Updated January 10, 2023. Accessed March 3, 2024.Available at //www.fda.gov/consumers/consumer-updates/allergic-sesame-food-labels-now-must-list-sesame-allergen 9. WHO/IUIS Allergen Nomenclature Sub-Committee. Sesamum indicum - All Allergen. Accessed March 3, 2024.Available at www.allergen.org/search.php?allergensource=Sesamum+indicum 10. Pastorello EA, Varin E, Farioli L, et al. The major allergen of sesame seeds (Sesamum indicum) is a 2S albumin. J Chromatogr B Biomed Sci Appl. 2001;756(1-2):85-93 11. Moreno FJ, Clemente A. 2S albumin storage proteins: what makes them food allergens?. Open Biochem J. 2008;2:16-28 12. Maruyama N, Nakagawa T, Ito K, et al. Measurement of specific IgE antibodies to Ses i 1 improves the diagnosis of sesame allergy. Clin Exp Allergy. 2016;46(1):163-171 13. Dreskin SC, Koppelman SJ, Andorf S, et al. The importance of the 2S albumins for allergenicity and cross-reactivity of peanuts, tree nuts, and sesame seeds. J Allergy Clin Immunol. 2021;147(4):1154-1163 14. Brough HA, Caubet JC, Mazon A, et al. Defining challenge-proven coexistent nut and sesame seed allergy: a prospective multicenter European study. J Allergy Clin Immunol. 2020;145(4):1231-1239 15. Tuano KTS, Dillard KH, Guffey D, Guffey D, Davis CM. Development of sesame tolerance and cosensitization of sesame allergy with peanut and tree nut allergy in children. Ann Allergy. 2016;117(6):708-710 16. Yanagida N, Ejiri Y, Takeishi D, et al. Ses i 1-specific IgE and sesame oral food challenge results. J Allergy Clin Immunol Pract. 2019;7(6):2084-2086 17. Saf S, Sifers TM, Baker MG et al. Diagnosis of Sesame Allergy: Analysis of Current Practice and Exploration of Sesame Component Ses i 1. J Allergy Clin Immunol Pract. 2020;8(5):1681-1688 18. Sato S, Yanagida N, Ebisawa M. How to diagnose food allergy. Curr Opin Allergy Clin Immunol. 2018;18(3):214-221 19. Foong RX, Dantzer JA, Wood RA, Santos AF. Improving Diagnostic Accuracy in Food Allergy. J Allergy Clin Immunol Pract. 2021;9(1):71-80 20. Patel A, Bahna SL. Hypersensitivities to sesame and other common edible seeds. Allergy. 2016;71(10):1405-1413 21. Segal L, Ben-Shoshan M, Alizadehfar R, et al. Initial and accidental reactions are managed inadequately in children with sesame allergy. J Allergy Clin Immunol Pract. 2017;5(2):482-485

SCOF3
622027

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2) and Influenza Virus Type A and Type B RNA, Molecular Detection, PCR, Varies

Clinical Information: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense, single-stranded RNA virus that causes COVID-19. Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract illness. Symptoms can range from mild (ie, the common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19 disease, the symptoms maybe nonspecific and resemble other common respiratory infections, such as influenza. If testing for other respiratory infections is negative, specific testing for

SARS-CoV-2 (COVID-19) may be warranted. Severe acute respiratory syndrome coronavirus 2 is likely to be at the highest concentrations in the nasopharynx during the first 3 to 5 days of symptomatic illness. As the disease progresses, the viral load tends to decrease in the upper respiratory tract, at which point lower respiratory tract specimens (eg, sputum, tracheal aspirate, bronchoalveolar fluid) may be more likely to have detectable SARS-CoV-2. Influenza, otherwise known as the "flu," is an acute, contagious respiratory illness caused by influenza A, B, and C viruses. Of these, only influenza A and B are thought to cause significant disease, with infections due to influenza B usually being milder than infections with influenza A. Influenza A viruses are further categorized into subtypes based on the 2 major surface protein antigens: hemagglutinin (H) and neuraminidase (N). Common symptoms of influenza infection include fever, chills, sore throat, muscle pains, severe headache, weakness, fatigue, and a nonproductive cough. Certain patients, including infants, older individuals, patients who are immunocompromised, and those with impaired lung function, are at risk for serious complications. In the United States, influenza results in 10,000 to 30,000 deaths and more than 200,000 hospitalizations each year. In the northern hemisphere, annual epidemics of influenza typically occur during the fall or winter months. However, the peak of influenza activity can occur as late as April or May, and the timing and duration of flu seasons vary. Influenza infection may be treated with supportive therapy as well as antiviral drugs, such as the neuraminidase inhibitors, oseltamivir (Tamiflu) and zanamivir (Relenza). These drugs are most effective when given within the first 48 hours of infection, so prompt diagnosis and treatment are essential for proper management. Influenza viruses can be detected in respiratory secretions, including upper and lower respiratory tract specimens, by molecular test methods. Nasopharyngeal swabs or aspirates are the preferred specimen types for detection of SARS-CoV-2, influenza A virus, and influenza B virus. Nasal swabs have also been shown to provide comparable yield to nasopharyngeal specimens for molecular detection of SARS-CoV-2 RNA and influenza A and B viral RNA.

Useful For: Simultaneous detection and differentiation of SARS-CoV-2 (cause of COVID-19), influenza A virus, and influenza B virus in upper or lower respiratory tract specimens from individuals with flu-like illnesses

Interpretation:

Reference Values:
Undetected

Clinical References: 1. Loeffelholz MJ, Tang YW. Laboratory diagnosis of emerging human coronavirus infections-the state of the art. Emerg Microbes Infect. 2020;9(1):747-756. doi:10.1080/22221751.2020.1745095 2. Mohammadi A, Esmaeilzadeh E, Li Y, Bosch RJ, Li JZ. SARS-CoV-2 detection in different respiratory sites: a systematic review and meta-analysis. EBioMedicine. 2020;59:102903. doi:10.1016/j.ebiom.2020.102903 3. Centers for Disease Control and Prevention. Testing for COVID-19. CDC; Updated June 25, 2024. Accessed August 22, 2024. Available at www.cdc.gov/covid/testing/index.html 4. US Food and Drug Administration. FAQs on diagnostic testing for SARS-CoV-2. FDA; Updated November 8, 2023. Accessed August 22, 2024. Available at www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/faqs-testing-sars-cov-2 5. Centers for Disease Control and Prevention. Information for clinicians on influenza virus testing. CDC; Updated December 11, 2023. Accessed August 22, 2024. Available at www.cdc.gov/flu/professionals/diagnosis/index.htm

SFRB 617492 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2), Influenza A and B, and Respiratory Syncytial Virus, Molecular Detection, Bronchoalveolar Lavage

Clinical Information: Influenza, or the flu, is a contagious viral infection of the respiratory tract.

Transmission of influenza is primarily airborne (ie, coughing or sneezing); the peak of transmission usually occurs in the winter months. Symptoms commonly include fever, chills, headache, muscle aches, malaise, cough, and sinus congestion. Gastrointestinal symptoms (ie, nausea, vomiting, or diarrhea) may also occur, primarily in children, but are less common in adults. Symptoms generally appear within 2 days of exposure to an infected person. Pneumonia may develop as a complication of influenza infection, causing increased morbidity and mortality in pediatric, elderly, and immunocompromised populations. Influenza viruses are classified into types A, B, and C; types A and B cause most human infections. Influenza A is the most common type of influenza virus in humans and is generally responsible for seasonal flu epidemics and occasionally pandemics. Influenza A viruses are further divided into subtypes on the basis of 2 surface proteins: hemagglutinin (H) and neuraminidase (N). Seasonal flu is normally caused by subtypes H1, H2, H3, and N1 and N2. In addition to seasonal flu, a novel H1N1 strain was identified in humans in the United States in early 2009. Infections with influenza B virus are generally restricted to humans and are less frequent causes of epidemics. Respiratory syncytial virus (RSV), a member of the Paramyxoviridae family consisting of subgroups A and B, is also the cause of a contagious disease that afflicts primarily infants and the elderly who are immunocompromised (eg, patients with chronic lung or heart disease or undergoing treatment for conditions that reduce the strength of their immune system). The virus causes both upper respiratory infections, such as tracheobronchitis and lower respiratory infections manifesting as bronchiolitis and pneumonia. By the age of 2, most children have already been infected by RSV, but because only weak immunity develops, both children and adults can become reinfected. Symptoms usually appear 4 to 6 days after infection. The disease is typically self-limiting, lasting about 1 to 2 weeks in infants. In adults, the infection lasts about 5 days and presents with symptoms consistent with a cold, such as rhinorrhea, fatigue, headache, and fever. The RSV season overlaps with influenza season somewhat as infections begin to rise during the fall and continues through early spring. RSV infections may rarely occur at other times of the year. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense, single-stranded RNA virus that causes COVID-19. Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract infection. Symptoms can range from mild (ie, the common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19, symptoms may be nonspecific and resemble other common respiratory tract infections, such as influenza. If testing for other respiratory tract pathogens is negative, specific testing for SARS-CoV-2 may be warranted.

Useful For: Aiding in the diagnosis of influenza A and B, respiratory syncytial virus, and SARS-CoV-2 infections in conjunction with clinical and epidemiological risk factors This test should be requested only on patients meeting current clinical and/or epidemiologic criteria defined by institutional, federal, state, or local public health directives.

Interpretation: A "Detected" result indicates that target RNA is present. Test result should always be considered in the context of patient's clinical history, physical examination, and epidemiologic exposures when making the final diagnosis. An "Undetected" result indicates that target RNA is not present in the patient's specimen. However, this result may be influenced by the stage of the infection and the quality of the specimen collected for testing. Result should be correlated with patient's history and clinical presentation. An "Inconclusive" result indicates that the presence or absence of target RNA in the specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to reverse transcription-polymerase chain reaction (RT-PCR) inhibition. Submission of a new specimen for testing is recommended.

Reference Values:
Negative

Clinical References: 1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733. doi:10.1056/NEJMoa2001017 2. Patel A, Jernigan DB, 2019-nCoV CDC Response Team. Initial public health response and Interim Clinical

Guidance for the 2019 Novel Coronavirus Outbreak-United States, December 31, 2019-February 4, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(5):140-146. doi:10.15585/mmwr.mm6905e1 3. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929-936. doi:10.1056/NEJMoa2001191 4. Centers for Disease Control and Prevention. Influenza (Flu). Accessed February 18, 2025. Available at www.cdc.gov/flu/index.htm 5. Lee N, Lui GC, Wong KT, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. Clin Infect Dis. 2013;57(8):1069-1077 6. Meerhoff TJ, Houben ML, Coenjaerts FE, et al. Detection of multiple respiratory pathogens during primary respiratory infection: nasal swab versus nasopharyngeal aspirate using real-time polymerase chain reaction. Eur J Clin Microbiol Infect Dis. 2010;29(4):365-371 7. Heikkinen T, Marttila J, Salmi AA, Ruuskanen O. Nasal swab versus nasopharyngeal aspirate for isolation of respiratory viruses. J Clin Microbiol. 2002;40(11):4337-4339

SCOF4
622031

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2), Influenza Virus Type A and Type B RNA, and Respiratory Syncytial Virus (RSV) Molecular Detection, PCR, Varies

Clinical Information: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense, single-stranded RNA virus that causes COVID-19. Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract illness. Symptoms can range from mild (ie, the common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19 disease, the symptoms may be nonspecific and resemble other common respiratory infections, such as influenza. If testing for other respiratory infections is negative, specific testing for SARS-CoV-2 (COVID-19) may be warranted. Severe acute respiratory syndrome coronavirus 2 is likely to be at the highest concentrations in the nasopharynx during the first 3 to 5 days of symptomatic illness. As the disease progresses, the viral load tends to decrease in the upper respiratory tract, at which point lower respiratory tract specimens (eg, sputum, tracheal aspirate, bronchoalveolar fluid) may be more likely to have detectable SARS-CoV-2. Influenza, otherwise known as the "flu," is an acute, contagious respiratory illness caused by influenza A, B, and C viruses. Of these, only influenza A and B are thought to cause significant disease, with infections due to influenza B usually being milder than infections with influenza A. Influenza A viruses are further categorized into subtypes based on the 2 major surface protein antigens: hemagglutinin (H) and neuraminidase (N). Common symptoms of influenza infection include fever, chills, sore throat, muscle pains, severe headache, weakness, fatigue, and a nonproductive cough. Certain patients, including infants, older individuals, patients who are immunocompromised, and those with impaired lung function, are at risk for serious complications. In the United States, influenza results in 10,000 to 30,000 deaths and more than 200,000 hospitalizations each year. In the northern hemisphere, annual epidemics of influenza typically occur during the fall or winter months. However, the peak of influenza activity can occur as late as April or May, and the timing and duration of flu seasons vary. Influenza infection may be treated with supportive therapy as well as antiviral drugs, such as the neuraminidase inhibitors, oseltamivir (Tamiflu) and zanamivir (Relenza). These drugs are most effective when given within the first 48 hours of infection, so prompt diagnosis and treatment are essential for proper management. Respiratory syncytial virus (RSV) is a respiratory virus that also infects the human respiratory tract, causing an influenza-like illness. Most otherwise healthy people recover from RSV infection in 1 to 2 weeks, but infection can be severe in infants, young children, and older adults. RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children younger than 1 year in the United States. It is increasingly recognized as a frequent cause of respiratory illness in older adults. The Influenza viruses and RSV can be detected in respiratory secretions, including upper and lower respiratory tract specimens, by molecular test methods. Nasopharyngeal swabs or aspirates are the preferred specimen types for detection of influenza A virus, influenza B virus, SARS-CoV-2, and RSV. Nasal swabs have also been shown to provide comparable yield to nasopharyngeal specimens for molecular detection of SARS-CoV-2 RNA and influenza A and B

viral RNA but not RSV RNA.

Useful For: Simultaneous detection and differentiation of SARS-CoV-2 (cause of COVID-19), influenza A virus, influenza B virus, and respiratory syncytial virus in upper or lower respiratory tract specimens from individuals with flu-like illnesses

Interpretation:

Reference Values:
Undetected

Clinical References: 1. Loeffelholz MJ, Tang YW. Laboratory diagnosis of emerging human coronavirus infections-the state of the art. Emerg Microbes Infect. 2020;9(1):747-756. doi:10.1080/22221751.2020.1745095 2. Mohammadi A, Esmaeilzadeh E, Li Y, Bosch RJ, Li JZ. SARS-CoV-2 detection in different respiratory sites: a systematic review and meta-analysis. EBioMedicine. 2020;59:102903. doi:10.1016/j.ebiom.2020.102903 3. Centers for Disease Control and Prevention. Testing for COVID-19. CDC; Updated June 25, 2024. Accessed August 22, 2024. Available at www.cdc.gov/covid/testing/index.html 4. US Food and Drug Administration. FAQs on diagnostic testing for SARS-CoV-2. FDA; Updated November 8, 2023. Accessed August 22, 2024. Available at www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/faqs-testing-sars-cov-2 5. Centers for Disease Control and Prevention. Information for clinicians on influenza virus testing. CDC; Updated December 11, 2023. Accessed August 22, 2024. Available at www.cdc.gov/flu/professionals/diagnosis/index.htm 6. Centers for Disease Control and Prevention. Respiratory syncytial virus infection (RSV). Updated July 21, 2023. Accessed August 4, 2023. Available at www.cdc.gov/rsv/index.html

HPCOV 614020 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2), Molecular Detection, Varies

Clinical Information: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)is a positive-sense, single-stranded RNA virus that causes COVID-19. Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract illness. Symptoms can range from mild (ie, the common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19 disease, the symptoms maybe nonspecific and resemble other common respiratory infections, such as influenza. If testing for other respiratory infections is negative, specific testing for SARS-CoV-2 (COVID-19) may be warranted. Severe acute respiratory syndrome coronavirus 2 is likely to be at the highest concentrations in the nasopharynx during the first 3 to 5 days of symptomatic illness. As the disease progresses, the viral load tends to decrease in the upper respiratory tract, at which point lower respiratory tract specimens (eg, sputum, tracheal aspirate, bronchoalveolar fluid) may be more likely to have detectable SARS-CoV-2.

Useful For: Diagnosis of COVID-19 illness due to SARS-CoV-2

Interpretation: A "Detected" (positive) result indicates that SARS-CoV-2 RNA is present and suggests the diagnosis of COVID-19. The test result should always be considered in the context of patient's clinical history, physical examination, and epidemiologic exposures when making the final diagnosis. An "Undetected" (negative) result indicates that SARS-CoV-2 is not present in the patient's specimen. However, this result may be influenced by the stage of the infection, as well as the quality and type of the specimen collected for testing. Result should be correlated with patient's history and clinical presentation. An "Inconclusive" result indicates that the presence or absence of SARS-CoV-2

RNA in the specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to inhibition. Submission of a new specimen for testing is recommended.

Reference Values:
Undetected

Clinical References: 1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733. doi:10.1056/NEJMoa2001017 2. Loeffelholz MJ, Tang YW. Laboratory diagnosis of emerging human coronavirus infections-the state of the art. Emerg Microbes Infect. 2020;9(1):747-756. doi:10.1080/22221751.2020.1745095 3. Mohammadi A, Esmaeilzadeh E, Li Y, Bosch RJ, Li JZ. SARS-CoV-2 detection in different respiratory sites: a systematic review and meta-analysis. EBioMedicine. 2020;59:102903. doi:10.1016/j.ebiom.2020.102903 4. Centers for Disease Control and Prevention. Testing for COVID-19. CDC; Updated June 25, 2024. Accessed August 22, 2024. Available at www.cdc.gov/covid/testing/index.html 5. US Food and Drug Administration. FAQs on diagnostic testing for SARS-CoV-2. Updated November 8, 2023. Accessed August 22, 2024. Available at www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/faqs-testing-sars-cov-2

RSARS
609414

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2), Molecular Detection, Varies

Clinical Information: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense, single-stranded RNA virus that causes COVID-19. Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract infection. Symptoms can range from mild (ie, the common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19, symptoms maybe nonspecific and resemble other common respiratory tract infections, such as influenza. If testing for other respiratory tract pathogens is negative, specific testing for SARS-CoV-2 may be warranted.

Useful For: Rapid diagnostic test for detection of COVID-19 illness due to SARS-CoV-2 This test should be requested only on patients meeting current clinical and/or epidemiologic criteria defined by federal, state, or local public health directives: www.cdc.gov/coronavirus/2019-ncov/index.html

Interpretation: A "Detected" result indicates that SARS-CoV-2 RNA is present and suggests the diagnosis of COVID-19. Test result should always be considered in the context of patient's clinical history, physical examination, and epidemiologic exposures when making the final diagnosis. An "Undetected" result indicates that SARS-CoV-2 is not present in the patient's specimen. However, this result may be influenced by the stage of the infection and the quality of the specimen collected for testing. Result should be correlated with patient's history and clinical presentation. An "Indeterminate" result suggests that the patient may be infected with a variant SARS-CoV-2 or SARS-related coronavirus. Additional testing with an alternative molecular method is recommended on a newly collection specimen. An "Inconclusive" result indicates that the presence or absence of SARS-CoV-2 RNA in the specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to real-time, reverse transcription polymerase chain reaction inhibition. Submission of a new specimen for testing is recommended.

Reference Values:
Negative

Clinical References: 1. Zhu N, Zhang D, Wang W, et al: A novel coronavirus from patients with

pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733. doi:10.1056/NEJMoa2001017 2. Patel A, Jernigan DB: Initial public health response and Interim Clinical Guidance for the 2019 Novel Coronavirus Outbreak United States, December 31, 2019 - February 4, 2020. Morb Mortal Wkly Rep. 2020;69(5):140-146. doi:10.15585/mmwr.mm6905e1 3. Holshue M, DeBolt C, Lindquist S, et al: First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929-936. doi:10.1056/NEJMoa2001191

COVID
608874

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA Detection, PCR, Varies

Clinical Information: SARS-CoV-2 is a positive-sense, single-stranded RNA virus that causes COVID-19. Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract infection. Symptoms can range from mild (ie, the common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19, symptoms maybe nonspecific and resemble other common respiratory tract infections, such as influenza. If testing for other respiratory tract pathogens is negative, specific testing for SARS-CoV-2 may be warranted. SARS-CoV-2 is likely to be at the highest concentrations in the nasopharynx during the first 3 to 5 days of symptomatic illness. As the disease progresses, the viral load tends to decrease in the upper respiratory tract, at which point lower respiratory tract specimens (eg, sputum, tracheal aspirate, bronchoalveolar fluid) would be more likely to have detectable SARS-CoV-2.

Useful For: Detection of COVID-19 illness due to SARS-CoV-2 Recommended only for patients who meet current clinical and/or epidemiologic criteria defined by federal, state, or local public health directives: www.cdc.gov/covid/hcp/clinical-care/overview-testing-sars-cov-2.html

Interpretation: A "Detected" result indicates that SARS-CoV-2 RNA is present and suggests the diagnosis of COVID-19. Test result should always be considered in the context of patient's clinical history, physical examination, and epidemiologic exposures when making the final diagnosis. An "Undetected" result indicates that SARS-CoV-2 is not present in the patient's specimen. However, this result may be influenced by the stage of the infection, quality, and type of the specimen collected for testing. Result should be correlated with patient's history and clinical presentation. An "Indeterminate" result suggests that the patient may be infected with a variant SARS-CoV-2 or -SARS-related coronavirus. Additional testing with an alternative molecular method may be considered if the patient does not have signs or symptoms of COVID-19. An "Inconclusive" result indicates that the presence or absence of SARS-CoV-2 RNA in the specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to real-time, reverse transcription polymerase chain inhibition. Submission of a new specimen for testing is recommended.

Reference Values:
Undetected

Clinical References: 1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733. doi:10.1056/NEJMoa2001017 2. Loeffelholz MJ, Tang YW. Laboratory diagnosis of emerging human coronavirus infections-the state of the art. Emerg Microbes Infect. 2020;9(1):747-756. doi:10.1080/22221751.2020.1745095 3. Mohammadi A, Esmaeilzadeh E, Li Y, Bosch RJ, Li JZ. SARS-CoV-2 detection in different respiratory sites: a systematic review and meta-analysis. EBioMedicine. 2020;59:102903. doi:10.1016/j.ebiom.2020.102903 4. Centers for Disease Control and Prevention. Overview of testing for SARS-CoV-2. Accessed November 14, 2024 Available at www.cdc.gov/covid/hcp/clinical-care/overview-testing-sars-cov-2.html#cdc_generic_section_2-diagnostic-testing 5. United States Food and Drug Administration. COVID-19 Test Uses: FAQs on Testing for SARS-CoV-2. Updated

September 29, 2023. Accessed January 27, 2025. Available at www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/covid-19-test-uses-faqs-testing-sars-cov-2

CVOOA 610435 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA Detection, Varies

Clinical Information: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense, single-stranded RNA virus that causes coronavirus disease 2019 (COVID-19). Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract infection. Symptoms can range from mild (ie, common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. During the early stages of COVID-19, symptoms maybe nonspecific and resemble other common respiratory tract infections, such as influenza. If testing for other respiratory tract pathogens is negative, specific testing for SARS-CoV-2 may be warranted. SARS-CoV-2 is likely to be at the highest concentrations in the nasopharynx during the first 3 to 5 days of symptomatic illness. As the disease progresses, the viral load tends to decrease in the upper respiratory tract, at which point lower respiratory tract specimens (eg, sputum, tracheal aspirate, bronchoalveolar fluid) would be more likely to have detectable SARS-CoV-2.

Useful For: Diagnosis of coronavirus disease 2019 (COVID-19) illness due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Recommended only for patients who meet current clinical and/or epidemiologic criteria defined by federal, state, or local public health directives

Interpretation: A "Detected" result indicates that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA is present and suggests the diagnosis of coronavirus disease 2019 (COVID-19). Test result should always be considered in the context of patient's clinical history, physical examination, and epidemiologic exposures when making the final diagnosis. An "Undetected" result indicates that SARS-CoV-2 is not present in the patient's specimen. However, this result may be influenced by the stage of the infection, as well as the quality and type of the specimen collected for testing. Result should be correlated with patient's history and clinical presentation. An "Inconclusive" result indicates that the presence or absence of SARS-CoV-2 RNA in the specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to real-time reverse transcription polymerase chain reaction (RT-PCR) inhibition. Submission of a new specimen for testing is recommended.

Reference Values:
Undetected

Clinical References: 1. Zhu N, Zhang D, Wang W, et al: A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733 doi: 10.1056/NEJMoa2001017 2. Loeffelholz MJ, Tang YW: Laboratory diagnosis of emerging human coronavirus infections-the state of the art. Emerg Microbes Infect. 2020;9(1):747-756 doi: 10.1080/22221751.2020.1745095 3. Mohammadi A, Esmaeilzadeh E, Li Y, Bosch RJ, Li JZ: SARS-CoV-2 detection in different respiratory sites: a systematic review and meta-analysis. EBioMedicine. 2020 Sep;59:102903. doi: 10.1016/j.ebiom.2020.102903 4. Centers for Disease Control and Prevention. Overview of testing for SARS-CoV-2. Available at www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html 5. Food and Drug Administration. FAQs on diagnostic testing for SARS-CoV-2. Available at www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-diagnostic-testing-sars-cov-2

COVTA 622465 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Nucleocapsid, Total Antibody, Serum

Clinical Information: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, single-stranded RNA virus of the family Coronaviridae, genus Betacoronavirus. All coronaviruses share similarities in the organization and expression of their genome, which encodes 16 nonstructural proteins and the 4 structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N). Detection of antibodies against the SARS-CoV-2 nucleocapsid indicates recent or prior infection with the virus. This assay will not detect an immune response to SARS-CoV-2 vaccination as the N antigen is not in current vaccine preparations.

Useful For: Aiding in identifying individuals with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection

Interpretation: Negative: No antibodies to SARS-CoV-2 detected. Negative results may occur in serum collected too soon following infection, in patients who are immunosuppressed, or in patients with mild or asymptomatic infection. This test does not rule out active or recent COVID-19 infection and will not detect SARS-CoV-2 vaccine-induced antibodies. Follow-up testing with a molecular test is recommended in symptomatic patients. Positive: Severe acute respiratory syndrome coronavirus 2 antibodies to the nucleocapsid protein detected. Results suggest recent or prior infection with SARS-CoV-2. Serologic results should not be used to diagnose recent SARS-CoV-2 infection.

Reference Values:
Negative

Clinical References:

SCOVT
610689

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), RNA Detection, ddPCR, Tissue

Clinical Information: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is a positive-sense, single-stranded RNA virus that causes coronavirus disease 2019 (COVID-19). Like other coronaviruses that infect humans, SARS-CoV-2 can cause both upper and lower respiratory tract illness. Symptoms can range from mild (ie, the common cold) to severe (ie, pneumonia) in both healthy and immunocompromised patients. SARS-CoV-2 transmission occurs primarily via respiratory droplets. As the disease progresses, the viral load tends to decrease in the upper respiratory tract, at which point, lower respiratory tract specimens (eg, sputum, tracheal aspirate, bronchoalveolar fluid, transbronchial biopsy, wedge biopsy of lung, autopsy lung specimen) would be more likely to have detectable SARS-CoV-2. Infection of other tissue has been reported. The SARS-CoV-2 RNA detection in formalin-fixed and paraffin-embedded (FFPE) tissue by droplet digital polymerase chain reaction (ddPCR) assay will be used to detect the nucleocapsid N1 and N2 target sequences of SARS-CoV-2 virus in FFPE surgical and autopsy tissue. The identification of SARS-CoV-2 in surgical tissue may aid in the diagnosis of COVID-19 and may lead to a better understanding of unusual disease presentations. Detection of SARS-CoV-2 in deceased patients (autopsy tissue) may similarly confirm a suspected diagnosis among individuals with clinical or pathologic manifestations of COVID-19 (ie, pulmonary, cardiac) and may increase understanding of SARS-CoV-2 pathobiology.

Useful For: Detection of severe respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19) in formalin-fixed, paraffin-embedded tissue

Interpretation: This test will be reported as positive, negative, or indeterminate. An "indeterminate" result indicates that the presence or absence of severe respiratory syndrome coronavirus 2 (SARS-CoV-2 RNA) in the specimen could not be determined with certainty after repeated testing in the laboratory. This could be due to reverse transcriptase polymerase chain reaction (RT-PCR) inhibition or

very low viral load. Submission of a new specimen for testing is recommended. Test results should always be considered in the context of patient's clinical history, physical examination, and epidemiologic exposures when making the final diagnosis.

Reference Values:
Not applicable

Clinical References: 1. Zhu N, Zhang D, Wang W, et al: A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020 Feb;382(8):727-733. doi: 10.1056/NEJMoa2001017 2. Holshue ML, DeBolt C, Lindquist S, et al: First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020 Mar 5;382(10):929-936. doi: 10.1056/NEJMoa2001191 3. Loeffelholz MJ, Tang YW: Laboratory diagnosis of emerging human coronavirus infections-the state of the art. Emerg Microbes Infect. 2020;9(1):747-756. doi.org/10.1080/22221751.2020.1745095 4. Liu X, Feng J, Zhang Q, et al: Analytical comparisons of SARS-COV-2 detection by qRT-PCR and ddPCR with multiple primer/probe sets. Emerg Microbes Infect. 2020 Dec;9(1):1175-1179 5. Suo T, Liu X, Feng J, et al: ddPCR: a more accurate tool for SARS-CoV-2 detection in low viral load specimens. Emerg Microbes Infect. 2020 Dec;9(1):1259-1268

COVSQ 622462 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Spike Antibody, Semi-Quantitative, Serum

Clinical Information: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, single-stranded RNA virus of the family Coronaviridae, genus Betacoronavirus. All coronaviruses share similarities in the organization and expression of their genome, which encodes 16 nonstructural proteins and the 4 structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N). Results are for the semiquantitative detection of total antibodies (without differentiation between immunoglobulin classes) against the SARS-CoV-2 spike protein, and specifically against the receptor binding domain. Antibodies to SARS-CoV-2 are detectable in over 90% of patients by 2 weeks after symptom onset or vaccination and can remain detectable for months to years following resolution of infection and after repeat vaccination.

Useful For: Aiding in the identification of individuals with an adaptive immune response to SARS-CoV-2, indicating prior infection or vaccination

Interpretation: This assay provides qualitative and semi-quantitative results for the presence of antibodies to the receptor binding domain on the SARS-CoV-2 spike glycoprotein. Both vaccine and recent infection can stimulate antibodies against this domain. Negative: No antibodies to SARS-CoV-2 spike glycoprotein detected. Negative results may occur in serum collected too soon following infection or vaccination, in immunosuppressed patients, or in patients with mild or asymptomatic infection. This test does not rule out active or recent COVID-19 infection. Follow-up testing with a molecular test for SARS-CoV-2 is recommended in symptomatic patients. Positive: Antibodies to the SARS-CoV-2 spike glycoprotein detected. Results suggest recent or prior SARS-CoV-2 infection or vaccination. Serologic results should not be used to diagnose recent SARS-CoV-2 infection as antibodies remain detectable for months to years after infection/vaccination. For the manufacture of COVID-19 convalescent plasma using the Roche Diagnostics anti-SARS-CoV-2 spike electro-chemiluminescence immunoassays, per current US Food and Drug Administration Emergency Use Authorization guidelines, high-titer convalescent plasma is defined as plasma units with a semi-quantitative value of 132 U/mL and above (see appendix A: www.fda.gov/media/141477/download).

Clinical References: 1. Zhang W, Du RH, Li B, et al. Molecular and serologic investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg Microbes Infect. 2020;9(1):386-389. doi:10.1080/22221751.2020.1729071 2. Okba N, Muller MA, Li W, et al. Severe

acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease 2019 patients. Emerg Infect Dis. 2020;26(7). doi:10.3201/eid2607.200841 3. Guo L, Ren L, Yang S, et al. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). Clin Infect Dis. 2020;ciaa310. doi:10.1093/cid/ciaa310 4. Wolfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465-469. doi:10.1038/s41586-020-2196-x 5. Su S, Wong G, Shi W, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol. 2016;24(6):490-502. doi:10.1016/j.tim.2016.03.003 6. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733. doi:10.1056/NEJMoa2001017 7. Liu L, Liu W, Zheng Y, et al. A preliminary study on serological assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 238 admitted hospital patients. Microbes Infect. 2020;22(4-5):206-211. doi:10.1016/j.micinf.2020.05.008 8. Zhang W, Du RH, Li B, et al. Molecular and serologic investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg Microbes Infect. 2020;9(1):386-389. doi:10.1080/22221751.2020.1729071

SCIDP
620134

Severe Combined Immunodeficiency (SCID) Gene Panel, Varies

Clinical Information: Severe combined immunodeficiency (SCID) is characterized by the absence or dysfunction of T lymphocytes, which affects both cellular and humoral adaptive immunity. This absence or dysfunction of T cells results in a severe form of inherited primary immunodeficiency that may be life-threatening. SCID typically presents in infancy with persistent respiratory and gastrointestinal infections, failure to thrive, or graft-versus-host disease (due to engraftment of maternal T cells). The absence of lymphoid tissue, immunoglobulins, and B lymphocytes may also be noted. Critically, having low T-cell numbers is not on its own sufficient for a diagnosis of SCID because other non-SCID disorders, such as thymic defects, may also present with significant T-cell lymphopenia. SCID results from genetic causes of hematopoietic stem cell intrinsic defects in T-lymphocyte development. Primary thymic function defects should be differentiated from SCID because hematopoietic stem cell transplantation is unlikely to be curative for thymic function defects, as the defect is in thymic stromal cell development, not in hematopoietic stem cells. SCID is suspected when the patient has fewer than 300 autologous CD3 T cells per microliter and additional suggestive features, such as having less than 20% of CD4+ cells with naive cell surface markers, an abnormal SCID newborn screen, a family history of SCID, recurrent or opportunistic infections, or features of Omenn syndrome. An important diagnostic criterion for typical SCID is having less than 50 autologous CD3 T cells per microliter in blood, which requires immediate medical intervention. Other diagnostic criteria may include the identification of a disease-causing variant or variants in a gene whose product is known to be essential for T-cell development and having no alternate explanation for low T-cell count and low to undetectable TREC (T cell receptor excision circles) or <20% of CD4 T cells with naive cell surface marker CD45RA. Alternatively, the presence of maternal T cells in peripheral blood due to failure to reject transplacentally transferred cells is a pathognomonic finding. Atypical or "leaky" SCID is the term used for patients with partial defects in T-cell number and function. Leaky SCID tends to present in patients older than 12 months of age with recurrent, severe, and prolonged viral infections, bronchiectasis, failure to thrive, and autoimmune manifestations, including cytopenias. Patients may display partial or restricted antigen-specific antibody responses. Leaky SCID is often caused by hypomorphic variants in genes normally associated with typical SCID. Leaky SCID can be diagnosed based on the following: low T-cell number for age; oligoclonal T cells; abnormal TREC or <20% of CD4+ T cells that are naive; the identification of disease-causing variants identified in a gene whose product is known to be essential for T-cell development; reduced T-cell proliferation tests (defined as a proliferative response to phytohemagglutinin, anti-CD3, or anti-CD3/CD28); and the exclusion of other SCID or combined immunodeficiency conditions with a known genotype, thymic disorder, and other disorders associated with low T-cell numbers. Omenn syndrome, a form of leaky SCID that typically presents in infancy, is characterized by erythroderma, alopecia, hepatosplenomegaly, and lymphadenopathy. Laboratory findings may include elevated IgE, eosinophilia, and lymphocytosis.

While RAG1 and RAG2 hypomorphic variants are most often associated with leaky SCID or Omenn syndrome, patients may have variants affecting other genes and the proteins they produce, such as Artemis or interleukin-7 receptor (IL-7R) alpha. There are forms of leaky SCID with hypomorphic variants in these genes that do not have the associated Omenn syndrome phenotype. SCID can be classified as T-B- or T-B+ SCID, with further subdivision possible based on the presence or absence of natural killer (NK) cells. T-B- SCID is typically caused by a defect in V(D)J recombination, the process that creates the antigen receptor diversity critical to the adaptive immune system. However, T-B- SCID may also be caused by certain enzyme deficiencies, such as adenosine deaminase deficiency, which results in accumulation of metabolic by-products that are toxic to lymphocytes. Reticular dysgenesis-the most severe form of combined immunodeficiency-is caused by a deficiency of the enzyme adenylate kinase 2 and genetic variants in the AK2 gene. Reticular dysgenesis is characterized by a T-B-NK- phenotype, congenital agranulocytosis, lymphopenia, lymphoid and thymic hypoplasia, and bilateral sensorineural deafness. T-B+ SCID is characterized by impaired development of mature T-cells and the presence of nonfunctional B cells. It is most often caused by genetic variants that affect cytokine-mediated signaling. X-linked T-B+ SCID is due to variants in the IL2RG gene, which encodes the common gamma chain that is a part of the IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors. Autosomal recessive forms of T-B+ SCID due to variants in JAK3 or IL7R also disrupt cytokine signaling. Genetic variants in one of the four CD3 genes (CD3G, CD3D, CD3E, and CD247[CD3Z]) inhibit CD3 signaling and cause T-B+ SCID. The T-B+ cellular phenotype may also be caused by thymic defects that must be differentiated from T-B+ SCID to guide treatment decisions as stated above. Causes of these thymic defects include coronin-1A deficiency, which causes disruption of thymic egress of T cells and defective T-cell locomotion, and CD45 deficiency caused by variants in the PTPRC gene. Thymic defects with additional congenital anomalies may be observed in DiGeorge syndrome (represented on this panel by TBX1), CHARGE (coloboma, heart defects, atresia choanae [also known as choanal atresia], growth retardation, genital abnormalities, and ear abnormalities) syndrome (due to variants in CHD7 or SEMA3E), and patients with genetic variants in FOXN1.

Useful For: Establishing a diagnosis of a severe combined immunodeficiency (SCID) associated with known causal genes Identifying variants within genes known to be associated with SCID, allowing for predictive testing of at-risk family members and/or determination of targeted management (anticipatory guidance, management changes, specific therapies)

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507. doi:10.1007/s10875-022-01289-3 2. Dvorak CC, Haddad E, Heimall J, et al. The diagnosis of severe combined immunodeficiency (SCID): The Primary Immune Deficiency Treatment Consortium (PIDTC) 2022 definitions. J Allergy Clin Immunol. 2023;151(2):539-546. doi:10.1016/j.jaci.2022.10.022 3. Bousfiha A, Moundir A, Tangye SG, et al. The 2022 update of IUIS Phenotypical Classification for human inborn errors of immunity. J Clin Immunol. 2022;42(7):1508-1520. doi:10.1007/s10875-022-01352-z 4. Raje N, Soden S, Swanson D, Ciaccio CE, Kingsmore SF, Dinwiddie DL. Utility of next generation sequencing in clinical primary immunodeficiencies. Curr Allergy Asthma Rep. 2014;14(10):468 5. DeSandro A, Nagarajan UM, Boss JM. The bare lymphocyte syndrome: Molecular clues to the transcriptional regulation of major histocompatability complex class II genes. Am J Hum Genet. 1999;65(2):279-286. doi: 10.1086/302519 6. Walkovich K, Vander Lugt M. ZAP70-related combined immunodeficiency. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2009. Updated

September 23, 2021. Accessed May 120, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK20221/ 7. Hershfield M. Adenosine deaminase deficiency. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated March 16, 2017. Accessed January 10, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1483/ 8. Allenspach E, Rawlings DJ, Scharenberg AM. X-linked severe combined immunodeficiency. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated August 5, 2021. Accessed May 12, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1410/ 9. Kwan A, Abraham RS, Currier R, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. JAMA. 2014;312(7):729-738. doi: 10.1001/jama.2014.9132

SCCNP
619872

Severe Congenital and Cyclic Neutropenia Gene Panel, Varies

Clinical Information: Inherited congenital neutropenia refers to a subset of primary immunodeficiencies impacting neutrophil maturation and function. The severity of the clinical manifestations in these disorders typically reflects the degree of neutropenia. Most cases of neutropenia are due to acquired (non-genetic) causes. Severe congenital neutropenia (SCN) is characterized by chronically low neutrophil count and recurrent, often life-threatening infections beginning in the first few months of life. Some individuals with SCN may also have an increased risk for myelodysplastic syndrome or acute myelogenous leukemia.(1-3) Cyclic neutropenia (CN) is characterized by periods of severe neutropenia and infections that last 3 to 5 days and recur at regular intervals.(1-5) Individuals with SCN or CN may also exhibit recurrent fevers, sinusitis, gingivitis, cellulitis, oral ulcers, colonic ulcers, and other manifestations of chronic infections.(1-5) Bone marrow biopsy on affected individuals may show arrest in myelopoiesis at the promyelocyte/myelocyte stage.(1-3) The prevalence of inherited severe congenital neutropenia and cyclic neutropenia is estimated to range from 1:500,000 to 1:100,000 live births.(1-5) The genetic etiology of inherited congenital neutropenia is most commonly due to disease-causing variants in genes that play a role in neutrophil differentiation.(1) Inheritance can be autosomal recessive, autosomal dominant, or X-linked. The most common causes of isolated congenital neutropenia are disease-causing variants in the ELANE and HAX1 genes, which encode neutrophil elastase and HCLS1(hematopoietic cell-specific Lyn substrate)-associated protein X-1, respectively. Autosomal dominant ELANE-related neutropenia is the most common cause of congenital neutropenia in children and may present with oral/colonic ulcers, recurrent upper and lower respiratory infections, and various infections of the soft tissue.(2,4,6) In addition, most cases of cyclic neutropenia are due to disease-causing variants in ELANE. Autosomal recessive Kostmann disease, caused by variants in the HAX1 gene, is the second most common cause of congenital neutropenia in children and presents similarly to ELANE-related neutropenia.(2,4,6) X-linked WAS-related disorders lead to a spectrum of congenital neutropenia phenotypes including Wiskott-Aldrich syndrome and X-linked congenital neutropenia.(5,6) Isolated severe congenital neutropenia may more rarely be due to disease-causing variants in several additional genes including CSF3R, CXCR2, GFI1 and WIPF1.(1,6) Severe neutropenia may also be present as part of a multisystem disorder.(1) This panel assesses for many conditions in which neutropenia is seen in conjunction with extra-hematologic features, including but not limited to: -Shwachman-Diamond syndrome, an autosomal dominant condition due to disease-causing variants in the SBDS gene, is also characterized by exocrine pancreatic dysfunction, bone abnormalities, and hematologic abnormalities. -GATA2-deficieny (monocytopenia and mycobacterial infection [MonoMAC] syndrome), an autosomal dominant condition due to disease-causing variants in the GATA2 gene, demonstrates a wide spectrum of clinical presentations ranging from mild chronic neutropenia with monocytopenia to Emberger syndrome and predisposition to acute myeloid malignancy. -Barth syndrome, an X-linked condition due to disease-causing variants in the TAZ gene, is also characterized cardiomyopathy, skeletal myopathy, growth delay, and distinctive facial features. -Cohen syndrome, an autosomal recessive condition due to disease-causing variants in the VSP13B gene, is also characterized by hypotonia, developmental delays, microcephaly, failure to thrive in infancy, truncal obesity, ophthalmologic findings, joint hypermobility, a cheerful disposition, and characteristic facial features. -WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome, an autosomal dominant condition caused by variants in the CXCR4 gene, is also

characterized by hypogammaglobulinemia and susceptibility to human papillomavirus.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of severe congenital neutropenia and/or cyclic neutropenia Establishing a diagnosis of an inherited congenital neutropenia and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Skokowa J, Dale DC, Touw IP, Zeidler C, Welte K: Severe congenital neutropenias. Nat Rev Dis Primers. 2017 Jun 8;3:17032. doi:10.1038/nrdp.2017.32 2. Fadeel B, Garwicz D, Carlsson G, Sandstedt B, Nordenskjold M: Kostmann disease and other forms of severe congenital neutropenia. Acta Paediatr. 2021 Nov;110(11):2912-2920. doi:10.1111/apa.16005 3. Tayal A, Meena JP, Kaur R, et al: A novel homozygous HAX1 mutation in a child With cyclic neutropenia: A case report and review. J Pediatr Hematol Oncol. 2022 Mar 1;44(2):e420-e423. doi:10.1097/MPH.0000000000002110 4. Dale DC, Makaryan V: ELANE-related neutropenia. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated August 23, 2018. Accessed January 19, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1533/ 5. Chandra S, Bronicki L, Nagaraj CB, et al: WAS-related disorders. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated September 22, 2016. Accessed January 19, 2023. Available at https://www.ncbi.nlm.nih.gov/books/NBK1178/ 6. Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022 Oct:42(7):1473-1507. doi: 10.1007/s10875-022-01289-3 7. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424

SCTF 35843 Sex Chromosome Determination, FISH, Tissue

Clinical Information: Genotypically normal females possess 2 X chromosomes (XX); genotypically normal males possess 1 X chromosome and 1 Y chromosome (XY). Determining the sex chromosome complement in a tissue specimen can be used to: -Identify opposite sex-donor cells post-transplant -Help resolve cases of suspected sample mix-up

Useful For: Identifying the sex chromosome complement in paraffin-embedded tissues

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Nakhleh RE, Zarbo RJ: Surgical pathology specimen identification and accessioning: A College of American Pathologists Q-Probes study of 1,004,115 cases from 417 institutions. Arch Pathol Lab Med. 1996 Mar;120:227-233 2. Riopel MA, Yu IT, Hruban RH, Lazenby

AJ, Griffin CA, Perlman EJ: Whose tumor is this: FISHing for the answer. Mod Pathol. 1995;8:456-457
3. Valenstein PN, Raab SS, Walsh MK: Identification errors involving clinical laboratories: a College of American Pathologists Q-Probes study of patient and specimen identification errors at 120 institutions. Arch Pathol Lab Med. 2006 Aug;130(8):1106-1113

SHBG1
608102

Sex Hormone-Binding Globulin, Serum

Clinical Information: Sex hormone-binding globulin (SHBG), a 95 kDa homodimer, is the blood transport protein for testosterone and estradiol. SHBG is mainly produced in the liver and has a half-life of approximately seven days. SHBG binds reversibly to sex steroids. SHBG has a relatively high-binding affinity to dihydrotestosterone (DHT), medium affinity to testosterone and estradiol, and exhibits a low affinity to estrone, dehydroepiandrosterone, androstenedione, and estriol. Albumin, which exists at physiologically higher concentrations than SHBG, also binds to sex steroids, although with a much lower binding affinity (eg, about 100 times lower for testosterone). Decreased SHBG serum concentrations are associated with conditions in which elevated androgen concentrations are present, or the effect of androgen on its target organs is excessive. Because of the high-binding affinity of SHBG to DHT, as compared to estradiol, SHBG has profound effects on the balance between bioavailable androgens and estrogens. Increased SHBG concentrations may be associated with signs and symptoms of hypogonadism in men, while decreased concentrations can result in androgenization in women. SHBG is regulated by insulin, and a low SHBG concentration often indicates insulin resistance and, consequently, may be a predictor of type 2 diabetes. Endogenous or exogenous thyroid hormones or estrogens increase SHBG concentrations. In men, there is also an age-related gradual rise, possibly secondary to the mild age-related fall in testosterone production. This process can result in bioavailable testosterone concentrations that are much lower than would be expected based on total testosterone measurements alone.

Useful For: Diagnosis and follow-up of women with signs or symptoms of androgen excess (eg, polycystic ovarian syndrome and idiopathic hirsutism) An adjunct in monitoring sex-steroid and antiandrogen therapy An adjunct in the diagnosis of disorders of puberty An adjunct in the diagnosis and follow-up of anorexia nervosa An adjunct in the diagnosis of thyrotoxicosis (tissue marker of thyroid hormone excess) A possible adjunct in diagnosis and follow-up of insulin resistance and cardiovascular and type 2 diabetes risk assessment, particularly in women

Interpretation: Many conditions of mild-to-moderate androgen excess in women, particularly polycystic ovarian syndrome, are associated with low sex hormone-binding globulin (SHBG) concentrations. A defect in SHBG production could lead to bioavailable androgen excess, in turn causing insulin resistance that depresses SHBG concentrations further. There are rare cases of SHBG variants that follow this pattern. SHBG concentrations are typically very low in these individuals. However, in most patients, SHBG concentrations are mildly depressed or possibly within the lower part of the reference interval. In these patients, the primary problem may be androgen overproduction, insulin resistance, or both. Adult SHBG concentrations in adolescent boys with signs of precocious puberty support the condition is testosterone driven, rather than representing premature adrenarche. Therapies/behavior alterations that may potentially increase SHBG concentrations include reducers of bioactivity of androgens (eg, androgen receptor antagonists, alpha-reductase inhibitors) or reduction of insulin resistance (eg, weight loss, metformin, peroxisome proliferator-activated receptor gamma agonists). Clinical assays may not be available for many therapeutic synthetic androgens and estrogens (eg, ethinyl-estradiol). In those instances, increasing SHBG concentrations may be associated with anti-androgen or estrogen therapy, while SHBG reduction can be associated with androgen treatment. Patients with anorexia nervosa have high SHBG concentrations. With successful treatment, concentrations start to decline as nutritional status improves. Normalization of SHBG precedes, and may be predictive of, future normalization of reproductive function. Thyrotoxicosis increases SHBG concentrations. In situations when assessment of true functional thyroid status may be difficult (eg, patients receiving amiodarone treatment, individuals with thyroid hormone transport-protein

abnormalities, patients with suspected thyroid hormone resistance or suspected inappropriate thyrotropin [TSH] secretion, such as a TSH-secreting pituitary adenoma), elevated SHBG concentrations suggest tissue thyrotoxicosis, while normal levels indicate euthyroidism or near-euthyroidism. SHBG is also produced by placental tissue and, therefore, values will be elevated during pregnancy. Reference ranges for pregnant women have not been established at our institution. In patients with known insulin resistance, "metabolic syndrome," or high risk of type 2 diabetes (eg, women with a history of gestational diabetes), low SHBG concentrations may predict progressive insulin resistance, cardiovascular complications, and progression to type 2 diabetes. An increase in SHBG concentrations may indicate successful therapeutic intervention. A genetic variant of SHBG (Asp327>Asn) introduces an additional glycosylation site in 10% to 20% of the population, resulting in significantly slower degradation. These individuals tend to have higher SHBG concentrations for any given level of other factors influencing SHBG. In laboratories without access to bioavailable testosterone or equilibrium dialysis-based "true" free testosterone assays, sex hormone-binding globulin measurement is crucial in cases when assessment of the free testosterone fraction (free androgen index or calculated free testosterone) is required. At Mayo Clinic Laboratories, both bioavailable testosterone (TTBS / Testosterone, Total and Bioavailable, Serum) and free testosterone (TGRP / Testosterone, Total and Free, Serum) measurements are available. Free testosterone (TGRP) is measured by equilibrium dialysis, obviating the need for sex hormone-binding globulin measurements to calculate free androgen fractions.

Reference Values:

CHILDREN: Males Tanner Stages	Mean Age	Reference Interval (nmol/L)
Stage I	10.4	17-135
Stage II	11.1	21-114
Stage III	12.7	12-138
Stage IV	14.5	7.7-67
Stage V	14.2	3.9-40
Females Tanner Stages	Mean Age	Reference Interval (nmol/L)
Stage I	10.5	16-182
Stage II	10.9	24-121
Stage III	12.5	18-87
Stage IV	14	7.7-108
Stage V	14.9	10-79

Clinical References:

SRYF
35301

Sex-Determining Region Y, Yp11.3 Deletion, FISH

Clinical Information: This test is appropriate for individuals with a 46,XX karyotype and male sex external genitalia, a 46,XY karyotype and female sex external genitalia, clinical features suggestive of 46,XX testicular disorder of sex development with normal male sex external genitalia, and clinical features suggestive of 46,XY complete gonadal dysgenesis. The SRY (sex-determining region on the Y chromosome) gene is required for normal embryonic wolffian (male sex) genital development, although

numerous other genes are involved in completing the process of normal phenotypic male development. Some gene variants block the action of SRY in development. Thus, a 46,XY individual with an SRY deletion or variant will have a normal female phenotype, and a 46,XX individual with translocation of SRY to one X chromosome will have a normal male phenotype. Structural abnormalities of the Y chromosome result in a spectrum of abnormalities from primary infertility (regardless of sex) to various forms of ambiguous genitalia. SRY-negative 46,XX individuals often have ambiguous genitalia, whereas those who are positive for SRY usually have a normal male phenotype with azoospermia. SRY-negative 46,XY phenotypic females may have another genetic variant, such as a SOX9 gene variant. A combination of conventional chromosome studies (CHRCB / Chromosome Analysis, Congenital Disorders, Blood; or CHRAF / Chromosome Analysis, Amniotic Fluid) to detect Y chromosome abnormalities and rule out other chromosome abnormalities or translocations, and fluorescence in situ hybridization studies to detect cryptic translocations involving the SRY region that are not demonstrated by conventional chromosome studies are recommended.

Useful For: Detecting the deletion or addition of the SRY gene in conjunction with conventional chromosome studies

Interpretation: Any phenotypic male individual with an SRY signal on a structurally normal Y chromosome is considered negative for a deletion in the region tested by this probe. Any patient with a fluorescence in situ hybridization (FISH) signal pattern indicating loss of the critical region will be reported as having a deletion of the regions tested by this probe. Any patient with a FISH signal on an X chromosome will be reported as having a cryptic X;Y translocation involving the critical region.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Mohnach l, Fechner PY, Keegan CE: Nonsyndromic disorders of testicular development overview. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews (Internet). University of Washington, Seattle; 2008. Updated August 18, 2022. Accessed June 13, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1547 2. Emmanule CD, Vilain EJ: Nonsyndromic 46,XX Testicular disorder of sex development. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews (Internet). University of Washington, Seattle; 2003. Updated May 26, 2022. Accessed June 13, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1416/

SZDIA
64750

Sezary Diagnostic Flow Cytometry, Blood

Clinical Information: Sezary syndrome (SS) and mycosis fungoides (MF) are two distinct but intimately related T-cell lymphoproliferative disorders involving the skin and are commonly referred to as cutaneous T-cell lymphomas (CTCLs). SS is defined by the triad of erythroderma, generalized lymphadenopathy, and the presence of circulating cells with irregular nuclear features (Sezary cells). MF typically presents with slowly progressing patch and plaque lesions. Detection of neoplastic CD4-positive T cells in peripheral blood (>1000 cells/microliter) is essential to establish a diagnosis of SS. Disease staging and assessment of therapy response in CTCL require a quantitative assessment of peripheral blood involvement in absolute number of neoplastic cells (Sezary cells) per microliter. Flow cytometry is now considered the method of choice to estimate the number of Sezary cells in peripheral blood, largely replacing the less reproducible and time-consuming morphologic quantitation of atypical lymphocytes on a peripheral blood smear, proposed by the International Society for Cutaneous Lymphomas, and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer. Typically, Sezary cells are immunophenotypically distinct and they are clonal.

Useful For: Identifying immunophenotypically aberrant T-cell populations with restricted expression of T-cell receptor beta-chain constant in peripheral blood, to roughly assess the circulating tumor

burden in cutaneous T-cell lymphomas

Interpretation: An immunophenotypically distinct T-cell population is suggestive of clonality when the subset exhibits a restricted T-cell receptor beta-chain constant (TRBC) staining pattern defined as either 1) >85% of TRBC1-positive events, 2) <15% TRBC1-positive events, or 3) homogenous TRBC1-dim expression. The immunophenotype of the distinct T-cell population, its percentage of total lymphocytes, and its percentage of total analyzed events will be reported. The test will be resulted as "No phenotypically aberrant T-cell population detected" if there is no specific immunophenotype that allows the detection of TRBC-restricted T cells.

Reference Values:
An interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and, if available, morphologic features will be provided by a board-certified hematopathologist for every case.

Clinical References:

SZMON 64749 Sezary Monitoring Flow Cytometry, Blood

Clinical Information: Sezary syndrome (SS) and mycosis fungoides (MF) are two distinct but intimately related T-cell lymphoproliferative disorders involving the skin and are commonly referred to as cutaneous T-cell lymphomas (CTCLs). SS is defined by the triad of erythroderma, generalized lymphadenopathy, and the presence of circulating cells with irregular nuclear features (Sezary cells). MF typically presents with slowly progressing patch and plaque lesions. Detection of neoplastic CD4-positive T-cells in peripheral blood (>1000 cells/microliter) is essential to establish a diagnosis of SS. Disease staging and assessment of therapy response in CTCL require a quantitative assessment of peripheral blood involvement in absolute number of neoplastic cells (Sezary cells) per microliter. Flow cytometry is now considered the method of choice to estimate the number of Sezary cells in peripheral blood, largely replacing the less reproducible and time-consuming morphologic quantitation of atypical lymphocytes on a peripheral blood smear, proposed by the International Society for Cutaneous Lymphomas, and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer. Typically, Sezary cells are immunophenotypically distinct, and they are clonal.

Useful For: Monitoring response to therapy in patients with previously diagnosed Sezary syndrome or mycosis fungoides

Interpretation: An immunophenotypically distinct T-cell population is suggestive of clonality when the subset exhibits a restricted T-cell receptor beta-chain (TRBC) staining pattern defined as either 1) >85% of TRBC1-positive events, 2) <15% TRBC1-positive events, or 3) homogenous TRBC1-dim expression. The immunophenotype of the distinct T-cell population, its percentage of total lymphocytes, and its percentage of total analyzed events will be reported. The test will be resulted as "No phenotypically aberrant T-cell population detected" if there is no specific immunophenotype that allows the detection of TRBC-restricted T cells.

Reference Values:
An interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and, if available, morphologic features will be provided by a board-certified hematopathologist for every case.

Clinical References: 1. Horna P, Deaver DM, Qin D, et al. Quantitative flow cytometric identification of aberrant T cell clusters in erythrodermic cutaneous T cell lymphoma. Implications for staging and prognosis. J Clin Pathol. 2014;67(5):431-436 2. Berg H, Otteson GE, Corley H, et al. Flow

cytometric evaluation of TRBC1 expression in tissue specimens and body fluids is a novel and specific method for assessment of T-cell clonality and diagnosis of T-cell neoplasms. Cytometry B Clin Cytom. 2021;100(3):361-369 3. Horna P, Shi M, Olteanu H, Johansson U. Emerging role of T-cell receptor constant beta chain-1 (TRBC1) expression in the flow cytometric diagnosis of T-cell malignancies. Int J Mol Sci. 2021;22(4):1817 4. Wilcox RA. Cutaneous T-cell lymphoma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016;91(1):152-165. doi:10.1002/ajh.24233 5. Horna P, Olteanu H, Jevremovic D, et al. Single-antibody evaluation of T-cell receptor beta constant chain monotypia by flow cytometry facilitates the diagnosis of T-cell large granular lymphocytic leukemia. Am J Clin Pathol. 2021;156(1):139-148 6. Horna P, Shi M, Jevremovic D, Craig FE, Comfere NI, Olteanu H. Utility of TRBC1 expression in the diagnosis of peripheral blood involvement by cutaneous T-cell lymphoma. J Invest Dermatol. 2021;141(4):821-829 7. Scarisbrick JJ, Hodak E, Bagot M, et al. Blood classification and blood response criteria in mycosis fungoides and Sezary syndrome using flow cytometry: recommendations from the EORTC cutaneous lymphoma task force. Eur J Cancer. 2018;93:47-56 8. Illingworth A, Johansson U, Huang S, et al. International guidelines for the flow cytometric evaluation of peripheral blood for suspected Sezary syndrome or mycosis fungoides: Assay development/optimization, validation, and ongoing quality monitors. Cytometry B Clin Cytom. 2021;100(2):156-182

SF1
72121

SF-1 Immunostain, Technical Component Only

Clinical Information: Steroidogenic factor 1 (SF-1) is a transcription factor involved in the development of the anterior pituitary and is useful in the classification of pituitary adenomas. Expression of SF-1 is observed in gonadotropic hormone producing tumors (follicular stimulating or luteinizing hormone).

Useful For: Classification of pituitary adenomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Reference Values:
Not applicable

Clinical References: 1. Mete O, Asa SL. Clinicopathological correlations in pituitary adenomas. Brain Pathol. 2012;22:443-453 2. Mete O, Asa SL. Therapeutic implications of accurate classification of pituitary adenomas. Semin Diagn Pathol. 2013;30(3):158-164 3. McDonald WC, Banerji N, McDonald KN, Ho B, Macias V, Kajdacsy-Balla A. Steroidogenic factor 1, Pit-1, and adrenocorticotropic hormone: A rational starting place for the immunohistochemical characterization of pituitary adenoma. Arch Pathol Lab Med. 2017;141(1):104-112. doi: 10.5858/arpa.2016-0082-OA 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

SHWL
82747

Sheep Wool, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to

allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to sheep wool Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

STFRP
35148

Shiga Toxin, Molecular Detection, PCR, Feces

Clinical Information: Shiga toxins (also known as Shiga-like toxins, Vero toxins, or Vero-like toxins) are encoded by some strains of Escherichia coli, most notably O157:H7. Shiga toxin can also be produced by other serogroups of enterohemorrhagic E coli (EHEC), as well as Shigella dysenteriae type 1. Generally, Shiga toxin-producing organisms cause bloody diarrhea, although this is not universal. Unlike some bacterial gastrointestinal infections, antimicrobial therapy is contraindicated as antimicrobials may exacerbate disease. Treatment is primarily supportive (eg, hydration). A complication of infection by an organism producing Shiga toxin is hemolytic uremic syndrome (HUS). The percentage of people that

develop HUS varies among outbreaks of E coli O157:H7, but generally ranges from 3% to 20%. HUS is characterized by a triad of findings: hemolytic anemia, thrombocytopenia, and kidney failure. Most people recover completely; however, some require permanent dialysis, and some die due to complications. Several diagnostic methods are available for the detection of EHEC but lack sensitivity, are labor intensive, or have a long turnaround time. There are more than 160 serogroups of EHEC; the first serogroup to be associated with HUS was O157:H7. This is also the serogroup that is most frequently implicated in outbreaks. EHEC O157:H7 is detectable as non-fermenting colonies when cultured on sorbitol MacConkey (SMAC) agar, but the majority of non-O157:H7 Shiga toxin-producing E coli strains ferment sorbitol and, therefore, are undetectable by this method. The Vero cell line is susceptible to the Shiga toxin, but the assay can take up to 48 hours and is nonspecific. Commercial enzyme-linked immunosorbent assay (ELISA) antigen detection kits have a sensitivity of 90% when compared to culture, but an overnight enrichment step is necessary for adequate sensitivity. Polymerase chain reaction (PCR) detection of stx, the gene encoding Shiga toxin, directly from fecal specimens is a sensitive and specific technique, providing same-day results. The PCR assay identifies non-O157:H7 Shiga toxin-producing bacteria, extending the utility beyond strains identifiable on SMAC agar.

Useful For: Sensitive, specific, and rapid detection of the presence of Shiga toxin-producing organisms such as Escherichia coli O157:H7 and Shigella dysenteriae type 1 in stool This test is not recommended as a test of cure.

Interpretation: A positive polymerase chain reaction (PCR) result indicates the likely presence of Shiga toxin-producing Escherichia coli in the specimen. Although Shigella dysenteriae serotype 1 may produce a positive result, it is extremely rare in the United States. A negative result indicates the absence of detectable Shiga toxin DNA in the specimen, but does not rule out the presence of Shiga toxin-producing E coli and may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of Shiga toxin DNA in quantities less than the limit of detection of the assay. Shiga toxins are encoded on mobile genetic elements and can theoretically be lost by their bacterial host.

Reference Values:
Not applicable

Clinical References: 1. Gould LH, Bopp C: Recommendations for diagnosis of Shiga toxin-producing Escherichia coli infection by clinical laboratories. MMWR Morb Mortal Wkly Rep. 2009 Oct;16:v58 2. Nyre LM, Kiemele DL, Zomok CD, et al: Clinical experience with rapid PCR for detection of Shiga toxin in stool. Abstract of the Annual Meeting of the American Society for Microbiology, 2010 General Meeting, San Diego, CA, May 23-27, 2010 3. Procop GW, Church DL, Hall GS, et al: The Enterobacteriaceae. In: Koneman's Color Atlas and Textbook of Diagnostic Microbiology. 7th ed. Wolters Kluwer; 2017:213-315

SHIGC
606221

Shigella Culture, Feces

Clinical Information: Diarrhea may be caused by a number of agents, including bacteria, viruses, parasites, and chemicals; these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the healthcare professional determine the appropriate testing to be performed. Shigella species are common causative agents of bacterial diarrheal disease worldwide. The infectious dose is low; Shigella transmission can occur via contaminated food and water or from direct person-to-person contact.

Useful For: Determining whether Shigella species may be the cause of diarrhea Reflexive testing for Shigella species from nucleic acid amplification test-positive stool This test is generally not useful for

patients hospitalized more than 3 days because the yield from specimens from these patients is very low, as is the likelihood of identifying a pathogen that has not been detected previously.

Interpretation: The growth of Shigella species identifies a potential cause of diarrhea.

Reference Values:
No growth of Shigella species.

Clinical References: 1. Pillai DR, Griener T. Culture for Campylobacter and related organisms. In: Leber AL, Church DL, eds. Clinical Microbiology Procedures Handbook. 4th ed. ASM Press; 2016:Section 3.8.2 2. DuPont HL. Persistent diarrhea: A clinical review. JAMA. 2016;315(24):2712-2723. doi:10.1001/jama.2016.7833 3. DuPont HL, Levine MM, Hornick RB, Formal SB. Inoculum size in shigellosis and implications for expected mode of transmission. J Infect Dis. 1989;159(6):1126-1128 4. Maurelli AT, Lampel KA. Shigella. In: Hui YH, Gorham JR, Murrell KD, Cliver DO, eds. Foodborne Disease Handbook. Marcel Dekker;1994:321 5. CDC Health Alert Network. CDC Recommendations for diagnosing and managing Shigella Strains with possible reduced susceptibility to ciprofloxacin. April 18, 2017. Accessed September 22, 2023. Available at https://emergency.cdc.gov/han/han00401.asp

SQTSG
617463

Short QT Syndrome Gene Panel, Varies

Clinical Information: Short QT syndrome (SQTS) is a genetic cardiac arrhythmia condition characterized by a shortened QT interval and T-wave abnormalities on electrocardiogram (ECG).(1) SQTS may result in or present with recurrent syncope, ventricular arrhythmia, sudden cardiac arrest, and sudden cardiac death.(1) The prevalence of SQTS is unknown, but the condition is thought to be rare.(2) The overall diagnostic yield of genetic testing for SQTS is estimated to be 5% to 20%.(2,3) While disease-causing variants in several genes have been reported in association with SQTS, the strongest evidence of association is currently limited to gain-of- function variants in the cardiac ion change genes KCNH2, KCNJ2, and KCNQ1,(4) and loss-of-function variants in the SLC4A3 gene.(5) Based on current knowledge, SQTS follows an autosomal dominant pattern of inheritance. Genetic testing in SQTS is recommended to confirm the clinical diagnosis, assist with risk stratification, guide management, and identify at-risk family members. Even individuals with a normal QT interval may still be at risk for a cardiac event and sudden cardiac death; thus, ECG analysis alone is insufficient to rule out the diagnosis, and genetic testing is necessary to confirm the presence or absence of disease in at-risk family members.(1-5)

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of short QT syndrome Establishing a diagnosis of short QT syndrome

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Campuzano O, Fernandez-Falgueras A, Lemus X, et al: Short QT syndrome: A comprehensive genetic interpretation and clinical translation of rare variants. J Clin Med. 2019 Jul 16;8(7):1035. doi:10.3390/jcm8071035 2. Mazzanti A, Underwood K, Nevelev D, Kofman S, Priori SG: The new kids on the block of arrhythmogenic disorders: Short QT syndrome and early repolarization. J Cardiovasc Electrophysiol. 2017 Oct;28(10):1226-1236. doi: 10.1111/jce.13265 3. Priori SG, Blomstrom-

Lundqvist C, Mazzanti A, et al; ESC Scientific Document Group: 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015 Nov 1;36(41):2793-2867. doi: 10.1093/eurheartj/ehv316 4. Walsh R, Adler A, Amin AS, et al: Evaluation of gene validity for CPVT and short QT syndrome in sudden arrhythmic death. Eur Heart J. 2022 Apr 14:43(15):1500-1510. doi: 10.1093/eurheartj/ehab687 5. Thorsen K, Dam VS, Kjaer-Sorensen K, et al: Loss-of-activity-mutation in the cardiac chloride-bicarbonate exchanger AE3 causes short QT syndrome. Nat Commun. 2017 Nov 22;8(1):1696. doi: 10.1038/s41467-017-01630-0 6. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

SRW
82667

Short Ragweed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to short ragweed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive

4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FSHRG
57542

Shrimp IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

SHRI
82677

Shrimp, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to shrimp Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SAU
620916

Sialic Acid, Free and Total, Random, Urine

Clinical Information: Sialic acid (SA), or N-acetyl-neuraminic acid, is a component of carbohydrates, glycoproteins, and gangliosides which are important for the human nervous system. SA can be measured in urine as free sialic acid or in a conjugated form, bound to oligosaccharides. Sialic acid disorders are a subset of lysosomal disorders caused by defective protein transport or enzyme deficiency that result in multisystem organ disease. Analysis of free and total sialic acid and their ratio in urine can detect the following conditions: free sialic acid storage disorder, sialuria, N-acetylneuraminate pyruvate lyase (NPL) deficiency, sialidosis, and galactosialidosis. Free sialic acid storage disorder (FSASD) is a rare lysosomal disorder caused by a defect in sialin, a sialic acid membrane exporter also known as SLC17A5. This defect results in increased stored free sialic acid in the lysosomes. Individuals with FSASD demonstrate the hallmark feature of progressive neurologic issues such as hypotonia, cerebellar ataxia, short stature, and cognitive impairment. Brain imaging may show central hypomyelination, cerebellar atrophy, and thinning of the corpus callosum. Infants and children with more severe disease may also have coarse facial features and organomegaly, such as enlarged liver and heart. A congenital form of the disease has been reported in which patients present with nonimmune hydrops fetalis. Historically, FSASD was divided into several conditions based on early to later age at disease presentation and severity: infantile free sialic acid storage disease, intermediate severe Salla disease, and Salla disease. These conditions are now considered to represent the spectrum of FSASD. There are no approved therapies for FSASD at present. Urine sialic acid analysis will show elevated free sialic acid and a high ratio of free to total sialic acid in individuals with FSASD. FSASD is an autosomal recessive condition caused by disease-causing variants in the SLC17A5 gene. There are two additional rare disorders that show elevated free sialic acid: sialuria and N-acetylneuraminate pyruvate lyase (NPL) deficiency. Sialuria is an autosomal recessive disorder caused by disease-causing variants in the GNE gene that results in onset of symptoms such as organomegaly and developmental delay in infancy. NPL deficiency is also inherited in an autosomal recessive manner due to pathogenic variants in the NPL gene. Individuals with NPL deficiency develop progressive cardiomyopathy and mild skeletal myopathy in childhood. There are no approved therapies for these conditions, and so treatment is supportive. Sialidosis is caused by a deficiency of the enzyme neuraminidase which results in accumulation of sialyloligosaccharides in lysosomes. Individuals with

sialidosis can present with a continuum of clinical features ranging from severe disease (type II) to a milder and more slowly progressive course (type I). These clinical features range from early developmental delay, coarse facial features, short stature, dysostosis multiplex, and hepatosplenomegaly to late onset cherry-red spot myoclonus syndrome. Seizures, hyperreflexia, and ataxia have been reported in more than 50% of later onset patients. A congenital form of the disease has been reported in which patients present with fetal hydrops or neonatal ascites. Urine sialic acid analysis will show a low ratio of free to total sialic acid in individuals with sialidosis, as they have increased excretion of conjugated SA. Analysis of urine oligosaccharides (OLIGU / Oligosaccharide Screen, Random, Urine) is also recommended for patients with a suspected diagnosis of sialidosis. Sialidosis an autosomal recessive condition caused by disease-causing variants in the NEU1 gene. Galactosialidosis also presents with a continuum of clinical features ranging from severe and rapidly progressive disease to a milder and more slowly progressive course; clinical features of the early infantile type include fetal hydrops, edema, ascites, visceromegaly, dysostosis multiplex, coarse facies, and cherry red spot(s) in the retina. Most patients have milder presentations, which include ataxia, myoclonus, angiokeratoma, cognitive and neurologic decline. Urine sialic acid will show a low ratio of free to total sialic acid in individuals with galactosialidosis, as they have increased excretion of conjugated SA. Analysis of urine oligosaccharides is also recommended for patients with a suspected diagnosis of galactosialidosis. Galactosialidosis is an autosomal recessive condition caused by disease-causing variants in the CTSA gene. Patients with an abnormal urine sialic acid result suggestive of any of the sialic acid disorders should have follow up confirmatory testing with the appropriate enzyme or molecular test.

Useful For: Screening for sialic acid disorders

Interpretation: An elevated result of total/free sialic acid ratio may be indicative of sialidosis or galactosialidosis. A decreased result of total/free sialic acid ratio may be indicative of free sialic acid storage disorder. Abnormal results or clinical suspicion should be confirmed with biochemical or molecular genetic analysis.

Reference Values:

Free Sialic Acid:
< or =4 weeks: < or =208 mmol/mol creatinine
5 weeks-12 months: < or =104 mmol/mol creatinine
13 months-18 years: < or =100 mmol/mol creatinine
> or =19 years: < or =38 mmol/mol creatinine

Total Sialic Acid
< or =4 weeks: < or =852 mmol/mol creatinine
5 weeks-12 months: < or =656 mmol/mol creatinine
13 months-18 years: < or =335 mmol/mol creatinine
> or =19 years: < or =262 mmol/mol creatinine

Total/Free Ratio:
< or =4 weeks: 1.94-18.68
5 weeks-12 months: 2.34-13.85
13 months-18 years: 2.63-9.18
> or =19 years: 3.35-15.81

An interpretive report will also be provided.

Clinical References: 1.Adams D, Wasserstein M. Free Sialic Acid Storage Disorders. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle;1993-2023. Updated January 23, 2020. Accessed June 10, 2025.Available at: www.ncbi.nlm.nih.gov/books/NBK1470/ 2. Huizing M, Hackbarth ME, Adams DR, et al. Free sialic acid storage disorder: Progress and promise. Neurosci Lett. 2021;755:135896.

doi:10.1016/j.neulet.2021.135896 3. Khan A, Sergi C. Sialidosis: A review of morphology and molecular biology of a rare pediatric disorder. Diagnostics (Basel). 2018;8(2):29. Published 2018 Apr 25. doi:10.3390/diagnostics8020029 4. Annunziata I, d'Azzo A. Galactosialidosis: historic aspects and overview of investigated and emerging treatment options. Expert Opin Orphan Drugs. 2017;5(2):131-141. doi:10.1080/21678707.2016.1266933

SDEX 9180 Sickle Solubility, Blood

Clinical Information: Homozygous hemoglobin (Hb) S (sickle cell disease) is a serious chronic hemolytic anemia most commonly found in those of African or Middle Eastern descent. Hb S is freely soluble when fully oxygenated; when oxygen is removed, polymerization of the abnormal hemoglobin occurs, forming tactoids that are rigid and deformed cells. This leads to sickling of the cells, hemolysis, and many other complications. Heterozygous Hb S (sickle cell trait) is the most common hemoglobinopathy in the United States. This condition is present in about 8% of African Americans. Usually, Hb S trait exhibits no clinical or hematological effects. A small fraction of people with sickle cell trait have recurrent hematuria.

Useful For: Screening for presence or absence of hemoglobin (Hb) S (sickle cell disease)

Interpretation: A positive result should be followed by a complete hemoglobin (Hb) evaluation (HBEL1 / Hemoglobin Electrophoresis Evaluation, Blood) to confirm the presence and concentration of Hb S.

Reference Values:
Negative

Clinical References: 1. Fairbanks VF. Laboratory methods and case studies. In: Decker BC, ed. Hemoglobinopathies and Thalassemias. Thieme-Stratton Inc; 1980:105-107 2. Sauntharajah Y, Vichinsky EP: Sickle cell disease: Clinical features and management. In Hoffman R, Benz EJ, Silberstein LE, et al, eds. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018:584-607

STAT6 70554 Signal Transducer and Activator of Transcription 6 (STAT6), Technical Component Only

Clinical Information: Signal transducer and activator of transcription 6 (STAT6) is a signal transducer/transcription activator expressed in the cytoplasm of various normal tissues including bladder epithelium, bronchial epithelium, and epidermis. NAB2-STAT6 fusions have recently been described in the majority of solitary fibrous tumors, and lead to aberrant strong nuclear STAT6 staining.

FSILS 75690 Silicon, Serum

Interpretation: Specimens for elemental testing should be collected in certified metal-free containers. Elevated results for elemental testing may be caused by environmental contamination at the time of specimen collection and should be interpreted accordingly. It is recommended that unexpected elevated results be verified by testing another specimen in a trace metal free container.

Reference Values:
Reporting limit determined each analysis.
Generally: Less than 0.05 mg/dL

Silicon concentrations are influenced by diet, especially vegetable intake.

BIR
82674

Silver Birch, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to silver birch Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FSINS
75400

Sinemet, Serum

Interpretation: Levodopa The target plasma concentration of levodopa in Parkinsonian patients is 2 +/- 0.5 mcg/mL. The average peak plasma levodopa concentration following a single oral dose of Sinemet containing 200 mg levodopa was 1.2 mcg/mL at 0.5 hours for normal release and 3.3 mcg/mL at 2 hours for controlled release. At steady-state, the average trough plasma levodopa concentration following oral Sinemet containing 200 mg levodopa was 0.07 mcg/mL for normal release and 0.16 mcg/mL for controlled release. Carbidopa Following a single oral dose of 250 mg levodopa and 25 mg carbidopa, peak plasma concentrations of carbidopa averaged 0.11 mcg/mL at 2.9 hours post dose. Carbidopa concentrations can decrease rapidly after collection unless flash frozen with dry ice.

Reference Values:

SIIRO
35144

Sirolimus, Whole Blood

Clinical Information:

Useful For: Monitoring whole blood sirolimus concentration during therapy, particularly in individuals coadministered cytochrome P450 (CYP) 3A4 substrates, inhibitors, or inducers Adjusting dose to optimize immunosuppression while minimizing toxicity Evaluating patient compliance

Interpretation: Most individuals display optimal response to sirolimus with trough whole blood levels 4 to 20 ng/mL. Preferred therapeutic ranges may vary by transplant type, protocol, and comedications. Therapeutic ranges are based on specimens collected at trough (ie, immediately before a scheduled dose). Higher results will be obtained when the blood is collected at other times. The assay is specific for sirolimus; it does not cross-react with cyclosporine, cyclosporine metabolites, tacrolimus, tacrolimus metabolites, or sirolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry are approximately 30% less than by immunoassay.

Reference Values:
4-20 ng/mL (Trough)

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.

Clinical References: 1. Milone MC, Shaw LM: Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453 2. Kahan BD. Ten years of mTOR inhibitor therapy. Transplant Proc. 2003;35(3A):3S-240S 3. Yakupoglu YK, Kahan BD. Sirolimus: a current perspective. Exp Clin Transplant 2003;1(1):8-18 4. Groth CG, Backman L, Morales JM, et al. Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine. Sirolimus European Renal Transplant Study Group. Transplantation. 1999;67(7):1036-1042

SMAD4
613980

SMAD4 Immunostain, Technical Component Only

Clinical Information: SMAD4 (mothers against decapentaplegic homolog 4 drosophila) is a tumor suppressor and transcription factor that is part of the transforming growth factor beta signaling pathway.

Normally SMAD4 is expressed within the nucleus of epithelial cells, while loss of SMAD4 expression is caused by inactivation of the SMAD4 gene due to sporadic genetic variants. The status of SMAD4 expression is useful in the diagnosis of pancreatic adenocarcinoma.

Useful For: Identification of loss of SMAD4 (mothers against decapentaplegic homolog 4 drosophila) expression within pancreatic ductal adenocarcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Hata T, Suenaga M, Marchionni L, et al. Genome-wide somatic copy number alterations and mutations in high-grade pancreatic intraepithelial neoplasia. Am J Pathol. 2018;188(7):1723-1733 2. Voorneveld PW, Jacobs RJ, Kodach LL, Hardwick JC. A meta-analysis of SMAD4 immunohistochemistry as a prognostic marker in colorectal cancer. Transl Oncol. 2015;8(1):18-24 3. Chen YW, Hsiao PJ, Weng CC, et al. SMAD4 loss triggers the phenotypic changes of pancreatic ductal adenocarcinoma cells. BMC Cancer. 2014;14:181 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5

SDLDL
619974

Small Dense Low Density Lipoprotein Cholesterol, Serum

Clinical Information: Low-density lipoprotein cholesterol (LDL-C) has long been known to be causally associated with atherosclerotic plaque development and progression and is the main target of lowering cardiovascular disease risk. Subfractions of LDL, particularly the concentration of small dense LDL-C, have been shown to also be associated with increased risk for coronary heart disease (CHD). It is thought that the smaller particles are especially pro-atherogenic given their higher probability to transverse the arterial wall and a longer circulating half-life, likely from a lower binding affinity to the LDL receptor. Several epidemiological and pathological studies have reported an association between the concentration of small dense LDL-C and CHD. Results should be used in conjunction with the patient's medical history and other laboratory and clinical results.

Useful For: Aiding in risk management of lipoprotein disorders associated with cardiovascular disease when used in conjunction with other lipid measurements and clinical evaluation

Interpretation: Results of 50 mg/dL or greater indicate increased risk of incident coronary heart disease (CHD) (myocardial infarction, fatal CHD, or cardiac procedure).

Reference Values:
> or =18 years: <50 mg/dL
Reference values have not been established for patients who are younger than 18 years.

Clinical References: 1. Tsai MY, Steffen BT, Guan W, et al. New automated assay of small dense low-density lipoprotein cholesterol identifies risk of coronary heart disease: the multi-ethnic study of atherosclerosis. Arterioscler Thromb Vasc Biol. 2014;34(1):196-201. doi:10.1161/ATVBAHA.113.302401 2. Hoogeveen RC, Gaubatz JW, Sun W, et al. Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: the atherosclerosis riskiIn ommunities (ARIC) study. Arterioscler Thromb Vasc Biol. 2014;34(5):1069-1077. doi:10.1161/ATVBAHA.114.303284 3. Hirano T, Ito Y, Yoshino G. Measurement of small dense low-density lipoprotein particles. J Atheroscler Thromb. 2005;12(2):67-72 4. Ogita K, Ai M, Tanaka A, et al.

Circadian rhythm of serum concentration of small dense low-density lipoprotein cholesterol. Clin Chim Acta. 2007;376(1-2):96-100 5. Balling M, Nordestgaard BG, Langsted A, Varbo A, Kamstrup PR, Afzal S. Small dense low-density lipoprotein cholesterol predicts atherosclerotic cardiovascular disease in the Copenhagen general population study. J Am Coll Cardiol. 2020;75(22):2873-2875. doi:10.1016/j.jacc.2020.03.072

SLL
65884

Small Lymphocytic Lymphoma, FISH, Tissue

Clinical Information: Small lymphocytic lymphoma (SLL) is the nonleukemic form of chronic lymphocytic leukemia (CLL), one of the most common leukemias in adults. The most frequently seen cytogenetic abnormalities in SLL involve chromosomes 6, 11, 12, 13 and 17. These are detected and quantified using the SLL fluorescence in situ hybridization (FISH) panel. Cytogenetics has proven to be a reliable predictor of outcome for patients with CLL. It is unknown if SLL has the same prognostic significance when these genetic abnormalities are observed. This FISH test detects an abnormal clone in approximately 65% of patients with SLL. Patients with t(11;14)(q13;q32) associated with CCND1::IGH fusion, have mantle cell lymphoma which can be distinguished from SLL and other B-cell lymphomas with this assay. Patients with t(14;19)(q32;q13.3) associated with IGH::BCL3 fusion, may have an atypical form of SLL or another B-cell lymphoma.

Useful For: Recurrent common chromosome abnormalities in patients with small lymphocytic lymphoma (SLL) Distinguishing patients with 11;14 translocations who have mantle cell lymphoma (MCL) from patients who have SLL Detecting patients with atypical SLL or other forms of B-cell lymphoma associated with translocations between IGH and BCL3

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. A positive result is not diagnostic for small lymphocytic lymphoma but may provide relevant prognostic information. The absence of an abnormal clone does not rule out the presence of an SLL clone or another neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow SH, Campo E, Harris NL eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC; 2017. WHO Classification of Tumours, Vol 2 2. Shanafelt TD. Predicting clinical outcome in CLL: how and why. Hematology Am Soc Hematol Educ Program. 2009;421-429 3. Van Dyke DL, Werner L, Rassenti LZ, et al. The Dohner fluorescence in situ hybridization prognostic classification of chronic lymphocytic leukaemia (CLL): the CLL Research Consortium experience. Br J Haematol. 2016;173(1):105-113

SM
81358

Smith (Sm) Antibodies, IgG, Serum

Clinical Information:

Useful For: Evaluating patients with clinical features suggestive of antinuclear antibody associated connective tissue disease and the confirmation of a diagnosis of systemic lupus erythematosus. Testing for Smith antibodies is not useful in patients without demonstrable antinuclear antibodies.

Interpretation: A positive anti-Smith antibody result in the appropriate clinical context is consistent with a diagnosis of systemic lupus erythematosus.

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References: 1. Tan EM, Kunkel HG. Characteristics of a soluble nuclear antigen precipitating with sera of patients with systemic lupus erythematosus. J Immunol. 1966;96(3):464-471 2. Zieve GW, Khusial PR. The anti-Sm immune response in autoimmunity and cell biology. Autoimmun Rev. 2003;2(5):235-240 3. Billings PB, Hoch SO. Characterization of U small nuclear RNA-associated proteins. J Biol Chem. 1984;259(20):12850-12856 4. Battle DJ, Kasim M, Yong J, et al. The SMN complex: an assembly machine for RNPs. Cold Spring Harb Symp Quant Biol. 2006;71:313-320 5. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol. 2019;71(9):1400-1412 6. van Beers JJBC, Schreurs MWJ. Anti-Sm antibodies in the classification criteria of systemic lupus erythematosus. J Transl Autoimmun. 2022;5:100155 7. Migliorini P, Baldini C, Rocchi V, Bombardieri S. Anti-Sm and anti-RNP antibodies. Autoimmunity. 2005;38(1):47-54 8. Kwon OC, Park MC. Risk of systemic lupus erythematosus flares according to autoantibody positivity at the time of diagnosis. Sci Rep. 2023;13(1):3068 9. Llorente MJ, Jimenez J, Gonzalez C, et al. Effectiveness of different methods for anti-Sm antibody identification. A multicentre study. Clin Chem Lab Med. 2005;43(7):748-752

DHCRZ
608025

Smith Lemli Opitz Syndrome, DHCR7 Gene, Full Gene Analysis, Varies

Clinical Information: Cholesterol plays an essential role in many cellular and developmental processes. In addition to its role as a membrane lipid, it is the precursor to numerous molecules that play important roles in cell growth and differentiation, protein glycosylation, and signaling pathways. The biosynthesis of cholesterol and its subsequent conversion to other essential compounds is complex, involving a number of intermediates and enzymes. Disorders that result from a deficiency of these enzymes lead to an accumulation of specific intermediates and inhibit the formation of important biomolecules. Clinical findings common to cholesterol biosynthesis disorders include congenital skeletal malformations, dysmorphic facial features, psychomotor retardation, and failure to thrive. Smith-Lemli-Opitz syndrome (SLO) is an autosomal recessive disorder caused by alterations in the DHCR7 gene leading to a deficiency of the 7-dehydrocholesterol reductase enzyme. It is characterized biochemically by markedly increased plasma concentrations of 7-dehydrocholesterol (7-DHC) and 8-dehydrocholesterol (8-DHC) levels. Clinically, features can include microcephaly, growth retardation, developmental delay, dysmorphic facial features, cleft palate, limb abnormalities (especially 2-3 syndactyly of the toes and postaxial polydactyly), and heart and kidney malformations. The clinical spectrum ranges from mild to severe, with some mildly affected individuals presenting with only 2 to 3 toe syndactyly and mild cognitive impairment. SLO is inherited in an autosomal recessive manner, caused by disease-causing variants in both alleles of the DHCR7 gene. The reported incidence is from 1 in 20,000 to 1 in 40,000, but it may be more prevalent due to underdiagnosis of mildly affected individuals. Measurement of cholesterol precursors in plasma (SLO / Smith-Lemli-Opitz Screen, Plasma) should be performed as a first-tier test to screen for SLO. Cholesterol supplementation may result in clinical improvement but is not curative.

Useful For: Follow up for abnormal biochemical results suggestive of Smith-Lemli-Opitz syndrome Establishing a molecular diagnosis for patients with Smith-Lemli-Opitz syndrome Identifying alterations within DHCR7 allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or

possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Haas D, Herman GE, Hoffmann GF. Defects of cholesterol biosynthesis. In: Sarafoglou K, Hoffman GF, Roth KS, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. 2nd ed. McGraw-Hill Education; 2017:413-426 3. Nowaczyk MJM, Wassif CA. Smith-Lemli-Opitz Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated January 30, 2020. Accessed March 8, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1143/ 4. Hall P, Michels V, Gavrilov D, et al. Aripiprazole and trazodone cause elevations of 7-dehydrocholesterol in the absence of Smith-Lemli-Opitz Syndrome. Mol Genet Metab. 2013;110(1-2):176-178

SLO
81595

Smith-Lemli-Opitz Screen, Plasma

Clinical Information: Cholesterol plays an essential role in many cellular and developmental processes. In addition to its role as a membrane lipid, it is the precursor to numerous molecules that play important roles in cell growth and differentiation, protein glycosylation, and signaling pathways. The biosynthesis of cholesterol and its subsequent conversion to other essential compounds is complex, involving a number of intermediates and enzymes. Disorders that result from a deficiency of these enzymes lead to an accumulation of specific intermediates and inhibit the formation of important biomolecules. Clinical findings common to cholesterol biosynthesis disorders include congenital skeletal malformations, dysmorphic facial features, psychomotor retardation, and failure to thrive. Smith-Lemli-Opitz syndrome (SLO) is an autosomal recessive disorder caused by variants in the DHCR7 gene leading to a deficiency of the 7-dehydrocholesterol reductase enzyme. It is characterized biochemically by markedly increased plasma concentrations of 7-dehydrocholesterol and 8-dehydrocholesterol levels. Clinical features can include microcephaly, growth retardation, developmental delay, dysmorphic facial features, cleft palate, limb abnormalities (especially 2-3 syndactyly of the toes and postaxial polydactyly), and heart and kidney malformations. However, the clinical spectrum ranges from mild to severe with some mildly affected individuals presenting with only 2-3 toe syndactyly and mild cognitive impairment. The reported incidence is between 1 in 10,000 and 1 in 60,000, but it may be more prevalent due to underdiagnoses of mildly affected individuals. Other disorders of cholesterol biosynthesis, including desmosterolosis (desmosterol reductase deficiency) and sitosterolemia, may present with similar manifestations. These disorders can be detected biochemically by performing a quantitative profile of plasma sterols (STER / Sterols, Plasma).

Useful For: Diagnosing Smith-Lemli-Opitz syndrome (7-dehydrocholesterol reductase deficiency)

Interpretation: Elevated plasma concentrations of 7-dehydrocholesterol (7-DHC) and 8-dehydrocholesterol are highly suggestive of a biochemical diagnosis of Smith-Lemli-Opitz (SLO) syndrome. Mild elevations of these cholesterol precursors can be detected in patients with hypercholesterolemia and patients treated with some antipsychotic or antidepressant medications, including haloperidol, aripiprazole, and trazodone. However, the 7-DHC to cholesterol ratio is typically elevated only in patients with SLO syndrome.

Reference Values:
7-DEHYDROCHOLESTEROL

< or =2.0 mg/L

8-DEHYDROCHOLESTEROL
< or =0.3 mg/L

Clinical References: 1. Donoghue SE, Pitt JJ, Boneh A, White SM. Smith-Lemli-Opitz syndrome: clinical and biochemical correlates. J Pediatr Endocrinol Metab. 2018;31(4):451-459 2. Nowaczyk MJM, Wassif CA. Smith-Lemli-Opitz syndrome. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated January 30, 2020.Accesses November 02, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1143/ 3. Hall P, Michels V, Gavrilov D, et al. Aripiprazole and trazodone cause elevations of 7-dehydrocholesterol in the absence of Smith-Lemli-Opitz syndrome. Mol Genet Metab. 2013;110(1-2):176-178 4. Genaro-Mattos TC, Tallman KA, Allen LB, et al. Dichlorophenyl piperazines, including a recently-approved atypical antipsychotic, are potent inhibitors of DHCR7, the last enzyme in cholesterol biosynthesis. Toxicol Appl Pharmacol. 2018;349:21-28. doi:10.1016/j.taap.2018.04.029

SMN1Z
65941

SMN1 Gene, Full Gene Analysis, Varies

Clinical Information: Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by motor neuron degeneration leading to muscular atrophy with progressive paralysis. It is a genetically complex condition that is traditionally divided into 5 subtypes, depending on the age at which symptoms present and the motor milestones that are achieved. Presentation can range from in utero joint contractures and lack of fetal movement (type 0), to loss of ambulation in adolescence or adulthood (type IV). All patients with SMA develop symmetrical loss of muscle control, most commonly affecting proximal muscles. The American College of Medical Genetics and Genomics (ACMG) recommends offering SMA carrier screening to all couples, regardless of race or ethnicity, before conception or early in pregnancy. The most common form of SMA is associated with the loss of survival motor neuron (SMN) protein, which is encoded by 2 or more genes on chromosome 5. The majority of SMN protein is expressed by the survival motor neuron 1 (SMN1) gene, but a small portion of SMN is also contributed by the survival motor neuron 2 (SMN2) gene. Indeed, SMN1 produces more than 90% of SMN protein, while SMN2 produces less than 10% of residual SMN protein. This occurs because SMN2 differs from SMN1 by 5 nucleotides, 1 of which leads to alternative exon 7 splicing, and a reduction of SMN2 expression. Most individuals have 2 copies of SMN1, but individuals with as many as 5 copies of SMN1 are detected. In addition, individuals may also have 0 to 5 copies of SMN2. SMA is most commonly caused by a homozygous deletion of exon 7 in SMN1. However, some patients with this disorder may be compound heterozygotes, with a deletion of 1 copy of SMN1 and a nucleotide variant in the other allele. The severity of a patient's disease course is associated with the number of copies of SMN2 that are present, and 3 or more SMN2 copies are associated with a milder SMA phenotype. This test aims to specifically identify nucleotide variants in SMN1 by direct sequencing and to distinguish these nucleotide variants from changes within SMN2. However, SMN1 exon 1 variants are still unable to be distinguished from changes within SMN2 exon 1.

Useful For: Confirming a diagnosis of spinal muscular atrophy due to nucleotide variants in SMN1 gene Second-tier carrier screening when there is a family history of spinal muscular atrophy, but an affected individual is not available for testing, or when disease-causing variants are unknown Second-tier carrier screening for the reproductive partner of a known SMA carrier

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 2. Wirth B: An update of the mutation spectrum of the survival motor neuron gene (SMN1) in autosomal recessive spinal muscular atrophy (SMA). Hum Mutat. 2000;15:228-237 3. Clermont O, Burlet P, Benit P, et al: Molecular analysis of SMA patients without homozygous SMN1 deletions using a new strategy for identification of SMN1 subtle mutations. Hum Mutat. 2004;24:417-427 4. Kubo Y, Nishio H, Saito K: A new method for SMN1 and hybrid SMN gene analysis in spinal muscular atrophy using long-range PCR followed by sequencing. J Hum Genet. 2015;60: 233-239 5. Prior T, Leach ME, Finanger E: Spinal muscular atrophy. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. Gene Reviews [Internet]. University of Washington, Seattle; 2000. Updated November 14, 2019. Accessed September 28, 2020. Available at www.ncbi.nlm.nih.gov/sites/books/NBK1352/ 6. The Human Gene Mutation Database (HGMD), Professional version 2017.2 from BIOBASE. A database of germline mutations in genes associated with human inherited disease. Accessed Sep 12, 2017. Available at https://portal.biobase-international.com/hgmd/pro/start.php

SMAS
609515

Smooth Muscle Antibody Screen, Serum

Clinical Information: Autoimmune hepatitis (AIH) is a chronic disease resulting from immune-mediated liver injury with varied clinical manifestations.(1-2) The precise factors leading to disease initiation and perpetuation are unknown, but likely reflect a combination of genetic predisposition relating to defects in immunological control of autoreactivity, as well as environmental triggers, which precipitate a persistent breakdown in self-tolerance.(2) Initially, patients with AIH may be clinically asymptomatic, and are usually identified only through an incidental finding of abnormal liver function tests.(1-4) At a more advanced stage, patients may manifest with symptoms such as jaundice, pruritus, or ascites, which are secondary to the more extensive liver damage. As implied by the name, AIH has many characteristics of an autoimmune disease, including female predominance, hypergammaglobulinemia, association with specific HLA alleles, responsiveness to immunosuppression, and the presence of autoantibodies.(1-3) The clinical features of AIH are nonspecific and can be seen in variety of liver diseases such as drug/alcohol-associated hepatitis, viral hepatitis, and primary sclerosing cholangitis. Therefore, the diagnosis can be challenging. A set of diagnostic criteria for AIH has been published and includes the presence of various autoantibodies, elevated total IgG, evidence of hepatitis on liver histology, and absence of viral markers.(1,3,4) Based on the specific autoantibodies present, AIH can be categorized in three categories.(4) The most prevalent is AIH type 1, linked to the presence of smooth muscle autoantibodies (SMA), antinuclear antibodies (ANA) and perinuclear anti-neutrophil cytoplasmic antibodies. SMA are generally identified by indirect immunofluorescence using a smooth muscle substrate. The antigen specificity of SMA in the context of AIH has been identified as filamentous-actin (F-actin).(3) The combination of autoantibody serology, specifically SMA and anti-F-actin antibodies with liver histology and thorough clinical evaluation are useful in the evaluation of patients with suspected autoimmune hepatitis. SMAs are detected in up to 85% of patients with AIH, either alone or in conjunction with ANA.(1,4,5) The SMA titer can also contribute to International Autoimmune Hepatitis Group diagnostic score in patients with a probable or definite diagnosis of AIH.(1,4,5) These antibodies have also been reported in 33% to 65% of cases of primary biliary cholangitis/AIH overlap syndrome (6), the concomitant presence of SMA and AMA being highly suggestive in this setting.

Useful For: Evaluation of patients with hepatitis of unknown origin associated with hypergammaglobulinemia and/or abnormal liver enzymes

Interpretation: Positivity for smooth muscle antibodies (SMA) may help support a diagnosis of autoimmune hepatitis (AIH) following exclusion of other causes of hepatitis. A negative result for SMA does not exclude a diagnosis of AIH.

Reference Values:

Negative
Reference values apply to all ages.

Clinical References:

SMAT
608956

Smooth Muscle Antibody Titer, Serum

Clinical Information: Autoimmune hepatitis (AIH) is a chronic disease resulting from immune-mediated liver injury with varied clinical manifestations (1,2) The precise factors leading to disease initiation and perpetuation are unknown, but likely reflect a combination of genetic predisposition relating to defects in immunological control of autoreactivity, as well as environmental triggers, which precipitate a persistent breakdown in self-tolerance.(2) Initially, patients with AIH may be clinically asymptomatic, and are usually identified only through an incidental finding of abnormal liver function tests.(1-4) At a more advanced stage, patients may manifest with symptoms such as jaundice, pruritus, or ascites, which are secondary to the more extensive liver damage. As implied by the name, AIH has many characteristics of an autoimmune disease, including female predominance, hypergammaglobulinemia, association with specific HLA alleles, responsiveness to immunosuppression, and the presence of autoantibodies.(1-3) The clinical features of AIH are nonspecific and can be seen in variety of liver diseases (drug/alcohol-associated hepatitis, viral hepatitis, primary sclerosing cholangitis, etc), the diagnosis can be challenging. A set of diagnostic criteria for AIH has been published and includes the presence of various autoantibodies, elevated total IgG, evidence of hepatitis on liver histology, and absence of viral markers.(1,3,4) Based on the specific autoantibodies present, AIH can be categorized in three categories.(4) The most prevalent is AIH type 1, linked to the presence of smooth muscle autoantibodies,(SMA) antinuclear antibodies (ANA) and perinuclear anti-neutrophil cytoplasmic antibodies. SMA are generally identified by indirect immunofluorescence using a smooth muscle substrate. The antigen specificity of SMA in the context of AIH has been identified as filamentous-actin (F-actin).(3) The combination of autoantibody serology, specifically SMA and anti-F-actin antibodies with liver histology and thorough clinical evaluation are useful in the evaluation of patients with suspected autoimmune hepatitis. SMA are detected in up to 85% of patients with AIH, either alone or in conjunction with ANA.(1,4,5) The SMA titer can also contribute to International Autoimmune Hepatitis Group diagnostic score in patients with a probable or definite diagnosis of AIH.(1,4,5) These antibodies have also been reported in 33% to 65% of cases of primary biliary cholangitis/AIH overlap syndrome(6), the concomitant presence of SMA and AMA being highly suggestive in this setting.

Useful For: Antibody titer testing as a part of the evaluation of patients with hepatitis of unknown origin associated with hypergammaglobulinemia and/or abnormal liver enzymes

Interpretation: Positivity for smooth muscle antibodies (SMA) may help support a diagnosis of autoimmune hepatitis (AIH) following exclusion of other causes of hepatitis. A negative result for SMA does not exclude a diagnosis of AIH.

Reference Values:

Only orderable as part of a reflex. For more information see SMAS / Smooth Muscle Antibody Screen, Serum.

Negative
Reference values apply to all ages.

Clinical References: 1. European Association for the Study of the Liver. EASL clinical practice guidelines: autoimmune hepatitis. J Hepatol. 2015;63(4):971-1004 2. Mieli-Vergani G, Vergani D, Czaja AJ, et al. Autoimmune hepatitis. Nat Rev Dis Primers. 2018;4:18017 3. Sebode M, Weiler-Normann C, Liwinski T, Schramm C. Autoantibodies in autoimmune liver disease-clinical and diagnostic relevance. Front Immunol. 2018;9:609 4. Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D. Autoimmune hepatitis: Serum autoantibodies in clinical practice. Clin Rev Allergy Immunol. 2022;63(2):124-137 5. Bogdanos DP, Invernizzi P, Mackay IR, Vergani D. Autoimmune liver serology: current diagnostic and clinical challenges. World J Gastroenterol. 2008;14(21):3374-3387 6. Muratori P, Granito A, Pappas G, et al. The serological profile of the autoimmune hepatitis/primary biliary cirrhosis overlap syndrome. Am J Gastroenterol. 2009;104(6):1420-1425

SMOTH
70552

Smoothelin Immunostain, Technical Component Only

Clinical Information: Smoothelin is a smooth muscle-specific marker expressed only in terminally differentiated smooth muscle cells as part of the cytoskeleton. It is expressed normally in the smooth muscle of the muscularis of the bowel as well as in smooth muscle in other organs.

Useful For: Distinguishing muscularis mucosae from muscularis propria

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Paner GP, Brown JG, Lapetino S, et al. Diagnostic use of antibody to smoothelin in the recognition of muscularis propria in transurethral resection of urinary bladder tumor (TURBT) specimens. Am J Surg Pathol. 2010;34(6):792-799 2. Miyamoto H, Sharma RB, Illei PB, Epstein JI. Pitfalls in the use of smoothelin to identify muscularis propria invasion by urothelial carcinoma. Am J Surg Pathol. 2010;34(3):418-422 3. Bovio IM, Al-Quran SZ, Rosser CJ, Algood CB, Drew PA, Allan RW. Smoothelin immunohistochemistry is a useful adjunct for assessing muscularis propria invasion in bladder carcinoma. Histopathology. 2010;56(7):951-956 4. Paner GP, Shen SS, Lapetino S, et al. Diagnostic utility of antibody to smoothelin in the distinction of muscularis propria from muscularis mucosae of the urinary bladder: a potential ancillary tool in the pathologic staging of invasive urothelial carcinoma. Am J Surg Pathol. 2009;33(1):91-98 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5

SNAIL
82344

Snail, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to

inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to snail Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SOD1Z
617740

SOD1 Gene, Full Gene Analysis, Varies

Clinical Information: Amyotrophic lateral sclerosis (ALS) is a motor neuron disease with progressive loss of upper and lower motor neurons. ALS typically presents with progressive muscle wasting, hyperreflexia, and spasticity. Death from respiratory failure usually occurs within 3 to 5 years of disease onset. The SOD1 gene is the second most commonly known cause of familial ALS (fALS) and is reported to occur in around 12% of fALS cases. Variants in SOD1 are believed to cause ALS through a toxic gain-of-function caused by aggregation of misfolded SOD1 protein. Although most cases of SOD1-related fALS are inherited in an autosomal dominant manner, rare cases with autosomal recessive inheritance have been reported.

Useful For: Establishing a molecular diagnosis for patients with amyotrophic lateral sclerosis (ALS) Identifying variants within SOD1 known to be associated with ALS, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Roggenbuck J, Quick A, Kolb SJ. Genetic testing and genetic counseling for amyotrophic lateral sclerosis: an update for clinicians. Genet Med. 2017;19(3):267-274

NAU
610734

Sodium, 24 Hour, Urine

Clinical Information: Sodium (Na+) is the primary extracellular cation. Sodium is responsible for almost one half the osmolality of the plasma and, therefore, plays a central role in maintaining the normal distribution of water and the osmotic pressure in the extracellular fluid compartment. The amount of Na+ in the body is a reflection of the balance between Na+ intake and output. The normal daily diet contains 8 to 15 grams of sodium chloride (NaCl) which is nearly completely absorbed from the gastrointestinal tract. The body requires only 1 to 2 mmol/day, and the excess is excreted by the kidneys, which are the ultimate regulators of the amount of Na+ (and thus water) in the body. Sodium is freely filtered by the glomeruli. Approximately 70% to 80% of the filtered Na+ is actively reabsorbed in the proximal tubules, with chloride and water passively following in an iso-osmotic and electrically neutral manner. Another 20% to 25% is reabsorbed in the loop of Henle along with chloride and more water. In the distal tubules, interaction of the adrenocortical hormone aldosterone with the coupled sodium-potassium and sodium-hydrogen exchange systems directly results in the reabsorption of Na+ and indirectly of chloride from the remaining 5% to 10% of the filtered load. It is the regulation of this latter fraction of filtered Na+ that determines the amount of Na+ excreted in the urine.

Useful For: Assessing acid-base balance, water balance, water intoxication, and dehydration

Interpretation: Urinary sodium (Na+) excretion varies with dietary intake, and there is a large diurnal variation with the rate of Na+ excretion during the night, being only 20% of the peak rate during the day. Sodium may be lost in the kidneys as a result of diuretic therapy, salt-losing nephropathies, or adrenal insufficiency, with the urinary Na+ concentration usually more than 20 mEq/L. In these hypovolemic states, urine Na+ values <10 mEq/L indicate extrarenal Na+ loss. In hypervolemic states, a low urine Na+ (<10 mEq/L) may indicate nephrotic syndrome in addition to non-kidney causes.

Reference Values:
> or =18 years: 22-328 mmol/24 hours

Reference values have not been established for patients who are less than 18 years of age.

Clinical References: Delaney MP, Lamb EJ: Kidney disease. In: Rifai NF, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1308-1309

RNAUR
610785

Sodium, Random, Urine

Clinical Information: Sodium (Na+) is the primary extracellular cation. Na+ is responsible for almost one-half the osmolality of the plasma and, therefore, plays a central role in maintaining the normal distribution of water and the osmotic pressure in the extracellular fluid compartment. The amount of Na+ in the body is a reflection of the balance between Na+ intake and output. The normal daily diet contains 8 to 15 grams of sodium chloride (NaCl), which is nearly completely absorbed from the gastrointestinal tract. The body requires only 1 to 2 mmol/day, and the excess is excreted by the kidneys, which are the ultimate regulators of the amount of Na+ (and thus water) in the body. Na+ is freely filtered by the glomeruli. Approximately 70% to 80% of the filtered Na+ is actively reabsorbed in the proximal tubules with chloride and water passively following in an iso-osmotic and electrically neutral manner. Another 20% to 25% is reabsorbed in the loop of Henle along with chloride and more water. In the distal tubules, interaction of the adrenocortical hormone aldosterone with the coupled sodium-potassium and sodium-hydrogen exchange systems directly results in the reabsorption of Na+ and indirectly of chloride from the remaining 5% to 10% of the filtered load. It is the regulation of this latter fraction of filtered Na+ that determines the amount of Na+ excreted in the urine.

Useful For: Assessing acid-base balance, water balance, water intoxication, and dehydration

Interpretation: Urinary sodium (Na+) excretion varies with dietary intake, and there is a large diurnal variation with the rate of Na+ excretion during the night being only 20% of the peak rate during the day. Na+ may be lost in the kidneys as a result of diuretic therapy, salt-losing nephropathies, or adrenal insufficiency, with the urinary Na+ concentration usually more than 20 mEq/L. In these hypovolemic states, urine Na+ values less than 10 mEq/L indicate extrarenal Na+ loss. In hypervolemic states, a low urine Na+ (<10 mEq/L) may indicate nephrotic syndrome in addition to non-kidney causes.

Reference Values:
No established reference values.
Random urine sodium may be interpreted in conjunction with serum sodium, using both values to calculate fractional excretion of sodium.

The calculation for fractional excretion (FE) of sodium (Na) is
FE(Na)= ([Na(urine)XCreat(serum)]/[Na(serum)XCreat(urine)])X100

Clinical References: 1. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1308-1309

NAS
602353

Sodium, Serum

Clinical Information: Sodium is the primary extracellular cation. Sodium is responsible for almost one-half the osmolality of the plasma and, therefore, plays a central role in maintaining the normal distribution of water and the osmotic pressure in the extracellular fluid compartment. The amount of sodium in the body is a reflection of the balance between sodium intake and output. Hyponatremia (low sodium) is a predictable consequence of decreased intake of sodium, particularly that precipitated or complicated by unusual losses of sodium from the gastrointestinal tract (eg, vomiting and diarrhea), kidneys, or sweat glands. Renal loss may be caused by inappropriate choice, dose, or use of diuretics; by primary or secondary deficiency of aldosterone and other mineralocorticoids; or by severe polyuria. It is common in metabolic acidosis. Hyponatremia also occurs in nephrotic syndrome, hypoproteinemia, primary and secondary adrenocortical insufficiency, and congestive heart failure. Symptoms of hyponatremia are a result of brain swelling and range from weakness to seizures, coma, and death. Hypernatremia (high sodium) is often attributable to excessive loss of sodium-poor body fluids. Hypernatremia is often associated with hypercalcemia and hypokalemia and is seen in liver disease, cardiac failure, pregnancy, burns, and osmotic diuresis. Other causes include decreased production of

antidiuretic hormone (ADH; also known as vasopressin) or decreased tubular sensitivity to the hormone (ie, diabetes insipidus), inappropriate forms of parenteral therapy with saline solutions, or high salt intake without corresponding intake of water. Hypernatremia occurs in dehydration, increased renal sodium conservation in hyperaldosteronism, Cushing syndrome, and diabetic acidosis. Severe hypernatremia may be associated with volume contraction, lactic acidosis, and increased hematocrit. Symptoms of hypernatremia range from thirst to confusion, irritability, seizures, coma, and death.

Useful For: Assessing acid-base balance, water balance, water intoxication, and dehydration

Interpretation: Symptoms of hyponatremia depend primarily upon the rate of change in sodium concentration, rather than the absolute level. Typically, sodium values less than 120 mEq/L result in weakness; values less than 100 mEq/L result in bulbar or pseudobulbar palsy; and values between 90 and 105 mEq/L result in severe signs and symptoms of neurological impairment. Symptoms associated with hypernatremia depend upon the degree of hyperosmolality present.

Reference Values:
<1 year: not established
> or =1 year: 135-145 mmol/L

Clinical References: Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. WB Saunders Company. Philadelphia, PA, 1994

SOLEF
86310

Sole, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to sole Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FSFM
58015

Soluble Fibrin Monomer

Reference Values:
Negative

SOLFM
602175

Soluble Fibrin Monomer, Plasma

Clinical Information: Fibrin monomers are intermediate products formed during the proteolysis of fibrinogen by thrombin. During intravascular coagulation, low levels of thrombin are available in the blood, but the quantity of fibrin monomers formed are not sufficient to aggregate and form a clot; instead, they associate themselves with fibrinogen or fibrinogen-degradation products to form soluble complexes (ie, soluble fibrin monomer complex). Disseminated intravascular coagulation (DIC)/intravascular coagulation and fibrinolysis (ICF), collectively termed DIC/ICF is a clinical diagnosis; no single test is completely sensitive or specific for DIC/ICF.

Useful For: Assisting in the diagnosis of arterial or venous prethrombotic states in various pathological and clinical situations including disseminated intravascular coagulation/intravascular coagulation and fibrinolysis and postoperative monitoring of surgeries with a high risk of thromboses

Interpretation: A normal soluble fibrin monomer complex (SFMC) does not exclude the presence of thrombosis or early disseminated intravascular coagulation (DIC)/intravascular coagulation and fibrinolysis (ICF). An elevated SFMC may be seen in patients with venous or arterial thromboembolism or DIC/ICF. It may also be mildly elevated in clotted specimens.

Reference Values:
Only orderable as a reflex. For more information see:
ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
AATHR / Thrombophilia Profile, Plasma and Whole Blood
APROL / Prolonged Clot Time Profile, Plasma

ADIC / Disseminated Intravascular Coagulation/Intravascular Coagulation and Fibrinolysis (DIC/ICF) Profile, Plasma

< or =8 mcg/mL

Clinical References: Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. Humana Press; 2017

FSLAA
57735

Soluble Liver Antigen (SLA) Autoantibody

Clinical Information: Anti-soluble liver antigen antibodies are detected in 10-30% of patients with type 1 autoimmune hepatitis (AIH), but not in patients with type 2 AIH, primary sclerosing cholangitis or primary biliary cirrhosis. The antibody is directed against a UGA suppressor tRNA associated protein. In some patients with AIH, this antibody may be the only autoantibody detected by current assays.

Reference Values:

Negative 0.0-20.0 U
Equivocal 20.1-24.9 U
Positive >25.0 U

Antibodies to soluble liver antigen (SLA) appear to be directed against the UGA-suppressor tRNA associated protein. These antibodies are highly specific for autoimmune hepatitis (AIH) and may rarely, be the only autoantibodies detected in serum from such patients. Antibodies to SLA are most closely associated with AIH type 1; the presence of these antibodies in patients with cryptogenic hepatitis suggests that these patients may have AIH type 1.

Anti-SLA antibodies may be detected in some patients with the primary biliary cirrhosis-AIH overlap syndrome, but not in healthy controls.

STFR
84283

Soluble Transferrin Receptor (sTfR), Serum

Clinical Information: Iron uptake into cells is mediated through internalizing iron-transferrin complexes. The iron-transferrin complex binds to transferrin receptors present on the external face of the plasma membrane and is internalized through endosomes with ultimate release of iron into the cytoplasm. Plasma membrane-bound transferrin receptor is released by proteolytic cleavage of the extracellular domain, resulting in the formation of a truncated soluble transferrin receptor (sTfR) that circulates freely in the blood. The concentration of sTfR is an indicator of iron status. Iron deficiency causes overexpression of transferrin receptor and sTfR levels, while iron repletion results in decreased sTfR levels. While ferritin measurement is the accepted method for assessment of iron deficiency, ferritin is an acute-phase reactant and elevates in response to processes that do not correlate with iron status, including inflammation, chronic disease, malignancy, and infection. sTfR is not an acute-phase reactant and the interpretation of iron status using sTfR measurement is not affected by these confounding pathologies.(1)

Useful For: Evaluation of suspected iron deficiency in patients who may have inflammation, infection, or chronic disease and other conditions in which ferritin concentration does not correlate with iron status, including: -Cystic fibrosis patients who frequently have inflammation or infections(2-3) -Evaluating insulin-dependent diabetics who may have iron-deficiency resulting from gastric autoimmunity and atrophic gastritis(4)

Interpretation: Soluble transferrin receptor (sTfR) concentrations are inversely related to iron status; sTfR elevates in response to iron deficiency and decreases in response to iron repletion.

Reference Values:
1.8-4.6 mg/L
It is reported that African Americans may have slightly higher values.

Clinical References:

SLC1Q
610061

Solute Carrier Organic Anion Transporter Family Member 1B1 (SLCO1B1) Genotype, Statin, Varies

Clinical Information: The most common adverse drug reaction associated with statins is skeletal muscle toxicity, which can include myalgia (with and without elevated creatine kinase levels), muscle weakness, muscle cramps, myositis, and rhabdomyolysis.(1) Rhabdomyolysis, while rare, is of clinical concern because of the risk for death as a result of cardiac arrhythmia, renal failure, and disseminated intravascular coagulation. While the underlying causes of statin-associated myopathy are not known, several hypotheses have been formulated, including those related to the biochemical pathway of cholesterol synthesis inhibition and statin metabolism. SLCO1B1 encodes the organic anion-transporting polypeptide 1B1 (OATP1B1) influx transporter located on the basolateral membrane of hepatocytes. OATP1B1 facilitates the hepatic uptake of statins as well as other endogenous compounds (eg, bilirubin). Changes in the activity of this transporter (eg, through genetic variations or drug-drug interactions) can increase the severity of statin-associated myopathy (ie, statin intolerance).(2) SLCO1B1 rs4149056 (c.521T>C, p.V174A), which is found in *5, *15, and *17, interferes with localization of the transporter to the plasma membrane and can lead to increased systemic statin concentrations.(3-4) All statins are substrates of OATP1B1, but the association of SLCO1B1 c.521T>C with statin intolerance varies depending on statin and dose and is most pronounced with higher doses of simvastatin therapy. A case-control study of simvastatin-induced myopathy observed an odds ratio (OR) for myopathy of 4.5 for *5 heterozygotes and 16.9 for *5 homozygotes (compared to individuals who did not carry *5) among patients receiving high-dose (80 mg/day) simvastatin therapy.(4) A dose relationship was also demonstrated in a replication cohort of patients taking 40 mg/day simvastatin with a relative risk of 2.6 per copy of the *5 allele. While the SLCO1B1 c.521T>C genotype has also been shown to affect systemic exposure of other statins (eg, atorvastatin, pravastatin, rosuvastatin) in addition to simvastatin,(3) there is less evidence demonstrating a clinical association between the SLCO1B1 genotype and myopathy with statins other than simvastatin.(2) Frequency of the SLCO1B1 alleles varies across different racial and ethnic groups.

Useful For: Predicting risk for statin-associated myopathy in patients beginning statin therapy, especially simvastatin therapy Determining a potential statin lipid lowering response, especially when using pravastatin

Interpretation: An interpretive report will be provided. The complementary DNA positions are based on NM_006446.4. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Wilke RA, Lin DW, Roden DM, et al. Identifying genetic risk factors for serious adverse drug reactions: current progress and challenges [published correction appears in Nat Rev

Drug Discov. 2008;7(2):185]. Nat Rev Drug Discov. 2007;6(11):904-916. doi: 10.1038/nrd2423 2. Ramsey LB, Johnson SG, Caudle KE, et al. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. Clin Pharmacol Ther. 2014;96(4):423-428. doi: 10.1038/clpt.2014.125 3. Niemi M. Transporter pharmacogenetics and statin toxicity. Clin Pharmacol Ther. 2010;87(1):130-133. doi: 10.1038/clpt.2009.197 4. SEARCH Collaborative Group, Link E, Parish S, et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. N Engl J Med. 2008;359(8):789-799. doi: 10.1056/NEJMoa0801936

FSOM1 75906 Somatostatin (Somatotropin Release-Inhibiting Factor, SRIF)

Reference Values:
Up to 25 pg/mL

SOMAT 70553 Somatostatin Immunostain, Technical Component Only

Clinical Information: Somatostatin is a cyclic polypeptide hormone originally isolated from the hypothalamus and characterized by its ability to inhibit the release of growth hormone from the pituitary. In the digestive system, somatostatin production occurs in the intrinsic nerves of the intestinal wall, endocrine cells of the digestive mucosa, and in the D cells of pancreatic islets. Antibodies to somatostatin can be used to characterize pancreatic islet cell tumors or other neuroendocrine tumors.

Useful For: Aids in the characterization of pancreatic islet cell tumors or other neuroendocrine tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Govindarajan M, Mohan V, Deepa R, Ashok S, Pitchumoni CS. Histopathology and immunohistochemistry of pancreatic islets in fibrocalculous pancreatic diabetes. Diabetes Res Clin Pract. 2001;51(1):29-38 2. Kasacka I, Lebkowski W, Janiuk I, Lapinska J, Lewandowska A. Immunohistochemical identification and localisation of gastrin and somatostatin in endocrine cells of human pyloric gastric mucosa. Folia Morphol (Warsz). 2012;71(1):39-44 3. Sporrong B, Falkmer S, Robboy SJ, et al. Neurohormonal peptides in ovarian carcinoids: an immunohistochemical study of 81 primary carcinoids and of intraovarian metastases from six mid-gut carcinoids. Cancer. 1982;49(1):68-74 4. Zalatnai A, Galambos E, Perjesi E. Importance of immunohistochemical detection of somatostatin receptors. Pathol Oncol Res. 2019;25(2):521-525. doi:10.1007/s12253-018-0426-4 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5

SSTR2 113597 Somatostatin Receptor 2 (SSTR2), Immunostain, Technical Component Only

Clinical Information: Somatostatin receptor 2 (SSTR2) is expressed in the secretory cells of the pancreas and the neurons of the central nervous system. SSTR2 is overexpressed in neuroendocrine tumors and can help predict response to targeted radiopeptide therapy. SSTR2 expression can also play

a role in guiding imaging studies and treatment choice.

Useful For: Aids in the identification of neuroendocrine tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Kiseljak-Vassiliades K, Xu M, Mills TS, et al. Differential somatostatin receptor (SSTR) 1-5 expression and downstream effectors in histologic subtypes of growth hormone pituitary tumors. Mol Cell Endocrinol. 2015;417:73-83 2. Brunner P, Jorg AC, Glatz K, et al. The prognostic and predictive value of sstr2-immunohistochemistry and sstr2-targeted imaging in neuroendocrine tumors. Eur J Nucl Med Mol Imaging. 2017;44(3):468-475 3. Sizdahkhani S, Feldman MJ, Piazza MG, et al. Somatostatin receptor expression on von Hippel-Lindau-associated hemangioblastomas offers novel therapeutic target. Sci Rep. 2017;7:40822 4. Shen Z, Chen X, Li Q, et al. SSTR2 promoter hypermethylation is associated with the risk and progression of laryngeal squamous cell carcinoma in males. Diagn Pathol. 2016;11:10 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5

SORBU
614934

Sorbitol and Mannitol, Quantitative, Random, Urine

Clinical Information: Phosphomannomutase 2 deficiency, or PMM2-CDG, is the most common congenital disorder of glycosylation (CDG) accounting for about 50% of known CDG patients. In many patients with PMM2-CDG, the urine polyols, sorbitol and mannitol, are elevated relative to controls. Sorbitol, in particular, has been shown to be positively correlated with severely affected patients in contrast to patients in the mild or moderate categories. It is also higher in patients with moderate peripheral neuropathy. Both mannitol and sorbitol were increased in patients with mild liver dysfunction.(1) Treatment options for PMM2-CDG remain limited however; current literature reports that the aldose reductase inhibitor, epalrestat, can correct the underlying enzyme deficiency in a majority of patients with PMM2-CDG.(2) Recent trials suggest that treatment with epalrestat, in addition to other therapeutic benefits, resulted in nearly normalized levels of sorbitol and mannitol relative to controls.(1)

Useful For: Monitoring effectiveness of treatment in patients with phosphomannomutase 2 deficiency (PMM2-CDG) Establishing a baseline level prior to initiating treatment for PMM2-CDG This test is not useful for diagnosing congenital disorders of glycosylation (CDG) in general or PMM2-CDG in particular

SORD
620920

Sorbitol and Xylitol, Quantitative, Random, Urine

Clinical Information: Sorbitol dehydrogenase (SORD) deficiency is an autosomal recessive condition caused by biallelic variants in the SORD gene resulting in peripheral neuropathy, which may present as clinically similar to Charcot-Marie-Tooth disease type 2 or distal hereditary motor neuropathy. The SORD enzyme catalyzes the breakdown of sorbitol to fructose. In patients with SORD deficiency-related peripheral neuropathy, the urine polyols, sorbitol and xylitol, are elevated when compared to controls. Polyols are sugar alcohols that have been identified in blood, urine, and cerebrospinal fluid. An abnormal urine polyol result suggestive of SORD deficiency-related peripheral neuropathy should be confirmed with molecular genetic analysis. For molecular confirmation, genetic testing for SORD can be performed (CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify gene list ID: NEUROLOGY-S3NL4H).

Useful For: Screening for sorbitol dehydrogenase deficiency-related neuropathy

Interpretation: An interpretive report will be provided. All profiles are reviewed by the laboratory director and interpretation is based on pattern recognition. A detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, and recommendations for in vitro confirmatory studies (molecular analysis).

Reference Values:
Sorbitol:
<35 mmol/mol creatinine

Xylitol:
<351 mmol/mol creatinine

Clinical References: 1. Cortese A, Zhu Y, Rebelo AP, et al. Biallelic mutations in SORD cause a common and potentially treatable hereditary neuropathy with implications for diabetes. Nat Genet 2020;52(5):473-481. doi:10.1038/s41588-020-0615-4 2. Lassuthova P, Mazanec R, Stanek D, et al. Biallelic variants in the SORD gene are one of the most common causes of hereditary neuropathy among Czech patients. Sci Rep 2021;11(1):8443. doi:10.1038/s41598-021-86857-0 3. Pons N, Fernandez-Eulate G, Pegat A, et al. SORD-related peripheral neuropathy in a French and Swiss cohort: Clinical features, genetic analyses, and sorbitol dosages. Eur J Neurol 2023. doi:10.1111/ene.15793

FSOTA
91123

Sotalol (Betapace)

Reference Values:
Reference Range: 500 - 4000 ng/mL

Serum Sotalol concentrations producing beta-blockade:
500 - 4000 ng/mL

Toxic range has not been established.

SOX10
70555

SOX10 Immunostain, Technical Component Only

Clinical Information: SOX10 (SRY-box transcription factor 10) is a nuclear transcription factor that plays an important role in schwannian and melanocytic cell differentiation and has been shown to be a useful marker in the diagnosis of melanocytic and schwannian tumors. SOX10 is expressed in benign melanocytic naevi and melanomas, including desmoplastic melanoma and spindle cell melanoma. It is also expressed by tumors with schwannian differentiation, including malignant peripheral nerve sheath tumors, Schwannomas, and neurofibromas. SOX10 is expressed in normal tissues, including Schwann cells, melanocytes, and myoepithelial cells of salivary, bronchial, and mammary glands.

Useful For: Identification of malignant melanomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Ramos-Herberth FI, Karamchandani J, Kim J, Dadras SS. SOX10 immunostaining distinguishes desmoplastic melanoma from excision scar. J Cutan Pathol.

2010;37(9):944-952 2. Blochin E, Nonaka D. Diagnostic value of Sox10 immunohistochemical staining for the detection of metastatic melanoma in sentinel lymph nodes. Histopathology. 2009;55(5):626-628 3. Flammiger A, Besch R, Cook AL, Maier T, Sturm RA, Berking C. SOX9 and SOX10 but not BRN2 are required for nestin expression in human melanoma cells. J Invest Dermatol. 2009;129(4):945-953 4. Nonaka D, Chiriboga L, Rubin BP. Sox10: a pan-schwannian and melanocytic marker. Am J Surg Pathol. 2008;32(9):1291-1298 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5

SOX11
70556

SOX11 Immunostain, Technical Component Only

Clinical Information: SOX11 (SRY-box transcription factor 11) is a transcription factor involved in embryonic neurogenesis and tissue remodeling. Nuclear SOX11 is expressed in most B- and T-lymphoblastic leukemia/lymphomas and a proportion of Burkitt lymphomas, but only weakly expressed in some hairy cell leukemias. Mantle cell lymphomas show SOX11 expression and it has been suggested to correlate with overall survival.

Useful For: Identification of mantle cell lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chen YH, Gao J, Fan G, Peterson LC. Nuclear expression of sox11 is highly associated with mantle cell lymphoma but is independent of t(11;14)(q13;q32) in non-mantle cell B-cell neoplasms. Mod Pathol. 2010;23(1):105-112 2. Dictor M, Ek S, Sundberg M, et al. Strong lymphoid nuclear expression of SOX11 transcription factor defines lymphoblastic neoplasms, mantle cell lymphoma and Burkitt's lymphoma. Haematologica. 2009;94(11):1563-1568 3. Ek S, Dictor M, Jerkeman M, Jirstrom K, Borrebaeck CA. Nuclear expression of the non B-cell lineage Sox11 transcription factor identifies mantle cell lymphoma. Blood. 2008;111(2):800-805 4. Fernandez V, Salamero O, Espinet B, et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. Cancer Res. 2010;70(4):1408-1418 5. Mozos A, Royo C, Hartmann E, et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype [published correction appears in Haematologica. 2010 Sep;95(9):1620]. Haematologica. 2009;94(11):1555-1562 6. Soldini D, Valera A, Sole C, et al. Assessment of SOX11 expression in routine lymphoma tissue sections: characterization of new monoclonal antibodies for diagnosis of mantle cell lymphoma. Am J Surg Pathol. 2014;38(1):86-93 7. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5

FSOYG
57551

Soybean IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:

Reference ranges have not been established for food-specific IgG tests.

FSYG4
57574

Soybean IgG4

Interpretation: The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests.

SOY
82886

Soybean, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to soybean Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive

4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

PBC2
620736

SP100 and GP210 Antibodies, IgG, Serum

Clinical Information: Primary biliary cholangitis (PBC) is a chronic and progressive autoimmune liver disease characterized by the destruction of the small intrahepatic bile ducts and a variable clinical course, which may include fatigue and pruritus. Untreated patients with PBC have a high risk of liver cirrhosis and related complications, liver failure, and death.(1,2) The serological hallmark of PBC is the presence of anti-mitochondrial antibody (AMA) characterized by cytoplasmic reticular/AMA (anti-cell 21 [AC-21] based on the International Consensus on Antinuclear Antibody Patterns [ICAP] nomenclature) staining pattern on HEp-2 substrate by indirect immunofluorescence assay (IFA).(3) In addition, autoantibodies associated with the HEp-2 IFA nuclear patterns have been reported in a subset of patients with PBC who are seronegative for AMA or may be positive for AMA but have uncertain clinical or phenotypic attributes.(1,2,4,5) The HEp-2 IFA nuclear patterns in PBC include multiple nuclear dots (MND or AC-6) and punctate nuclear envelope (AC-12), which are associated with anti-Sp100 and anti-gp210 antibodies, respectively.(3) The diagnosis of PBC can be established if 2 out of the 3 following criteria are met: sustained elevated levels of alkaline phosphatase (ALP), evidence AMA or specific antinuclear antibody (ANA) (anti-Sp100 and anti-gp210 antibodies) and diagnostic liver histology.(2) Based on these criteria, a biopsy can be avoided in case of high ALP levels and detection of these PBC-specific autoantibodies.(1,2) Therefore, reliable and accurate serologic determination of PBC-specific autoantibodies play a critical role in disease evaluation. Of the PBC-specific antibodies, the AMA is the most common, with the M2-type AMA (AMA-M2) the dominant target of the 9 subunits of the mitochondrial antigenic complex.(1,2) AMA-M2 target components of the 2-oxo-acid dehydrogenase complex: pyruvate dehydrogenase complex (PDC), 2-oxoglutarate dehydrogenase complex (OGDC), and branched-chain 2-oxoacid dehydrogenase complex (BCOADC). Specifically, autoantibodies mainly recognize the E2 subunits of these complexes: PDC-E2 (80%-90% of cases), BCOADC-E2 (50%-80% of cases) and OGDC-E2 (20%-60% of cases) and, to a lesser extent, the E1 and E3 subunits.(2). In addition to the diagnostic relevance of anti-gp210 IgG antibody, a few studies have suggested a role for their use in the risk stratification and prognosis in PBC; however, the significance of these remain contentious. In one study, the presence of anti-gp210 antibodies was reported to pose a significant risk for hepatic failure type progression, more severe interface hepatitis, and lobular inflammation compared to those with centromere antibodies who had relatively higher ductular reaction.(6) In other investigations, anti-gp210 and/or anti-Sp100 antibodies were reported to be useful in confirming a diagnosis of PBC or predicting development of disease in the context of AMA positivity in nonestablished PBC cases.(5,7) The anti-Sp100 and anti-gp210 antibodies can also be determined using analyte-specific enzyme-linked immunosorbent assay, line blot immunoassay, and dot immunoassay.(4-8) In addition to the solid-phase immunoassays (SPA) for detecting antibodies to AMA, Sp100 and gp210, the use HEp-2 substrate by IFA provides a simple and strategic approach for confirming the presence of AMA cytoplasmic staining if positive by enzyme immunoassay (EIA) with the possibility of identifying patients who may be AMA-negative but positive to nuclear antibodies. In PBC patients, the nuclear envelope pattern is associated with anti-gp210 antibody, while the multiple nuclear dots pattern is specific for anti-Sp100 antibodies. However, expression of the multiple nuclear dot and the nuclear envelope patterns may not be easily identified in the presence of other antibodies. Testing for these antibodies is indicated in patients who are AMA positive by EIA as well as patients at-risk for PBC but are AMA negative. In addition to providing additional support for

PBC diagnosis in AMA-positive and AMA-negative patients, the use of HEp-2 substrate offers the possibility to identify patients at-risk for PBC who may present with coexisting systemic autoimmune rheumatic diseases (systemic lupus erythematosus, systemic sclerosis, and Sjogren syndrome) or autoimmune liver disease (autoimmune hepatitis) through additional pattern recognition.(9,10) The use of SPA for ANA testing do not provide these additional diagnostic insights. For more information see First-Line Screening for Autoimmune Liver Disease Algorithm.

Useful For: Evaluating the risk of primary biliary cholangitis in anti-mitochondrial antibody (AMA)-negative patients by identification of Sp100 and gp210 antibodies Estimating risk in AMA-positive patients with incomplete feature of disease

Interpretation: A positive result for anti-gp210 antibodies or anti-Sp100 antibodies in the setting of chronic cholestasis after exclusion of other causes of liver disease is highly suggestive of primary biliary cholangitis.

Reference Values:

Negative: < or =20.0 Units
Equivocal: 20.1-24.9 Units
Positive: > or =25.0 Units

Clinical References: 1. Younossi ZM, Bernstein D, Shiffman ML, et al. Diagnosis and management of primary biliary cholangitis. Am J Gastroenterol. 2019;114(1):48-63 2. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance update from the American Association for the Study of Liver Diseases. Hepatology. 2019;69(1):394-419 3. International Consensus on ANA Patterns. AC-20 Cytoplasmic fine speckled. ICAP; 2015. Accessed August 18, 2023. Available at www.anapatterns.org/view_pattern.php?pattern=20 4. Zhang Q, Liu Z, Wu S, et al. Meta-analysis of antinuclear antibodies in the diagnosis of antimitochondrial antibody-negative primary biliary cholangitis. Gastroenterol Res Pract. 2019;2019:8959103 5. Dahlqvist G, Gaouar F, Carrat F, et al. Large-scale characterization study of patients with antimitochondrial antibodies but nonestablished primary biliary cholangitis. Hepatology. 2017;65(1):152-163 6. Nakamura M, Kondo H, Mori T, et al. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. Hepatology. 2007;45(1):118-127 7. Jaskowski TD, Nandakumar V, Novis CL, Palmer M, Tebo AE. Presence of anti-gp210 or anti-sp100 antibodies in AMA-positive patients may help support a diagnosis of primary biliary cholangitis. Clin Chim Acta. 2023;540:117219 8. Munoz-Sanchez G, Perez-Isidro A, Ortiz de Landazuri I, et al. Working algorithms and detection methods of autoantibodies in autoimmune liver disease: A nationwide study. Diagnostics (Basel). 2022;12:697 9. Favoino E, Grapsi E, Barbuti G, et al. Systemic sclerosis and primary biliary cholangitis share an antibody population with identical specificity. Clin Exp Immunol. 2023;212(1):32-38 10. Wei Q, Jiang Y, Xie J, et al. Investigation and analysis of HEp 2 indirect immunofluorescence titers and patterns in various liver diseases [published correction appears in Clin Rheumatol. 2021 Apr;40(4):1667]. Clin Rheumatol. 2020;39(8):2425-2432. doi:10.1007/s10067-020-04950-7

SP100
620725

SP100 Antibody, IgG, Serum

Clinical Information:

Useful For: Evaluating the risk of primary biliary cholangitis in anti-mitochondrial antibody (AMA) negative patients by identification of Sp100 antibodies Estimating risk in AMA-positive patients with incomplete feature of disease

Interpretation: A positive result for anti-Sp100 antibodies in the setting of chronic cholestasis after

exclusion of other causes of liver disease is highly suggestive of primary biliary cholangitis.

Reference Values:
Negative: < or =20.0 Units
Equivocal: 20.1-24.9 Units
Positive: > or =25.0 Units

Clinical References: 1. Younossi ZM, Bernstein D, Shiffman ML, et al. Diagnosis and management of primary biliary cholangitis. Am J Gastroenterol. 2019;114(1):48-63 2. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance update from the American Association for the Study of Liver Diseases. Hepatology. 2019;69(1):394-419 3. International Consensus on ANA Patterns. AC-20 Cytoplasmic fine speckled. ICAP; 2015. Accessed August 18, 2023. Available at www.anapatterns.org/view_pattern.php?pattern=20 4. Zhang Q, Liu Z, Wu S, et al. Meta-analysis of antinuclear antibodies in the diagnosis of antimitochondrial antibody-negative primary biliary cholangitis. Gastroenterol Res Pract. 2019;2019:8959103 5. Dahlqvist G, Gaouar F, Carrat F, et al. Large-scale characterization study of patients with antimitochondrial antibodies but nonestablished primary biliary cholangitis. Hepatology. 2017;65(1):152-163 6. Nakamura M, Kondo H, Mori T, et al. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. Hepatology. 2007;45(1):118-127 7. Jaskowski TD, Nandakumar V, Novis CL, Palmer M, Tebo AE. Presence of anti-gp210 or anti-sp100 antibodies in AMA-positive patients may help support a diagnosis of primary biliary cholangitis. Clin Chim Acta. 2023;540:117219 8. Munoz-Sanchez G, Perez-Isidro A, Ortiz de Landazuri I, et al. Working algorithms and detection methods of autoantibodies in autoimmune liver disease: A nationwide study. Diagnostics (Basel). 2022;12:697 9. Favoino E, Grapsi E, Barbuti G, et al. Systemic sclerosis and primary biliary cholangitis share an antibody population with identical specificity. Clin Exp Immunol. 2023;212(1):32-38 10. Wei Q, Jiang Y, Xie J, et al. Investigation and analysis of HEp 2 indirect immunofluorescence titers and patterns in various liver diseases [published correction appears in Clin Rheumatol. 2021 Apr;40(4):1667]. Clin Rheumatol. 2020;39(8):2425-2432. doi:10.1007/s10067-020-04950-7

SPAGR
113392

Special Red Cell Antigen Typing, Whole Blood

Clinical Information: The presence or absence of a cellular antigen is an inherited trait. Generally, individuals will not make antibody directed against an antigen present on their own red blood cells.

Useful For: Additional proof of alloantibody specificity Determining possible antibody specificities in complex cases This test is not useful for the purpose of establishing paternity

Interpretation: Each antigen typed will be listed by name, followed by "pos" or "+" indicating that the antigen is present, or by "neg" or "-" indicating that the antigen is absent.

Reference Values:
Reported as positive or negative

Clinical References: Cohn CS, Delaney M, Johnson ST, Katz LM, Schwartz J, eds. Technical Manual. 21st ed. AABB; 2023

SGUR
606565

Specific Gravity, Random, Urine

Clinical Information: Specific gravity (SG), the ratio of the mass of a solution compared to the mass of an equal volume of water, is an estimate of the concentration of substances dissolved in the solution.

Urine SG can be used to assess the kidney's ability to concentrate or dilute urine. However, because protein, glucose, and contrast dye have molecular masses that are relatively large compared to other major components of urine (eg, sodium, chloride, potassium), they disproportionately affect SG. In these cases, urine osmolality is a better measure of urine concentration

Useful For: As a partial assessment of the kidney's ability to concentrate urine

Interpretation: Low specific gravity (SG) (1.001-1.003) may indicate the presence of diabetes insipidus, a disease caused by impaired functioning of antidiuretic hormone (ADH). Low SG also can occur in patients with glomerulonephritis, pyelonephritis, and other renal abnormalities. In these cases, the kidney has lost its ability to concentrate due to tubular damage. High SG may occur in patients with adrenal insufficiency, hepatic disease, congestive heart failure, or in patients experiencing excessive water loss due to sweating, fever, vomiting, or diarrhea.

Reference Values:
1.002-1.030

Clinical References: 1. Schumann GB, Schweitzer SC: Examination of urine. In: Kaplan LA, Pesce AJ, eds. Clinical Chemistry, Theory, Analysis and Correlation. 3rd ed. Mosby-Year Book Inc; 1996:1118-1119 2. Free HM, ed: Modern Urine Chemistry (Manual). 8th ed. Bayer Corp; 1996:36-37 3. Perrier ET, Bottin JH, Vecchio M, Lemetais G: Criterion values for urine-specific gravity and urine color representing adequate water intake in healthy adults. Eur J Clin Nutr. 2017 Feb;71:561-563

FSPNG
57678

Spinach IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

SPIN
86312

Spinach, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to spinach Defining the allergen responsible for

eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SMNCS 65574 Spinal Muscular Atrophy Carrier Screening, Deletion/Duplication Analysis, Varies

Clinical Information:

Useful For: General population carrier screening for spinal muscular atrophy (SMA) Carrier screening for reproductive partners of known SMA carriers Carrier screening for parents of a child with a known deletion of the survival motor neuron 1 gene (SMN1) or other family history of SMA

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. D'Amico A, Mercuri E, Tiziano FD, Bertini E: Spinal muscular atrophy. Orphanet J Rare Dis 2011;6:71 2. Hendrickson BC, Donohoe C, Akmaev VR, et al: Differences in SMN1 allele frequencies among ethnic groups within North America. J Med Genet 2009;46:641-644 3. Carre A,

Empey C: Review of Spinal Muscular Atrophy (SMA) for Prenatal and Pediatric Genetic Counselors. 2016;25:32-43 4. Committee on Genetics: Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine. Obstet Gynecol 2017;129:e35-e40 5. Committee on Genetics: Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol March 2017;129;e41-e55 6. Luo M, Liu L, Peter I, et al: An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy. Genet Med 2014;16:149-156 7. Prior TW, Nagan N: Spinal muscular atrophy: overview of molecular diagnostic approaches. Curr Protoc Hum Genet 2016;1:88 unit 9.27 8. Prior TW, Nagan N, Sugarman EA, et al: Technical standards and guidelines for spinal muscular atrophy testing. Genet Med 2011;13:686-694

SMNDX
65575

Spinal Muscular Atrophy Diagnostic Assay, Deletion/Duplication Analysis, Varies

Clinical Information: Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by motor neuron degeneration leading to muscular atrophy with progressive paralysis. It is a genetically complex condition that is traditionally divided into 5 subtypes, depending on the age at which symptoms present and the motor milestones that are achieved. Presentation can range from in utero joint contractures and lack of fetal movement (type 0), to loss of ambulation in adolescence or adulthood (Type IV). All patients with SMA develop symmetrical loss of muscle control, most commonly affecting proximal muscles. The American College of Medical Genetics and Genomics (ACMG) and The American Congress of Obstetricians and Gynecologists (ACOG) currently recommend offering SMA carrier screening to all couples, regardless of race or ethnicity, before conception or early in pregnancy. The most common form of SMA is associated with the loss of survival motor neuron (SMN) protein, which is encoded by 2 or more genes on chromosome 5. The majority of SMN protein is expressed by the SMN1 gene but a small portion of SMN is also contributed by the SMN2 gene. In fact, SMN1 produces more than 90% of SMN protein, while SMN2 produces less than 10% of residual SMN protein. This occurs because SMN2 differs from SMN1 by 5 nucleotide changes, one of which leads to alternative exon 7 splicing, and a reduction of SMN2 expression. Most individuals have 2 copies of SMN1, but individuals with as many as 5 copies of SMN1 have been observed. In addition, individuals may also have 0 to 5 copies of SMN2. SMA is most commonly caused by a homozygous deletion of exon 7 in SMN1. However, some patients with this disorder may be compound heterozygotes, with a deletion of 1 copy of SMN1 and a point alteration in the other allele. The severity of a patient's disease is associated with the number of copies of SMN2 that are present and 3 or more SMN2 copies are associated with a milder SMA phenotype. As the SMA test is a quantitative assay for the number of SMN1 exon 7 deletions, any result showing 2 or more SMN1 copies may, in fact, have 2 copies of SMN1 in cis (on the same chromosome) and a copy of SMN1 with the exon 7 deletion on the other chromosome (in trans). This is called the "2+0" carrier genotype. The frequency of the "2+0" carrier genotype differs by ancestry. Previously, it was not possible to distinguish a "2+0" carrier from an individual with one copy of SMN1 on each chromosome. However, following a study performed by Luo et al,(2) it is now possible to provide an adjusted genetic residual carrier risk specific to one's ancestry, based on the presence or absence of the SMN1 alteration g.27134T>G. The presence of this alteration is linked to being a "2+0" carrier in the Ashkenazi Jewish and Asian populations, and it increases the chances that one is a "2+0" carrier in other populations. See the table below for details. SMA carrier residual risk estimates.(2) Ancestry Carrier frequency Detection rate based on copy number alone Residual risk after detection of 2 copies of SMN1 Detection rate with addition of SMN1 g.27134T>G Residual risk of being a 2+0 carrier after absence of SMN1 g.27134T>G Residual risk of being a 2+0 carrier after presence of SMN1 g.27134T>G Ashkenazi Jewish 1 in 41.1 90% 1 in 345 94% 1 in 580 2+0 Carrier Asian 1 in 53 92.6% 1 in 628 93.3% 1 in 701.8 2+0 Carrier African American 1 in 66 71.1% 1 in 121 N/A 1 in 395.7 1 in 33.5 Hispanic 1 in 117 90.6% 1 in 1,061 N/A 1 in 1,762 1 in 139.6 European 1 in 35 94.9% 1 in 632 N/A 1 in 769.3 1 in 28.6

Useful For: First-tier newborn screening for spinal muscular atrophy (SMA) Prenatal testing for

SMA Diagnostic testing to confirm a suspected diagnosis of SMA

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Newborn Screening ACT Sheet [Exon 7 Deletion (Pathogenic Variant) in Survival Motor Neuron Gene (SMN1)] Spinal Muscular Atrophy (SMA). American College of Medical Genetics and Genomics; 2020. Accessed September 25, 2024. Available at www.acmg.net/PDFLibrary/SMA-ACT-Sheet.pdf 2. Luo M, Liu L, Peter I, et al: An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy. Genet Med. 2014;16:149-156. doi: 10.1038/gim.2013.84 3. Hendrickson BC, Donohoe C, Akmaev VR, et al: Differences in SMN1 allele frequencies among ethnic groups within North America. J Med Genet. 2009;46:641-644. doi:10.1136/jmg.2009.066969 4. Carre A, Empey C: Review of spinal muscular atrophy (SMA) for prenatal and pediatric genetic counselors. J Genet Couns. 2016;25:32-43. doi:10.1007/s10897-015-9859-z 5. Committee on Genetics: Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine. Obstet Gynecol. 2017;129:e35-e40. doi:10.1097/AOG.0000000000001951 6. Committee on Genetics: Committee Opinion No. 691: Carrier Screening for Genetic Conditions. Obstet Gynecol. March 2017;129;e41-e55. doi:10.1097/AOG.0000000000001952 7. D'Amico A, Mercuri E, Tiziano FD, Bertini E: Spinal muscular atrophy. Orphanet J Rare Dis. 2011;6:71. doi: 10.1186/1750-1172-6-71 8. Prior TW, Nagan N: Spinal muscular atrophy: overview of molecular diagnostic approaches. Curr Protoc Hum Genet. 2016;1:88 unit 9.27. doi:10.1002/0471142905.hg0927s88 9. Prior TW, Nagan N, Sugarman EA, Batish SD, Braastad C: Technical standards and guidelines for spinal muscular atrophy testing. Genet Med, 2011;13:686-694. doi:10.1097/GIM.0b013e318220d523

SBULB
35542

Spinobulbar Muscular Atrophy (Kennedy Disease), Molecular Analysis, Varies

Clinical Information: X-linked spinal and bulbar muscular atrophy (spinobulbar muscular atrophy [SBMA] or Kennedy disease) is characterized by onset of progressive muscle weakness, atrophy, and fasciculations typically in the fourth or fifth decade of life. Affected patients also have signs of androgen insensitivity such as gynecomastia, reduced fertility, and testicular atrophy. The clinical severity and age at onset can be quite variable, even within families. Because this is an X-linked disease, males manifest this disorder and females are generally asymptomatic carriers. However, there have been reports of female carriers who exhibit symptoms such as muscle weakness and cramping. Spinobulbar muscular atrophy is caused by an expansion of the CAG trinucleotide repeat in exon 1 of the human androgen receptor (AR) gene. This trinucleotide repeat is polymorphic in the general population, with the number of repeats ranging from 11 to 34. The number of repeats found in affected individuals can range from 38 to 62. There is no consensus as to the clinical significance of alleles of 35 CAG repeats and literature suggests that alleles of 36 to 37 CAG repeats may be associated with reduced penetrance. As with other trinucleotide repeat disorders, anticipation is frequently observed, and larger CAG expansions are associated with earlier onset and a more rapid clinical progression.

Useful For: Molecular confirmation of clinically suspected cases of sporadic or familial spinobulbar muscular atrophy (SBMA) Presymptomatic testing for individuals with a family history of SBMA and a documented expansion in the androgen receptor (AR) gene

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
Normal alleles: 11-34 CAG repeats

Abnormal alleles: 36-62 CAG repeats

The interpretive report includes an overview of the findings as well as the associated clinical significance.

Clinical References: 1. Pinsky L, Beitel LK, Trifiro MA: Spinobulbar Muscular Atrophy. In Scriver CR, Beaudet AL, Sly WS, et al. The Metabolic and Molecular Basis of Inherited Disease. Vol 4. 8th ed. McGraw-Hill Book Company, 2001;4147-4157 2. Breza M, Koutsis G. Kennedy's disease (spinal and bulbar muscular atrophy): a clinically oriented review of a rare disease. J Neurol. 2019;266(3):565-573. doi:10.1007/s00415-018-8968-7

SCAP
609505

Spinocerebellar Ataxia Repeat Expansion Panel, Varies

Clinical Information: Spinocerebellar Ataxia Type 1: Spinocerebellar ataxia type 1 (SCA1) is characterized by progressive ataxia, dysarthria, eventual deterioration of bulbar functions, and ophthalmoplegia. Onset typically occurs in the third to fourth decade of life. Most individuals present with difficulties in gait or slurred speech. SCA1 is caused by an expansion of the CAG (cytosine-adenine-guanine) trinucleotide repeat in the ATXN1 gene. This trinucleotide repeat is polymorphic in the general population, with the number of benign repeats ranging from 6 to 37. The pathogenicity of the repeat is dependent on the presence or absence of CAT (cytosine-adenine-thymine) trinucleotide repeats that interrupt the CAG repeats. Therefore, individuals with 36 to 37 uninterrupted CAG repeats are predisposed to having a child with an expanded allele. In affected individuals, the CAG expansions are greater than 38 uninterrupted CAG repeats or greater than 44 repeats, regardless of the presence or absence of CAT repeat interruptions. The presence of CAT repeats in an individual with 36 to 43 CAG repeats is considered normal and not disease-causing. In contrast, 38 CAG repeats without CAT repeats are of uncertain significance. There is a report of an individual with very last onset SCA1 with 38 CAG repeats. Reduced penetrance has been associated with 44 CAG repeats. As with other trinucleotide repeat disorders, large CAG expansions are associated with earlier onset and a more severe clinical course. Spinocerebellar Ataxia Type 2:Spinocerebellar ataxia type 2 (SCA2) is characterized by slowly progressive ataxia, dysarthria, and slow saccadic eye movements. The mean age of onset is in the fourth decade, but symptoms may appear from childhood to later adulthood. SCA2 is caused by an expansion of the CAG trinucleotide repeat in the ATXN2 gene. This trinucleotide repeat is polymorphic in the general population, with the number of benign repeats less than 32. However, 29 to 31 heterozygous repeats have been associated with an increased exponential risk for amyotrophic lateral sclerosis (ALS). Additionally, there has been a report of an individual homozygous for 31 repeats with late-onset cerebellar ataxia. In contrast, 27 repeats have been associated with a protective effect for ALS. In affected individuals, the CAG expansion is greater than 34 repeats, with the most common disease-causing alleles having 37 to 39 repeats. Larger CAG expansions are associated with an earlier age of onset but repeat length cannot predict age of onset or disease severity. A CAG expansion of 32 repeats is of unclear clinical significance. Repeats in the 33 to 34 range are associated with reduced penetrance. Spinocerebellar Ataxia Type 3: Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease, is characterized by progressive cerebellar ataxia and pyramidal signs. The age of onset is highly variable but most commonly occurs in the second to fifth decade of life. Individuals may present with gait problems, speech difficulties, clumsiness, or visual blurring. SCA3 is caused by an expansion of the CAG trinucleotide repeat in the ATXN3 gene. This trinucleotide repeat is polymorphic in the general population, with the number of benign repeats ranging from 12 to 44. In affected individuals, the CAG expansion ranges from 60 to 87 repeats. A loose correlation exists between repeat length and clinical phenotype. Individuals with 45 to 59 CAG repeats are predisposed to having a child with an expanded allele and may or may not have symptoms themselves. There have been reports of reduced penetrant and nonpenetrant alleles with repeats in this range. Spinocerebellar Ataxia Type 6: Spinocerebellar

ataxia type 6 (SCA6) is characterized by adult-onset, slowly progressive cerebellar ataxia, dysarthria, and nystagmus. The mean age of onset is 43 to 52 years. Initial symptoms include unsteadiness, stumbling, and imbalance. SCA6 is caused by an expansion of the CAG trinucleotide repeat in the CACNA1A gene. This trinucleotide repeat is polymorphic in the general population, with the number of benign repeats less than 19. In affected individuals, the CAG expansion ranges from 20 to 33 repeats. Larger CAG expansions are associated with an earlier age of onset. A CAG expansion of 19 repeats is of unclear clinical significance. Individuals with 19 CAG repeats are predisposed to having a child with an expanded allele. Additionally, homozygous abnormal expansions have been reported in individuals with younger age of onset and a more severe phenotype. Spinocerebellar Ataxia Type 7: Spinocerebellar ataxia type 7 (SCA7) is characterized by progressive cerebellar ataxia, including dysarthria and dysphagia, and con-rod and retinal dystrophy. Onset ranges from infancy to the fifth or sixth decade of life. SCA7 is caused by an expansion of the CAG trinucleotide repeat in the ATXN7 gene. This trinucleotide repeat is polymorphic in the general population, with the number of benign repeats less than 19. In affected individuals, the CAG expansion is greater than 36 repeats. A CAG expansion of 19 to 27 repeats is of unclear clinical significance. Individuals with 28 to 33 repeats are predisposed to having a child with an expanded allele but are unlikely to have symptoms themselves. Thirty-four to 36 repeats are associated with reduced penetrance, and when symptoms do occur, they are more likely to be associated with later onset and a milder phenotype.

Useful For:

Interpretation: An interpretive report will be provided.

Reference Values:

SPINOCEREBELLAR ATAXIA TYPE 1
Normal alleles: <36 CAG repeats
Normal alleles with CAT interruptions: 36-43 repeats
Intermediate alleles without CAT interruptions: 36-37 repeats
Uncertain significance: 38 repeats
Expanded alleles without CAT interruptions: >38 CAG repeats
Expanded alleles with CAT interruptions: >43 CAG repeats

SPINOCEREBELLAR ATAXIA TYPE 2
Normal alleles: <32 repeats
Uncertain significance: 31 homozygous and 32 repeats
Reduced penetrance: 33-34 repeats
Expanded alleles: >34 repeats

SPINOCEREBELLAR ATAXIA TYPE 3
Normal alleles: <45 repeats
Intermediate alleles: 45-59 repeats
Expanded alleles: >59 repeats

SPINOCEREBELLAR ATAXIA TYPE 6
Normal alleles: <19 repeats
Intermediate alleles: 19 heterozygous repeats
Uncertain significance: 19 homozygous repeats
Expanded alleles: >19 repeats

SPINOCEREBELLAR ATAXIA TYPE 7
Normal alleles: <19 repeats
Uncertain significance: 19-27 repeats
Intermediate alleles: 28-33 repeats
Reduced penetrance: 34-36 repeats

Expanded alleles: >36 repeats

An interpretive report will be provided.

Clinical References: 1. Soong BW, Morrison PJ: Spinocerebellar ataxias. Handb Clin Neurol. 2018;155:143-174. doi: 10.1016/B978-0-444-64189-2.00010-X 2. Buijsen RAM, Toonen LJA, Gardiner SL, van Roon-Mom WMC: Genetics, mechanisms, and therapeutic progress in polyglutamine spinocerebellar ataxias. Neurotherapeutics. 2019 Apr;16(2):263-286. doi: 10.1007/s13311-018-00696-y

SCARA
609698

Spinocerebellar Ataxia Type 1, 2, 3, 6, or 7, Repeat Expansion Analysis, Varies

Clinical Information: Spinocerebellar Ataxia Type 1: Spinocerebellar ataxia type 1 (SCA1) is characterized by progressive ataxia, dysarthria, eventual deterioration of bulbar functions, and ophthalmoplegia. Onset typically occurs in the third to fourth decade of life. Most individuals present with difficulties in gait or slurred speech. SCA1 is caused by an expansion of the CAG (cytosine-adenine-guanine) trinucleotide repeat in the ATXN1 gene. This trinucleotide repeat is polymorphic in the general population, with the number of benign repeats ranging from 6 to 37. The pathogenicity of the repeat is dependent on the presence or absence of CAT (cytosine-adenine-thymine) trinucleotide repeats that interrupt the CAG repeats. Therefore, individuals with 36 to 37 uninterrupted CAG repeats are predisposed to having a child with an expanded allele. In affected individuals, the CAG expansions are greater than 38 uninterrupted CAG repeats or greater than 44 repeats, regardless of the presence or absence of CAT repeat interruptions. The presence of CAT repeats in an individual with 36 to 43 CAG repeats is considered normal and not disease-causing. In contrast, 38 CAG repeats without CAT repeats are of uncertain significance. There is a report of an individual with very last onset SCA1 with 38 CAG repeats. Reduced penetrance has been associated with 44 CAG repeats. As with other trinucleotide repeat disorders, large CAG expansions are associated with earlier onset and a more severe clinical course. Spinocerebellar Ataxia Type 2: Spinocerebellar ataxia type 2 (SCA2) is characterized by slowly progressive ataxia, dysarthria, and slow saccadic eye movements. The mean age of onset is in the fourth decade, but symptoms may appear from childhood to later adulthood. SCA2 is caused by an expansion of the CAG trinucleotide repeat in the ATXN2 gene. This trinucleotide repeat is polymorphic in the general population, with the number of benign repeats less than 32. However, 29 to 31 heterozygous repeats have been associated with an increased exponential risk for amyotrophic lateral sclerosis (ALS). Additionally, there has been a report of an individual homozygous for 31 repeats with late-onset cerebellar ataxia. In contrast, 27 repeats have been associated with a protective effect for ALS. In affected individuals, the CAG expansion is greater than 34 repeats, with the most common disease-causing alleles having 37 to 39 repeats. Larger CAG expansions are associated with an earlier age of onset but repeat length cannot predict age of onset or disease severity. A CAG expansion of 32 repeats is of unclear clinical significance. Repeats in the 33 to 34 range are associated with reduced penetrance. Spinocerebellar Ataxia Type 3: Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease, is characterized by progressive cerebellar ataxia and pyramidal signs. The age of onset is highly variable but most commonly occurs in the second to fifth decade of life. Individuals may present with gait problems, speech difficulties, clumsiness, or visual blurring. SCA3 is caused by an expansion of the CAG trinucleotide repeat in the ATXN3 gene. This trinucleotide repeat is polymorphic in the general population, with the number of benign repeats ranging from 12 to 44. In affected individuals, the CAG expansion ranges from 60 to 87 repeats. A loose correlation exists between repeat length and clinical phenotype. Individuals with 45 to 59 CAG repeats are predisposed to having a child with an expanded allele and may or may not have symptoms themselves. There have been reports of reduced penetrant and nonpenetrant alleles with repeats in this range. Spinocerebellar Ataxia Type 6: Spinocerebellar ataxia type 6 (SCA6) is characterized by adult-onset, slowly progressive cerebellar ataxia, dysarthria, and nystagmus. The mean age of onset is 43 to 52 years. Initial symptoms include unsteadiness, stumbling, and imbalance. SCA6 is caused by an expansion of the CAG trinucleotide repeat in the

CACNA1A gene. This trinucleotide repeat is polymorphic in the general population, with the number of benign repeats less than 19. In affected individuals, the CAG expansion ranges from 20 to 33 repeats. Larger CAG expansions are associated with an earlier age of onset. A CAG expansion of 19 repeats is of unclear clinical significance. Individuals with 19 CAG repeats are predisposed to having a child with an expanded allele. Additionally, homozygous abnormal expansions have been reported in individuals with younger age of onset and a more severe phenotype. Spinocerebellar Ataxia Type 7: Spinocerebellar ataxia type 7 (SCA7) is characterized by progressive cerebellar ataxia, including dysarthria and dysphagia, and con-rod and retinal dystrophy. Onset ranges from infancy to the fifth or sixth decade of life. SCA7 is caused by an expansion of the CAG trinucleotide repeat in the ATXN7 gene. This trinucleotide repeat is polymorphic in the general population, with the number of benign repeats less than 19. In affected individuals, the CAG expansion is greater than 36 repeats. A CAG expansion of 19 to 27 repeats is of unclear clinical significance. Individuals with 28 to 33 repeats are predisposed to having a child with an expanded allele but are unlikely to have symptoms themselves. Thirty-four to 36 repeats are associated with reduced penetrance, and when symptoms do occur, they are more likely to be associated with later onset and a milder phenotype.

Useful For: Diagnostic or predictive testing when clinical symptoms or a family history are specific to only one type of spinocerebellar ataxia

Interpretation: An interpretive report will be provided.

Reference Values:

SPINOCEREBELLAR ATAXIA TYPE 1
Normal alleles: <36 CAG repeats
Normal alleles with CAT interruptions: 36-43 repeats
Intermediate alleles without CAT interruptions: 36-37 repeats
Uncertain significance: 38 repeats
Expanded alleles without CAT interruptions: >38 CAG repeats
Expanded alleles with CAT interruptions: >43 CAG repeats

SPINOCEREBELLAR ATAXIA TYPE 2
Normal alleles: <32 repeats
Uncertain significance: 31 homozygous and 32 repeats
Reduced penetrance: 33-34 repeats
Expanded alleles: >34 repeats

SPINOCEREBELLAR ATAXIA TYPE 3
Normal alleles: <45 repeats
Intermediate alleles: 45-59 repeats
Expanded alleles: >59 repeats

SPINOCEREBELLAR ATAXIA TYPE 6
Normal alleles: <19 repeats
Intermediate alleles: 19 heterozygous repeats
Uncertain significance: 19 homozygous repeats
Expanded alleles: >19 repeats

SPINOCEREBELLAR ATAXIA TYPE 7
Normal alleles: <19 repeats
Uncertain significance: 19-27 repeats
Intermediate alleles: 28-33 repeats
Reduced penetrance: 34-36 repeats
Expanded alleles: >36 repeats

An interpretive report will be provided.

Clinical References: 1. Soong BW, Morrison PJ: Spinocerebellar ataxias. Handb Clin Neurol. 2018;155:143-174. doi: 10.1016/B978-0-444-64189-2.00010-X 2. Buijsen RAM, Toonen LJA, Gardiner SL, van Roon-Mom WMC: Genetics, mechanisms, and therapeutic progress in polyglutamine spinocerebellar ataxias. Neurotherapeutics. 2019 Apr;16(2):263-286. doi: 10.1007/s13311-018-00696-y

SPIRO
619428

Spirochete Immunostain, Technical Component Only

Clinical Information: This test will identify spirochete organisms in cases of intestinal spirochetosis, as well as cases of syphilis caused by infection with the spirochete Treponema pallidum.

Useful For: This test will identify spirochete organisms in cases of intestinal spirochetosis, as well as cases of syphilis caused by infection with the spirochete Treponema pallidum.

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Muller H, Eisendle K, Brauninger W, Kutzner H, Cerroni L, Zelger B. Comparative analysis of immunohistochemistry, polymerase chain reaction and focus-floating microscopy for the detection of Treponema pallidum in mucocutaneous lesions of primary, secondary and tertiary syphilis. Br J Dermatol. 2011;165(1):50-60 2. Theel ES, Katz SS, Pillay A. Molecular and direct detection tests for Treponema pallidum subspecies pallidum: a review of the literature, 1964-2017. Clin Infect Dis. 2020;71(Suppl 1):S4-S12. doi: 10.1093/cid/ciaa176 3. Fukuda H, Takahashi M, Kato K, Oharaseki T, Mukai H. Multiple primary syphilis on the lip, nipple-areola and penis: An immunohistochemical examination of Treponema pallidum localization using an anti-T. pallidum antibody. J Dermatol. 2015;42(2):515-517

SFGP
83679

Spotted Fever Group Antibody, IgG and IgM, Serum

Clinical Information: Species of Rickettsia are small (0.3-0.5 mcm x 1-2 mcm) obligately intracellular bacteria (Proteobacteria). They have a gram-negative cell wall structure. Rickettsiae are found in arthropod hosts for at least part of their life cycle. Rickettsial infections in the United States are caused by 2 major groups within the genus Rickettsia: spotted fever group and typhus fever group. The spotted fever group includes Rickettsia rickettsii (Rocky Mountain spotted fever), Rickettsia akari, Rickettsia conorii (Boutonneuse fever), Rickettsia australis (Queensland tick typhus), and Rickettsia sibirica (North Asian tick typhus). The typhus fever group includes Rickettsia typhi (murine typhus; endemic typhus) and Rickettsia prowazekii (epidemic typhus). R rickettsiae is the most common rickettsial species encountered in the United States and is transmitted through a tick vector (Dermacentor species or, less commonly, Rhipicephalus sanguineus). Following a 2- to 14-day incubation period, patients most commonly present with fever, chills, and myalgia. A maculopapular rash typically appears 2 to 5 days after fever onset, though approximately 10% of patients will not develop a rash. Antibodies to the spotted fever group agents are detectable within 7 to 10 days after illness onset. Demonstration of either seroconversion or a 4-fold change in IgG-specific antibody titers in acute and convalescent serum samples is consistent with acute or ongoing disease.

Useful For: Aiding in the diagnosis of spotted fever group rickettsial infections

Interpretation: This test detects reactivity to the group-specific rickettsia. For example, antibody reactivity to the Rickettsia rickettsii will also react with other organisms within the spotted fever group. IgG Titer results of 1:256 and above: -Serum end point titers of 1:256 and above are considered presumptive evidence of recent or current infection by organisms of appropriate rickettsial antigen group. Titer results from 1:64 to 1:256: -Single serum end point titers from 1:64 to 1:256 are suggestive of infection at an undetermined time and may indicate either past infection or early response to a recent rickettsial infection. -A 4-fold or greater increase in IgG titer between 2 serum specimens collected 1 to 2 weeks apart and tested in parallel is considered presumptive evidence of a recent or current infection. -In patients infected with organisms within the rickettsial groups, IgG antibody is generally detectable within 1 to 2 weeks of onset of symptoms, peaking within 1 to 2 months and declining thereafter. Following prompt antimicrobial treatment, titers generally decline below detectable levels within 8 to 11 months. With relapse, prior immunization, or delayed antibiotic treatment, IgG levels may remain elevated for more than a year post-onset. IgM Titer results of 1:64 and above: -Titers of 1:64 and above are considered presumptive evidence of recent or current infection by organisms of appropriate rickettsial antigen group. Titer results below 1:64: -Titers below 1:64 suggest that the patient does not have an acute rickettsial infection. -IgM class antibody is transiently detected within 1 to 2 weeks of onset of symptoms, usually declining rapidly within 3 months following prompt antibiotic treatment. These levels will also be elevated for an extended period with relapse, prior immunization, or delayed antibiotic treatment.

Reference Values:
IgG: <1:64
IgM: <1:64
Reference values apply to all ages.

Clinical References: 1. Walker DH, Bouyer DH: Rickettsia: In: Murray PR, Baron EJ, Jorgenson JH, et al, eds. Manual of Clinical Microbiology. 8th ed. ASM Press; 2003:1005-1014 2. Helmick C, Bernard K, D'Angelo L: Rocky Mountain spotted fever. Clinical laboratory and epidemiological features of 262 cases. J Infect Dis. 1984;150(4):480-488 3. Centers for Disease Control and Prevention: Tickborne diseases of the United States. A Reference Manual for HealthCare Providers. 6th ed. 2022. Accessed December 11, 2024. Available at www.cdc.gov/ticks/tickbornediseases/TickborneDiseases-P.pdf

SPRU
82394

Spruce, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to spruce Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SCCA
610033

Squamous Cell Carcinoma Antigen, Serum

Clinical Information: Squamous cell carcinoma (SCC) of the skin is the second most common form of skin cancer, characterized by abnormal, accelerated cellular growth. SCC antigen (SCCA) represents a subfraction of tumor-associated antigens related to squamous cell carcinoma and is used as a serum tumor marker for squamous cell carcinoma of the head and neck, lung (including esophagus), and other types of SCC. Additionally, associations between serum SCCA concentrations and tumor stage, size, and progression have been observed in SCCs of the cervix and esophagus. SCC is the most common histological type of cervical cancer, accounting for more than 70% of cervical cancer cases in the US. Squamous cell carcinoma antigen is a cytoplasmic glycoprotein found in normal squamous epithelia and elevated concentrations in serum from patients with SCCs. SCCA exists as two isoforms, SCCA1 and SCCA2, which are 91% identical at the amino acid level. Total SCCA assays (which measure both SCCA 1 and 2), like this assay, may be used in conjunction with clinical evaluation in the follow-up/monitoring of patients with SCC of the cervix, lung, head and neck, and esophagus. Serum concentrations of SCCA may be used for monitoring response to treatment in patients with cervical cancer. Notably, in 46% to 92% of patients who experience recurrence, an elevated level of SCCA after treatment was observed before the clinical manifestation of relapse, with a median lead time of 2 to 8 months. While pretreatment serum SCCA concentrations in patients with cervical cancer are more correlated with tumor burden and prognosis, there is some evidence that it may also help to differentiate patients with and without risk for lymph node metastasis. Furthermore, it has been shown that SCCA is a useful marker in follow-up and therapy monitoring, and increasing SCCA levels may predict relapse. Increased serum SCCA values have also been associated with benign inflammatory diseases, including various skin disorders, such as psoriasis and atopic dermatitis, in addition to inflammatory disorders, such as asthma. In one report, 70% of patients with psoriasis and dermatitis had SCCA concentrations greater than 2.4 ng/mL (radioimmunoassay reference value), with some patients having SCCA

concentrations between 20 and 60 ng/mL. Another study found that median concentrations of SCCA2 were higher in psoriasis (2.7 ng/mL, interquartile range: 1.25-7.75 ng/mL) than in controls (0.7 ng/mL, interquartile range: 0.40-0.80 ng/mL).

Useful For: Aiding in the evaluation and monitoring of squamous cell carcinoma of the head and neck, lung, and cervix This test should not be used to screen for carcinoma or other disorders including those of the liver, lung, or skin.

Interpretation: Squamous cell carcinoma antigen (SCCA) concentrations alone should not be interpreted as evidence of the presence or absence of malignancy. Although the sensitivity of this assay for the presence of squamous cell carcinoma (SCC) is not ideal, SCCA remains one of the few clinically viable potential circulating markers used for the detection and monitoring of SCC. Previous estimates of sensitivity are 20% to 53% for lung SCC(1,2) and 38% for tonsil and tongue SCC.(3) In a previous study, SCCA was elevated (>2 ng/ml) in 21.6% of untreated cervical squamous cell carcinomas.(4) Serum levels of SCCA in cervical cancer were significantly related to tumor stage, size, and depth of infiltration(5) and may also serve as a prognostic predictor of overall outcome.(6) Squamous cell carcinoma antigen is expressed in normal epithelial tissues and may be elevated in nonmalignant conditions such as tuberculosis, sarcoidosis, eczema, erythroderma, and psoriasis. Psoriasis, in particular, is known to exhibit elevated SCCA concentrations. Additionally, serum concentrations of squamous cell carcinoma antigen have been reported to be elevated in severe cases of atopic dermatitis and asthma. Although there are conflicting reports, SCCA has been shown to be elevated in hepatocellular carcinoma (HCC) and may serve as a potential marker of HCC. A study of 961 patients (HCC, n =499)(7) indicated that at a serum SCCA cut-off of 3.8 ng/mL, sensitivity was 42% with a specificity of 83% for patients with HCC. This Brahms Kryptor total SCCA assay detects both SCCA1 and SCCA2 antigen isoforms with a 90% and 72% measured recovery, respectively.

Reference Values:
Males: < or =2.00 mcg/L
Females: < or =1.67 mcg/L

Reference values have not been established for patients younger than 18 years.

Clinical References: 1. Fischbach W, Rink C. SCC-Antigen: ein sensitiver und spezifischer Tumormarker fur Plattenepithelkarzinome? [SCC antigen: a sensitive and specific tumor marker for squamous cell carcinoma?]. Dtsch Med Wochenschr. 1988;113(8):289-293. doi:10.1055/s-2008-1067632 2. Tas F, Aydiner A, Topuz E, Yasasever V, Karadeniz A, Saip P. Utility of the serum tumor markers: CYFRA 21.1, carcinoembryonic antigen (CEA), and squamous cell carcinoma antigen (SCC) in squamous cell lung cancer. J Exp Clin Cancer Res. 2000;19(4):477-481 3. Fischbach W, Meyer T, Barthel K. Squamous cell carcinoma antigen in the diagnosis and treatment follow-up of oral and facial squamous cell carcinoma. Cancer. 1990;65(6):1321-1324 4. Bolger BS, Dabbas M, Lopes A, Monaghan JM. Prognostic value of preoperative squamous cell carcinoma antigen level in patients surgically treated for cervical carcinoma. Gynecol Oncol. 1997;65(2):309-313 5. Gaarenstroom KN, Kenter GG, Bonfrer JM, et al. Can initial serum cyfra 21-1, SCC antigen, and TPA levels in squamous cell cervical cancer predict lymph node metastases or prognosis? Gynecol Oncol. 2000;77(1):164-170. doi:10.1006/gyno.2000.5732 6. Liu Z, Shi H. Prognostic role of squamous cell carcinoma antigen in cervical cancer: A meta-analysis. Dis Markers. 2019;2019:6710352. doi:10.1155/2019/6710352 7. Giannelli G, Marinosci F, Sgarra C, Lupo L, Dentico P, Antonaci S. Clinical role of tissue and serum levels of SCCA antigen in hepatocellular carcinoma. Int J Cancer. 2005;116(4):579-583. doi:10.1002/ijc.20847 8. Bae SN, Namkoong SE, Jung JK, et al. Prognostic significance of pretreatment squamous cell carcinoma antigen and carcinoembryonic antigen in squamous cell carcinoma of the uterine cervix. Gynecol Oncol. 1997;64(3):418-424 9. Beale G, Chattopadhyay D, Gray J, et al. AFP, PIVKAII, GP3, SCCA-1 and follisatin as surveillance biomarkers for hepatocellular cancer in non-alcoholic and alcoholic fatty liver disease. BMC Cancer. 2008:200. doi:10.1186/1471-2407-8-200 10. Duk JM, van Voorst Vader PC, ten Hoor KA, Hollema H, Doeglas HM, de Bruijn HW. Elevated levels of squamous cell carcinoma antigen in patients with a benign disease

of the skin. Cancer. 1989 Oct 15;64(8):1652-1656. doi:10.1002/1097-0142(19891015)64:8<1652:aid-cncr2820640816>3.0.co;2-m 11. Watanabe Y, Yamaguchi Y, Komitsu N, et al. Elevation of serum squamous cell carcinoma antigen 2 in patients with psoriasis: associations with disease severity and response to the treatment. Br J Dermatol. 2016;174(6):1327-1336. doi:10.1111/bjd.14426 12. Mitsuishi K, Nakamura T, Sakata Y, et al: The squamous cell carcinoma antigens as relevant biomarkers of atopic dermatitis. Clin Exp Allergy. 2005 Oct;35(10):1327-33. doi:10.1111/j.1365-2222.2005.02353.x 13. Ohta S, Shibata R, Nakao Y, et al. The usefulness of combined measurements of squamous cell carcinoma antigens 1 and 2 in diagnosing atopic dermatitis. Ann Clin Biochem. 2012;49(Pt 3):277-284. doi:10.1258/acb.2011.011065 14. Liu Y, Cao Y, He S, Cai W. Technical and clinical performance of two methods to detect squamous cell carcinoma antigen levels for comparing pathological diagnosis coincidence rates in lung, cervical, and head and neck cancers. Clin Lab. 2020;66(7). doi:10.7754/Clin.Lab.2019.190912 15. Zhou Z, Li W, Zhang F, Hu K. The value of squamous cell carcinoma antigen (SCCa) to determine the lymph nodal metastasis in cervical cancer: A meta-analysis and literature review. PLoS One. 2017;12(12):e0186165 16. Zheng NN, Zhang RC, Yang XX, Tao YK, Zhong LS. Squamous cell carcinoma antigen is useful in the differential diagnosis of erythroderma. Int J Derm. 2019;58(8):e158-e159. doi:10.1111/ijd.14498 17. Fatica EM, Larson BJ, Algeciras-Schimnich A, Bornhorst JA. Performance characteristics of the BRAHMS KRYPTOR automated squamous cell carcinoma antigen assay. J Immunol Methods. 2022;504:113257. doi:10.1016/j.jim.2022.113257

SQUA
82797

Squash, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to squash Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SQUID
82631

Squid, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to squid Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SSAB
82403

SS-A and SS-B Antibodies, IgG, Serum

Clinical Information: Sjogren syndrome (SjS) is a heterogeneous systemic autoimmune rheumatic disorder characterized by diverse immunologic responses to SS-A/Ro and SS-B/La antigens.(1) These immune reactivities have been implicated in the destruction of exocrine gland epithelium with demonstration of typical peri-epithelial lymphocytic infiltration, which can vary from sicca syndrome to systemic disease and lymphoma.(2) The SS-A/Ro and SS-B/La system is considered to be a heterogeneous antigenic complex made up of three different proteins (Ro52, Ro60 and La) and four small RNA particles.(1,2) The SS-B/La antigen is a 48 kDa phosphorylated protein that can be found in the nucleus and the cytoplasm and binds to several RNA molecules.(3) SS-B/La appears to be susceptible to proteolysis and degrades into smaller, but immunoreactive, polypeptides.(4) Unlike antibodies to SS-A/Ro, which are present in SjS and other connective tissue diseases (CTD; systemic lupus erythematosus, systemic sclerosis, inflammatory myopathies, overlap CTD) and primary biliary cholangitis, anti-SS-B/La antibodies are found primarily in patients with SjS.(2,5,6) In addition, SS-A/Ro antibodies may be found alone in many patients with SjS; however, anti-SS-B/La autoantibodies without SS-A/Ro have limited significant association for SjS diagnosis or phenotypic categorization.(2,6,7) Lastly, testing for anti-SS-A/Ro antibodies is included in the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary SjS; whereas, evaluation of anti-SS-B/La antibodies is not required.(8) In a recent multicenter study of more than 10,500 patients with primary SjS, anti-SS-B/La antibodies were detected in 58% of anti-SS-A/Ro antibody-positive cases.(9) SS-A/Ro is an extractable nuclear antigen composed of two distinct antigens of 52 kDa (Ro52) and 60 kDa (Ro60) combined with cytoplasmic RNA species.(10-12) SS-A/Ro (Ro52 and/or Ro60) antibodies occur in patients with several different connective tissue diseases including SjS, an autoimmune disease that involves primarily the salivary and lachrymal glands, systemic lupus erythematosus (SLE), rheumatoid arthritis, systemic sclerosis (SSc), and idiopathic inflammatory myopathies (IIM).(10-14) SS-A/Ro antibodies are associated with childhood SLE, neonatal SLE, and with congenital heart block in infants born to mothers with SLE.(12,14) Traditionally, anti-Ro antibodies were detected by indirect immunofluorescence assay on HEp-2 substrates and confirmed by immunodiffusion, immunoblot, or enzyme-linked immunosorbent assay (ELISA), mostly using a mixture of both Ro52 and Ro60 as the antigens.(10) With technological advances in the expression and purification of recombinant proteins, solid-phase immunoassays that allow the separate detection of anti-Ro52 and anti-Ro60 antibodies, such as ELISA, fluorometric enzyme-linked immunoassays (FEIA),

chemiluminescence immunoassays (CIA), addressable laser bead immunoassay (ALBIA), particle-based multianalyte technology (PMAT), or autoantigen arrays, became available.(11,12) Based on separate determination of Ro52 and Ro60 antibodies, there is substantial evidence that differential associations of these autoantibodies in patients may corelate with specific phenotypes in SLE (neonatal lupus, and fetal atrioventricular blockade), SjS, SSc, IIM, or primary biliary cholangitis.(10-13,15) Patients who have SjS with antibodies to both Ro52 and Ro60 are characterized by higher prevalence of markers of B-cell hyperactivity and glandular inflammation compared to those with single positivity.(13,15) Although these antibodies are often found together, both autoantibodies have important and distinct diagnostic and predictive attributes and should be distinguished when SS-A/Ro antibody is positive or tested singly.(11,13,15) Like anti-Ro52 and anti-Ro60 antibodies, anti-SS-B/La autoantibodies are detected using a variety of solid-phase (such as plate, bead or membrane) immunoassays, such ELISAs, FEIA, CIA, ALBIA, PMAT, and dot or line immunoassays.(16) For more information see Connective Tissue Disease Cascade.

Useful For: Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive, especially those with signs and symptoms consistent with Sjogren syndrome or lupus erythematosus This test is not useful in patients without demonstrable antinuclear antibodies.

Interpretation: A positive result for SSA (Ro) or SSB (La) antibodies is highly suggestive of a diagnosis of Sjogren syndrome. The presence of isolated anti-SS-B/La antibody has low positive predictive value of Sjogren syndrome. A positive result for SS-A/Ro antibodies may be suggestive of connective tissue disease (CTD) such as Sjogren syndrome, systemic lupus erythematosus (SLE), systemic sclerosis, inflammatory myopathies (especially in patients with anti-synthetase syndrome), CTD-associated with interstitial lung diseases, or rheumatoid arthritis. A positive result for SS-A/Ro antibodies in a woman with SLE prior to delivery indicates an increased risk of congenital heart block in the neonate. Differential testing for Ro52 and Ro60 antibodies in patients positive for SS-A/Ro may be useful in the diagnosis of specific CTD clinical subset, disease stratification, and prognosis. Consider testing for Ro52 and Ro60 antibodies (ROPAN / Ro52 and Ro60 Antibodies, IgG, Serum) if the patient is positive for SS-A/Ro.

Reference Values:

SS-A/Ro ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

SS-B/La ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 (positive)
Reference values apply to all ages.

Clinical References:

SSA
81360

SS-A/Ro Antibodies, IgG, Serum

Clinical Information: SS-A/Ro is an extractable nuclear antigen composed of two distinct antigens of 52 kDa (Ro52) and 60 kDa (Ro60) combined with cytoplasmic RNA species.(1,2) SS-A/Ro (Ro52 and/or Ro60) antibodies occur in patients with several different connective tissue diseases including Sjogren syndrome (SjS), an autoimmune disease that involves primarily the salivary and lachrymal glands,systemic lupus erythematosus (SLE), rheumatoid arthritis, systemic sclerosis (SSc) and idiopathic inflammatory myopathies (IIM).(1-5) SS-A/Ro antibodies are associated with childhood SLE, neonatal

SLE, and with congenital heart block in infants born to mothers with SLE.(3-5) Traditionally, anti-SS-A/Ro antibodies were detected by indirect immunofluorescence assay on HEp-2 substrates and confirmed by immunodiffusion, immunoblot or ELISA, mostly using a mixture of both Ro52 and Ro60 as the antigens.(1) With technological advances in the expression and purification of recombinant proteins, solid-phase immunoassays such as ELISA, CLIA, LIA, ALBIA or autoantigen arrays became available that allow the separate detection of anti-Ro52 and anti-Ro60 antibodies.(2,3) Based on separate determination of Ro52 and Ro60 antibodies, there is substantial evidence that differential associations of these autoantibodies in patients may corelate with specific phenotypes in SLE (neonatal lupus, and fetal atrioventricular blockade), SjS, SSc, IIM, or primary biliary cholangitis.(1-4, 6) SjS patients with antibodies to both Ro52 and Ro60 are characterized by higher prevalence of markers of B-cell hyperactivity and glandular inflammation compared to those with single positivity.(4,6) Although these antibodies are often found together, both autoantibodies have important and distinct diagnostic and predictive attributes and should be distinguished when SS-A/Ro antibody is positive or tested singly.(6) For more information see Connective Tissue Disease Cascade.

Useful For: Evaluating patients at-risk for connective tissue disease with or without interstitial lung disease Detection of both anti-SS-A 52 (Ro52) and SS-A 60 (Ro60) antibodies in serum

Interpretation: A positive result for SS-A/Ro antibodies may be suggestive of connective tissue disease (CTD) such as Sjogren syndrome, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), inflammatory myopathies especially in patients with anti-synthetase syndrome, CTD-associated with interstitial lung diseases (CTD-ILD), or rheumatoid arthritis. A positive result for SS-A/Ro antibodies in a woman with SLE prior to delivery may suggest an increased risk of congenital heart block in the neonate. Differential testing for Ro52 and Ro60 antibodies in SS-A/Ro positive patients may be useful in the diagnosis of specific CTD clinical subset, disease stratification, and prognosis. Consider testing for Ro52 and Ro60 antibodies (ROPAN / Ro52 and Ro60 Antibodies, IgG, Serum) if the patient is positive for SS-A/Ro.

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References: 1. Lee AYS, Reed JH, Gordon TP: Anti-Ro60 and anti-Ro52/TRIM21: Two distinct autoantibodies in systemic autoimmune diseases. J Autoimmun. 2021 Nov;124:102724. doi: 10.1016/j.jaut.2021.102724 2. Armagan B, Robinson SA, Bazoberry A, et al: Antibodies to both Ro52 and Ro60 for identifying Sjogren's syndrome patients best suited for clinical trials of disease-modifying therapies. Arthritis Care Res (Hoboken). 2021 Mar 20;10.1002/acr.24597. Epub ahead of print. 3. Homburger H, Larsen S: Detection of specific antibodies. In: Rich R, Fleisher T, Schwartz B, et al, eds. Clinical Immunology: Principles and Practice. 1st ed. Mosby-Year Book; 1996:2096-2109 4. Kotzin B, West S: Systemic lupus erythematosus. In: Rich R, Fleisher T, Shearer W, et al, eds. Clinical Immunology Principles and Practice. 2nd ed. Mosby-Year Book; 2001:60.1-60.24

SSB
81359

SS-B/La Antibodies, IgG, Serum

Clinical Information: Sjogren syndrome (SjS) is a heterogeneous systemic autoimmune rheumatic disorder characterized by diverse immunologic responses to SS-A/Ro and SS-B/La antigens.(1) These immune reactivities have been implicated in the destruction of the epithelium of the exocrine glands with the demonstration of typical peri-epithelial lymphocytic infiltration that can vary from sicca syndrome to systemic disease and lymphoma.(2) The SS-A/Ro and SS-B/La system is considered as a heterogeneous antigenic complex which is made up of three different proteins (Ro52, Ro60 and La) and four small RNAs particles.(1,2) The SS-B/La antigen is a 48 kDa phosphorylated protein which can be

found in the nucleus and the cytoplasm and binds to several RNA molecules.(3) SS-B/La appears to be susceptible to proteolysis and degrades into smaller but immunoreactive polypeptides.(4) Unlike antibodies to SS-A/Ro that are present in SjS and other connective tissue diseases (CTD) [systemic lupus erythematosus, systemic sclerosis, inflammatory myopathies, overlap CTD] and primary biliary cholangitis, anti-SS-B/La antibodies are found primarily in patients with SjS.(2,5,6) In addition, SS-A/Ro antibodies may be found alone in many patients with SjS, however, anti-SS-B/La autoantibodies without SS-A/Ro has limited significant association for SjS diagnosis or phenotypic categorization.(2,6,7) Lastly, whereas testing for anti-SS-A/Ro antibodies is included in the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary SjS, evaluation of anti-SS-B/La antibodies is not required.(8) In a recent multicenter study of more than 10,500 patients with primary SjS, anti-SSB/La antibodies were detected in 58% of anti-SSA/Ro antibody-positive cases.(9) Anti-SS-B/La antibodies are detected using a variety of solid-phase (eg, plate, bead, or membrane) immunoassays such as enzyme-linked immunosorbent assay, fluorometric enzyme-linked immunoassays, chemiluminescence immunoassays, addressable laser bead immunoassay particle-based multianalyte technology and dot or line immunoassays.(10) For more information see Connective Tissue Disease Cascade.

Useful For:

Interpretation: A positive result for anti-SS-B/La antibodies may be suggestive of a diagnosis of primary or secondary connective tissue disease including Sjogren syndrome if compatible autoantibody profile and clinical symptoms are present. The positive predictive value for primary Sjogren syndrome is increased with positivity for antibodies to Ro52, Ro60, and SS-B/La. Combination of anti-SSB-B/A and anti-Ro52 and/or anti-Ro60 antibodies may also be useful in the phenotypic stratification of patients with primary Sjogren syndrome.

Reference Values:

<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Clinical References:

STLPC
83956

St. Louis Encephalitis Antibody, IgG and IgM, Serum, Spinal Fluid

Clinical Information: The onset of St. Louis encephalitis is characterized by generalized malaise, fever, chilliness, headache, drowsiness, nausea, and sore throat or cough followed in 1 to 4 days by the meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Areas of outbreaks since 1933 have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence of St. Louis encephalitis is associated with summer and early autumn.

Useful For: Aiding in the diagnosis of St. Louis encephalitis using serum specimens

Interpretation: In patients infected with the St. Louis encephalitis virus, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. A single serum specimen IgG of 1:10 or greater indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). While a 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicates recent infection. Infections with St. Louis encephalitis can occur at any

age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age and sex, as well as the occupational, vocational, and recreational habits of the individuals. St. Louis encephalitis tends to produce the most severe clinical infections in older persons.

Reference Values:

IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

Clinical References: 1. Gonzalez-Scarano F, Nathanson N. Bunyaviruses. In: Fields BN, Knipe DM, eds. Fields Virology. Vol 1. 2nd ed. Raven Press; 1990:1195-1228 2. Donat JF, Rhodes KH, Groover RV, Smith TF. Etiology and outcome in 42 children with acute nonbacterial meningoencephalitis. Mayo Clin Proc. 1980;55(3):156-160 3. Tsai TF. Arboviruses. In: Murray PR, Baron EJ, Pfaller MA, et al, eds. Manual of Clinical Microbiology. 7th ed. American Society for Microbiology; 1999:1107-1124 4. Calisher CH. Medically important arboviruses of the United States and Canada. Clin Microbiol Rev. 1994;7(1):89-116 5. Diaz A, Coffey LL, Burkett-Cadena N, Day JF. Reemergence of St. Louis Encephalitis Virus in the Americas. Emerg Infect Dis. 2018;24(12):2150-2157. doi:10.3201/eid2412.180372

FSTAB
57891

Stachybotrys chartarum/atra IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 17.50-49.99 Very High Positive 5 50.00-99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:

<0.35 kU/L

STRC
83316

Standard Renal Clearance, Plasma and Random Urine

Clinical Information: The assessment of glomerular filtration rate (GFR) is an important parameter of renal function utilized by clinicians in the care of patients with varying renal diseases, and for clinical research when precise assessment of renal function is necessary. The GFR is the sum of all the filtration rates of the individual nephrons within the kidney and, as such, reflects the number of functioning nephrons. GFR can fall due to a chronic renal disease that causes a permanent loss of nephrons, or due to an acute renal injury that is potentially reversible. In addition, a decline in renal blood flow, ie, secondary to volume depletion, can result in a fall in GFR that is functional and (potentially) quickly reversible. GFR increases when factors that decreased renal blood flow are corrected, or the kidney heals after an acute injury. GFR also increases transiently during pregnancy, as well as in response to other physiologic stimuli that include hyperglycemia or a dietary protein load. Measurement of GFR can be performed by several methodologies including creatinine clearance, iothalamate clearance, and inulin clearance. Of these methods, the latter 2 are significantly more accurate and reproducible than the former. Renal clearance of inulin, a fructose polymer, has traditionally been considered the gold standard for determination of GFR. Disadvantages to the use of inulin are its high cost, limited availability, and analytical expense. Previous studies have shown close correlation between iothalamate and inulin GFR determinations. The short renal clearance test, which utilizes a subcutaneous injection of nonradiolabeled iothalamate and a single (1 hour) urine specimen, is the preferred method for measurement of GFR in most situations since it is less time consuming and less costly. The Standard Renal Clearance test, which utilizes continuous intravenous infusion of iothalamate (or inulin) and additional urine and plasma collections, is an alternative means of measuring GFR and may be preferable in patients with low urine flows (eg, patients with severe liver failure). The Standard Renal

Clearance test also measures renal plasma flow (RPF). Intravenously administered para-aminohippurate (PAH) is used to determine RPF because PAH is nearly completely removed from the renal circulation in a single pass, by a combination of glomerular filtration and tubular secretion.

Useful For: Precise measurement of glomerular filtration rate and renal plasma flow

Interpretation: Iothalamate Clearance: Low glomerular filtration rate (GFR) values indicate abnormal renal function, which may be either reversible/transient or irreversible/permanent. GFR tends to decline with age. Para-Aminohippurate (PAH) Clearance: The renal clearance of PAH, calculated from measurements of PAH in serum and timed urine specimens, equals renal plasma flow (RPF). However, it is important to note that only 85% to 90% of PAH is cleared from the circulation in a single pass, so the PAH clearance may underestimate RPF by 10% to 15%. Filtration Fraction (FF): The FF is the fraction of plasma perfusing the kidneys that is filtered (FF=GFR/RPF). Under normal conditions, FF is approximately 20%. Values significantly different from this provide an index to changes in GFR relative to RPF. For example, in states of decreased renal perfusion due to congestive heart failure, both RPF and GFR are decreased, whereas the FF is >20%.

Reference Values:

GLOMERULAR FILTRATION RATE

20 years: 87-141 mL/min/SA

(Iothalmate) Decreases by 4.95 mL/min/decade

< or = 19 years: Not established
20 years: 87-141
21 years: 86-140
22 years: 86-140
23 years: 85-139
24 years: 85-139
25 years: 84-138
26 years: 84-138
27 years: 83-137
28 years: 83-137
29 years: 82-136
30 years: 81-136
31 years: 81-136
32 years: 81-135
33 years: 80-135
34 years: 80-134
35 years: 79-134
36 years: 79-133
37 years: 78-133
38 years: 78-132
39 years: 77-132
40 years: 77-131
41 years: 76-131
42 years: 76-130
43 years: 75-130
44 years: 75-129
45 years: 74-129
46 years: 74-128
47 years: 73-128
48 years: 73-127
49 years: 72-127
50 years: 72-126

51 years: 72-126
52 years: 71-125
53 years: 71-125
54 years: 70-124
55 years: 70-124
56 years: 69-123
57 years: 69-123
58 years: 68-122
59 years: 68-122
60 years: 67-121
61 years: 67-121
62 years: 66-120
63 years: 66-120
64 years: 65-119
65 years: 65-119
66 years: 65-119
67 years: 64-118
68 years: 64-118
69 years: 63-117
70-150 years: 62-116

PARA-AMINOHIPPURATE (PAH) CLEARANCE
PAH Clearance
0-19 years: not established
20-29 years: >448 mL/min/SA
30-39 years: >413 mL/min/SA
40-49 years: >378 mL/min/SA
50-59 years: >343 mL/min/SA
60-69 years: >308 mL/min/SA
70-79 years: >273 mL/min/SA
80-89 years: >238 mL/min/SA
90-99 years: >203 mL/min/SA

Note: Reference range decreases by 35mL/decade.

FILTRATION FRACTION
>or=16 years: 18-22%

Clinical References: 1. Seegmiller JC, Burns BE, Fauq AH, et al: Iothalamate quantification by tandem mass spectrometry to measure glomerular filtration rate. Clin Chem 2010;56:568-574 2. Slack TK, Wilson DM: Normal renal function CIN and CPAH in healthy donors before and after nephrectomy. Mayo Clin Proc 1976;51:296-300 3. Liedtke RR, Durate CG: Laboratory protocols and methods for the measurement of glomerular filtration rate and renal plasma flow. In Renal Function Tests. Edited by CG Duarte. Boston, Little Brown and Co., 1980, pp 49-63 4. Kasiske BL, Keane WF: Laboratory assessment of renal disease: clearence, urinalysis, and renal biopsy. In Brenner and Rector's The Kidney. Sixth edition. Edited by BM Brenner. Philadelphia, PA, WB Saunders Co, 2000, pp 1129-1142 5. Wilson DM, Bergert JH, Larson TS, Liedtke RR: GFR determined by nonradiolabeled iothalamate using capillary electrophoresis. Am J Kid Dis 1997;30:646-652

STEM
82696

Stemphyllium, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from

IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Stemphyllium Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

STER
82079

Sterols, Plasma

Clinical Information:

Useful For: Investigation of possible desmosterolosis (desmosterol reductase deficiency), cerebrotendinous xanthomatosis, lathosterolosis, sitosterolemia, sterol C4 methyl oxidase deficiency,

MEND (male EBP disorder with neurologic defects) syndrome, and X-linked chondrodysplasia punctata 2

Interpretation: A quantitative report of the patient's sterol profile and a Biochemical Genetics consultant's interpretation is provided for each specimen.

Reference Values:

7-DEHYDROCHOLESTEROL
< or =2.0 mg/L

8-DEHYDROCHOLESTEROL
< or =0.3 mg/L

8(9)-CHOLESTENOL
< or =5.0 mg/L

CAMPESTEROL
< or =8.0 mg/L

CHOLESTANOL
< or =6.0 mg/L

DESMOSTEROL
< or =2.5 mg/L

DIHYDRO T-MAS
< or =0.3 mg/L

LATHOSTEROL
< or =6.0 mg/L

SITOSTEROL
< or =15.0 mg/L

SQUALENE
< or =1.0 mg/L

STIGMASTEROL
< or =0.5 mg/L

Clinical References: 1. Simonen P, Lehtonen J, Lampi AM, et al. Desmosterol accumulation in users of amiodarone. J Intern Med. 2018;283(1):93-101. doi:10.1111/joim.12682 2. Hall P, Michels V, Gavrilov D, et al. Aripiprazole and trazodone cause elevations of 7-dehydrocholesterol in the absence of Smith-Lemli-Opitz syndrome. Mol Genet Metab. 2013;110(1-2):176-178 3. Lupatelli G, De Vuono S, Mannarino E. Patterns of cholesterol metabolism: Pathophysiological and therapeutic implications for dyslipidemias and the metabolic syndrome. Nutr Metab Cardiovasc Dis. 2011;21(9):620-627. doi:10.1016/j.numecd.2011.04.010 4. Zolotushko J, Flusser H, Markus B, et al. The desmosterolosis phenotype: spasticity, microcephaly and micrognathia with agenesis of corpus callosum and loss of white matter. Eur J Hum Genet. 2011;19(9):942-946. doi:10.1038/ejhg.2011.74 5. Bjorkhem I, Boberg K, Leitersdorf E. Inborn errors in bile acid biosynthesis and storage of sterols other than cholesterol. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed November 02, 2023. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225540623 6. Lu K, Lee MH, Hazard S, et al. Two genes that map to the STSL locus cause sitosterolemia: genomic structure and

spectrum of mutations involving sterolin-1 and sterolin-2, encoded by ABCG5 and ABCG8, respectively. Am J Hum Genet. 2001;69(2):278-290 7. Pilo de la Fuente B, Sobrido MJ, Giros M, et al. Usefulness of cholestanol levels in the diagnosis and follow-up of patients with cerebrotendinous xanthomatosis. Neurologia. 2011;26(7):397-404 8. Herman GE, Kratz L. Disorders of sterol synthesis: beyond Smith-Lemli-Optiz syndrome. Am J Med Genet C Semin Med Genet. 2012;106C(4):301-321 9. Kumble S, Savarirayan R. Chondrodysplasia punctata 2, X-linked. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds: GeneReviews [Internet]. University of Washington, Seattle; 2011. Updated January 09, 2020. Accessed November 02, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK55062/ 10. Parraga I, Lopez-Torres J, Andres F, et al. Effect of plant sterols on the lipid profile of patients with hypercholesterolaemia. Randomised, experimental study. BMC Complement Altern Med. 2011;11:73. doi:10.1186/1472-6882-11-73

SPPS
614599

Stiff-Person Spectrum Disorders Evaluation, including Progressive Encephalomyelitis with Rigidity and Myoclonus, Serum

Clinical Information: Stiff-person spectrum disorders include classical stiff-person syndrome, focal stiff-person forms (stiff-limb and stiff-trunk), and a severe encephalomyelitic form known as progressive encephalomyelitis with rigidity and myoclonus (PERM). Paraneoplastic and idiopathic autoimmune causes may be differentiated by a neuronal IgG antibody profile. The unifying clinical and electrophysiologic characteristic is central nervous system hyperexcitability. Clinical manifestations include stiffness, spasms, heightened startle responses, and falls. For the classical stiff-person form, the low back and lower extremities are principally affected. The stiff-limb phenotype may affect one or more limbs without truncal involvement. Truncal manifestations include low back spasms and deformity with sudden chest wall spasms and breathing difficulties. In addition, patients with PERM have encephalopathy (often with seizures), myoclonus (muscle jerking), and dysautonomia. The most common IgG biomarker detected in stiff-person spectrum is glutamic acid decarboxylase 65 (GAD65) antibody. These patients generally have a classical or limited stiff-person form, almost always have antibody values above 20.0 nmol/L, have accompanying nonneurological autoimmune disease in 50% (type 1 diabetes and thyroid disease being most common), and almost always without accompanying cancer. Amphiphysin-IgG positivity is most frequently encountered in patients with occult breast adenocarcinoma presenting with limb stiffness and spasms; neurogenic changes are usually detectable on clinical exam and electromyography. Patients with glycine receptor (GlyR [alpha1 1 subunit]) autoimmunity present more commonly with PERM or stiff-limb phenotype rather than the classical stiff-person form. Associated neoplasms in patients who are GlyR antibody positive include thymoma, but a general search for age- and sex-pertinent cancers should also be undertaken. Dipeptidyl-peptidase-like protein-6 (DPPX) antibody is associated with diverse central and autonomic presentations, including PERM. B-cell blood dyscrasias should be tested for in DPPX-IgG positive cases. All patients with stiff-person spectrum, both seropositive and seronegative, may be immune therapy responsive. GlyR-IgG may be predictive of immune therapy response, including in patients with coexisting GAD65 antibody.

Useful For: Evaluating patients with suspected stiff-person syndrome (classical or focal forms, such as stiff-limb or stiff-trunk) and progressive encephalomyelitis with rigidity and myoclonus using serum specimens

Interpretation: Seropositivity supports the clinical diagnosis of stiff-person spectrum disorder (classical stiff-person, stiff-limb, stiff-trunk, or progressive encephalomyelitis with rigidity and myoclonus). A paraneoplastic basis should be considered.

Reference Values:

Test ID	Reporting name	Methodology*	Reference value
SPPSI	Stiff-Person/PERM Interp, S	Medical interpretation	Interpretive report
AMPHS	Amphiphysin Ab, S	IFA	Negative
DPPCS	DPPX Ab CBA, S	CBA	Negative
GD65S	GAD65 Ab Assay, S	RIA	< or =0.02 nmol/L Reference values apply to all ages.
GLYCS	Glycine Alpha1 LCBA, S	LCBA	Negative
Reflex Information Test ID	Reporting name	Methodology	Reference value
AMIBS	Amphiphysin Immunoblot, S	IB	Negative
APHTS	Amphiphysin Ab Titer, S	IFA	
DPPTS	DPPX Ab IFA Titer, S	IFA	

Clinical References: 1. Hinson SR, Lopez-Chiriboga AS, Bower JH, et al. Glycine receptor modulating antibody predicting treatable stiff-person spectrum disorders. Neurol Neuroimmunol Neuroinflamm. 2018;5:e438 2. Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology. 2008;71(16):1291-1292 3. Martinez-Hernandez E, Arino H, McKeon A, et al. Clinical and immunologic investigations in patients with stiff-person spectrum disorder. JAMA Neurol. 2016;73(6):714-720 4. McKeon A, Martinez-Hernandez E, Lancaster E, et al. Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. JAMA Neurol. 2013;70(1):44-50 5. McKeon A, Robinson MT, McEvoy KM, et al. Stiff-man syndrome and variants: clinical course, treatments, and outcomes. Arch Neurol. 2012;69(2):230-238 6. Pittock SJ, Lucchinetti CF, Parisi JE, et al: Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol. 2005;58(1):96-107 7. Pittock SJ, Yoshikawa H, Ahlskog JE, et al. Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal, and spinal cord dysfunction. Mayo Clin Proc. 2006;81(9):1207-1214 8. Tobin WO, Lennon VA, Komorowski L, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. Neurology. 2014;83(20):1797-1803 9. Walikonis JE, Lennon VA. Radioimmunoassay for glutamic acid decarboxylase (GAD65) autoantibodies as a diagnostic aid for stiff-man syndrome and a correlate of susceptibility to type 1 diabetes mellitus. Mayo Clin Proc. 1998;73(12):1161-1166

SPPC
614600

Stiff-Person Spectrum Disorders Evaluation, including Progressive Encephalomyelitis with Rigidity and Myoclonus, Spinal Fluid

Clinical Information: Stiff-person spectrum disorders include classical stiff-person syndrome, focal stiff-person forms (stiff-limb and stiff-trunk), and a severe encephalomyelitic form known as progressive encephalomyelitis with rigidity and myoclonus (PERM). Paraneoplastic and idiopathic autoimmune causes may be differentiated by a neuronal IgG antibody profile. The unifying clinical and electrophysiologic characteristic is central nervous system hyperexcitability. Clinical manifestations include stiffness, spasms, heightened startle responses, and falls. For the classical stiff-person form, the

low back and lower extremities are principally affected. The stiff-limb phenotype may affect one or more limbs without truncal involvement. Truncal manifestations include low back spasms and deformity with sudden chest wall spasms and breathing difficulties. In addition, patients with PERM have encephalopathy (often with seizures), myoclonus (muscle jerking), and dysautonomia. The most common IgG biomarker detected in stiff-person spectrum is glutamic acid decarboxylase 65 (GAD65) antibody. These patients generally have a classical or limited stiff-person form, almost always have antibody values above 20.0 nmol/L, have accompanying nonneurological autoimmune disease in 50% (type 1 diabetes and thyroid disease being most common), and almost always without accompanying cancer. Amphiphysin-IgG positivity is most frequently encountered in patients with occult breast adenocarcinoma presenting with limb stiffness and spasms; neurogenic changes are usually detectable on clinical exam and electromyography. Patients with glycine receptor (GlyR [alpha1 1 subunit]) autoimmunity present more commonly with PERM or stiff-limb phenotype rather than the classical stiff-person form. Associated neoplasms in patients who are GlyR antibody positive include thymoma, but a general search for age- and sex-pertinent cancers should also be undertaken. Dipeptidyl-peptidase-like protein-6 (DPPX) antibody is associated with diverse central and autonomic presentations, including PERM. B-cell blood dyscrasias should be tested for in DPPX-IgG positive cases. All patients with stiff-person spectrum, both seropositive and seronegative, may be immune therapy responsive. GlyR-IgG may be predictive of immune therapy response, including in patients with coexisting GAD65 antibody.

Useful For: Evaluating patients with suspected stiff-person syndrome (classical or focal forms, such as stiff-limb or stiff-trunk) and progressive encephalomyelitis with rigidity and myoclonus using spinal fluid specimens

Interpretation: Spinal fluid antibody positivity supports the clinical diagnosis of stiff-person spectrum disorder (classical stiff-person, stiff-limb, stiff-trunk, or progressive encephalomyelitis with rigidity and myoclonus). A paraneoplastic basis should be considered.

Reference Values:

Test ID	Reporting name	Methodology*	Reference value
SPPCI	Stiff-Person/PERM Interp, CSF	Medical interpretation	Interpretive report
AMPHC	Amphiphysin Ab, CSF	IFA	Negative
DPPCC	DPPX Ab CBA, CSF	CBA	Negative
GD65C	GAD65 Ab Assay, CSF	RIA	< or =0.02 nmol/L Reference values apply to all ages.
GLYCC	Glycine Alpha1 LCBA, CSF	LCBA	Negative
Reflex information Test ID	Reporting name	Methodology	Reference value
AMIBC	Amphiphysin Immunoblot, CSF	IB	Negative
APHTC	Amphiphysin Ab Titer, CSF	IFA	
DPPTC	DPPX Ab IFA Titer, CSF	IFA	

Clinical References: 1. Hinson SR, Lopez-Chiriboga AS, Bower JH, et al. Glycine receptor modulating antibody predicting treatable stiff-person spectrum disorders. Neurol Neuroimmunol Neuroinflamm. 2018;5(2):e438 2. Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology. 2008;71(16):1291-1292 3. Martinez-Hernandez E, Arino H, McKeon A, et al. Clinical and immunologic investigations in patients with stiff-person spectrum disorder. JAMA Neurol. 2016;73(6):714-720 4. McKeon A, Martinez-Hernandez E, Lancaster E, et al. Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. JAMA Neurol. 2013;70(1):44-50 5. McKeon A, Robinson MT, McEvoy KM, et al. Stiff-man syndrome and variants: clinical course, treatments, and outcomes. Arch Neurol. 2012;69(2):230-238 6. Pittock SJ, Lucchinetti CF, Parisi JE, et al. Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol. 2005;58(1):96-107 7. Pittock SJ, Yoshikawa H, Ahlskog JE, et al. Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal, and spinal cord dysfunction. Mayo Clin Proc. 2006;81(9):1207-1214 8. Tobin WO, Lennon VA, Komorowski L, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. Neurology. 2014;83(20):1797-1803 9. Walikonis JE, Lennon VA. Radioimmunoassay for glutamic acid decarboxylase (GAD65) autoantibodies as a diagnostic aid for stiff-man syndrome and a correlate of susceptibility to type 1 diabetes mellitus. Mayo Clin Proc. 1998;73(12):1161-1166

SPPCI
614602

Stiff-Person Spectrum Disorders including Progressive Encephalomyelitis with Rigidity and Myoclonus, Interpretation, Spinal Fluid

Clinical Information: Stiff-person spectrum disorders include classical stiff-person syndrome, focal stiff-person forms (stiff-limb and stiff-trunk), and a severe encephalomyelitic form known as progressive encephalomyelitis with rigidity and myoclonus (PERM). Paraneoplastic and idiopathic autoimmune causes may be differentiated by a neuronal IgG antibody profile. The unifying clinical and electrophysiologic characteristic is central nervous system hyperexcitability. Clinical manifestations include stiffness, spasms, heightened startle responses, and falls. For the classical stiff-person form, the low back and lower extremities are principally affected. The stiff-limb phenotype may affect one or more limbs without truncal involvement. Truncal manifestations include low back spasms and deformity, with sudden chest wall spasms and breathing difficulties. In addition, patients with PERM have encephalopathy (often with seizures), myoclonus (muscle jerking), and dysautonomia. The most common IgG biomarker detected in stiff-person spectrum is glutamic acid decarboxylase 65 (GAD65) antibody. These patients generally have a classical or limited stiff-person form, almost always have antibody values above 20.0 nmol/L, have accompanying non-neurological autoimmune disease in 50% (type 1 diabetes and thyroid disease being most common), and almost always without accompanying cancer. Amphiphysin-IgG positivity is most frequently encountered in patients with occult breast adenocarcinoma presenting with limb stiffness and spasms; neurogenic changes are usually detectable on clinical exam and electromyography. Glycine receptor (GlyR [alpha1 1 subunit]) autoimmunity patients present more commonly with PERM or stiff-limb phenotype rather than the classical stiff-person form. Associated neoplasms in GlyR antibody positive patients include thymoma, but a general search for age- and sex-pertinent cancers should also be undertaken. Dipeptidyl-peptidase-like protein-6 (DPPX) antibody is associated with diverse central and autonomic presentations, including PERM. B-cell blood dyscrasias should be tested for in DPPX-IgG positive cases. All stiff-person spectrum patients, both seropositive and seronegative, may be immune therapy responsive. GlyR-IgG may be predictive of immune therapy response, including in patients with coexisting GAD65 antibody.

Useful For: Interpretation for the evaluation of stiff-person spectrum disorders, including the classical or focal forms, such as stiff-limb or stiff-trunk, and progressive encephalomyelitis with rigidity and myoclonus, using spinal fluid specimens

Interpretation: Spinal fluid antibody positivity supports the clinical diagnosis of stiff-person spectrum disorder (classical stiff-person, stiff-limb, stiff-trunk, or progressive encephalomyelitis with rigidity and myoclonus). A paraneoplastic basis should be considered.

Reference Values:
Only orderable as part of profile. For more information see SPPC / Stiff-Person Spectrum Disorders Evaluation, including Progressive Encephalomyelitis with Rigidity and Myoclonus, Spinal Fluid.

Clinical References: 1. Hinson SR, Lopez-Chiriboga AS, Bower JH, et al: Glycine receptor modulating antibody predicting treatable stiff-person spectrum disorders. Neurol Neuroimmunol Neuroinflamm. 2018 Jan;5:e438 2. Hutchinson M, Waters P, McHugh J, et al: Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology. 2008 Oct;71(16):1291-1292 3. Martinez-Hernandez E, Arino H, McKeon A, et al: Clinical and immunologic investigations in patients with stiff-person spectrum disorder. JAMA Neurol. 2016 Jun;73(6):714-720 4. McKeon A, Martinez-Hernandez E, Lancaster E, et al: Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. JAMA Neurol. 2013 Jan;70(1):44-50 5. McKeon A, Robinson MT, McEvoy KM, et al: Stiff-man syndrome and variants: clinical course, treatments, and outcomes. Arch Neurol. 2012 Feb;69(2):230-238 6. Pittock SJ, Lucchinetti CF, Parisi JE, et al: Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol. 2005 Jun;58(1):96-107 7. Pittock SJ, Yoshikawa H, Ahlskog JE, et al: Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal, and spinal cord dysfunction. Mayo Clin Proc. 2006 Sep;81(9):1207-1214 8. Tobin WO, Lennon VA, Komorowski L, et al: DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. Neurology. 2014 Nov;83(20):1797-1803 9. Walikonis JE, Lennon VA: Radioimmunoassay for glutamic acid decarboxylase (GAD65) autoantibodies as a diagnostic aid for stiff-man syndrome and a correlate of susceptibility to type 1 diabetes mellitus. Mayo Clin Proc. 1998 Dec;73(12):1161-1166

SPPSI
614601

Stiff-Person Spectrum Disorders, including Progressive Encephalomyelitis with Rigidity and Myoclonus, Interpretation, Serum

Clinical Information: Stiff-person spectrum disorders include classical stiff-person syndrome, focal stiff-person forms (stiff-limb and stiff-trunk), and a severe encephalomyelitic form known as progressive encephalomyelitis with rigidity and myoclonus (PERM). Paraneoplastic and idiopathic autoimmune causes may be differentiated by a neuronal IgG antibody profile. The unifying clinical and electrophysiologic characteristic is central nervous system hyperexcitability. Clinical manifestations include stiffness, spasms, heightened startle responses, and falls. For the classical stiff-person form, the low back and lower extremities are principally affected. The stiff-limb phenotype may affect one or more limbs without truncal involvement. Truncal manifestations include low back spasms and deformity, with sudden chest wall spasms and breathing difficulties. In addition, patients with PERM have encephalopathy (often with seizures), myoclonus (muscle jerking), and dysautonomia. The most common IgG biomarker detected in stiff-person spectrum is glutamic acid decarboxylase 65 (GAD65) antibody. These patients generally have a classical or limited stiff-person form, almost always have antibody values above 20.0 nmol/L, have accompanying non-neurological autoimmune disease in 50% (type 1 diabetes and thyroid disease being most common), and almost always without accompanying cancer. Amphiphysin-IgG positivity is most frequently encountered in patients with occult breast adenocarcinoma presenting with limb stiffness and spasms; neurogenic changes are usually detectable on clinical exam and electromyography. Glycine receptor (GlyR [alpha1 1 subunit]) autoimmunity patients present more commonly with PERM or stiff-limb phenotype rather than the classical stiff-person form. Associated neoplasms in GlyR antibody positive patients include thymoma, but a general search for age- and sex-pertinent cancers should also be undertaken. Dipeptidyl-peptidase-like protein-6 (DPPX) antibody is associated with diverse central and autonomic presentations, including PERM. B-cell blood dyscrasias should be tested for in DPPX-IgG positive cases. All stiff-person spectrum patients, both seropositive and

seronegative, may be immune therapy responsive. GlyR-IgG may be predictive of immune therapy response, including in patients with coexisting GAD65 antibody.

Useful For: Interpretation for the evaluation of stiff-person spectrum disorders including the classical or focal forms, such as stiff-limb or stiff-trunk, and progressive encephalomyelitis with rigidity and myoclonus, using serum specimens

Interpretation: Seropositivity supports the clinical diagnosis of stiff-person spectrum disorder (classical stiff-person, stiff-limb, stiff-trunk, or progressive encephalomyelitis with rigidity and myoclonus). A paraneoplastic basis should be considered.

Reference Values:
Only orderable as part of a profile. For more information see SPPS / Stiff-Person Spectrum Disorders Evaluation, including Progressive Encephalomyelitis with Rigidity and Myoclonus, Serum.

Clinical References: 1. Hinson SR, Lopez-Chiriboga AS, Bower JH, et al: Glycine receptor modulating antibody predicting treatable stiff-person spectrum disorders. Neurol Neuroimmunol Neuroinflamm. 2018 Jan;5:e438 2. Hutchinson M, Waters P, McHugh J, et al: Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology. 2008 Oct;71(16):1291-1292 3. Martinez-Hernandez E, Arino H, McKeon A, et al: Clinical and immunologic investigations in patients with stiff-person spectrum disorder. JAMA Neurol. 2016 Jun;73(6):714-720 4. McKeon A, Martinez-Hernandez E, Lancaster E, et al: Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. JAMA Neurol. 2013 Jan;70(1):44-50 5. McKeon A, Robinson MT, McEvoy KM, et al: Stiff-man syndrome and variants: clinical course, treatments, and outcomes. Arch Neurol. 2012 Feb;69(2):230-238 6. Pittock SJ, Lucchinetti CF, Parisi JE, et al: Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol. 2005 Jun;58(1):96-107 7. Pittock SJ, Yoshikawa H, Ahlskog JE, et al: Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal, and spinal cord dysfunction. Mayo Clin Proc. 2006 Sep;81(9):1207-1214 8. Tobin WO, Lennon VA, Komorowski L, et al: DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. Neurology. 2014 Nov;83(20):1797-1803 9. Walikonis JE, Lennon VA: Radioimmunoassay for glutamic acid decarboxylase (GAD65) autoantibodies as a diagnostic aid for stiff-man syndrome and a correlate of susceptibility to type 1 diabetes mellitus. Mayo Clin Proc. 1998 Dec;73(12):1161-1166

INSEC
31765

Stinging Insects Allergen Profile, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years of age due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to honeybee, yellow jacket, wasp, yellow faced hornet, and white-faced hornet venoms Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic

reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. Elsevier; 2017:1057-1070

FSTBG
57656

Strawberry IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

STBY
82676

Strawberry, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical

manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to strawberry Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SABP
86537

Streptococcal Antibodies Profile, Serum

Clinical Information: A number of bacterial antigens have been identified in cultures of group A streptococci. These extracellular products are primarily enzymatic proteins and include streptolysin O, streptokinase, hyaluronidase, deoxyribonucleases (DNases A, B, C, and D), and nicotinamide adenine nucleotidase. Infections by the group A streptococci are unique because they can be followed by the serious nonpurulent complications of rheumatic fever and glomerulonephritis. Recent information suggests that rheumatic fever is associated with infection by certain rheumatogenic serotypes (M1, M3, M5, M6, M18, and M19), while glomerulonephritis follows infection by nephritogenic serotypes (M2, M12, M49, M57, M59, and M60). Glomerulonephritis and rheumatic fever occur following the infection, after a period of latency following the infection, during which the patient is asymptomatic. The latency period for glomerulonephritis is approximately 10 days, and for rheumatic fever the latency

period is 20 days.

Useful For: Demonstration of acute or recent streptococcal infection using both antistreptolysin O and anti-DNase B titers

Interpretation: Elevated values are consistent with an antecedent infection by group A streptococci.

Reference Values:
ANTISTREP-O TITER
<5 years: < or =70 IU/mL
5-17 years: < or =640 IU/mL
> or =18 years: < or =530 IU/mL

ANTI-DNase B TITER
<5 years: < or =250 U/mL
5-17 years: < or =375 U/mL
> or =18 years: < or =300 U/mL

Clinical References: 1. Ayoub EM, Harden E. Immune response to streptococcal antigens: diagnostic methods. In: Rose NR, de Marco EC, Folds JD, et al. Manual of Clinical and Laboratory Immunology. 5th ed. ASM Press, 1997:450-457 2. Antistreptolysin O (ASO). Testing.com; Updated July 24, 2020. Accessed March 17, 2025. Available at www.testing.com/tests/antistreptolysin-o-aso/ 3. Anti-DNase B. Testing.com. Updated June 28, 2021. Accessed March 17, 2025. Available at www.testing.com/tests/anti-dnase-b/

GAPCR
610254

Streptococcus Group A, Molecular Detection, PCR, Throat

Clinical Information: Group A streptococci are gram-positive, beta-hemolytic disease-causing bacteria that commonly cause infections in the throat (pharyngitis or strep throat) or on skin (cellulitis and impetigo) and can cause a wide range of other infections (eg, sepsis, pneumonia, and meningitis). Pharyngitis may also be caused by other bacteria, including Neisseria gonorrhoeae and Corynebacterium diphtheriae, for which specific culture methods are required. If left untreated, mild infections can lead to more serious infections. The most severe but least common forms of invasive Group A streptococcal disease (GAS) are necrotizing fasciitis and streptococcal toxic shock syndrome. Several million cases of strep throat and impetigo occur each year with approximately 9000 to 11,500 cases of invasive GAS disease occurring in the United States, resulting in 1000 to 1800 deaths.(1) Treating an infected person with an appropriate antibiotic generally prevents the spread of the infection and reduces the risk of post-infectious complications, such as rheumatic fever and acute glomerular nephritis.(2)

Useful For: Detecting group A streptococcal infections in patients with signs and symptoms of pharyngitis using a throat swab specimen The test is not intended for monitoring treatment for group A Streptococcus infections.

Interpretation: Positive: Streptococcus pyogenes DNA is detected. Negative: Streptococcus pyogenes DNA is not detected.

Reference Values:
Negative

Clinical References: 1. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases, Division of Bacterial Diseases. Active Bacterial Core

Surveillance (ABCs) Report: group A Streptococcus, 2003. CDC. 2004. Accessed January 31, 2024. Available at www.cdc.gov/abcs/reports-findings/survreports/gas03.pdf 2. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases, Division of Bacterial Diseases. Scarlet Fever: All You Need to Know. CDC. Updated May 10, 2023. Accessed January 31, 2024. Available at www.cdc.gov/groupastrep/diseases-public/scarlet-fever.html 3. Package insert: Xpert Xpress Strep A. Cepheid; 301-9326 Rev. D, 06/2019

SPNEU
83150

Streptococcus pneumoniae Antigen, Random, Urine

Clinical Information: Streptococcus pneumoniae is the most frequently encountered bacterial agent of community-acquired pneumonia. Because of the significant morbidity and mortality associated with pneumococcal pneumonia, septicemia, and meningitis, it is important to have diagnostic test methods available that can provide a rapid diagnosis. In instances where empirical antibiotics are provided for community-acquired pneumonia without culture confirmation of S pneumoniae, antigen testing may be useful.

Useful For: Rapid diagnosis of pneumococcal pneumonia

Interpretation: A positive result is indicative of pneumococcal pneumonia. Negative: Negative for pneumococcal pneumonia, suggesting no current or recent pneumococcal infection. Infection due to Streptococcus pneumoniae cannot be ruled out since the antigen present in the sample may be below the detection limit of the test.

Reference Values:
Negative

Clinical References: 1. Plouffe JF, Moore SK, Davis R, Facklam RR. Serotypes of Streptococcus pneumoniae blood culture isolates from adults in Franklin County, Ohio. J Clin Microbiol. 1994;32(6):1606-1607 2. Johnston RB Jr. Pathogenesis of pneumococcal pneumonia. Rev Infect Dis. 1991;13 Suppl 6:S509-S517. doi:10.1093/clinids/13.supplement_6.s509 3. Janoff EN, Musher DM: Streptococcus pneumoniae. In Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2473-2491

SPNC
89971

Streptococcus pneumoniae Antigen, Spinal Fluid

Clinical Information: Streptococcus pneumoniae is the most frequently encountered bacterial agent of community-acquired pneumonia and can also be an agent of bacterial meningitis. Because of the significant morbidity and mortality associated with pneumococcal pneumonia, septicemia, and meningitis, it is important to have diagnostic test methods available that can provide a rapid diagnosis. In instances where empirical antibiotics are being considered prior to culture confirmation, antigen testing may be useful.

Useful For: Rapid diagnosis of pneumococcal meningitis

Interpretation: A positive result supports a diagnosis of pneumococcal meningitis. A negative result suggests that pneumococcal antigen is absent in the cerebrospinal fluid (CSF). However, infection due to Streptococcus pneumoniae cannot be ruled out since the antigen present in the specimen may be below the lower limit of detection of the test. If pneumococcal meningitis is suspected, bacterial culture and Gram stain analysis on CSF should be performed.

Reference Values:
Negative

Reference values apply to all ages.

Clinical References:

PN23M
619921

Streptococcus pneumoniae IgG Antibodies, 23 Serotypes, Serum

Clinical Information: Streptococcus pneumoniae (S pneumoniae) is a gram-positive bacterium that causes a variety of infectious diseases in children and adults, including invasive disease (bacteriemia and meningitis) and infections of the respiratory tract (pneumonia and otitis media).(1) More than 90 serotypes of S pneumoniae have been identified, based on varying polysaccharides found in the bacterial cell wall. The serotypes responsible for disease vary with age and geographic location. Bacterial polysaccharides induce a T-cell independent type II humoral immune response. In adults and older children, bacterial polysaccharides are effective in generating an immune response that results in production of IgG antibodies and generation of long-lived plasma cells and memory B cells.(2) S pneumoniae purified polysaccharide vaccines (PPSV) that contain a total of 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) are available; these are referred to as PPSV23.(3) These 23 serotypes were included because, as a group, they account for approximately 90% of invasive pneumococcal infections. Antibody responses develop in approximately 75% to 85% of nonimmunocompromised adults and older children approximately 4 to 6 weeks following immunization with purified polysaccharide vaccines. A meta-analysis estimated an efficacy of 74% for prevention of invasive pneumococcal disease in adults vaccinated with PPSV23.(4) In contrast, immune responses to polysaccharide antigens in children younger than 2 years of age are generally weak. Active immunization of children younger than 2 years requires vaccines prepared of polysaccharides conjugated to an immunogenic carrier protein (Corynebacterium diphtheria strain C7), which results in a T-cell dependent antibody response.(3) In children younger than age 6, prior to the availability of routine S pneumoniae vaccination, 7 serotypes (4, 6B, 9V, 18C, 19F, and 23F) accounted for 80% of invasive disease and up to 100% of all isolates that were found to be highly resistant to treatment with penicillin. The first pneumococcal conjugated vaccine (PCV) available for children younger than age 2 contained these 7 serotypes (PCV7). The vaccine was highly effective, with invasive disease in children younger than age 5 reduced from 99 to 21 cases per 100,000 population from 1998 to 2008.(5) In addition, it was demonstrated that after PCV7 became part of the routine vaccination schedule, only 2% of invasive disease was associated with any of the serotypes present in the vaccine. Instead, approximately 61% of the invasive disease was caused by an additional 6 serotypes (1, 3, 5, 6A, 7F, and 19A). This led to development of a 13-valent conjugated vaccine, known as PCV13. More recently, additional pneumococcal conjugate vaccines have been approved, specifically 15-valent (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F) and 20-valent (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) vaccines, known as PCV15 and PCV20, respectively. Conjugated pneumococcal vaccination is included in the routine childhood schedule, with 4 doses of PCV13 or PCV15 administered at 2, 4, 6, and 12 to 15 months.(6) For adults younger than 65 years, a single dose of PCV20 or a single dose of PCV15 followed 1 year later with a single dose of PPSV23 is recommended.(7) This same pneumococcal vaccination strategy is recommended for adults 19 to 64 years of age with immunocompromising conditions, cochlear implants, cerebrospinal fluid leaks, or other chronic health conditions. Patients with intrinsic defects in humoral immunity, such as common variable immunodeficiency, may have impaired antibody responses to pneumococcal vaccination.(8,9) Selective antibody deficiency is a recognized clinical entity in patients older than 2 years of age and is characterized by recurrent bacterial respiratory infections, absent or subnormal antibody response to a majority of polysaccharide antigens, and normal or increased immunoglobulin concentrations, including IgG subclasses, in the context of intact humoral response to protein antigens. In several other primary

immunodeficiencies, including Wiskott-Aldrich syndrome, autoimmune lymphoproliferate syndrome, and DiGeorge syndrome, IgG subclass deficiencies may also result in impaired antibody responses to polysaccharide antigens.

Useful For: Assessing the IgG antibody response to active immunization with nonconjugated, 23-valent pneumococcal vaccines Assessing the IgG antibody response to active immunization with conjugated 13-valent, 15-valent and 20-valent pneumococcal vaccines Determining the ability of an individual to produce an antibody response to polysaccharide antigens, as part of the evaluation for humoral or combined immunodeficiencies

Interpretation: As a general guideline, nonimmunocompromised adults develop IgG antibodies approximately 4 to 6 weeks following nonconjugated vaccination. Either of the following conditions is consistent with a normal response to Streptococcus pneumonia vaccination: 1. When comparing pre- and post-vaccination samples, antibody concentrations increased by at least 2-fold for a. >50% of serotypes in children <6 years of age b. >70% of serotypes for individuals >6 years of age 2. In either a pre- or post-vaccination sample, antibody concentrations >/= 1.0 mcg/mL for a. >50% of serotypes for children <6 years of age b. >70% of serotypes for individuals >6 years of age

Reference Values:

Results are reported in mcg/mL Serotype	Normal value
1 (1)	> or =1.0
2 (2)	> or =1.0
3 (3)	> or =1.0
4 (4)	> or =1.0
5 (5)	> or =1.0
8 (8)	> or =1.0
9N (9)	> or =1.0
12F (12)	> or =1.0
14 (14)	> or =1.0
17F (17)	> or =1.0
19F (19)	> or =1.0
20 (20)	> or =1.0
22F (22)	> or =1.0
23F (23)	> or =1.0
6B (26)	> or =1.0
10A (34)	> or =1.0
11A (43)	> or =1.0
7F (51)	> or =1.0
15B (54)	> or =1.0
18C (56)	> or =1.0
19A (57)	> or =1.0

9V (68)	> or =1.0
33F (70)	> or =1.0

Clinical References:

PNTO
608969

Streptococcus pneumoniae IgG Antibodies, Total, Serum

Clinical Information: Streptococcus pneumoniae is a gram-positive bacterium that causes a variety of infectious diseases in children and adults, including invasive disease (bacteriemia and meningitis) and infections of the respiratory tract (pneumonia and otitis media).(1) More than 90 serotypes of S. pneumoniae have been identified, based on varying polysaccharides found in the bacterial cell wall. The serotypes responsible for disease vary with age and geographic location. Bacterial polysaccharides induce a T-cell independent type II humoral immune response. In adults and older children, bacterial polysaccharides are effective in generating an immune response that results in production of IgG antibodies and generation of long-lived plasma cells and memory B cells.(2) S. pneumoniae purified polysaccharide vaccines (PPSV) that contain a total of 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) are available; these are referred to as PPSV23.(3) These 23 serotypes were included because, as a group, they account for approximately 90% of invasive pneumococcal infections. Antibody responses develop in 75% to 85% of nonimmunocompromised adults and older children approximately 4 to 6 weeks following immunization with purified polysaccharide vaccines. A meta-analysis estimated an efficacy of 74% for prevention of invasive pneumococcal disease in adults vaccinated with pneumococcal polysaccharide vaccine (PPSV23).(4) In contrast, immune responses to polysaccharide antigens in children younger than 2 years of age are generally weak. Active immunization of children younger than 2 years requires vaccines prepared of polysaccharides conjugated to an immunogenic carrier protein (Corynebacterium diphtheria strain C7), which results in a T-cell dependent antibody response.(3) In children younger than age 6, prior to the availability of routine S. pneumoniae vaccination, 7 serotypes (4, 6B, 9V, 18C, 19F, and 23F) accounted for 80% of invasive disease and up to 100% of all isolates that were found to be highly resistant to treatment with penicillin. The first pneumococcal conjugated vaccine (PCV) available for children younger than age 2 contained these 7 serotypes (PCV7). The vaccine was highly effective, with invasive disease in children younger than age 5 reduced from 99 to 21 cases per 100,000 population from 1998 to 2008.(5) In addition, it was demonstrated that after PCV7 became part of the routine vaccination schedule, only 2% of invasive disease was associated with any of the serotypes present in the vaccine. Instead, approximately 61% of the invasive disease was caused by an additional 6 serotypes (1, 3, 5, 6A, 7F, and 19A). This led to development of a 13-valent conjugated vaccine, known as pneumococcal conjugate vaccine (PCV13). More recently, additional pneumococcal conjugate vaccines have been approved, specifically 15-valent (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F) and 20-valent (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) vaccines, known as PCV15 and PCV20, respectively. Conjugated pneumococcal vaccination is included in the routine childhood schedule, with 4 doses of PCV13 or PCV15 administered at 2, 4, 6, and 12 to 15 months.(6) For adults younger than 65 years, a single dose of PCV20 or a single dose of PCV15 followed 1 year later with a single dose of PPSV23 is recommended.(7) This same pneumococcal vaccination strategy is recommended for adults 19 to 64 years of age with immunocompromising conditions, cochlear implants, cerebrospinal fluid leaks, or other chronic health conditions. Patients with intrinsic defects in humoral immunity, such as common variable immunodeficiency, may have impaired antibody responses to pneumococcal vaccination.(8,9) Selective antibody deficiency is a recognized clinical entity in patients older than 2 years of age and is characterized by recurrent bacterial respiratory infections, absent or subnormal antibody response to a majority of polysaccharide antigens, and normal or increased immunoglobulin concentrations, including IgG subclasses, in the context of intact humoral response to

protein antigens. In several other primary immunodeficiencies, including Wiskott-Aldrich syndrome, autoimmune lymphoproliferate syndrome, and DiGeorge syndrome, IgG subclass deficiencies may also result in impaired antibody responses to polysaccharide antigens.

Useful For: Assessing the IgG antibody response to active immunization with nonconjugated 23-valent pneumococcal vaccines Assessing the IgG antibody response to active immunization with conjugated 13-valent, 15-valent and 20-valent pneumococcal vaccines Determining the ability of an individual to produce an antibody response to polysaccharide antigens, as part of an evaluation for humoral or combined immunodeficiencies

Interpretation: Low anti-pneumococcal antibody concentrations (<9.7 mcg/mL) indicate a poor response to the pneumococcal vaccine, while high concentrations (>270.0 mcg/mL) indicate a robust vaccine response. Results falling in the modest (9.7-40.9 mcg/mL), intermediate (41.0-180.9 mcg/mL), and moderate (181.0-270.0 mcg/mL) categories may warrant serotype-specific antibody testing, to be determined at the discretion of the physician. When comparing pre- and post-vaccination samples, an increase in antibody concentrations is generally considered to be indicative of a normal vaccine response. However, the specific fold increase is influenced substantially by the antibody concentration observed in the pre-vaccination sample.

Reference Values:
> or =9.7 mcg/mL

Clinical References: 1. Weisberg SS. Pneumococcus. Dis Mon. 2007;53(10):495-502. doi:10.1016/j.disamonth.2007.09.013 2. Grabenstein JD, Manoff SB. Pneumococcal polysaccharide 23-valent vaccine: long-term persistence of circulating antibody and immunogenicity and safety after revaccination in adults. Vaccine. 2012;30(30):4435-4444 3. Musher DM, Anderson R, Feldman C. The remarkable history of pneumococcal vaccination: an ongoing challenge. Pneumonia (Nathan). 2022;14(1):5. Published 2022 Sep 25. doi:10.1186/s41479-022-00097-y 4. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013;2013(1):CD000422 5. Paradiso PR. Advances in pneumococcal disease prevention: 13-valent pneumococcal conjugate vaccine for infants and children. Clin Infect Dis. 2011;52(10):1241-1247 6. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(4):109-117 7. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-Valent Pneumococcal Conjugate Vaccine Among U.S. Children: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(37):1174-1181 8. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015;136(5):1186-205.e2078 9. Orange JS, Ballow M, Stiehm ER, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2012;130(3 Suppl):S1-S24 10. Parker AR, Park MA, Harding S, Abraham RS. The total IgM, IgA and IgG antibody responses to pneumococcal polysaccharide vaccination (Pneumovax 23) in a healthy adult population and patients diagnosed with primary immunodeficiencies. Vaccine. 2019;37(10):1350-1355

PNTOR 608970 Streptococcus pneumoniae IgG Antibodies, Total, with Reflex, Serum

Clinical Information: Streptococcus pneumoniae is a gram-positive bacterium that causes a variety of infectious diseases in children and adults, including invasive disease (bacteriemia and meningitis)

and infections of the respiratory tract (pneumonia and otitis media).(1) More than 90 serotypes of S. pneumoniae have been identified, based on varying polysaccharides found in the bacterial cell wall. The serotypes responsible for disease vary with age and geographic location. Bacterial polysaccharides induce a T-cell independent type II humoral immune response. In adults and older children, bacterial polysaccharides are effective in generating an immune response that results in production of IgG antibodies and generation of long-lived plasma cells and memory B cells.(2) S. pneumoniae purified polysaccharide vaccines (PPSV) that contain a total of 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) are available; these are referred to as PPSV23.(3) These 23 serotypes were included because, as a group, they account for approximately 90% of invasive pneumococcal infections. Antibody responses develop in 75% to 85% of nonimmunocompromised adults and older children approximately 4 to 6 weeks following immunization with purified polysaccharide vaccines. A meta-analysis estimated an efficacy of 74% for prevention of invasive pneumococcal disease in adults vaccinated with pneumococcal polysaccharide vaccine (PPSV23).(4) In contrast, immune responses to polysaccharide antigens in children younger than 2 years of age are generally weak. Active immunization of children younger than 2 years requires vaccines prepared of polysaccharides conjugated to an immunogenic carrier protein (Corynebacterium diphtheria strain C7), which results in a T-cell dependent antibody response.(3) In children younger than age 6, prior to the availability of routine S. pneumoniae vaccination, 7 serotypes (4, 6B, 9V, 18C, 19F, and 23F) accounted for 80% of invasive disease and up to 100% of all isolates that were found to be highly resistant to treatment with penicillin. The first pneumococcal conjugated vaccine (PCV) available for children younger than age 2 contained these 7 serotypes (PCV7). The vaccine was highly effective, with invasive disease in children younger than age 5 reduced from 99 to 21 cases per 100,000 population from 1998 to 2008.(5) In addition, it was demonstrated that after PCV7 became part of the routine vaccination schedule, only 2% of invasive disease was associated with any of the serotypes present in the vaccine. Instead, approximately 61% of the invasive disease was caused by an additional 6 serotypes (1, 3, 5, 6A, 7F, and 19A). This led to development of a 13-valent conjugated vaccine, known as pneumococcal conjugate vaccine (PCV13). More recently, additional pneumococcal conjugate vaccines have been approved, specifically 15-valent (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F) and 20-valent (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) vaccines, known as PCV15 and PCV20, respectively. Conjugated pneumococcal vaccination is included in the routine childhood schedule, with 4 doses of PCV13 or PCV15 administered at 2, 4, 6, and 12 to 15 months.(6) For adults younger than 65 years, a single dose of PCV20 or a single dose of PCV15 followed 1 year later with a single dose of PPSV23 is recommended.(7) This same pneumococcal vaccination strategy is recommended for adults 19 to 64 years of age with immunocompromising conditions, cochlear implants, cerebrospinal fluid leaks, or other chronic health conditions. Patients with intrinsic defects in humoral immunity, such as common variable immunodeficiency, may have impaired antibody responses to pneumococcal vaccination.(8,9) Selective antibody deficiency is a recognized clinical entity in patients older than 2 years of age and is characterized by recurrent bacterial respiratory infections, absent or subnormal antibody response to a majority of polysaccharide antigens, and normal or increased immunoglobulin concentrations, including IgG subclasses, in the context of intact humoral response to protein antigens. In several other primary immunodeficiencies, including Wiskott-Aldrich syndrome, autoimmune lymphoproliferate syndrome, and DiGeorge syndrome, IgG subclass deficiencies may also result in impaired antibody responses to polysaccharide antigens.

Useful For: Assessing the IgG antibody response to active immunization with nonconjugated 23-valent pneumococcal vaccines Assessing the IgG antibody response to active immunization with conjugated 13-valent, 15-valent and 20-valent pneumococcal vaccines Determining the ability of an individual to produce an antibody response to polysaccharide antigens, as part of an evaluation for humoral or combined immunodeficiencies

Interpretation: Low antipneumococcal antibody concentrations (<9.7 mcg/mL) indicate a poor response to the pneumococcal vaccine, while high concentrations (>270.0 mcg/mL) indicate a robust vaccine response. Results falling in the modest (9.7-40.9 mcg/mL), intermediate (41.0-180.9 mcg/mL), and moderate (181.0-270.0 mcg/mL) categories may warrant serotype-specific antibody testing, to be

determined at the discretion of the physician. When comparing pre- and post-vaccination samples, an increase in antibody concentrations is generally considered to be indicative of a normal vaccine response. However, the specific fold increase is influenced substantially by the antibody concentration observed in the pre-vaccination sample.

Reference Values:
> or =9.7 mcg/mL

Clinical References: 1. Weisberg SS. Pneumococcus. Dis Mon. 2007;53(10):495-502. doi:10.1016/j.disamonth.2007.09.013 2. Grabenstein JD, Manoff SB. Pneumococcal polysaccharide 23-valent vaccine: long-term persistence of circulating antibody and immunogenicity and safety after revaccination in adults. Vaccine. 2012;30(30):4435-4444 3. Musher DM, Anderson R, Feldman C. The remarkable history of pneumococcal vaccination: an ongoing challenge. Pneumonia (Nathan). 2022;14(1):5. Published 2022 Sep 25. doi:10.1186/s41479-022-00097-y 4. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013;2013(1):CD000422 5. Paradiso PR. Advances in pneumococcal disease prevention: 13-valent pneumococcal conjugate vaccine for infants and children. Clin Infect Dis. 2011;52(10):1241-1247 6. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(4):109-117 7. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-Valent Pneumococcal Conjugate Vaccine Among U.S. Children: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(37):1174-1181 8. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015;136(5):1186-205.e2078 9. Orange JS, Ballow M, Stiehm ER, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2012;130(3 Suppl):S1-S24 10. Parker AR, Park MA, Harding S, Abraham RS. The total IgM, IgA and IgG antibody responses to pneumococcal polysaccharide vaccination (Pneumovax 23) in a healthy adult population and patients diagnosed with primary immunodeficiencies. Vaccine. 2019;37(10):1350-1355

MSTC
80749

Strict Criteria Sperm Morphology for Infertility Diagnosis and Treatment, Semen

Clinical Information: Infertility affects 1 out of 6 couples of child-bearing age. Approximately 40% of infertility has a female-factor cause and 40% a male-factor cause. The remaining 20% of infertility is due to a combination of male- and female-factor disorders or is unexplained. Abnormalities in sperm morphology are related to defects in sperm transport, sperm capacitation, the acrosome reaction, binding/penetration of the zona pellucida, and fusion with the oocyte vitelline membrane. All of these steps are essential to normal fertility. Strict criteria sperm morphology testing also greatly assists with selecting the most cost-effective in vitro sperm processing and insemination treatment for the couple's in vitro fertilization (IVF) cycle. Sperm with severe head abnormalities are unlikely to bind to the zona pellucida. These patients may require intracytoplasmic sperm injection in association with their IVF cycle to ensure optimal levels of fertilization are achieved. This, in turn, provides the patient with the best chance of pregnancy.

Useful For: Diagnosing male infertility Selecting the most cost-effective therapy for treating male-factor infertility Quantifying the number of germinal and white blood cells per mL of semen

Interpretation: Categorizing sperm according to strict criteria based on measurements of head and

tail sizes and shapes. Sperm with abnormalities in head/tail size/shape may not be capable of completing critical steps in sperm transport and fertilization.

Reference Values:
Normal forms
> or =4.0%
Germinal cells/mL
<4 x 10(6) (normal)
> or =4 x 10(6) (Elevated germinal cells in semen are of unknown clinical significance)
WBC/mL
<1 x 10(6) (normal)
> or =1 x 10(6) (Elevated white blood cells in semen are of questionable clinical significance)

Clinical References: 1. Kruger Morphology Conference, Boston, MA, October 9, 1993 2. Cooper TG, Aitken J, Auger J, et al, eds. WHO laboratory manual for the examination and processing of human semen. 5th ed. WHO Press; 2010 3. Bjorndahl L, Apolikhin O, Baldi E, et al, eds: WHO laboratory manual for the examination and processing of human semen. 6th ed. World Health Organization; 2021

MSTC1 35184 Strict Criteria Sperm Morphology for Infertility Diagnosis and Treatment, Semen

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Useful For: Diagnosing male infertility Selecting the most cost-effective therapy for treating male-factor infertility Quantifying the number of germinal and WBCs per mL of semen

Interpretation: Categorizing sperm according to strict criteria based on measurements of head and tail sizes and shapes. Sperm with abnormalities in head, tail size, or shape may not be capable of completing critical steps in sperm transport and fertilization.

Reference Values:
Normal forms: > or =4.0%
Germinal cells/mL
<4 x 10(6) (normal)
> or =4 x 10(6) (elevated germinal cells in semen are of unknown clinical significance)
WBC/mL
<1 x 10(6) (normal)
> or =1 x 10(6) (elevated white blood cells in semen are of questionable clinical significance)

Clinical References: 1. Kruger Morphology Conference, Boston, MA, October 9, 1993 2. WHO laboratory manual for the examination and processing of human semen. 5th ed. WHO Press; 2010 3.

WHO laboratory manual for the examination and processing of human semen. 6th ed. World Health Organization; 2021

STRNG
63866

Strongyloides Antibody, IgG, Serum

Clinical Information: Strongyloidiasis is caused by Strongyloides stercoralis, a nematode endemic to tropical and subtropical regions worldwide. S stercoralis is also prominent in the Southeastern US, including in rural areas of Kentucky, Tennessee, Virginia, and North Carolina. A small series of epidemiological studies in the US identified that 0% to 6.1% of individuals sampled had antibodies to S stercoralis. S stercoralis has a complex lifecycle that begins with maturation to the infective filariform larva in warm, moist soil. The larvae subsequently penetrate exposed skin and migrate hematogenously to the lungs, from where they ascend the bronchial tree and are swallowed. Once in the small intestine, filariform larva matures into the adult worms that burrow into the mucosa. Gravid female worms produce eggs that develop into noninfectious rhabditiform larvae in the gastrointestinal tract and are eventually released in the stool. The time from dermal penetration to appearance of Strongyloides in stool samples is approximately 3 to 4 weeks. The most common manifestations of infection are mild and may include epigastric pain, mild diarrhea, nausea, and vomiting. At the site of filariform penetration, skin may be inflamed and itchy-this is referred to as "ground itch." Migration of the larva through the lungs and up the trachea can produce a dry cough, wheezing, and mild hemoptysis. Eosinophilia, though common among patients with strongyloidiasis, is not a universal finding, and the absence of eosinophilia cannot be used to rule-out infection. In some patients, particularly those with a depressed immune system, the rhabditiform larvae may mature into the infectious filariform larvae in the gastrointestinal tract and lead to autoinfection. The filariform larvae subsequently penetrate the gastrointestinal mucosa, migrate to the lungs, and can complete their lifecycle. Low-level autoinfection can maintain the nematode in the host for years to decades. Among patients who become severely immunocompromised, however, autoinfection may lead to hyperinfection and fatal disseminated disease. Hyperinfection has also been associated with underlying human T-cell lymphotropic virus type 1 (HTLV-1) infection. Uncontrolled, the larvae can disseminate to the lungs, heart, liver, and central nervous system. Septicemia and meningitis are common in cases of Strongyloides hyperinfection due to seeding of the bloodstream and central nervous system with bacteria originating from the gastrointestinal tract.

Useful For: Screening for the presence of IgG-class antibodies to Strongyloides This test is not useful for monitoring patient response to therapy as IgG-class antibodies to Strongyloides may remain detectable following resolution of infection.

Interpretation: Positive: IgG antibodies to Strongyloides were detected, suggesting current or past infection. False-positive results may occur with other helminth infections (eg, Trichinella, Taenia solium). Clinical correlation is required. Negative: No detectable levels of IgG antibodies to Strongyloides. Repeat testing in 10 to 14 days if clinically indicated.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Ramanathan R, Burbelo PD, Groot S, Iadarola MJ, Neva FA, Nutman TB. A luciferase immunoprecipitation systems assay enhances the sensitivity and specificity of diagnosis of Strongyloides stercoralis infection. J Infect Dis. 2008;198(3):444-451 2. Starr MC, Montgomery SP. Soil-transmitted Helminthiasis in the United States: a systematic review-1940-2010. Am J Trop Med Hyg. 2011;85(4):680-684 3. Krolewiecki AJ, Ramanathan R, Fink V, et al. Improved diagnosis of Strongyloides stercoralis using recombinant antigen-based serologies in a community-wide study in northern Argentina. Clin Vaccine Immunol. 2010;17(10):1624-1630 4. Centers for Disease Control and

Prevention. Global Health. Division of Parasitic Diseases and Malaria: Parasites-Strongyloides: Epidemiology and Risk Factors. CDC; Updated February 16, 2024. Accessed December 9, 2024. Available at www.cdc.gov/parasites/strongyloides/epi.html

FSTYR
91094

Styrene, Occupational Exposure, Blood

Reference Values:
Normal (Unexposed population):
None detected

Exposed:
Biological Exposure Index (BEI):
0.55 mg/L (end of shift)

0.02 mg/L (prior to next shift)

Toxic:
Not established

SUAC
83635

Succinylacetone, Blood Spot

Clinical Information: Tyrosinemia type 1 (hepatorenal tyrosinemia, HT-1) is an autosomal recessive condition caused by a deficiency of the enzyme fumarylacetoacetate hydrolase (FAH). HT-1 primarily affects the liver, kidneys, and peripheral nerves, causing severe liver disease, renal tubular dysfunction, and neurologic crises. If left untreated, most patients die of liver failure in the first years of life and all are at risk of developing hepatocellular carcinoma. Treatment with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanedione (NTBC) is available and is particularly effective when initiated in newborns. The incidence of HT-1 is approximately 1 in 100,000 live births. While tyrosine can be determined by routine newborn screening, it is not a specific marker for tyrosinemia type I and often may be associated with common and benign transient tyrosinemia of the newborn. Succinylacetone is a specific marker for HT-1 but not consistently measured by newborn screening programs. This assay determines succinylacetone and tyrosine in newborn blood spots by tandem mass spectrometry. Additional follow-up testing may include confirmatory molecular analysis of the FAH gene.

Useful For: Second-tier newborn screen for tyrosinemia type 1 (HT-1) when primary screen showed nonspecific elevations of tyrosine Diagnosing HT-1 when used in conjunction with testing for urine organic acids, liver function, alpha-fetoprotein, and molecular genetic analysis of FAH

Interpretation: Elevations of succinylacetone (SUAC) above the reference range with or without elevations of tyrosine (TYR) are indicative of tyrosinemia type 1. Elevations of TYR above the reference range without elevations of SUAC may be suggestive of tyrosinemia type II, type III, transient hypertyrosinemia of the neonate, or nonspecific liver disease.

Reference Values:
SUCCINYLACETONE
< or =1.0 nmol/mL

TYROSINE
<4 weeks: 40-280 nmol/mL
> or =4 weeks: 25-150 nmol/mL

Clinical References: 1. Blackburn PR, Hickey RD, Nace RA, et al. Silent tyrosinemia type I without elevated tyrosine or succinylacetone associated with liver cirrhosis and hepatocellular carcinoma. Hum Mutat. 2016;37(10):1097-1105. doi:10.1002/humu.23047 2. Larochelle J, Alvarez F, Bussieres JF, et al. Effects of nitisinone (NTBC) treatment on the clinical course of hepatorenal tyrosinemia in Quebec. Mol Genet Metab. 2012;107(1-2):49-54 3. Sniderman King L, Trahms C, Scott CR. Tyrosinemia Type I. In: MP Adam, HH Ardinger, PA Pagon et al, eds: GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated May 25, 2017. Accessed December 7, 2023. Available at: www.ncbi.nlm.nih.gov/books/NBK1515/ 4. De Jesus VR, Adam BW, Mandel D, Cuthbert CD, Matern D. Succinylacetone as primary marker to detect tyrosinemia type I in newborns and its measurement by newborn screening programs. Mol Genet Metab. 2014;113(1-2)67-75 5. Chinsky JM, Singh R, Ficicioglu C et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. Genet Med. 2017;19(12) doi:10.1038/gim.2017.101

SUDC
606930

Sudden Cardiac Death Pathology Consultation

Clinical Information: Sudden, unexpected death in individuals less than 40 years of age with a strong probability of cardiac disease (including cases of obvious cardiomyopathy, with likely genetic underpinning). This evaluation is offered to provide the careful dissection and diagnostic experience that may be needed for subtle or overt cases of cardiovascular disease.

Useful For: Identifying specific causes contributing to sudden cardiac death

Interpretation: This request will be processed as a consultation. Appropriate stains and ancillary testing will be performed, and an interpretation provided.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Baudhuin LM, Leduc C, Train LJ, et al. Technical advances for the clinical genomic evaluation of sudden cardiac death: Verification of next-generation sequencing panels for hereditary cardiovascular conditions using formalin-fixed paraffin-embedded tissues and dried blood spots. Circ Cardiovasc Genet. 2017;10(6):e001844. doi:10.1161/CIRCGENETICS.117.001844 2. Ackerman JP, Bartos DC, Kapplinger JD, Tester DJ, Delisle BP, Ackerman MJ. The promise and peril of precision medicine: phenotyping still matters most. Mayo Clin Proc. Published online October 8, 2016. doi:10.1016/j.mayocp.2016.08.008

FSCNE
57543

Sugar Cane (Saccharum officinarum) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

SBSE
82382

Sugarbeet Seed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from

IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to sugar beet seed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SFZ
8238

Sulfamethoxazole, Serum

Clinical Information: Sulfamethoxazole is a sulfonamide antibiotic that is administered in conjunction with another antibacterial, trimethoprim. These agents are used to treat a variety of infections, including methicillin-resistant Staphylococcus aureus, and for prophylaxis in immunosuppressed patients, such as individuals who are HIV positive. Therapeutic drug monitoring is not commonly performed unless there are concerns about adequate absorption, clearance, or compliance. Monitoring of

sulfamethoxazole is indicated only when prolonged (>3 months) therapy is required. Sulfamethoxazole is absorbed readily after oral administration, with peak serum concentration occurring 1 to 4 hours after an oral dose. Its average elimination half-life is approximately 10 hours. Toxicity includes crystalluria with resultant calculi and kidney disease. Toxicity is due to a high concentration of acetylated, relatively insoluble forms of the drug. Excess fluid should be taken with sulfamethoxazole to avoid formation of urine sulfonamide crystals.

Useful For: Monitoring sulfamethoxazole therapy to ensure drug absorption, clearance, or compliance

Interpretation: Peak concentrations of sulfamethoxazole should be obtained 1 hour after the end of an intravenous dose or 2 to 3 hours after an oral dose, while peak concentrations of trimethoprim can be collected at least 1 hour after an oral dose. Serum drug concentrations should be interpreted with respect to the minimal inhibitory concentration of targeted organisms. Most patients will display peak steady-state serum concentrations greater than 50 mcg/mL when collected at least 1 hour after an oral dose. Target concentrations may be higher, depending on the intent of therapy. For Pneumocystis carinii pneumonia (PCP pneumonia), peak concentrations: 100-150 mcg/mL Toxicity: >200 mcg/mL Toxicity (formation of urinary crystals) associated with sulfamethoxazole occurs with prolonged exposure to serum concentrations greater than 125 mcg/mL. Trimethoprim: Most patients will display peak steady-state serum concentrations of more than 2.0 mcg/mL when the specimen is collected at least 1 hour after an oral dose. Target concentrations may be higher depending on the intent of therapy.

Reference Values:
>50 mcg/mL (Peak)

Clinical References: 1. Hughes WT, Feldman S, Chaudhary SC, Ossi MJ, Cox F, Sanyal SK. Comparison of pentamidine isethionate and trimethoprim-sulfamethoxazole in the treatment of Pneumocystis carinii pneumonia. J Pediatr. 1978;92(2):285-291. doi:10.1016/s0022-3476(78)80028-6 2. Dao BD, Barreto JN, Wolf RC, Dierkhising RA, Plevak MF, Tosh PK. Serum peak sulfamethoxazole concentrations demonstrate difficulty in achieving a target range: a retrospective cohort study. Curr Ther Res Clin Exp. 2014;76:104-109. doi:10.1016/j.curtheres.2014.08.003 3. Young T, Oliphant C, Araoyinbo I, Volmink J. Co-trimoxazole prophylaxis in HIV: the evidence. S Afr Med J. 2008;98(4):258-259 4. Avdic E, Cosgrove SE. Management and control strategies for community-associated methicillin-resistant Staphylococcus aureus. Expert Opin Pharmacother. 2008;9(9):1463-1479. doi:10.1517/14656566.9.9.1463 5. Kamme C, Melander A, Nilsson N. Serum and saliva concentrations of sulfamethoxazole and trimethoprim in adults in children: relation between saliva concentrations and in vitro activity against nasopharyngeal pathogens. Scand J Infect Dis. 1983;15(1):107-113. doi:10.3109/inf.1983.15.issue-1.18 6. Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 13th ed. McGraw-Hill Publishing; 2018

SULFU
606479

Sulfate, 24 Hour, Urine

Clinical Information: Urinary sulfate is a reflection of dietary protein intake, particularly meat, fish, and poultry, which are rich in sulfur-containing amino acids methionine and cysteine. Urinary sulfate can be used to assess dietary protein intake for nutritional purposes. A protein-rich diet has been associated with an increased risk for stone formation, possibly due, in part, to an increase in urinary calcium excretion caused by acid production from metabolism of sulfur-containing amino acids.(1,2) Indeed, urinary sulfate excretion is higher in patients who have kidney stones than in individuals who do not form stones. Thus, urinary sulfate excretion may provide an index for protein-induced calciuria.(1) Sulfate is a major anion in the urine that has significant affinity for cations and modulates the availability of cations for reacting with other anions in the urine. It thus is an important factor of

urinary supersaturation(3) for various crystals or stones such as calcium oxalate, hydroxyapatite, and brushite. For example, a high sulfate concentration may modulate the availability of calcium for reacting with oxalate and thus affect the propensity for calcium oxalate stone or crystal formation. Urinary sulfate also has a major impact on buffering or providing hydrogen ions and as such modulates the supersaturation of uric acid.

Useful For: Assessing the nutrition intake of animal protein The calculation of urinary supersaturation of various crystals or stones

Interpretation: Urinary sulfate is a reflection of dietary protein intake, particularly of meat, and thus can be used as an index of nutritional protein intake. It also is used in the calculation of urinary supersaturation of various crystals or stones.

Reference Values:
7-47 mmol/24 hours

Clinical References: 1. Rodgers A, Gauvin D, Edeh S, et al. Sulfate but not thiosulfate reduces calculated and measured urinary ionized calcium and supersaturation: implications for the treatment of calcium renal stones. PLoS ONE. 2014;9(7):e103602. doi:10.1371/journal.pone.0103602 2. Magee EA, Curno R, Edmond LM, Cummings JH. Contribution of dietary protein and inorganic sulfur to urinary sulfate: toward a biomarker of inorganic sulfur intake. Am J Clin Nutr. 2004;80(1):137-142 3. Houterman S, van Faassen A, Ocke MC, et al. Is urinary sulfate a biomarker for the intake of animal protein and meat?. Cancer Lett. 1997;114(1-2):295-296

FSUAB 75230 Sulfatide Autoantibody Test

Clinical Information: Background information: Peripheral neuropathies (PNs) are a group of neurological disorders affecting one or more of the peripheral nerves (1,2). Causes of PN include nerve compression, genetic mutations, inflammation, metabolic abnormalities, vitamin deficiencies, exposure to toxins or drugs, or the presence of autoimmune antibodies (1). Symptoms of PN vary based on location and mechanism of nerve damage but can include sensory impairment, distal weakness, loss of sensation, muscle weakness, and pain (1,2). PNs are typically classified based on the types of nerves affected, predominantly motor, predominantly sensory, or a combination of both (2). IgG and more commonly IgM Antibodies to sulfatide have been associated with sensory and sensory-motor neuropathies sometimes accompanied by pain (3,4,5). Additionally, IgG anti-sulfatide antibodies have been associated with distal sensory polyneuropathy (DSP) in individuals with HIV (6).

Reference Values:
A final report will be attached in MayoAccess.

Clinical References: 1. Andreoli et al. (2007) Cecil Essentials of Medicine. 7th ed. Sauders Elsevier. (ISBN-13: 978-1-4160-2933-5) 2. Latov, N. (2007) Peripheral Neuropathy: When the Numbness, Weakness and Pain Won't Stop. AAN press. (ISBN-13: 978-1-932603-59-0) 3. Pestronk, A, et al. (1991) Neurology 41: 357-62, (PMID: 1706491) 4. Lopate, G, et al. (1997) J Neurol Neurosurg Psychiatry 62: 581-5. (PMID: 9219742) 5. van den Berg, LH, et al. (1993) J Neurol Neurosurg Psychiatry 56: 1164-8. (PMID: 8229027) 6. Lopate, G, et al. (2005) Neurology 64: 1632-4. (PMID: 15883332)

FSLFU 57710 Sulfonylurea Screen, Urine

Reference Values:

Reference Range: Not Established

Acetohexamide, UR	ug/mL
Chlorpropamide, UR	ug/mL
Tolazamide, UR	ug/mL
Tolbutamide, UR	ug/mL
Glimepiride, UR	ng/mL
Glipizide, UR	ng/mL
Glyburide, UR	ng/mL
Nateglinide, UR	ng/mL
Repaglinide, UR	ng/mL

FSUNG
57681

Sunflower Seed IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

SUNFS
82813

Sunflower Seed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to sunflower seed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SUNF
82615

Sunflower, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to sunflower Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SUP24
616180

Supersaturation Profile, 24 Hour, Urine

Clinical Information: Urine is often supersaturated, which favors precipitation of several crystalline phases, such as calcium oxalate, calcium phosphate, and uric acid. However, crystals do not always form in supersaturated urine because supersaturation is balanced by crystallization inhibitors that are present in the urine. Urinary inhibitors include ions (eg, citrate) and macromolecules but remain poorly understood. Urine supersaturation is calculated by measuring the concentration of all the ions that can interact (potassium, calcium, phosphorus, oxalate, uric acid, citrate, magnesium, sodium, chloride, sulfate, and pH). Once the concentrations of all the relevant urinary ions are known, a computer program can calculate the theoretical supersaturation with respect to the important crystalline phases (eg, calcium oxalate).(1) Since the supersaturation of urine has been shown to correlate with stone type,(2) therapy is often targeted towards decreasing the urinary supersaturations identified. Treatment strategies include alterations in diet and fluid intake as well as drug therapy; all designed to decrease the urine supersaturation.

Useful For: Diagnosis and management of patients with renal lithiasis: -Predicting the likely composition of the stone, in patients who have a radiopaque stone, for whom stone analysis is not available -May aid in designing a treatment program Aiding in identification of specific risk factors for stones using a 24-hour urine collection Monitoring the effectiveness of therapy by confirming that the crystallization potential has indeed decreased Evaluating kidney excretion of acid and urine pH Estimating a patient's protein intake

Interpretation: Delta G (DG), the Gibbs free energy of transfer from a supersaturated to a saturated solution, is negative for undersaturated solutions and positive for supersaturated solutions. In most cases, the supersaturation levels are slightly positive, even in normal individuals, but are balanced by an inhibitor activity. While the DG of urine is often positive, even in the urine of non-stone formers, on average, the DG is more positive in those individuals who do form kidney stones. The reference values were derived by comparing urinary DG values for the important stone-forming crystalline phases between a population of stone formers and a population of non-stone formers. DG values that are outside the expected range in a population of non-stone formers are marked abnormal. If the urine citrate is low, secondary causes should be excluded, including hypokalemia, renal tubular acidosis, gastrointestinal bicarbonate losses (eg, diarrhea or malabsorption), or an exogenous acid load (eg,

excessive consumption of meat protein). A normal or increased citrate value suggests that potassium citrate may be a less effective choice for treatment of a patient with calcium oxalate or calcium phosphate stones. An increased urinary oxalate value may prompt a search for genetic abnormalities of oxalate production (ie, primary hyperoxaluria). Secondary hyperoxaluria can result from diverse gastrointestinal disorders that result in malabsorption. Milder hyperoxaluria could result from excess dietary oxalate consumption or reduced calcium (dairy) intake, perhaps even in the absence of gastrointestinal disease. High urine ammonium and low urinary pH suggest ongoing gastrointestinal losses. Such patients are at risk of uric acid and calcium oxalate stones. Low urine ammonium and high urine pH suggest renal tubular acidosis. Such patients are at risk of calcium phosphate stones. Patients with calcium oxalate and calcium phosphate stones are often treated with citrate to raise the urine citrate (a natural inhibitor of calcium oxalate and calcium phosphate crystal growth). However, since citrate is metabolized to bicarbonate (a base), this drug can also increase the urine pH. If the urine pH gets too high with citrate treatment, one may unintentionally increase the risk of calcium phosphate stones. Monitoring the urine ammonium concentration is one way to titrate the citrate dose and avoid this problem. A good starting citrate dose is about one-half of the urine ammonium excretion (in mEq of each). One can monitor the effect of this dose on urine ammonium, citrate, and pH values and adjust the citrate dose based on the response. A fall in urine ammonium levels should indicate whether the current citrate is enough to partially (but not completely) counteract the daily acid load of that given patient. The protein catabolic rate is calculated from urine urea. Under routine conditions, the required protein intake is often estimated as 0.8 g/ kg body weight. The results can be used to determine the likely effect of a therapeutic intervention on stone-forming risk. For example, taking oral potassium citrate will raise the urinary citrate excretion, which should reduce calcium phosphate supersaturation (by reducing free ionic calcium), but citrate administration also increases urinary pH (because it represents an alkali load), which promotes calcium phosphate crystallization. The net result of this or any therapeutic manipulation could be assessed by collecting a 24-hour urine and comparing the supersaturation calculation for calcium phosphate before and after therapy. Important stone-specific factors: -Calcium oxalate stones: urine volume, calcium, oxalate, citrate, and uric acid excretion are all risk factors that are possible targets for therapeutic intervention. -Calcium phosphate stones (apatite or brushite): urinary volume, calcium, pH, and citrate significantly influence the supersaturation of calcium phosphate. Of note, a urine pH below 6 may help reduce the tendency for these stones to form. -Uric acid stones: urine pH, volume, and uric acid excretion levels influence the supersaturation. Urine pH is especially critical, in that uric acid is unlikely to crystallize if the pH is above 6. -Sodium urate stones: alkaline pH and high uric acid excretion promote stone formation. A low urine volume is a universal risk factor for all types of kidney stones.

Reference Values:

SUPERSATURATION REFERENCE MEANS (Delta G: DG)

Men:
Calcium oxalate: 1.89 DG
Brushite: 0.46 DG
Hydroxyapatite: 4.19 DG
Uric acid: 1.18 DG

Women:
Calcium oxalate: 1.59 DG
Brushite: -0.11 DG
Hydroxyapatite: 3.62 DG
Uric acid: 0.89 DG

INDIVIDUAL URINE ANALYTES

OSMOLALITY, 24 HOUR, URINE
0-11 months: 50-750 mOsm/kg
> or =12 months: 150-1,150 mOsm/kg

pH, 24 HOUR, URINE
4.5-8.0

SODIUM, 24 HOUR, URINE
> or =18 years: 22-328 mmol/24 h
Reference values have not been established for patients who are younger than 18 years.

POTASSIUM, 24 HOUR, URINE
> or =18 years: 16-105 mmol/24 h
Reference values have not been established for patients who are younger than 18 years.

CALCIUM, 24 HOUR, URINE
Males: <250 mg/24 h
Females: <200 mg/24 h
Reference values have not been established for patients who are younger than 18 years.

MAGNESIUM, 24 HOUR, URINE
51-269 mg/24 h
Reference values have not been established for patients who are younger than 18 years.

CHLORIDE, 24 HOUR, URINE
> or =18 years: 34-286 mmol/24 h
Reference values have not been established for patients who are younger than 18 years.

PHOSPHORUS, 24 HOUR, URINE
> or =18 years: 226-1,797 mg/24 h
Reference values have not been established for patients who are younger than 18 years.

SULFATE, 24 HOUR, URINE
7-47 mmol/24 h

CITRATE EXCRETION, 24 HOUR, URINE
0-19 years: Not established
20 years: 150-1,191 mg/24 h
21 years: 157-1,191 mg/24 h
22 years: 164-1,191 mg/24 h
23 years: 171-1,191 mg/24 h
24 years: 178-1,191 mg/24 h
25 years: 186-1,191 mg/24 h
26 years: 193-1,191 mg/24 h
27 years: 200-1,191 mg/24 h
28 years: 207-1,191 mg/24 h
29 years: 214-1,191 mg/24 h
30 years: 221-1,191 mg/24 h
31 years: 228-1,191 mg/24 h
32 years: 235-1,191 mg/24 h
33 years: 242-1,191 mg/24 h
34 years: 250-1,191 mg/24 h
35 years: 257-1,191 mg/24 h
36 years: 264-1,191 mg/24 h
37 years: 271-1,191 mg/24 h
38 years: 278-1,191 mg/24 h
39 years: 285-1,191 mg/24 h

40 years: 292-1,191 mg/24 h
41 years: 299-1,191 mg/24 h
42 years: 306-1,191 mg/24 h
43 years: 314-1,191 mg/24 h
44 years: 321-1,191 mg/24 h
45 years: 328-1,191 mg/24 h
46 years: 335-1,191 mg/24 h
47 years: 342-1,191 mg/24 h
48 years: 349-1,191 mg/24 h
49 years: 356-1,191 mg/24 h
50 years: 363-1,191 mg/24 h
51 years: 370-1,191 mg/24 h
52 years: 378-1,191 mg/24 h
53 years: 385-1,191 mg/24 h
54 years: 392-1,191 mg/24 h
55 years: 399-1,191 mg/24 h
56 years: 406-1,191 mg/24 h
57 years: 413-1,191 mg/24 h
58 years: 420-1,191 mg/24 h
59 years: 427-1,191 mg/24 h
60 years: 434-1,191 mg/24 h
>60 years: Not established

OXALATE, 24 HOUR, URINE
0.11-0.46 mmol/24 h
9.7-40.5 mg/24 h
Reference values have not been established for patients who are younger than 16 years.

URIC ACID, 24 HOUR, URINE
Males: > or =18 years: 200-1,000 mg/24 h
Females: > or =18 years: 250-750 mg/24 h
Reference values have not been established for patients who are younger than 18 years.

CREATININE, 24 HOUR, URINE
Males: > or =18 years: 930-2,955 mg/24 h
Females: > or =18 years: 603-1,783 mg/24 h
Reference values have not been established for patients who are younger than 18 years.

AMMONIUM, 24 HOUR, URINE
15-56 mmol/24 h
Reference values have not been established for patients who are younger than 18 years or older than 77 years.

UREA NITROGEN, 24 HOUR, URINE
> or =18 years: 7-42 g/24 h
Reference values have not been established for patients who are younger than 18 years.

PROTEIN CATABOLIC RATE, 24 HOUR, URINE
56-125 g/24 h

Clinical References: 1. Werness PG, Brown CM, Smith LH, Finlayson B. EQUIL2: a BASIC computer program for the calculation of urinary saturation. J Urol. 1985;134(6):1242-1244 2. Parks JH, Coward M, Coe FL. Correspondence between stone composition and urine supersaturation in nephrolithiasis. Kidney Int. 1997;51(3):894-900 3. Finlayson B. Calcium stones: Some physical and

clinical aspects. In: David DS, ed. Calcium Metabolism in Renal Failure and Nephrolithiasis. John Wiley and Sons; 1977:337-382 4. Burtis CA, Bruns DE: Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics. 7th ed. Saunders; 2014 5. Tiselius HG, Daudon M, Thomas K, Seitz C. Metabolic work-up of patients with urolithiasis: indications and diagnostic algorithm. Eur Urol Focus. 2017 Feb;3(1):62-71. doi:10.1016/j.euf.2017.03.014

SUPRA
616375

Supersaturation Profile, Random, Urine

Clinical Information: Urine is often supersaturated, which favors precipitation of several crystalline phases such as calcium oxalate, calcium phosphate, and uric acid. However, crystals do not always form in supersaturated urine because supersaturation is balanced by crystallization inhibitors that are present in the urine. Urinary inhibitors include ions (eg, citrate) and macromolecules but remain poorly understood. Urine supersaturation is calculated by measuring the concentration of all the ions that can interact (potassium, calcium, phosphorus, oxalate, uric acid, citrate, magnesium, sodium, chloride, sulfate, and pH). Once the concentrations of all the relevant urinary ions are known, a computer program can calculate the theoretical supersaturation with respect to the important crystalline phases (eg, calcium oxalate).(1) Since the supersaturation of urine has been shown to correlate with stone type,(2) therapy is often targeted towards decreasing the urinary supersaturations identified. Treatment strategies include alterations in diet and fluid intake as well as drug therapy; all designed to decrease the urine supersaturation.

Useful For: Diagnosis and management of patients with renal lithiasis: -Predicting the likely composition of the stone, in patients who have a radiopaque stone, for whom stone analysis is not available which may help in designing a treatment program -Identifying specific risk factors for stones formation using a random urine collection -Monitoring the effectiveness of therapy by confirming that the crystallization potential has indeed decreased -Evaluation of kidney excretion of acid and urine pH

Interpretation: Delta G (DG), the Gibbs free energy of transfer from a supersaturated to a saturated solution, is negative for undersaturated solutions and positive for supersaturated solutions. In most cases, the supersaturation levels are slightly positive, even in normal individuals, but are balanced by an inhibitor activity. While the DG of urine is often positive, even in the urine of non-stone formers, on average, the DG is more positive in those individuals who do form kidney stones. The reference values are derived by comparing urinary DG values for the important stone-forming crystalline phases between a population of stone formers and a population of non-stone formers. Those DG values that are outside the expected range in a population of non-stone formers are marked abnormal. A normal or increased citrate value suggests that potassium citrate may be a less effective choice for treatment of a patient with calcium oxalate or calcium phosphate stones. If the urine citrate is low, secondary causes should be excluded including hypokalemia, renal tubular acidosis, gastrointestinal bicarbonate losses (eg, diarrhea or malabsorption), or an exogenous acid load (eg, excessive consumption of meat protein). An increased urinary oxalate value may prompt a search for genetic abnormalities of oxalate production (ie, primary hyperoxaluria). Secondary hyperoxaluria can result from diverse gastrointestinal disorders that result in malabsorption. Milder hyperoxaluria could result from excess dietary oxalate consumption or reduced calcium (dairy) intake, perhaps even in the absence of gastrointestinal disease. Low urine ammonium and high urine pH suggest renal tubular acidosis. Such patients are at risk of calcium phosphate stones. The results can be used to determine the likely effect of a therapeutic intervention on stone-forming risk. For example, taking oral potassium citrate will raise the urinary citrate excretion, which should reduce calcium phosphate supersaturation (by reducing free ionic calcium), but citrate administration also increases urinary pH (because it represents an alkali load), which promotes calcium phosphate crystallization. The net result of this or any therapeutic manipulation could be assessed by collecting a 24-hour urine and comparing the supersaturation calculation for calcium phosphate before and after therapy. Important stone-specific factors: -Calcium oxalate stones: Urine volume, calcium, oxalate, citrate, and uric acid excretion are all risk factors that are possible targets for therapeutic intervention. -Calcium phosphate stones (apatite or brushite): Urinary volume, calcium, pH, and citrate significantly

influence the supersaturation of calcium phosphate. Of note, a urine pH below 6 may help reduce the tendency for these stones to form. -Uric acid stones: Urine pH, volume, and uric acid excretion levels influence the supersaturation. Urine pH is especially critical, in that uric acid is unlikely to crystallize if the pH is above 6. -Sodium urate stones: Alkaline pH and high uric acid excretion promote stone formation. A low urine volume is a universal risk factor for all types of kidney stones. The following reference means for calculated supersaturation apply to 24-hour timed collections. No information is available for random collections. Supersaturation Reference Means (Delta G: DG) Men: Calcium oxalate: 1.89 DG Brushite: 0.46 DG Hydroxyapatite: 4.19 DG Uric acid: 1.18 DG Women: Calcium oxalate: 1.59 DG Brushite: -0.11 DG Hydroxyapatite: 3.62 DG Uric acid: 0.89 DG Values for individual analytes that are part of this panel on a random urine collection are best interpreted as a ratio to the creatinine excretion. Following are pediatric reference ranges for the important analytes for which pediatric data is available. Oxalate/Creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 <0.175 0.5-1 <0.139 1-2 <0.103 2-3 <0.08 3-5 <0.064 5-7 <0.056 7-17 <0.048 Matos V, Van Melle G, Werner D, Bardy D, Guignard JP. Urinary oxalate and urate to creatinine ratios in a healthy pediatric population. Am J Kidney Dis. 1999;34(2):e1 Uric Acid/Creatinine (mg/mg) Age (year) 5th Percentile 95th Percentile 0-0.5 >1.189 <2.378 0.5-1 >1.040 <2.229 1-2 >0.743 <2.080 2-3 >0.698 <1.932 3-5 >0.594 <1.635 5-7 >0.446 <1.189 7-10 >0.386 <0.832 10-14 >0.297 <0.654 14-17 >0.297 <0.594 Matos V, Van Melle G, Werner D, Bardy D, Guignard JP. Urinary oxalate and urate to creatinine ratios in a healthy pediatric population. Am J Kidney Dis. 1999;34(2):e1 Phosphate/Creatinine (mg/mg) Age (year) 5th Percentile 95th Percentile 0-1 >0.34 <5.24 1-2 >0.34 <3.95 2-3 >0.34 <3.13 3-5 >0.33 <2.17 5-7 >0.33 <1.19 7-10 >0.32 <0.97 10-14 >0.22 <0.86 14-17 >0.21 <0.75 Matos V, van Melle G, Boulat O, Markert M, Bachmann C, Guignard JP. Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. J Pediatr. 1997;131(2):252-257 Magnesium/Creatinine (mg/g) Age (year) 95th Percentile 0-1 <0.48 1-2 <0.37 2-3 <0.34 3-5 <0.29 5-7 <0.21 7-10 <0.18 10-14 <0.15 14-17 <0.13 Matos V, van Melle G, Boulat O, Markert M, Bachmann C, Guignard JP. Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. J Pediatr. 1997;131(2):252-257 Citrate/Creatinine (mg/mg) Age (year) 95th Percentile 5-18 <1.311 Srivastava T, Winston MJ, Auron A, Alon US. Urine calcium/citrate ratio in children with hypercalciuric stones. Pediatr Res. 2009;66(1):85-90

SSH24 616228 Supersaturation Profile, Self-Collect, 24 Hour, Urine

Clinical Information: Urine is often supersaturated, which favors precipitation of several crystalline phases, such as calcium oxalate, calcium phosphate, and uric acid. However, crystals do not always form in supersaturated urine because supersaturation is balanced by crystallization inhibitors that are present in the urine. Urinary inhibitors include ions (eg, citrate) and macromolecules but remain poorly understood. Urine supersaturation is calculated by measuring the concentration of all the ions that can interact (potassium, calcium, phosphorus, oxalate, uric acid, citrate, magnesium, sodium, chloride, sulfate, and pH). Once the concentrations of all the relevant urinary ions are known, a computer program can calculate the theoretical supersaturation with respect to the important crystalline phases (eg, calcium oxalate).(1) Since the supersaturation of urine has been shown to correlate with stone type,(2) therapy is often targeted towards decreasing the urinary supersaturations identified. Treatment strategies include alterations in diet and fluid intake as well as drug therapy; all designed to decrease the urine supersaturation.

Useful For: Diagnosis and management of patients with renal lithiasis: -Predicting the likely composition of the stone, in patients who have a radiopaque stone, for whom stone analysis is not available -May aid in designing a treatment program Aiding in identification of specific risk factors for stones using a 24-hour urine collection Monitoring the effectiveness of therapy by confirming that the crystallization potential has indeed decreased Evaluating kidney excretion of acid and urine pH Estimating a patient's protein intake

Interpretation: Delta G (DG), the Gibbs free energy of transfer from a supersaturated to a saturated solution, is negative for undersaturated solutions and positive for supersaturated solutions. In most cases, the supersaturation levels are slightly positive, even in normal individuals, but are balanced by an inhibitor activity. While the DG of urine is often positive, even in the urine of non-stone formers, on average, the DG is more positive in those individuals who do form kidney stones. The reference values were derived by comparing urinary DG values for the important stone-forming crystalline phases between

a population of stone formers and a population of non-stone formers. DG values that are outside the expected range in a population of non-stone formers are marked abnormal. If the urine citrate is low, secondary causes should be excluded including hypokalemia, renal tubular acidosis, gastrointestinal bicarbonate losses (eg, diarrhea or malabsorption), or an exogenous acid load (eg, excessive consumption of meat protein). A normal or increased citrate value suggests that potassium citrate may be a less effective choice for treatment of a patient with calcium oxalate or calcium phosphate stones. An increased urinary oxalate value may prompt a search for genetic abnormalities of oxalate production (ie, primary hyperoxaluria). Secondary hyperoxaluria can result from diverse gastrointestinal disorders that result in malabsorption. Milder hyperoxaluria could result from excess dietary oxalate consumption or reduced calcium (dairy) intake, perhaps even in the absence of gastrointestinal disease. High urine ammonium and low urinary pH suggest ongoing gastrointestinal losses. Such patients are at risk of uric acid and calcium oxalate stones. Low urine ammonium and high urine pH suggest renal tubular acidosis. Such patients are at risk of calcium phosphate stones. Patients with calcium oxalate and calcium phosphate stones are often treated with citrate to raise the urine citrate (a natural inhibitor of calcium oxalate and calcium phosphate crystal growth). However, since citrate is metabolized to bicarbonate (a base), this drug can also increase the urine pH. If the urine pH gets too high with citrate treatment, one may unintentionally increase the risk of calcium phosphate stones. Monitoring the urine ammonium concentration is one way to titrate the citrate dose and avoid this problem. A good starting citrate dose is about one-half of the urine ammonium excretion (in mEq of each). One can monitor the effect of this dose on urine ammonium, citrate, and pH values and adjust the citrate dose based upon the response. A fall in urine ammonium levels should indicate whether the current citrate is enough to partially (but not completely) counteract the daily acid load of that given patient. The protein catabolic rate is calculated from urine urea. Under routine conditions, the required protein intake is often estimated as 0.8 g/ kg body weight. The results can be used to determine the likely effect of a therapeutic intervention on stone-forming risk. For example, taking oral potassium citrate will raise the urinary citrate excretion, which should reduce calcium phosphate supersaturation (by reducing free ionic calcium), but citrate administration also increases urinary pH (because it represents an alkali load), which promotes calcium phosphate crystallization. The net result of this or any therapeutic manipulation could be assessed by collecting a 24-hour urine and comparing the supersaturation calculation for calcium phosphate before and after therapy. Important stone-specific factors: -Calcium oxalate stones: urine volume, calcium, oxalate, citrate, and uric acid excretion are all risk factors that are possible targets for therapeutic intervention. -Calcium phosphate stones (apatite or brushite): urinary volume, calcium, pH, and citrate significantly influence the supersaturation of calcium phosphate. Of note, a urine pH below 6 may help reduce the tendency for these stones to form. -Uric acid stones: urine pH, volume, and uric acid excretion levels influence the supersaturation. Urine pH is especially critical, in that uric acid is unlikely to crystallize if the pH is above 6. -Sodium urate stones: alkaline pH and high uric acid excretion promote stone formation. A low urine volume is a universal risk factor for all types of kidney stones.

Reference Values:

SUPERSATURATION REFERENCE MEANS (Delta G: DG)

Men:

Calcium oxalate: 1.89 DG
Brushite: 0.46 DG
Hydroxyapatite: 4.19 DG
Uric acid: 1.18 DG

Women:

Calcium oxalate: 1.59 DG
Brushite: -0.11 DG
Hydroxyapatite: 3.62 DG
Uric acid: 0.89 DG

OSMOLALITY, 24 HOUR, URINE

0-11 months: 50-750 mOsm/kg
> or =12 months: 150-1,150 mOsm/kg

pH, 24 HR, U
4.5-8.0

SODIUM, 24 HOUR, URINE
> or =18 years: 22-328 mmol/24 h
Reference values have not been established for patients who are younger than 18 years.

POTASSIUM. 24 HOUR, URINE
> or =18 years: 16-105 mmol/24 h
Reference values have not been established for patients who are younger than 18 years.

CALCIUM, 24 HOUR, URINE
Males: <250 mg/24 h
Females: <200 mg/24 h
Reference values have not been established for patients who are younger than 18 years.

MAGNESIUM, 24 HOUR URINE
> or =18 years: 51-269 mg/24 h
Reference values have not been established for patients who are younger than 18 years.

CHLORIDE, 24 HOUR URINE
> or =18 years: 34-286 mmol/24 h
Reference values have not been established for patients who are younger than 18 years.

PHOSPHORUS, 24 HOUR, URINE
> or =18 years: 226-1,797 mg/24 h
Reference values have not been established for patients who are younger than 18 years of.

SULFATE, 24 HOUR, URINE
7-47 mmol/24 h

CITRATE EXCRETION, 24 HOUR, URINE
0-19 years: Not established
20 years: 150-1,191 mg/24 h
21 years: 157-1,191 mg/24 h
22 years: 164-1,191 mg/24 h
23 years: 171-1,191 mg/24 h
24 years: 178-1,191 mg/24 h
25 years: 186-1,191 mg/24 h
26 years: 193-1,191 mg/24 h
27 years: 200-1,191 mg/24 h
28 years: 207-1,191 mg/24 h
29 years: 214-1,191 mg/24 h
30 years: 221-1,191 mg/24 h
31 years: 228-1,191 mg/24 h
32 years: 235-1,191 mg/24 h
33 years: 242-1,191 mg/24 h
34 years: 250-1,191 mg/24 h
35 years: 257-1,191 mg/24 h
36 years: 264-1,191 mg/24 h
37 years: 271-1,191 mg/24 h

38 years: 278-1,191 mg/24 h
39 years: 285-1,191 mg/24 h
40 years: 292-1,191 mg/24 h
41 years: 299-1,191 mg/24 h
42 years: 306-1,191 mg/24 h
43 years: 314-1,191 mg/24 h
44 years: 321-1,191 mg/24 h
45 years: 328-1,191 mg/24 h
46 years: 335-1,191 mg/24 h
47 years: 342-1,191 mg/24 h
48 years: 349-1,191 mg/24 h
49 years: 356-1,191 mg/24 h
50 years: 363-1,191 mg/24 h
51 years: 370-1,191 mg/24 h
52 years: 378-1,191 mg/24 h
53 years: 385-1,191 mg/24 h
54 years: 392-1,191 mg/24 h
55 years: 399-1,191 mg/24 h
56 years: 406-1,191 mg/24 h
57 years: 413-1,191 mg/24 h
58 years: 420-1,191 mg/24 h
59 years: 427-1,191 mg/24 h
60 years: 434-1,191 mg/24 h
>60 years: Not established

OXALATE, 24 HOUR, URINE
0.11-0.46 mmol/24 h
9.7-40.5 mg/24 h

URIC ACID, 24 HOUR, URINE
Male: > or =18 years: 200-1,000 mg/24 h
Female: > or =18 years: 250-750 mg/24 h
Reference values have not been established for patients who are younger than 18 years.

CREATININE, 24 HOUR, URINE
Male: > or =18 years: 930-2,955 mg/24 h
Female: > or =18 years: 603-1,783 mg/24 h
Reference values have not been established for patients who are younger than 18 years.

AMMONIUM, 24 HOUR, URINE
15-56 mmol/24 h
Reference values have not been established for patients who are younger than18 years or older than 77 years.

UREA NITROGEN, 24 HOUR, URINE
> or =18 years: 7-42 g/24 h
Reference values have not been established for patients who are younger than 18 years.

PROTEIN CATABOLIC RATE, 24 HOUR, URINE
56-125 g/24 h

Clinical References: 1. Werness PG, Brown CM, Smith LH, Finlayson B. EQUIL2: a BASIC computer program for the calculation of urinary saturation. J Urol. 1985;134(6):1242-1244 2. Parks JH, Coward M, Coe FL. Correspondence between stone composition and urine supersaturation in

nephrolithiasis. Kidney Int. 1997;51(3):894-900 3. Finlayson B. Calcium stones: Some physical and clinical aspects. In: David DS, ed. Calcium Metabolism in Renal Failure and Nephrolithiasis. John Wiley and Sons; 1977:337-382 4. Burtis CA, Bruns DE. Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics. 7th ed. Saunders, 2014 5. Tiselius HG, Daudon M, Thomas K, Seitz C. Metabolic work-up of patients with urolithiasis: indications and diagnostic algorithm. Eur Urol Focus. 2017;3(1):62-71. doi: 10.1016/j.euf.2017.03.014

SNS
82594

Supplemental Newborn Screen, Blood Spot

Clinical Information: Newborn screening as a public health measure was initiated in the early 1960s to identify infants affected with phenylketonuria (PKU). Since then, additional genetic and nongenetic conditions have been included in state screening programs. The goal of newborn screening is to detect diagnostic markers of the selected disorders in blood spots collected from presymptomatic newborns. Inherited disorders of amino acid, fatty acid, and organic acid metabolism typically manifest during the first 2 years of life as acute metabolic crises and usually result in severe neurologic impairment or death. These metabolic decompensations are typically triggered by intermittent febrile illness, such as common viral infections leading to prolonged fasting and increased energy demands. Early identification of affected newborns allows for early initiation of treatment to avoid mortality, morbidity, and disabilities due to these disorders. Tandem mass spectrometry (MS/MS) is a powerful multianalyte screening method ideally suited for population-wide testing. Since the early 1990s, MS/MS has made screening possible for more than 30 genetic disorders affecting the metabolism of amino acids, fatty acids, and organic acids based on the profiling of amino acids and acylcarnitines in blood spots. The simultaneous MS/MS analysis of amino acids, acylcarnitines, and succinylacetone in dried blood spots can be performed in less than 3 minutes per specimen, generating metabolite profiles that allow for the biochemical diagnosis of multiple disorders. This is in contrast to conventional screening techniques traditionally based on the principle of one separate test for each disorder. In Mayo Clinic's experience, the combined incidence of the disorders identifiable by MS/MS in a single blood spot analysis is approximately 1 in 1700 newborns. Supplemental newborn screening by MS/MS as described here does not replace current state screening programs because MS/MS does not provide primary screening for galactosemia, congenital hypothyroidism, congenital adrenal hyperplasia, cystic fibrosis, biotinidase, sickle cell disease, mucopolysaccharidosis type I, adrenoleukodystrophy, Pompe disease, severe combined immune deficiency, spinal muscular atrophy, critical congenital heart disease, and congenital hearing loss. The Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children recommends all programs screen for 34 core disorders. These conditions are considered to fulfill 3 basic principles: -Condition is identifiable at a period of time (24-48 hours after birth) at which it would not ordinarily be clinically detected. -Test with appropriate sensitivity and specificity is available. -Demonstrated benefits of early detection, timely intervention, and efficacious treatment. *This test does not screen for critical congenital heart disease and congenital hearing loss, both of which are tested in the nursery using methods other than blood spots (audiometry, pulse oximetry). Screening tests do not conclusively determine disease status but measure analytes that, in most cases, are not specific for a particular disease. This is the reason why the Health and Human Services Secretary also recognizes more than 25 additional conditions as secondary targets that do not meet all inclusion criteria but are identified nevertheless because most are components of the differential diagnosis of screening results observed in core conditions. Even for the secondary conditions, the possibility of making a diagnosis early in life not only helps avoid unnecessary diagnostic testing but is also beneficial to patients' families, as genetic counseling and prenatal diagnosis can be offered. Guanidinoacetate methyltransferase (GAMT), a disorder of creatine synthesis recently added to the recommended uniform screening panel, is a condition included in the Mayo Clinic Laboratories' supplemental newborn screen. When untreated, this disorder results in a depletion of cerebral creatine, leading to global developmental delays, intellectual disability, severe speech delays, and seizures. Patients with GAMT deficiency exhibit behavioral problems and features of autism. Treatment consists of lifelong supplementation with creatine monohydrate, ornithine, and dietary protein restriction to decrease cerebral guanidinoacetic acid levels. Individuals with GAMT who are treated before the appearance of symptoms may exhibit normal neurodevelopmental outcomes.

Useful For: Presymptomatic identification of disorders to allow for early initiation of treatment and consequent improvement in the long-term prognosis of affected patients The conditions identifiable by amino acid and acylcarnitine analysis are detected by supplemental newborn screening using tandem mass spectrometry (MS/MS) as described here. Analyte (assay platform) ACMG recommended conditions Additional conditions/treatment detectable by MS/MS Core condition Secondary targets Amino acids (MS/MS) Phe PKU BS HPA REG TPN Leu/Ile, Val MSUD TPN Met HCY Met TPN, nonspecific liver disease Cit, Arg, ASA ASA CIT ARG CIT-II Tyr TYR-I TYR-II TYR-III Nonspecific liver disease GUAC GAMT Acylcarnitines (MS/MS) C0 CUD Maternal CUD, maternal GA-I, maternal MCAD C3 CblA, Cbl B MUT PA Cbl C, Cbl D C4 IBDH SCAD FIGLU C5 IVA SBCAD Antibiotics containing pivalic acid C5-OH BKT HMG MCC MCD MGA-I MHBD Maternal MCC, biotinidase deficiency C8 MCAD GA-II MCKAT M/SCHAD C3-DC MAL C10:2 DR C5-DC GA-I C14:1, C16, C18:1 VLCAD CACT CPT-I CPT-II C16-OH LCHAD TFP m/z 225<399<473 Dextrose infusion m/z 342 (C8:1) Artifact often observed in premature neonates m/z 470 (C16:1OH) Cefotaxime metabolite Succinylacetone TYR-I This test is not appropriate for metabolic screening of symptomatic patients.

Interpretation: The quantitative measurements of the various amino acids, acylcarnitines, and succinylacetone support the interpretation of the complete profile but, for the most part, are not diagnostic by themselves. The interpretation is by pattern recognition. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered by Mayo Clinic Laboratories. The reports are in text form only; values for the more than 60 analytes and analyte ratios are not provided. A report for a normal screening result is reported as: "In this blood spot sample, the amino acid and acylcarnitine profiles by tandem mass spectrometry showed no biochemical evidence indicative of an underlying metabolic disorder." A report for an abnormal screening result includes a quantitative result of the abnormal metabolites, a detailed interpretation of the results, including an overview of the results significance, possible differential diagnoses, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis), and a phone number for a contact at Mayo Clinic if the referring physician has additional questions.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Watson MS, Mann MY, Lloyd-Puryear MA, Rinaldo P, Howell RR. Newborn screening: toward a uniform screening panel and system. Genet Med. 2006;8 Suppl 1(Suppl 1):1S-252S 2. Rinaldo P, Zafari S, Tortorelli S, Matern D. Making the case for objective performing metrics in newborn screening by tandem mass spectrometry. Ment Retard Dev Disabil Res Rev. 2006;1294):255-261 3. Matern D, Tortorelli S, Oglesbee D, Gavrilov D, Rinaldo P. Reduction of the false-positive rate in newborn screening by implementation of MS/MS-based second-tier tests: The Mayo Clinic experience (2004-2007). J Inherit Metab Dis. 2007;30(4):585-592 4. McHugh DMS, Cameron CA, Abdenur JE, et al. Clinical validation of cutoff target ranges in newborn screening of metabolic disorders by tandem mass spectrometry: a worldwide collaborative project. Genet Med. 2011;13(3):230-254 5. Marquardt G, Currier R, McHugh DMS, et al. Enhanced interpretation of newborn screening results without analyte cutoff values. Genet Med. 2012;14(7):648-655 6. Hall PL, Marquardt G, McHugh DMS, et al. Post-analytical tools improve performance of newborn screening by tandem mass spectrometry. Genet Med. 2014;16(12):889-895

TBPZA
34549

Susceptibility, Mycobacterium tuberculosis Complex, Pyrazinamide, Varies

Clinical Information: Initial treatment regimens for Mycobacterium tuberculosis complex often include isoniazid, rifampin, ethambutol, and pyrazinamide (PZA). Susceptibility testing of M

tuberculosis complex isolates against these antimycobacterial agents is a key component of patient management. The Clinical and Laboratory Standards Institute provides consensus protocols for the methods, antimycobacterial agents, and critical concentrations of each agent to be tested to permit standardized interpretation of M tuberculosis complex susceptibility test results. This test uses a US Food and Drug Administration cleared commercial system for rapid broth susceptibility testing of M tuberculosis complex against PZA. The literature indicates that broth testing of PZA can, at times, produce falsely resistant results, so resistance to PZA by the broth method is automatically confirmed by pncA DNA sequencing. Variants in the pncA gene and upstream promoter region have been reported to account for the majority (70%-97%) of PZA-resistant isolates. However, 3% to 30% of PZA-resistant isolates do not have a corresponding pncA variant and other genes (eg, rpsA) may also play a role. A separate test is available for testing of the other primary agents (isoniazid, rifampin and ethambutol). If desired, this must be ordered separately; TB1LN / Antimicrobial Susceptibility, Mycobacterium tuberculosis Complex, First Line, Varies.

Useful For: Susceptibility testing of Mycobacterium tuberculosis complex isolates growing in pure culture against pyrazinamide This test is not useful for Mycobacterium bovis and Myocobacterium bovis bacille Calmette-Guerin (BCG) isolates as they are intrinsically resistant to pyrazinamide.

Interpretation: Mycobacterium tuberculosis complex isolates are reported as susceptible or resistant to pyrazinamide at the critical concentration.

Reference Values:
Results are reported as susceptible or resistant.

Clinical References: 1. Nahid P, Mase SR, Migliori GB, et al. Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline [published correction appears in Am J Respir Crit Care Med. 2020 Feb 15;201(4):500-501 2. Dormandy J, Somoskovi A, Kreiswirth BN, Driscoll JR, Ashkin D, Salfinger M. Discrepant results between pyrazinamide susceptibility testing by the reference BACTEC 460TB method and pncA DNA sequencing in patients infected with multidrug-resistant W-Beijing Mycobacterium tuberculosis strains. Chest. 2007;131(2):497-501. doi:10.1378/chest.06-1899 3. Chedore P, Bertucci L, Wolfe J. Potential for erroneous results indicating resistance when using the BACTEC MGIT 960 system for testing susceptibility of mycobacterium tuberculosis to Pyrazinamide. J Clin Microbiol 2010;48(1):300-301 4. Campbell PJ, Morlock GP, Sikes RD, et al. Molecular resistance of mutations associated with first- and second-line drug resistance compared with conventional drug susceptibility testing of Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2011;55(5):2032-2041 5. Shi W, Zhang X, Jiang X, et al. Pyrazinamide inhibits trans-translation in Mycobacterium tuberculosis. Science. 2011;333(6049):1630-1632 6. Clinical and Laboratory Standards Institute (CLSI). Susceptibility Testing of Mycobacteria, Nocardia spp., and Other Aerobic Actinomycetes. 3rd ed. CLSI standard M24. CLSI; 2018 7. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Susceptibility Testing of Mycobacteria, Nocardia spp., and Other Aerobic Actinomycetes. 2nd ed. CLSI supplement M24S. CLSI; 2023 8. Espasa M, Salvado M, Vicente E, et al. Evaluation of the versaTREK system compared to the Bactec MGIT 960 system for first-line drug susceptibility testing of Mycobacterium tuberculosis. J Clin Microbiol. 2012;50:488-491 9. Somoskovi A, Dormandy J, Parson LM, et al. Sequencing of the pncA gene in members of the Mycobacterium tuberculosis complex has important diagnostic applications: Identification of a species-specific pncA mutation in "Mycobacterium canettii" and the reliable and rapid predictor of pyrazinamide resistance. Confirmation of pyrazinamide resistance is done using Sanger dideoxy sequencing of approximately 700bp of the pncA gene and promoter region. J Clin Microbiol. 2007;45(2):595-599 10. Jureen P, Werngren J, Toro JC, Hoffner S: Pyrazinamide resistance and pncA gene mutations in Mycobacterium tuberculosis. Antimicrob Agents Chemother 2008;52(5):1852-1854

TB2LN 34550 Susceptibility, Mycobacterium tuberculosis Complex, Second

Line, Varies

Clinical Information: The Clinical and Laboratory Standards Institute (CLSI) provides a consensus protocol for the methods, antimycobacterial agents, and concentrations of each agent to be tested to permit standardized interpretation of Mycobacterium tuberculosis complex susceptibility testing results. CLSI guidelines suggest that additional agents should be tested when an isolate of M tuberculosis complex is resistant to rifampin, is monoresistant to the critical concentration of isoniazid and the physician intends to use a fluoroquinolone for therapy or is resistant to any combination of two first-line agents. This test uses a broth microdilution minimal inhibitory concentration (MIC) method for susceptibility testing of M tuberculosis complex against antimycobacterial agents. Agents tested are amikacin, ethionamide, kanamycin, moxifloxacin, ofloxacin, p-aminosalicylic acid, rifabutin, and streptomycin.

Useful For: Determination of Mycobacterium tuberculosis complex minimal inhibitory concentrations to second-line antimicrobial agents

Interpretation: Results are reported as minimal inhibitory concentrations in mcg/mL. This test is used as an alternative to TB1LN / Antimicrobial Susceptibility, Mycobacterium tuberculosis Complex, First Line, Varies for ethambutol, isoniazid and rifampin when reagents are not available to perform the TB1LN test. Ethambutol, isoniazid, and rifampin are not routinely reported with this test.

Reference Values:
Interpretive criteria and reporting guidelines are followed using the Clinical Laboratory Standards Institute (CLSI) M24S document.

Clinical References: 1. Hall L, Jude KP, Clark SL, et al. Evaluation of the Sensititre MycoTB plate for susceptibility testing of the Mycobacterium tuberculosis complex against first- and second-line agents. J Clin Microbiol. 2012;50:3732-3734 2. Nahid P, Mase SR, Migliori GB, et al. Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline [published correction appears in Am J Respir Crit Care Med. 2020 Feb 15;201(4):500-501 3. Clinical and Laboratory Standards Institute (CLSI). Susceptibility Testing of Mycobacteria, Nocardia spp., and Other Aerobic Actinomycetes. 3rd ed. CLSI standard M24. CLSI; 2018 4. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Susceptibility Testing of Mycobacteria, Nocardia spp., and Other Aerobic Actinomycetes. 2nd ed. CLSI supplement M24S. CLSI; 2023

SV40
618827

SV40 Immunostain, Technical Component Only

Clinical Information: Simian virus 40 (SV40) polyomavirus immunohistochemistry can be used in the diagnosis of polyomavirus-associated diseases, such as BK virus-associated nephropathy and JC virus-associated progressive multifocal leukoencephalopathy. The SV40 assay does not identify the specific polyomavirus detected, as BK and JC viruses show approximately 70% similarity to SV40. This test has been shown to not crossreact with Merkel cell polyomavirus.

Useful For: Identifying BK or JC polyomavirus

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Hirsch HH, Randhawa PS. AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13528 2. Atkinson AL, Atwood WJ. Fifty years of JC polyomavirus: A brief overview and remaining questions. Viruses. 2020;12(9):969 3. Nili F, Mohammadhoseini M, Khatami SM, Seirafi G, Haghzare M. Routine immunohistochemistry study for polyomavirus BK nephropathy in transplanted kidney biopsies, is it recommended?. BMC Nephrol. 2021;22(1):226 4. Myint TM, Chong CHY, Wyld M, Nankivell B, Kable K, Wong G. Polyoma BK virus in kidney transplant recipients: Screening, monitoring, and management. Transplantation. 2022;106(1):e76-e89 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

SGUM
82483

Sweet Gum, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to sweet gum Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive

6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SPOT
82799

Sweet Potato, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to sweet potato Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

VERG
82909

Sweet Vernal Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to sweet vernal grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SWORD
82346

Swordfish, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to swordfish Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

SYNAP
70557

Synaptophysin (SYNAPTO) Immunostain, Technical Component Only

Clinical Information: Synaptophysin is a calcium-binding protein present in the presynaptic vesicles of neurons as well as vesicles in the neuroendocrine cells. Synaptophysin is expressed in neuronal tumors and tumors with neuroendocrine differentiation, including neuroblastoma, ganglioneuroblastoma, ganglioneuroma, pheochromocytoma/paraganglioma and carcinoid/neuroendocrine carcinoma. Antibodies to synaptophysin strongly stain the cytoplasm of all the neuroendocrine cells in the pancreatic islets and is also seen in adrenal cortical cells, probably due to a closely related protein.

Useful For: Identification of neuronal tumors and tumors with neuroendocrine differentiation

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Coffin CM, Braun JT, Wick MR, Dehner LP. A clinicopathologic and immunohistochemical analysis of 53 cases of medulloblastoma with emphasis on synaptophysin expression. Mod Pathol. 1990;3(2):164-170 2. Gould VE, Wiedenmann B, Lee I, et al. Synaptophysin expression in neuroendocrine neoplasms as determined by immunocytochemistry. Am J Pathol. 1987;126(2):243-257 3. Miller DC, Koslow M, Budzilovich GN, Burstein DE. Synaptophysin: a sensitive and specific marker for ganglion cells in central nervous system neoplasms. Hum Pathol. 1990;21(3):271-276 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

SS18F 35303 Synovial Sarcoma (SS), 18q11.2 (SS18 or SYT) Rearrangement, FISH, Tissue

Clinical Information: Synovial sarcoma (SS) is a malignant soft tissue tumor that predominantly occurs in the lower limbs of children and young adults. This tumor accounts for approximately 5% to 10% of soft tissue tumors, has a poor prognosis, and may occur in other areas of the body such as the head and neck, heart, abdominal wall, mediastinum, and lung, in addition to the extremities. Histologically, SS is grouped either into the monophasic subtype consisting of mostly spindle cells or the biphasic subtype consisting of epithelial and spindle cells. Depending on the site of origin, the differential diagnosis of SS can include mesothelioma, fibrosarcoma, solitary fibrous tumor, leiomyosarcoma, malignant peripheral nerve sheath tumors, epithelioid sarcoma, and clear cell sarcoma. In addition, when the SS is poorly differentiated, the differential diagnosis broadens to include the small round-blue cell tumors (Ewing sarcoma, alveolar rhabdomyosarcoma, and neuroblastoma). Accurate diagnosis of SS is important for appropriate clinical management of patients. Although immunohistochemical markers can be helpful in the correct diagnosis of these various tumor types, recent molecular studies have shown the superior specificity of molecular makers in differentiating SS from other tumors. A recurrent, tumor-specific translocation t(X;18)(p11.2;q11.2) is observed in approximately 90% of synovial sarcomas. A single gene, SS18 (SYT), has been implicated on 18q11.2, while 1 of 3 related genes, SSX1, SSX2, or infrequently SSX4, is usually involved on Xp11.2. The prevalence of SS18-SSX1 is about twice that of SS18-SSX2 in most studies. Detection of these transcripts is usually performed by reverse transcriptase-PCR (RT-PCR) (SYT / Synovial Sarcoma RT-PCR), which allows specific identification of SS18-SSX1 or SS18-SSX2. Identification of the SS18-SSX1 fusion is associated with an unfavorable outcome with significantly shorter overall survival when compared to the SS18-SSX2 fusion. Unfortunately, RT-PCR results may be equivocal or falsely negative due to many reasons such as when the available RNA is of poor quality or if a rare translocation partner is present. In these cases, FISH testing can be used to identify SS18 gene rearrangements in these tumors, which supports the diagnosis of SS.

Useful For: Supporting the diagnosis of synovial sarcoma when used in conjunction with an anatomic

pathology consultation

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the SS18 (SYT) FISH probe. A positive result suggests rearrangement of the SS18 (SYT) gene region at 18q11.2 and supports the diagnosis of synovial sarcoma (SS). A negative result suggests no rearrangement of the SS18 (SYT) gene region at 18q11.2. However, this result does not exclude the diagnosis of SS.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. Edited by CDM Fletcher, K Unni, F Mertens. IARC: Lyon 2002, pp 200-204 2. Sandberg AA, Bridge JA: Updates on the cytogenetics and tissue tumors. Synovial sarcoma. Cancer Genet Cytogenet 2002 Feb;133(1):1-23 3. Kokovic I, Bracko M, Golouh R, et al: Are there geographical chimeric transcripts in synovial sarcoma? Cancer Detect Prev 2004;28(4):294-301 4. dos Santos NR, de Bruijn DR, van Kessel AG: Molecular mechanisms underlying human synovial sarcoma development. Genes Chromosomes Cancer 2001 Jan;30(1):1-14

SSX18
610609

Synovial Sarcoma Panel, Technical Component Only

Clinical Information: The SS18-SSX fusion-specific antibody and SSX C-terminal antibody are markers used for the diagnosis of synovial sarcoma. The SS18-SSX fusion-specific antibody recognizes SS18-SSX fusion proteins, which are a result of the SS18 gene fusing with SSX gene on chromosome 18. This translocation is unique to synovial sarcoma. SSX C-terminal antibody recognizes endogenous levels of SSX (1-4) proteins and the SS18-SSX fusion protein. Using these two antibodies together will aid in distinguishing synovial sarcomas from other histologically similar sarcomas.

Useful For: Aiding in distinguishing synovial sarcomas from similar sarcomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Baranov E, McBride M, Bellizzi A, et al. A novel SS18-SSX fusion-specific antibody for the diagnosis of synovial sarcoma. Am J Surg Pathol. 2020;44(7):922-933 2. Kadoch C, Crabtree G. Reversible disruption of mSWI/SNF (BAF) complexes by the SS18-SSX oncogenic fusion in synovial sarcoma. Cell. 2013;153(1):71-85 3. McBride M, Pulice J, Beird H, et al. The SS18-SSX fusion oncoprotein hijacks BAF complex targeting and function to drive synovial sarcoma. Cancer Cell. 2018;33(6):1128-1141 4. Thway K, Fisher C. Synovial sarcoma: defining features and diagnostic evolution. Annals of Diag Path. 2014;18(6):369-380 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FCSC
75761

Synthetic Cannabinoid Metabolites Screen, Expanded, Urine

Reference Values:

Reporting limit determined each analysis. Test	Result	Units
5F-PINACA 3-methylbutanoic acid	None Detected	ng/mL
4F-BINACA 3,3-dimethylbutanoic acid	None Detected	ng/mL
5F-PICA 3,3-dimethylbutanoic acid	None Detected	ng/mL
5F-PINACA 3,3-dimethylbutanoic acid	None Detected	ng/mL
MDMB-4en-PINACA butanoic acid	None Detected	ng/mL
FUBINACA 3-methylbutanoic acid	None Detected	ng/mL
FUBINACA 3,3-dimethylbutanoic acid	None Detected	ng/mL
4-carboxy-NA-PIM	None Detected	ng/mL

SGSU
81035

Synthetic Glucocorticoid Screen, Random, Urine

Clinical Information: Synthetic glucocorticoids are widely used and have important clinical utility both as anti-inflammatory and immunosuppressive agents. The medical use of these agents, as well as their surreptitious use, can sometimes lead to a confusing clinical presentation. Patients exposed to these steroids may present with clinical features of Cushing syndrome but with suppressed cortisol levels and evidence of hypothalamus-pituitary-adrenal axis suppression.

Useful For: Confirming the presence of the listed synthetic glucocorticoids Confirming the cause of secondary adrenal insufficiency

Interpretation: This test screens for and quantitates, if present, the following synthetic glucocorticoids: betamethasone, budesonide, dexamethasone, fludrocortisone, megestrol acetate, methylprednisolone, prednisolone, prednisone, and triamcinolone acetonide. The presence of synthetic glucocorticoids in urine indicates current or recent use of these compounds. Since several of these compounds exceed the potency of endogenous cortisol by 1 or more orders of magnitude, even trace levels may be associated with cushingoid features.

Reference Values:

Negative
Cutoff concentrations
Betamethasone: 0.10 mcg/dL
Budesonide: 0.20 mcg/dL
Dexamethasone: 0.10 mcg/dL
Fludrocortisone: 0.10 mcg/dL
Megestrol acetate: 0.10 mcg/dL

Methylprednisolone: 0.10 mcg/dL
Prednisolone: 0.10 mcg/dL
Prednisone: 0.10 mcg/dL
Triamcinolone acetonide: 0.10 mcg/dL

Values for normal patients not taking these synthetic glucocorticoids should be less than the cutoff concentration (detection limit).

Clinical References: 1. Cave A, Arlett P, Lee E. Inhaled and nasal corticosteroids: factors affecting the risks of systemic adverse effects. Pharmacol Ther. 1999;83(3):153-179 2. Bijlsma JWJ, Van Everdingen AA, Huisman M, De Nijs RNJTL, Jacobs JWG. Glucocorticoids in rheumatoid arthritis: effects on erosions and bone. Ann NY Acad Sci. 2002;966:82-90 3. Sandborn WJ. Steroid-dependent Crohn's disease. Can J Gastroenterol. 2000;14 Suppl C:17C-22C 4. Benvenuti S, Brandi ML. Corticosteroid-induced osteoporosis: pathogenesis and prevention. Clin Exp Rheumatol. 2000;18(4 Suppl 20):S64-S66 5. Loke TK, Sousa AR, Corrigan CJ, Lee TH. Glucocorticoid-resistant asthma. Curr Allergy Asthma Rep. 2002;2(2):144-150 6. Fardet L, Petersen I, Nazareth I. Monitoring of patients on long-term glucocorticoid therapy: a population-based cohort study. Medicine (Baltimore). 2015;94(15):e647. doi:10.1097/MD.0000000000000647 7. Cronin JJ, McCoy S, Kennedy U, et al. A randomized trial of single-dose oral dexamethasone versus multidose prednisolone for acute exacerbations of asthma in children who attend the emergency department. Ann Emerg Med. 2016;67(5):593-601.e3. doi:10.1016/j.annemergmed.2015.08.001

SGSS
81031

Synthetic Glucocorticoid Screen, Serum

Clinical Information: Synthetic glucocorticoids are widely used and have important clinical utility both as anti-inflammatory and immunosuppressive agents. The medical use of these agents, as well as their surreptitious use, can sometimes lead to a confusing clinical presentation. Patients exposed to these steroids may present with clinical features of Cushing syndrome but with suppressed cortisol levels and evidence of hypothalamus-pituitary-adrenal axis suppression.

Useful For: Confirming the presence of listed synthetic glucocorticoids (see Interpretation) Confirming the cause of secondary adrenal insufficiency This test is not useful for detection of fluticasone propionate.

Interpretation: This test screens for and quantitates, if present, the following synthetic glucocorticoids: betamethasone, budesonide, dexamethasone, fludrocortisone, megestrol acetate, methylprednisolone, prednisolone, prednisone, and triamcinolone acetonide. The presence of synthetic glucocorticoids in serum indicates current or recent use of these compounds. Since several of these compounds exceed the potency of endogenous cortisol by 1 or more orders of magnitude, even trace levels may be associated with cushingoid features.

Reference Values:
Negative
Cutoff concentrations
Betamethasone: 0.10 mcg/dL
Budesonide: 0.20 mcg/dL
Dexamethasone: 0.10 mcg/dL
Fludrocortisone: 0.10 mcg/dL
Megestrol acetate: 0.10 mcg/dL
Methylprednisolone: 0.10 mcg/dL
Prednisolone: 0.10 mcg/dL
Prednisone: 0.10 mcg/dL

Triamcinolone acetonide: 0.10 mcg/dL

Values for normal patients not taking these synthetic glucocorticoids should be less than the cutoff concentration (detection limit).

Clinical References: 1. Cave A, Arlett P, Lee E: Inhaled and nasal corticosteroids: factors affecting the risks of systemic adverse effects. Pharmacol Ther. 1999 Sep;83(3):153-179 2. Bijlsma JWJ, Van Everdingen AA, Huisman M, De Nijs RNJTL, Jacobs JWG: Glucocorticoids in rheumatoid arthritis: effects on erosions and bone. Ann NY Acad Sci. 2002 Jun;966:82-90 3. Sandborn WJ: Steroid-dependent Crohn's disease. Can J Gastroenterol. 2000 Sep;14 Suppl C:17C-22C 4. Benvenuti S, Brandi ML: Corticosteroid-induced osteoporosis: pathogenesis and prevention. Clin Exp Rheumatol. 2000 Jul-Aug;18(4 Suppl 20):S64-S66 5. Loke TK, Sousa AR, Corrigan CJ, Lee TH: Glucocorticoid-resistant asthma. Curr Allergy Asthma Rep. 2002 Mar;2(2):144-150 6. Fardet L, Petersen I, Nazareth I: Monitoring of patients on long-term glucocorticoid therapy: a population-based cohort study. Medicine (Baltimore). 2015 Apr;94(15):e647. doi: 10.1097/MD.0000000000000647 7. Cronin JJ, McCoy S, Kennedy U, et al: A randomized trial of single-dose oral dexamethasone versus multidose prednisolone for acute exacerbations of asthma in children who attend the emergency department. Ann Emerg Med. 2016 May;67(5):593-601.e3. doi: 10.1016/j.annemergmed.2015.08.001

TPPA
61480

Syphilis Antibody, Treponema pallidum Particle Agglutination, Serum

Clinical Information: Syphilis is a disease caused by infection with the spirochete Treponema pallidum subspecies pallidum. The infection is systemic, and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Syphilis is categorized by an early primary infection in which patients may have nonspecific symptoms and, potentially, genital lesions. Patients tested by serology during the primary phase may be negative for antibodies, especially if testing is performed during the first 1 to 2 weeks after symptom onset. As the disease progresses into the secondary phase, antibodies to T pallidum reach peak titers and may persist indefinitely regardless of the disease state or prior therapy. Therefore, detection of antibodies to nontreponemal antigens, such as cardiolipin (a lipoidal antigen released by host cells damaged by T pallidum) may help to differentiate between active and past syphilis infection. Non-treponemal antibodies are detected by the rapid plasma reagin (RPR) assay, which is typically positive during current infection and negative following treatment or during late/latent forms of syphilis. Historically, the serologic testing algorithm for syphilis included an initial nontreponemal screening test, such as the RPR or VDRL tests. Because these tests measure the host's antibody response to nontreponemal antigens, they may lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the T pallidum particle agglutination (TP-PA) assay. Although technically simple to perform, the TP-PA assay is labor intensive and requires subjective interpretation by testing personnel. Due to the increased specificity of treponemal assays and the objective result interpretation of automated treponemal immunoassays, many large clinical laboratories have switched to screening for syphilis using a reverse algorithm. Per this algorithm, serum samples are first tested by an automated treponemal immunoassay, and positive samples are reflexed to the RPR assay to provide an indication of the patient's disease state and history of treatment. For specimens testing positive by the screening treponemal assay and negative by RPR, a second treponemal test (eg, TP-PA) is performed. The results of TP-PA assist in determining whether the results of a screening treponemal test are truly or falsely positive.

Useful For: An aid to resolve discrepant results between screening treponemal and non-treponemal assays This test is not recommended for general screening purposes for syphilis. This test should not be used to evaluate response to therapy. This test is not intended for medical-legal use.

Interpretation:

Reference Values:
Negative

Clinical References: 1. Park IU, Tran A, Pereira L, Fakile Y. Sensitivity and specificity of treponemal-specific tests for diagnosis of syphilis. Clinical Infectious Diseases. 2020;71:S13-S20 2. Tuddenham S, Katz SS, Ghanem KG. Syphilis laboratory guidelines: performance characteristics of nontreponemal antibody tests. Clinical Infectious Diseases. 20201;71:S21-S42 3. Ortiz DA, Shukla MR, Loeffelholz MJ. The traditional or reverse algorithm for diagnosis of syphilis: pros and cons. Clinical Infectious Diseases. 2020;71:S43-S51

NSYPH
616862

Syphilis IgG Enzyme Immunoassay, Serum

Clinical Information: Syphilis is caused by infection with the spirochete Treponema pallidum subspecies pallidum. The infection is systemic, and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial non-treponemal screening test, such as the rapid plasma reagin (RPR) or the VDRL tests. Because these tests measure the host's immune response to nontreponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorption (FTA-ABS) or microhemagglutination (MHA-TP) assay. Although the FTA-ABS and MHA-TP assays are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. As an alternative to the traditional syphilis screening algorithm, many laboratories utilize the reverse syphilis screening algorithm. This algorithm starts with an automated treponemal assay to detect antibodies specific to T pallidum. If this screening assay is positive, the sample is reflexed for testing by RPR, which, if positive, is reported with a titer and is indicative of active or recent syphilis infection. If the RPR is negative, the sample is reflexed to a second treponemal assay, such as the T pallidum particle agglutination (TP-PA) assay. If the TP-PA is positive, this would indicate previously treated or late-stage syphilis infection. Alternatively, if the TP-PA is negative, the initial positive screen is interpreted as a false-positive result. Syphilis screening at Mayo Clinic is performed using the reverse algorithm, which first tests sera for T pallidum specific IgG antibodies using an automated enzyme immunoassay. A positive treponemal test suggests infection with T pallidum but does not distinguish between recent, past, treated, or untreated infection. This is because treponemal tests may remain reactive for life, even following adequate therapy. Therefore, the results of a nontreponemal assay, such as RPR, are needed to provide information on a patient's disease state and history of therapy.(Table) In some patients, the results of the treponemal screening test and RPR may be discordant (eg, syphilis IgG positive and RPR negative). To discriminate between a falsely reactive screening result and past syphilis, a second treponemal-specific antibody test is recommended using a method that is different from the initial screen test (eg, TP-PA). In the setting of a positive syphilis IgG screening result and a negative RPR, a positive TP-PA result is consistent with either 1) past, successfully treated syphilis, 2) early syphilis with undetectable RPR, or 3) late/latent syphilis in patients who do not have a history of treatment for syphilis. Further historical evaluation is necessary to distinguish between these scenarios.(Table) In the setting of a positive syphilis IgG screening result and a negative RPR, a negative TP-PA result is most consistent with a falsely reactive syphilis IgG screen.(Table) If syphilis remains clinically suspected, a second specimen should be submitted for testing. Table. Interpretation and follow-up of reverse screening results: Test and result Patient history Syphilis IgG Ab by EIA RPR TP-PA Interpretation Follow-up Unknown history of syphilis Nonreactive NA NA No serologic evidence of syphilis None, unless clinically indicated (eg, early/acute/primary syphilis) Unknown history of syphilis Reactive Reactive NA Untreated or recently treated syphilis See Centers for Disease Control and Prevention treatment guidelines Unknown history of syphilis Reactive Nonreactive Nonreactive Probable false-positive screening test No follow-up testing, unless clinically

indicated (eg, acute/primary syphilis) Unknown history of syphilis Reactive Nonreactive Reactive Possible syphilis (eg, early or latent) or previously treated syphilis Historical and clinical evaluation required Unknown history of syphilis Equivocal NA NA NA Unknown history of syphilis Known history of syphilis Reactive Nonreactive Reactive or NA Past, successfully treated syphilis None EIA, enzyme immunoassay; NA, not applicable; RPR, rapid plasma reagin; TP-PA, Treponema pallidum particle agglutination

Useful For: An aid in the diagnosis of infection with Treponema pallidum Routine prenatal screening This test is not useful for diagnosis of congenital syphilis. This test is not offered as a screening or confirmatory test for blood donor specimens.

Interpretation: Nonreactive: No serologic evidence of exposure to Treponema pallidum (syphilis). Repeat testing may be considered in patients with suspected acute or primary syphilis. Equivocal: Recommend follow-up testing in 10 to 14 days if clinically indicated. Reactive: Results suggest infection with T pallidum at some point in time. Results do not distinguish between recent or past infection, or between treated and untreated syphilis as treponema-specific IgG may remain elevated despite appropriate therapy. Falsely reactive treponemal results may occur; additional testing by a non-treponemal assay is recommended if not previously performed on this sample.

Reference Values:
Nonreactive
Reference values apply to all ages

Clinical References: 1. Centers for Disease Control and Prevention (CDC): Discordant results from reverse sequence syphilis screening-five laboratories, United States, 2006-2010. Morb Mortal WKLY Rep. 2011 Feb 11;60(5):133-137 2. Radolf JD, Tramont EC, Salazar JC: Syphilis (Treponema pallidum). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2865-289291 3. Binnicker MJ, Jespersen DJ, Rollins LO: Direct comparison of the traditional and reverse syphilis screening algorithms in a population with a low prevalence of syphilis. J Clin Microbiol. 2012 Jan;50(1):148-150

SYPH1
616860

Syphilis IgG with Reflex, Enzyme Immunoassay, Serum

Clinical Information: Syphilis is caused by infection with the spirochete Treponema pallidum subspecies pallidum. The infection is systemic, and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial nontreponemal screening test, such as the rapid plasma reagin (RPR) or the VDRL tests. Because these tests measure the host's immune response to nontreponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorption (FTA-ABS) or microhemagglutination (MHA-TP) assay. Although the FTA-ABS and MHA-TP assays are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. As an alternative to the traditional syphilis screening algorithm, many laboratories utilize the reverse syphilis screening algorithm. This algorithm starts with an automated treponemal assay to detect antibodies specific to T pallidum. If this screening assay is positive, the sample is reflexed for testing by RPR, which, if positive, is reported with a titer and is indicative of active or recent syphilis infection. If the RPR is negative, the sample is reflexed to a second treponemal assay, such as the T pallidum particle agglutination (TP-PA) assay. If the TP-PA is positive, this would indicate previously treated or late-stage syphilis infection. Alternatively, if the TP-PA is negative, the initial positive screen is interpreted as a false-positive result. Syphilis screening at Mayo Clinic is performed using the reverse algorithm, which first tests sera for T pallidum specific IgG antibodies using an automated enzyme immunoassay. A

positive treponemal test suggests infection with T pallidum but does not distinguish between recent, past, treated, or untreated infections. This is because treponemal tests may remain reactive for life, even following adequate therapy. Therefore, the results of a nontreponemal assay, such as RPR, are needed to provide information on a patient's disease state and history of therapy.(Table) In some patients, the results of the treponemal screening test and RPR may be discordant (eg, syphilis IgG positive and RPR negative). To discriminate between a falsely reactive screening result and past syphilis, a second treponemal-specific antibody test is recommended using a method that is different from the initial screen test (eg, TP-PA). In the setting of a positive syphilis IgG screening result and a negative RPR, a positive TP-PA result is consistent with either 1) past, successfully treated syphilis, 2) early syphilis with undetectable RPR, or 3) late/latent syphilis in patients who do not have a history of treatment for syphilis. Further historical evaluation is necessary to distinguish between these scenarios.(Table) In the setting of a positive syphilis IgG screening result and a negative RPR, a negative TP-PA result is most consistent with a falsely reactive syphilis IgG screen.(Table) If syphilis remains clinically suspected, a second specimen should be submitted for testing. Table. Interpretation and follow-up of reverse screening results: Test and result Patient history Syphilis IgG antibody by EIA RPR TP-PA Interpretation Follow-up Unknown history of syphilis Nonreactive NA NA No serologic evidence of syphilis None, unless clinically indicated (eg, early/acute/ primary syphilis) Unknown history of syphilis Reactive Reactive NA Untreated or recently treated syphilis See Centers for Disease Control and Prevention treatment guidelines Unknown history of syphilis Reactive Nonreactive Nonreactive Probable false-positive screening test No follow-up testing, unless clinically indicated (eg, acute/primary syphilis) Unknown history of syphilis Reactive Nonreactive Reactive Possible syphilis (eg, early or latent) or previously treated syphilis Historical and clinical evaluation required Unknown history of syphilis Equivocal NA NA NA Unknown history of syphilis Known history of syphilis Reactive Nonreactive Reactive or NA Past, successfully treated syphilis None EIA-enzyme immunoassay NA-not applicable RPR-rapid plasma reagin TP-PA-T pallidum particle agglutination

Useful For: Aid for the diagnosis of infection with Treponema pallidum using an algorithmic approach Routine prenatal screening This test is not offered as a screening or confirmatory test for blood donor specimens. This test is not useful for diagnosis of congenital syphilis.

Interpretation: Nonreactive: No serologic evidence of infection to Treponema pallidum (syphilis). Repeat testing may be considered in patients with suspected acute or primary syphilis in 2 to 4 weeks. Equivocal: Rapid plasma reagin (RPR) has been ordered to help distinguish between infection with T pallidum (syphilis) versus a falsely reactive treponemal antibody result. Reactive: RPR has been ordered to help distinguish between infection with T pallidum (syphilis) versus a falsely reactive treponemal antibody result.

Reference Values:

SYPHILIS IgG SCREEN
Nonreactive

RAPID PLASMA REAGIN SCREEN
Negative

RAPID PLASMA REAGIN TITER
Negative

SYPHILIS ANTIBODY, Treponema pallidum-PARTICLE AGGLUTINATION
Negative

Reference values apply to all ages

Clinical References: 1. Centers for Disease Control and Prevention (CDC). Discordant results from reverse sequence syphilis screening-five laboratories, United States, 2006-2010. MMWR Morb

Mortal Wkly Rep. 2011;605):133-137 2. Radolf JD, Tramont EC, Salazar JC: Syphilis (Treponema pallidum). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2865-2892 3. Binnicker MJ, Jespersen DJ, Rollins LO. Direct comparison of the traditional and reverse syphilis screening algorithms in a population with a low prevalence of syphilis. J Clin Microbiol. 2012;;50(1):148-150

SYPHT
603264

Syphilis Total Antibody with Reflex, Serum

Clinical Information: Syphilis is a disease caused by infection with the spirochete Treponema pallidum. The infection is systemic, and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial nontreponemal screening test, such as the rapid plasma reagin (RPR) or the VDRL tests. Because these tests measure the host's antibody response to non-treponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorption (FTA-ABS) or microhemagglutination (MHA-TP) assay. Although the FTA-ABS and MHA-TP assays are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. As an alternative to the traditional syphilis screening algorithm, many laboratories utilize the reverse syphilis screening algorithm. This algorithm starts with an automated treponemal assay, such as an enzyme immunoassay and multiplex flow immunoassay (MFI), to detect antibodies specific to T pallidum. If the screening assay is positive, the sample is reflexed to a RPR assay, which, if positive, is reported with a titer and is indicative of active or recent syphilis infection. If the RPR is negative, the sample is reflexed to a second treponemal assay, such as the T pallidum particle agglutination (TP-PA) assay. If the TP-PA is positive, this would indicate previously treated or late-stage syphilis infection. Alternatively, if the TP-PA is negative, the initial positive screen is interpreted as a false positive result. Syphilis screening at Mayo Clinic is performed by using the reverse algorithm, which first tests sera for T pallidum specific IgG/IgM antibodies using an automated MFI. A positive treponemal test suggests infection with T pallidum but does not distinguish between recent, past, treated or untreated infections. This is because treponemal tests may remain reactive for life, even following adequate therapy. Therefore, the results of a nontreponemal assay, such as RPR, are needed to provide information on a patient's disease state and history of therapy.(Table) In some patients, the results of the treponemal screening test and RPR may be discordant (eg, syphilis IgG/IgM positive and RPR negative). To discriminate between a falsely reactive screening result and past syphilis, a second treponemal-specific antibody test is recommended using a method that is different from the initial screen test (eg, TP-PA). In the setting of a positive syphilis IgG/IgM screening result and a negative RPR, a positive TP-PA result is consistent with either 1) past, successfully treated syphilis, 2) early syphilis with undetectable RPR titers, or 3) late/latent syphilis in patients who do not have a history of treatment for syphilis. Further historical evaluation is necessary to distinguish between these scenarios.(Table) In the setting of a positive syphilis IgG/IgM screening result and a negative RPR, a negative TP-PA result is most consistent with a falsely reactive syphilis IgG/IgM screen.(Table) If syphilis remains clinically suspected, a second specimen should be submitted for testing. Table. Interpretation and follow-up of reverse screening results: Test and result Patient history Syphilis total antibody by MFI RPR TP-PA Interpretation Follow-up Unknown history of syphilis Nonreactive NA NA No serologic evidence of syphilis None, unless clinically indicated (eg, early/acute/ primary syphilis) Unknown history of syphilis Reactive Reactive NA Untreated or recently treated syphilis See Centers for Disease Control and Prevention treatment guidelines Unknown history of syphilis Reactive Nonreactive Nonreactive Probable false-positive screening test No follow-up testing, unless clinically indicated (eg, acute/primary syphilis) Unknown history of syphilis Reactive Nonreactive Reactive Possible syphilis (eg, early or latent) or previously treated syphilis Historical and clinical evaluation required Unknown history of syphilis Equivocal NA NA NA Unknown history of syphilis Known history of syphilis Reactive Nonreactive Reactive or NA Past, successfully treated syphilis None MFI - multiplex flow immunoassay NA - not applicable RPR - rapid plasma reagin TP-PA -T pallidum particle agglutination

Useful For: Aiding in the diagnosis of recent or past Treponema pallidum infection Routine prenatal screening This test is not offered as a screening or confirmatory test for blood donor specimens. This test is not useful for diagnosis of congenital syphilis.

Interpretation: Nonreactive: No serologic evidence of infection to Treponema pallidum (syphilis). Repeat testing may be considered in patients with suspected acute or primary syphilis in 2 to 4 weeks. Equivocal: Rapid plasma reagin (RPR) has been ordered to help distinguish between infection with T pallidum (syphilis) versus a falsely reactive treponemal antibody result. Reactive: RPR has been ordered to help distinguish between infection with T pallidum (syphilis) versus a falsely reactive treponemal antibody result.

Reference Values:

SYPHILIS TOTAL ANTIBODY
Nonreactive

RAPID PLASMA REAGIN SCREEN
Negative

RAPID PLASMA REAGIN TITER
Negative

SYPHILIS ANTIBODY, Treponema pallidum-PARTICLE AGGLUTINATION
Negative

Reference values apply to all ages

Clinical References: 1. Centers for Disease Control and Prevention (CDC): Discordant results from reverse sequence syphilis screening-five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011;60(5):133-137 2. Radolf JD, Tramont EC, Salazar JC: Syphilis (Treponema pallidum). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2865-2892 3. Binnicker MJ, Jespersen DJ, Rollins LO: Direct comparison of the traditional and reverse syphilis screening algorithms in a population with a low prevalence of syphilis. J Clin Microbiol. 2012: Jan;50(1):148-150

TBNY
82589

T, B and NK Lymphocyte Quantitation, New York, Blood

Clinical Information: Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer (NK) cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/mcL) and relative (%) quantitation for the main categories of T cells, B cells, and NK cells, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of 1 or more cell surface markers. The CD3 antigen is a pan-T-cell marker, and T cells can be further divided into 2 broad categories based on the expression of CD4 or CD8 coreceptors. B cells can be identified by expression of CD19, while NK cells are typically identified by the coexpression of CD16 and CD56. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon with no change between noon and afternoon. NK-cell counts, on the other hand, are constant throughout the day.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with

plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening(5) and during summer compared to winter.(6) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of T (CD3+, CD4+, CD8+), B (CD19), and NK (CD16+CD56) lymphocytes have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T lymphocytes in patients infected with HIV is associated with increased infections and complications. The US Public Health Service has recommended that all patients who are HIV-positive be tested every 3 to 6 months for the level of CD4 T lymphocytes. Lymphocyte subset quantitation is also very useful in the evaluation of patients with primary immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, or any other relevant clinical condition where immunomodulatory treatment is used. It is also helpful as a preliminary screening assay for gross quantitative anomalies in any lymphocyte subset, whether related to malignancies or infection. The 2008 guidelines for diagnosis and treatment of chronic lymphocytic leukemia (CLL) from the International Workshop on Chronic Lymphocytic Leukemia(7) recommend changing the diagnostic criteria for CLL from an absolute lymphocyte count greater than 5 x 10(9)/L to a circulating B-cell count greater than 5 x 10(9)/L(8,9) previously defined in the 1996 National Cancer Institute guidelines for CLL. This flow cytometric assay enables accurate quantitation of circulating B cells using a single platform technology with absolute quantitation through the use of flow cytometry beads.

Useful For: Only orderable by New York clients Serial monitoring of CD4 T-cell count in patients who are HIV-positive Follow-up and diagnostic evaluation of primary immunodeficiencies, including severe combined immunodeficiency Immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of immune reconstitution post-hematopoietic cell transplantation Early screening of gross quantitative anomalies in lymphocyte subsets in infection or malignancies Absolute quantitation of circulating B cells for diagnosis of patients with chronic lymphocytic leukemia as indicated in the 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines

Interpretation: HIV treatment guidelines from the US Department of Health and Human Services and the International Antiviral Society-USA Panel recommend antiviral treatment in all patients with HIV infection, regardless of CD4 T-cell count.(10,11) Additionally, antibiotic prophylaxis for Pneumocystis jiroveci infection is recommended for patients with CD4 count less than 200 cells/mcL. For other opportunistic infections, see the recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.(12)

Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References: 1. Carmichael KF, Abayomi A. Analysis of diurnal variation of lymphocyte subsets in healthy subjects and its implication in HIV monitoring and treatment. 15th Intl Conference on AIDS, Bangkok, Thailand, 2004, Abstract # B11052. Afr J Med Med Sci. 2006;35(1):53-57 2. Dimitrov S, Benedict C, Heutling D, Westermann J, Born J, Lange T. Cortisol and epinephrine control opposing circadian rhythms in T-cell subsets. Blood. 2009;113(21):5134-5143 3. Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating antigen presenting cells regulated by sleep. Sleep. 2007;30(4):401-411 4. Kronfol Z, Nair M, Zhang Q, Hill EE, Brown MB. Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Psychosom Med. 1997;59(1):42-50 5. Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS. Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J AIDS. 1990;3(2):144-151

6. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994;34(6):512-516 7. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on chronic lymphocytic leukemia updating the National Cancer Institute Working Group 1996 guidelines. Blood. 2008;111(12):5446-5456 8. Hanson CA, Kurtin PJ, Dogan A. The proposed diagnostic criteria change for chronic lymphocytic leukemia: unintended consequences? Blood. 2009;113(25):6495-6496 9. Hillmen P, Cheson BD, Catovsky D, et al: Response: Letters regarding Blood. 2008;111:5446-5456 by Hanson et al and Mulligan et al. . Blood. 2009 Jun;113(25):6497-6498. doi:10.1182/blood-2009-04-165324 10. Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services; Updated February 27, 2024. Accessed August 19, 2024. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf 11. Thompson MA, Horberg MA, Agwu AL, et al. Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2021;73(11):e3572-e3605. Erratum in: Clin Infect Dis. 2021 Dec 08 12. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Department of Health and Human Services; Updated February 17, 2022. Accessed August 19, 2024. Available at https://clinicalinfo.hiv.gov/en/guidelines

TBET
70559

T-Box Expressed in T Cells (TBET) Immunostain, Technical Component Only

Clinical Information: The T-box transcription factor, TBET, is a master regulator of Th1 lymphoid development. It is expressed in other hematopoietic cells, including stem cells, B cells, and natural killer cells. In normal tonsil, TBET staining is seen in scattered small interfollicular T lymphocytes, with virtually no staining in the germinal centers. It is preferentially positive in T-cell lymphomas with Th1 differentiation, B-cell lymphomas of memory B-cell origin, and both classical and nodular lymphocyte predominant Hodgkin lymphoma.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Atayar C, Poppema S, Blokzijl T, et al. Expression of the T-cell transcription factors, GATA-3 and T-bet, in the neoplastic cells of Hodgkin lymphomas. Am J Pathol. 2005;166(1):127-134 2. Dorfman DM, Hawang ES, Shahsafaei A, Glimcher LH. T-bet, a T-cell associated transcription factor, is expressed in a subset of B-cell lymphoproliferative disorders. Am J Clin Pathol. 2004;122(2):292-297 3. Dorfman DM, van den Elzen P, Weng AP, et al. Differential expression of T-bet, a T-box transcription factor required for Th1 T-cell development, in peripheral T-cell lymphomas. Am J Clin Pathol. 2003;120(6):866-873 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

COGTF
113529

T-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Children's Oncology Group Enrollment Testing, FISH, Varies

Clinical Information: In the United States, the incidence of acute lymphoblastic leukemia (ALL) is roughly 6000 new cases per year (as of 2019). ALL accounts for approximately 70% of all childhood leukemia cases (ages 0 to 19 years), making it the most common type of childhood cancer. Approximately 85% of pediatric cases of ALL are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). T-ALL is more common in adolescents than younger children and accounts for 25% of adult ALL. When occurring as a primary lymphoblastic lymphoma (LBL), approximately 90% are T-cell lineage versus only 10% B-cell lineage. T-LBL often present as a mediastinal mass in younger patients with or without concurrent bone marrow involvement. Specific genetic abnormalities are identified in the majority of cases of T-ALL, although many of the classic abnormalities are "cryptic" by conventional chromosome studies and must be identified by fluorescence in situ hybridization (FISH) studies. Each of the genetic subgroups are important to detect and can be critical prognostic markers. One predictive marker, amplification of the ABL1 gene region, has been identified in 5% of T-ALL, and these patients may be responsive to targeted tyrosine kinase inhibitors. A combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients to characterize the T-ALL clone for the prognostic genetic subgroups. A summary of the characteristic chromosome abnormalities identified in T-ALL are listed in the following table. Table. Common Chromosome Abnormalities in T-cell Acute Lymphoblastic Leukemia Cytogenetic change Genes involved del(1p33) TAL1/STIL t(5;14)(q35;q32) TLX3/BCL11B t(10;11)(p12;q14) MLLT10/PICALM Episomal amplification ABL1 del(9p) CDKN2A(p16) t(11q23;var) MLL(KMT2A) t(4;11)(q21;q23) AFF1/MLL(KMT2A) t(6;11)(q27;q23) MLLT4(AFDN)/MLL(KMT2A) t(9;11)(p22;q23) MLLT3/MLL(KMT2A) t(10;11)(p12;q23) MLLT10/MLL(KMT2A) t(11;19)(q23;p13.1) MLL(KMT2A)/ELL t(11;19)(q23;p13.3) MLL(KMT2A)/MLLT1 t(7q34;var) TRB t(6;7)(q23;q34) MYB/TRB t(7;10)(q34;q24) TRB/TLX1 t(7;11)(q34;p15) TRB/LMO1 t(7;11)(q34;p13) TRB/LMO2 t(14q11.2;var) TRAD t(8;14)(q24.1;q11.2) MYC/TRAD t(10;14)(q24;q11.2) TLX1/TRAD t(11;14)(p15;q11.2) LMO1/TRAD t(11;14)(p13;q11.2) LMO2/TRAD del(17p) TP53

Useful For: Evaluation of pediatric bone marrow and peripheral blood specimens by fluorescence in situ hybridization probe analysis for classic rearrangements and chromosomal copy number changes associated with T-cell acute lymphoblastic leukemia in patients being considered for enrollment in Children's Oncology Group clinical trials and research protocols

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow SH, Campo E, Harris NL, et al, eds: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press; 2017 2. Gesk S, Martin-Subero JI, Harder L, et al: Molecular cytogenetic detection of chromosomal breakpoints in T-cell receptor gene loci. Leukemia. 2003;17:738-745 3. Chin M, Mugishima H, Takamura M, et al: Hemophagocytic syndrome and hepatosplenic (gamma)(delta) T-cell lymphoma with isochromosome 7q and 8 trisomy. J Pediatr Hematol Oncol. 2004;26(6):375-378 4. Graux C, Cools J, Michaux L, et al: Cytogenetics and molecular genetics of T-cell acute lymphoblastic leukemia: from thymocyte to lymphoblast. Leukemia. 2006;20:1496-1510 5. Liu Y, Easton J, Shao Y, et al: The genomic landscape of pediatric and young adult T-lineage acute lymphoblastic leukemia. Nat Genet. 2017;49(8):1211-1218

TALAF
609557

T-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), FISH,

Adult, Varies

Clinical Information: T-cell acute lymphoblastic leukemia (T-ALL) accounts for approximately 25% of cases of adult lymphoblastic leukemia. An abnormal karyotype is found in 50% to 70% of T-ALL cases, although many of the classic abnormalities are "cryptic" by conventional chromosome studies and must be identified by fluorescence in situ hybridization studies and are associated with various prognoses. One predictive marker, amplification of the ABL1 gene region, has been identified in 5% of T-ALL, and these patients may be responsive to targeted tyrosine kinase inhibitors. A summary of the characteristic chromosome abnormalities identified in T-ALL is listed in the following table. Table. Common Chromosome Abnormalities in T-cell Acute Lymphoblastic Leukemia Cytogenetic change Genes involved del(1p33) TAL1/STIL t(5;14)(q35;q32) TLX3/BCL11B t(5q32;var) PDGFRB t(10;11)(p12;q14) MLLT10/PICALM Episomal amplification ABL1 t(11q23;var) MLL(KMT2A) t(4;11)(q21;q23) AFF1/MLL(KMT2A) t(6;11)(q27;q23) MLLT4(AFDN)/MLL(KMT2A) t(9;11)(p22;q23) MLLT3/MLL(KMT2A) t(10;11)(p12;q23) MLLT10)/MLL(KMT2A) t(11;19)(q23;p13.1) MLL(KMT2A)/ELL t(11;19)(q23;p13.3) MLL(KMT2A)/MLLT1 t(7q34;var) TRB t(7;10)(q34;q24) TRB/TLX1 t(7;11)(q34;p13) TRB/LMO2 t(14q11.2;var) TRAD t(10;14)(q24;q11.2) TLX1/TRAD t(11;14)(p13;q11.2) LMO2/TRAD t(9p24.1;var) JAK2 t(9q34;var) ABL1 Complex karyotype (> or =4 abnormalities)

Useful For: Detecting, at diagnosis, recurrent common chromosome abnormalities associated with T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) in adult patients As an adjunct to conventional chromosome studies in patients with T-ALL Evaluating specimens in which chromosome studies are unsuccessful This test should not be used to screen for residual T-ALL

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board, eds. Haematolymphoid tumours. 5th ed. IARC Press; 2024. WHO Classification of Tumours, Volume 11 2. Gesk S, Martin-Subero JI, Harder L, et al. Molecular cytogenetic detection of chromosomal breakpoints in T-cell receptor gene loci. Leukemia. 2003;17(4):738-745 3. Chin M, Mugishima H, Takamura M, et al. Hemophagocytic syndrome and hepatosplenic (gamma)(delta) T-cell lymphoma with isochromosome 7q and 8 trisomy. J Pediatr Hematol Oncol. 2004;26(6):375-378 4. Graux C, Cools J, Michaux L, Vandenberghe, P, Hagemeijer A. Cytogenetics and molecular genetics of T-cell acute lymphoblastic leukemia: from thymocyte to lymphoblast. Leukemia. 2006;20:1496-1510 5. Cayuela JM, Madani A, Sanhes L, Stern MH, Sigaux F. Multiple tumor-suppressor gene 1 inactivation is the most frequent genetic alteration in T-cell acute lymphoblastic leukemia. Blood. 1996;87:2180-2186 6. Hayette S, Tigaud I, Maguer-Satta V, et al. Recurrent involvement of the MLL gene in adult T-lineage acute lymphoblastic leukemia. Blood. 2002;99:4647-4649 7. Graux C, Cools J, Melotte C, et al. Fusion of NUP214 to ABL1 on amplified episomes in T-cell acute lymphoblastic leukemia. Nat Genet. 2004;36:1084-1089

TALPF
609567

T-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), FISH, Pediatric, Varies

Clinical Information: In the United States, the incidence of acute lymphoblastic leukemia (ALL) is roughly 6000 new cases per year (as of 2019). ALL accounts for approximately 70% of all childhood leukemia cases (ages 0 to 19 years), making it the most common childhood cancer. Approximately 85%

of pediatric cases of ALL are of B-cell lineage (B-ALL) and 15% are of T-cell lineage (T-ALL). T-ALL is more common in adolescents than younger children and accounts for 25% of adult ALL. When occurring as a primary lymphoblastic lymphoma (LBL), approximately 90% are T-cell lineage versus only 10% B-cell lineage. T-LBL often present as a mediastinal mass in younger patients with or without concurrent bone marrow involvement. An abnormal karyotype is found in 50% to 70% of T-ALL cases, although many of the classic abnormalities are "cryptic" by conventional chromosome studies and must be identified by fluorescence in situ hybridization studies and are associated with various prognoses. One predictive marker, amplification of the ABL1 gene region, has been identified in 5% of T-ALL, and these patients may be responsive to targeted tyrosine kinase inhibitors. A summary of the characteristic chromosome abnormalities identified in T-ALL are listed in the following table. Table. Common Chromosome Abnormalities in T-cell Acute Lymphoblastic Leukemia Cytogenetic change Genes involved del(1p33) TAL1/STIL t(5;14)(q35;q32) TLX3/BCL11B t(10;11)(p12;q14) MLLT10/PICALM Episomal amplification ABL1 del(9p) CDKN2A(p16) t(11q23;var) MLL(KMT2A) t(4;11)(q21;q23) AFF1/MLL(KMT2A) t(6;11)(q27;q23) MLLT4(AFDN)/MLL(KMT2A) t(9;11)(p22;q23) MLLT3/MLL(KMT2A) t(10;11)(p12;q23) MLLT10/MLL(KMT2A) t(11;19)(q23;p13.1) MLL(KMT2A)/ELL t(11;19)(q23;p13.3) MLL(KMT2A)/MLLT1 t(7q34;var) TRB t(6;7)(q23;q34) MYB/TRB t(7;10)(q34;q24) TRB/TLX1 t(7;11)(q34;p15) TRB/LMO1 t(7;11)(q34;p13) TRB/LMO2 t(14q11.2;var) TRAD t(8;14)(q24.1;q11.2) MYC/TRAD t(10;14)(q24;q11.2) TLX1/TRAD t(11;14)(p15;q11.2) LMO1/TRAD t(11;14)(p13;q11.2) LMO2/TRAD del(17p) TP53

Useful For: Detecting, at diagnosis, recurrent common chromosome abnormalities associated with T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) in pediatric/young adult patients As an adjunct to conventional chromosome studies in pediatric/young adult patients with T-ALL Evaluating specimens in which chromosome studies are unsuccessful This test should not be used to screen for residual T-ALL

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board, eds. Haematolymphoid tumours. 5th ed. IARC Press; 2024. WHO Classification of Tumours, Volume 11 2. Gesk S, Martin-Subero JI, Harder L, et al. Molecular cytogenetic detection of chromosomal breakpoints in T-cell receptor gene loci. Leukemia. 2003;17(4):738-745 3. Chin M, Mugishima H, Takamura M, et al: Hemophagocytic syndrome and hepatosplenic (gamma)(delta) T-cell lymphoma with isochromosome 7q and 8 trisomy. J Pediatr Hematol Oncol. 2004;26(6):375-378 4. Graux C, Cools J, Michaux L, et al. Cytogenetics and molecular genetics of T-cell acute lymphoblastic leukemia: from thymocyte to lymphoblast. Leukemia. 2006;20:1496-1510 5. Liu Y, Easton J, Shao Y, et al. The genomic landscape of pediatric and young adult T-lineage acute lymphoblastic leukemia. Nat Genet. 2017;49(8):1211-1218

TALMF 614323 T-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Specified FISH, Varies

Clinical Information: Acute lymphoblastic leukemia (ALL) accounts for approximately 70% of all childhood leukemia cases (ages 0 to 19 years), making it the most common childhood cancer. Approximately 85% of pediatric cases of ALL are of B-cell lineage (B-ALL) and 15% are of T-cell lineage (T-ALL). T-ALL is more common in adolescents than younger children and accounts for 25% of adult ALL. When occurring as a primary lymphoblastic lymphoma (LBL), approximately 90% are T-cell lineage versus only 10% B-cell lineage. T-LBL often present as a mediastinal mass in younger patients, with or without concurrent bone marrow involvement. An abnormal karyotype is found in 50% to 70% of

T-ALL cases, although many of the classic abnormalities are "cryptic" by conventional chromosome studies and must be identified by fluorescence in situ hybridization (FISH) studies and are associated with various prognoses. One predictive marker, amplification of the ABL1 gene region, has been identified in 5% of T-ALL, and these patients may be responsive to targeted tyrosine kinase inhibitors. A summary of the characteristic chromosome abnormalities identified in T-ALL is listed in the following table. Table. Common Chromosome Abnormalities in T-cell Acute Lymphoblastic Leukemia Cytogenetic change Genes involved del(1p33) TAL1/STIL t(5;14)(q35;q32) TLX3/BCL11B t(5q32;var) PDGFRB t(10;11)(p13;q14) MLLT10/PICALM Episomal amplification ABL1 del(9p) CDKN2A(p16) t(9p24.1;var) JAK2 t(9q34;var) ABL1 t(11q23;var) MLL(KMT2A) t(4;11)(q21;q23) AFF1/MLL(KMT2A) t(6;11)(q27;q23) MLLT4(AFDN)/MLL(KMT2A) t(9;11)(p22;q23) MLLT3/MLL(KMT2A) t(10;11)(p13;q23) MLLT10/MLL(KMT2A) t(11;19)(q23;p13.1) MLL(KMT2A)/ELL t(11;19)(q23;p13.3) MLL(KMT2A)/MLLT1 t(7q34;var) TRB t(6;7)(q23;q34) MYB/TRB t(7;10)(q34;q24) TRB/TLX1 t(7;11)(q34;p15) TRB/LMO1 t(7;11)(q34;p13) TRB/LMO2 t(14q11.2;var) TRAD t(8;14)(q24.1;q11.2) MYC/TRAD t(10;14)(q24;q11.2) TLX1/TRAD t(11;14)(p15;q11.2) LMO1/TRAD t(11;14)(p13;q11.2) LMO2/TRAD del(17p) TP53 Complex karyotype (> or =4 abnormalities)

Useful For: Detecting recurrent common chromosome abnormalities associated with T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) using client-specified probes An adjunct to conventional chromosome studies in patients with T-ALL Evaluating specimens in which standard cytogenetic studies are unsuccessful Identifying and tracking known chromosome abnormalities in patients with T-ALL and monitoring response to therapy

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board, eds. Haematolymphoid tumours. 5th ed. IARC Press; 2024. WHO Classification of Tumours, Volume 11 2. Gesk S, Martin-Subero JI, Harder L, et al. Molecular cytogenetic detection of chromosomal breakpoints in T-cell receptor gene loci. Leukemia. 2003;17:738-745 3. Chin M, Mugishima H, Takamura M, et al. Hemophagocytic syndrome and hepatosplenic (gamma)(delta) T-cell lymphoma with isochromosome 7q and 8 trisomy. J Pediatr Hematol Oncol. 2004;26(6):375-378 4. Graux C, Cools J, Michaux L, Vandenberghe P, Hagemeijer A. Cytogenetics and molecular genetics of T-cell acute lymphoblastic leukemia: from thymocyte to lymphoblast. Leukemia. 2006;20:1496-1510 5. Cayuela JM, Madani A, Sanhes L, Stern MH, Sigaux F. Multiple tumor-suppressor gene 1 inactivation is the most frequent genetic alteration in T-cell acute lymphoblastic leukemia. Blood. 1996;87:2180-2186 6. Hayette S, Tigaud I, Maguer-Satta V, et al. Recurrent involvement of the MLL gene in adult T-lineage acute lymphoblastic leukemia. Blood. 2002;99:4647-4649 7. Graux C, Cools J, Melotte C, et al. Fusion of NUP214 to ABL1 on amplified episomes in T-cell acute lymphoblastic leukemia. Nat Genet. 2004;36:1084-1089

BTIA1
605160

T-Cell Intracellular Antigen 1 (TIA-1) Immunostain, Bone Marrow, Technical Component Only

Clinical Information: T-cell intracellular antigen 1 (TIA-1) shows a granular cytoplasmic staining pattern due to its presence in cytotoxic granules. It is involved in cytotoxic cell-mediated immune responses. TIA-1 was first identified in cytotoxic T cells; it is also expressed in normal natural killer (NK) cells and granulocytes.

Useful For: Characterizing neoplasms of cytotoxic T cells or natural killer cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Fujimura T, Furudate S, Kambayashi Y, Aiba S: Potential use of bisphosphonates in invasive extramammary Paget's disease: an immunohistochemical investigation. Clin Dev Immunol. 2013;2013(3):164982. doi: 10.1155/2013/164982 2. Kiyasu J, Aoki R, Tanaka PY, et al: FOXP3(+) regulatory and TIA-1(+) cytotoxic T lymphocytes in HIV-associated Hodgkin lymphoma. Pathol Int. 2012 Feb;62(2):77-83. doi: 10.1111/j.1440-1827.2011.02754.x 3. Zlobec I, Karamitopoulou E, Terracciano L, et al: TIA-1 cytotoxic granule-associated RNA binding protein improves the prognostic performance of CD8 in mismatch repair-proficient colorectal cancer. PLoS One. 2010 Dec 10;5(12):e14282. doi: 10.1371/journal.pone.0014282

TIA1
70566

T-Cell Intracellular Antigen 1 (TIA-1) Immunostain, Technical Component Only

Clinical Information: T-cell intracellular antigen 1 (TIA-1) shows a granular cytoplasmic staining pattern due to its presence in cytotoxic granules. It is involved in cytotoxic cell-mediated immune responses. TIA-1 was first identified in cytotoxic T cells; it is also expressed in normal natural killer (NK) cells and granulocytes. TIA-1 antibody is useful in characterizing neoplasms of cytotoxic T cells or NK cells.

Useful For: Characterizing neoplasms of cytotoxic T cells or natural killer cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Zlobec I, Karamitopoulou E, Terracciano L, et al. TIA-1 cytotoxic granule-associated RNA binding protein improves the prognostic performance of CD8 in mismatch repair-proficient colorectal cancer. PLoS One. 2010;5(12):e14282. doi:10.1371/journal.pone.0014282 2. Kiyasu J, Aoki R, Tanaka P, et al. FOXP3+ regulatory and TIA-1+ cytotoxic T lymphocytes in HIV-associated Hodgkin lymphoma. Pathol Inter. 2012;62(2):77-83. doi:10.1111/j.1440-1827.2011.02754.x 3. Fujimura T, Furudate S, Kambayashi Y, Aiba S. Potential use of Bisphosphonates in Invasive Extramammary Paget's Disease: An Immunohistochemical Investigation. Clin Dev Immunol. 2013 2013:164982. doi:10.1155/2013/164982 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TCL1A
70561

T-Cell Leukemia/Lymphoma Protein 1A (TCL1A) Immunostain, Technical Component Only

Clinical Information: T-cell leukemia/lymphoma (TCL) proteins augment AKT signal transduction and enhance cell proliferation and survival. Inversion or translocations involving the TCL-1 gene are present in more than 90% of T-cell prolymphocytic leukemias, resulting in overexpression of the TCL-1 protein. TCL-1 is also found in plasmacytoid monocytes in reactive tissues, and the putative malignant counterpart, blastic plasmacytoid dendritic cell neoplasm. In normal tonsil, expression is limited to the B-cell compartment.

Useful For: Identification of T-cell leukemia and lymphoma protein overexpression in neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1.Said JW, Hoyer KK, French SW, et al. TCL1 oncogene expression in B cell subsets from lymphoid hyperplasia and distinct classes of B cell lymphoma. Lab Invest. 2001;81(4):555-564 2. Herling M, Teitell MA, Shen RR, et al. TCL1 expression in plasmacytoid dendritic cells (DC2s) and the related CD4+ CD56+ blastic tumors of skin. Blood. 2003;101(12):5007-5009 3. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TLPDF
614335

T-Cell Lymphoma, Diagnostic FISH, Varies

Clinical Information: T-cell malignancies account for approximately 10% of all non-Hodgkin lymphomas. There are subtypes of T-cell malignancies with diagnostic and prognostic genetic abnormalities. Fluorescence in situ hybridization (FISH) is available for specific abnormalities in the following T-cell lymphoma subtypes (see Table). Table. Common Chromosome Abnormalities in T-cell Lymphomas Lymphoma type Chromosome abnormality FISH probe T-cell prolymphocytic leukemia inv(14)(q11q32)/ (14;14)(q11;q32) 5'/3'TRAD 5'/3'TCLA1 Hepatosplenic T-cell lymphoma Isochromosome 7q D7Z1/ D7S486 Trisomy 8 D8Z2/MYC

Useful For: Detecting, at diagnosis, common chromosome abnormalities associated with specific T-cell lymphoma subtypes using a laboratory-designated probe set algorithm

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. Detection of an abnormal clone supports a diagnosis of T-cell lymphoma. The specific abnormality detected may help to determine a specific T-cell lymphoma subtype. The absence of an abnormal clone does not rule out the presence of lymphoma or another neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Volume 2. IARC Press; 2017 2. Gesk S, Martin-Subero JI, Harder L, et al. Molecular cytogenetic detection of chromosomal breakpoints in T-cell receptor gene loci. Leukemia. 2003;17(4):738-745. doi:10.1038/sj.leu.2402884 3. Chin M, Mugishima H, Takamura M, et al. Hemophagocytic syndrome and hepatosplenic gammadelta T-cell lymphoma with isochromosome 7q and 8 trisomy. J Pediatr Hematol Oncol. 2004;26(6):375-378. doi:10.1097/00043426-200406000-00008

TLYM
65911

T-Cell Lymphoma, FISH, Tissue

Clinical Information: T-cell malignancies account for approximately 10% of all non-Hodgkin lymphomas and there are numerous subtypes with diagnostic and prognostic genetic abnormalities that can be evaluated by fluorescence in situ hybridization (FISH) testing. FISH is available for specific abnormalities in T-cell lymphoma subtypes; see Table. Table. Common Chromosome Abnormalities in T-cell Lymphomas Lymphoma type Chromosome abnormality FISH probe Anaplastic large cell lymphoma 2p23 rearrangement 3′/5' ALK 3q28 rearrangement 5′/3' TP63 6p25.3 rearrangement 5′/3' IRF4 (DUSP22) T-cell prolymphocytic leukemia inv(14)(q11q32)/ t(14;14)(q11;q32) 5′/3' TRAD 5′/3' TCL1A Hepatosplenic T-cell lymphoma Isochromosome 7q D7Z1/ D7S486 trisomy 8 D8Z2/MYC

Useful For: Detecting common, recurrent chromosome abnormalities in various T-cell lymphomas in paraffin-embedded tissue specimens at diagnosis Providing prognostic information in patients with documented systemic ALK-negative anaplastic large cell lymphoma

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone is supportive of a diagnosis of a T-cell lymphoma. The specific abnormality detected may help determine a T-cell lymphoma subtype and/or contribute to the prognosis. The absence of an abnormal clone, or negative result, does not rule out the presence of a neoplastic disorder or change the pathologic diagnosis.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017. WHO Classification of Tumours. Vol 2. 2. Feldman AL, Law M, Remstein ED, et al. Recurrent translocations involving the IRF4 oncogene locus in peripheral T-cell lymphomas. Leukemia. 2009;23(3):574-580 3. Feldman AL, Dogan A, Smith Dl, et al. Discovery of recurrent t(6:7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomics sequencing. Blood. 2011;117(3):915-919 4. Parilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood. 2014;124(9):1473-1480 5. Vasmatzis G, Johnson SH, Knudson RA, et al. Genomics-wide analysis reveals recurrent structural abnormalities of TP63 and other p53-releated genes in peripheral T-cell lymphomas. Blood. 2012 Sep 13;120(11):2280-2289

TLPMF
614346

T-Cell Lymphoma, Specified FISH, Varies

Clinical Information: T-cell malignancies account for approximately 10% of all non-Hodgkin lymphomas. There are subtypes of T-cell lymphoma with diagnostic and prognostic genetic abnormalities. Fluorescence in situ hybridization (FISH) is available for specific abnormalities in the following T-cell lymphoma subtypes (see Table). Table. Common Chromosome Abnormalities in T-cell Lymphomas Lymphoma type Chromosome abnormality FISH probe T-cell prolymphocytic leukemia inv(14)(q11q32)/ (14;14)(q11;q32) 5′/3' TRAD 5′/3' TCL1A Hepatosplenic T-cell lymphoma Isochromosome 7q D7Z1/ D7S486 Trisomy 8 D8Z2/MYC

Useful For: Detecting, at diagnosis, common chromosome abnormalities associated with specific T-cell lymphoma subtypes using client specified probes

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. Detection of an abnormal clone supports a diagnosis of T-cell lymphoma. The specific abnormality detected may help to determine a specific T-cell lymphoma

subtype. The absence of an abnormal clone does not rule out the presence of lymphoma or another neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Swerdlow S, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press; 2017 2. Gesk S, Martin-Subero JI, Harder L, et al. Molecular cytogenetic detection of chromosomal breakpoints in T-cell receptor gene loci. Leukemia. 2003;17(4):738-745 3. Chin M, Mugishima H, Takamura M, et al. Hemophagocytic syndrome and hepatosplenic (gamma)(delta) T-cell lymphoma with isochromosome 7q and 8 trisomy. J Pediatr Hematol Oncol. 2004;26(6):375-378

TCRF1 70560 T-Cell Receptor Beta (TCR Beta F1) Immunostain, Technical Component Only

Clinical Information: T-cell receptor beta (TCR Beta F1) antibody is directed against the beta chain of the alpha/beta T-cell receptor, thus staining the majority of T lymphocytes. Staining is localized at cell membranes with weak cytoplasmic staining in some cells. Positive staining in malignant lymphomas can confirm T-cell lineage and further subtype as alpha/beta T cells.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chan WC, Borowitz MJ, Hammami A, et al. T-cell receptor antibodies in the immunohistochemical studies of normal and malignant lymphoid cells. Cancer. 1988;62(10):2118-2124 2. Chuang S, Young-Hyeh K. Cutaneous nonmycotic T- and natural killer/T-cell lymphomas: diagnostic challenges and dilemmas. J Am Acad Dermatol. 2014;70:724-735 3. Krajewski AS, Myskow MW, Salter DM, et al. Diagnosis of T-cell lymphoma using beta F1, anti-T-cell receptor beta chain antibody. Histopathology. 1989:15(3):239-247 4. Rudiger T, Weisenburger DD, Anderson JR, et al. Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. Annals of Oncol. 2002;13:140-149 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TRBC3 622845 T-Cell Receptor Constant Beta Chain (TRBC1) +CD3 Immunostain, Technical Component Only

Clinical Information: Each alpha beta T cell expresses a T-cell receptor (TCR) containing one of the two TCR beta chain constant regions (TRBC), TRBC1 or TRBC2. Reactive T-cell populations show a polytypic mixture of TRBC1 and TRBC2 expression. T-cell neoplasms show restricted expression with T-cells expressing either TRBC1 or TRBC2 in a mutually exclusive pattern, analogous to light chain expression in B-cells.

Useful For: Determination of T-cell clonality in T-cell neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Zhou T, Sardana R, Eren OC, et al. The diagnostic utility of TRBC1 immunohistochemistry in mature T-cell lymphomas. Mod Pathol. Published online January 28,2025.. doi:10.1016/j.modpat.2025.100725 2. Horna P, Weybright MJ, Ferrari M, et al. Dual T-cell constant beta chain (TRBC)1 and TRBC2 staining for the identification of T-cell neoplasms by flow cytometry. Blood Cancer J. 2024;14(1):34 3. Soilleux EJ, Rodgers DT, Situ JJ, et al. Demonstration of T-cell monotypia using anti-TCRbeta1/2 (TRBC1/2) immunostaining as a rapid and cost-effective alternative to PCR-based clonality studies for the diagnosis of T-cell lymphoma. Diagnostics (Basel). 2024;14(22):2479 4. Nocco SE, Ewalt MD, Moy AP, et al. TRBC1 immunohistochemistry distinguishes cutaneous T-cell lymphoma from inflammatory dermatitis: A retrospective analysis of 39 cases. J Am Acad Dermatol. 2024;90(4):839-841

TRBC1
622852

T-Cell Receptor Constant Beta Chain (TRBC1) Immunostain, Technical Component Only

Clinical Information: Each alpha beta T cell expresses a T-cell receptor (TCR) containing one of the two TCR beta chain constant regions (TRBC), TRBC1 or TRBC2. Reactive T-cell populations show a polytypic mixture of TRBC1 and TRBC2 expression. T-cell neoplasms show restricted expression with T-cells expressing either TRBC1 or TRBC2 in a mutually exclusive pattern, analogous to light chain expression in B-cells.

Useful For: Determination of T-cell clonality in T-cell neoplasms

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Zhou T, Sardana R, Eren OC, et al. The diagnostic utility of TRBC1 immunohistochemistry in mature T-cell lymphomas. Mod Pathol. Published online January 28,2025.. doi:10.1016/j.modpat.2025.100725 2. Horna P, Weybright MJ, Ferrari M, et al. Dual T-cell constant beta chain (TRBC)1 and TRBC2 staining for the identification of T-cell neoplasms by flow cytometry. Blood Cancer J. 2024;14(1):34 3. Soilleux EJ, Rodgers DT, Situ JJ, et al. Demonstration of T-cell monotypia using anti-TCRbeta1/2 (TRBC1/2) immunostaining as a rapid and cost-effective alternative to PCR-based clonality studies for the diagnosis of T-cell lymphoma. Diagnostics (Basel). 2024;14(22):2479 4. Nocco SE, Ewalt MD, Moy AP, et al. TRBC1 immunohistochemistry distinguishes cutaneous T-cell lymphoma from inflammatory dermatitis: A retrospective analysis of 39 cases. J Am Acad Dermatol. 2024;90(4):839-841

TCRGD
70562

T-Cell Receptor Delta Immunostain, Technical Component Only

Clinical Information: T-cell receptor delta expression is seen in a small proportion of total T cells.

Recognition of T-cell lymphomas that are derived from the delta T-cell subset is important as they often have a more aggressive clinical behavior. Normal tonsils show scattered cells staining in the interfollicular regions.

Useful For: Classification of lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Roullet M, Gheith SMF, Mauger J, et al. Percentage of gamma-delta T cells in panniculitis by paraffin immunohistochemical analysis. Am J Clin Pathol. 2009;131:820-826 2. Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-Cell lymphoma: Definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 38 cases. Blood. 2008;111:838-845 3. Vega F, Medeiros LJ, Gaulard P. Hepatosplenic and other gammadelta T-cell lymphomas. Am J Clin Pathol. 2007;127:869-880 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TRECS
610068

T-Cell Receptor Excision Circles Analysis, Blood

Clinical Information: T-cell generation is a critical feature of the adaptive immune response and has 2 main components: thymic output of new T cells and peripheral homeostatic expansion of preexisting T cells. It has been shown that although thymic function declines with age, a reasonable output is still maintained into late adult life.(1) In many clinical situations, thymic output is crucial to the maintenance and competence of the T-cell effector immune response. Thymic output of new T cells can be determined by T-cell receptor excision circles (TREC) analysis. TREC are extrachromosomal DNA byproducts of T-cell receptor (TCR) rearrangement, which are nonreplicative. TREC are produced only in T cells of thymic origin and each cell is thought to contain a single copy of the TREC measured in this test. Hence, TREC analysis provides a specific assessment of T-cell recovery (eg, after hematopoietic stem cell transplantation) or numerical T-cell competence. There are several TREC generated during the process of TCR rearrangement and the TCR delta deletion TREC (deltaREC psi-J-alpha signal joint TREC) has been shown to be the most accurate TREC for measuring thymic output.(2) This assay measures this specific TREC using quantitative, real-time polymerase chain reaction. Clinical use of TREC in HIV and Antiretroviral Therapy: HIV infection leads to a decrease in thymic function. Adult patients treated with highly active antiretroviral therapy (HAART) show a rapid and sustained increase in thymic output.(1) Clinical use of TREC in Hematopoietic Stem Cell Transplantation and Inborn Errors of Immunity (formerly Primary Immunodeficiencies)(3): There is a period of immunodeficiency following hematopoietic stem cell transplantation (HSCT) that varies depending on the nature and type of stem cell graft used and the conditioning regimen, among other factors. This secondary immunodeficiency also includes defects in thymopoiesis.(4-6) It has been shown that numerical T-cell recovery is usually achieved by day 100 post-transplant, although there is an inversion of the CD4:CD8 ratio that can persist for up to a year.(5) Also, recovery of T-cell function and diversity can take up to 12 months, although this can be more rapid in pediatric patients. However, recovery of T-cell function is only possible when there is numerical reconstitution of T cells. T cells, along with the other components of adaptive immunity, are key players in the successful response to vaccination post-HSCT.(7) In patients who have received HSCT for severe combined immunodeficiency, T-cell recovery early after transplant is crucial to long-term T-cell reconstitution.(8) Patients who demonstrated impaired reconstitution were shown to have poor early grafting, as opposed to immune failure caused by accelerated loss of thymic output or long-term graft failure. In this study,

the numbers of TREC early after HSCT were most predictive for long-term reconstitution. The data suggests that frequent monitoring of T-cell immunity and TREC numbers after HSCT can help identify patients who will fail to reconstitute properly, which would allow institution of additional therapies in a timely manner.(8) It would be reasonable to extrapolate such a conclusion to other diseases that are also treated by HSCT. TREC Copies and Thymic Output in Adults: Since the adult thymus involutes after puberty and is progressively replaced by fat with age, thymus-dependent T-cell recovery has been assumed to be severely limited in adults. However, with TREC analysis it has been shown that the change in thymic function in adults is a quantitative phenomenon rather than a qualitative one and thymic output is not totally eliminated.(1,9,10) Thus, after HSCT or HAART, the remaining thymic tissue can be mobilized in adults to replenish depleted immune systems with a potentially broader repertoire of naive T cells. Douek et al have shown that there is a significant contribution by the thymus to immune reconstitution after myeloablative chemotherapy and HSCT in adults.(9) In fact, this data show that there is both a marked increase in the TREC numbers and a significant negative correlation of TREC copies with age post-transplant. In addition to the specific clinical situations elucidated above, TREC analysis can be helpful in identifying patients with primary immunodeficiencies and assessing their numerical T-cell immune competence. It can also be used as a measure of immune competence in patients receiving immunotherapy or cancer vaccines, where maintenance of T-cell output is integral to the immune response against cancer. The absolute counts of lymphocyte subsets are influenced by a variety of biological factors, including genetic background, hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell counts throughout the day, while CD8 T cells and CD19 B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day.(11) Circadian variations in circulating T cells are negatively correlated with plasma cortisol concentration.(12-14) In fact, cortisol and catecholamine concentrations control distribution, and therefore numbers of naive versus effector CD4 and CD8 T cells.(12) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening,(15) and during summer compared to winter.(16) These data, therefore, indicate that consistency in timing of blood collection are critical when serially monitoring patients for lymphocyte subsets.

Useful For: Measuring T-cell output or reconstitution (thymopoiesis) following hematopoietic cell transplantation or highly active antiretroviral therapy Evaluating thymic function in patients with cellular or combined inborn errors of immunity (formerly primary immunodeficiencies), or receiving immunotherapy or cancer vaccines Assessing T-cell recovery following thymus transplants for DiGeorge syndrome

Interpretation: T-cell receptor excision circles (TREC) generally show an inverse correlation with age, although there can be substantial variations in TREC copies relative to T-cell count within a given age group. Following hematopoietic stem cell transplantation (HSCT), highly active antiretroviral therapy (HAART), thymic transplants, etc, TREC typically increases from absent or very low levels (below age-matched reference range) to baseline levels or exceeds baseline levels, showing evidence of thymic rebound, which is consistent with recovery of thymic output and T-cell reconstitution. When a patient is being monitored for thymic recovery post-transplant, it is recommended that a pre-transplant (prior to myeloablative or non-myeloablative conditioning) or a pretreatment baseline specimen is provided so that appropriate comparisons can be made between the pre- and post-transplant specimens. Since there is substantial variability between individuals in TREC copies, the best comparison is made to the patient's own baseline specimen rather than the reference range (which provides a guideline for TREC copies for age-matched healthy controls). A consultative report will be generated for each patient.

Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References: 1. Douek DC, McFarland RD, Keiser PH, et al: Changes in thymic function with age and during the treatment of HIV infection. Nature. 1998;396:690-694 2. Hazenberg MD, Verschuren MC, Hamann D, et al: T cell receptor excision circles as markers for recent thymic emigrants:

basic aspects, technical approach, and guidelines for interpretation. J Mol Med. 2001;79:631-640 3. Gaballa A, Clave E, Uhlin M, Toubert A, Arruda LCM: Evaluating thymic function after human hematopoietic stem cell transplantation in the personalized medicine era. Front Immunol. 2020 Jul 31;11:1341. doi: 10.3389/fimmu.2020.01341 4. Parkman R, Weinberg K: Immunological reconstitution following hematopoietic stem cell transplantation. In: Thomas ED, Blume KG, Forman SJ, eds. Hematopoietic Cell Transplantation. 2nd ed. Blackwell Scientific; 1999:704-711 5. Weinberg K, Blazar BR, Wagner JE, et al: Factors affecting thymic function after allogeneic hematopoietic stem cell transplantation. Blood. 2001;97:1458-1466 6. Weinberg K, Annett G, Kashyap A, et al: The effect of thymic function on immunocompetence following bone marrow transplantation. Biol Blood Marrow Transplant. 1995;1:18-23 7. Auletta JJ, Lazarus HM: Immune restoration following hematopoietic stem cell transplantation: an evolving target. Bone Marrow Transplant. 2005;35:835-857 8. Borghans JA, Bredius RG, Hazenberg MD, et al: Early determinants of long-term T cell reconstitution after hematopoietic stem cell transplantation for severe combined immunodeficiency. Blood. 2006;108:763-769 9. Douek DC, Vescio RA, Betts MR, et al: Assessment of thymic output in adults after hematopoietic stem cell transplantation and prediction of T cell reconstitution. Lancet. 2000;355:1875-1881 10. Jamieson BD, Douek DC, Killian S, et al: Generation of functional thymocytes in the human adult. Immunity. 1999;10:569-575 11. Carmichael KF, Abayomi A: Analysis of diurnal variation of lymphocyte subsets in healthy subjects and its implication in HIV monitoring and treatment. 15th Intl Conference on AIDS, Bangkok, Thailand, 2004, Abstract B11052 12. Dimitrov S, Benedict C, Heutling D, et al: Cortisol and epinephrine control opposing circadian rhythms in T-cell subsets. Blood. 2009 May 21;113(21):5134-5143 13. Dimitrov S, Lange T, Nohroudi K, Born J: Number and function of circulating antigen presenting cells regulated by sleep. Sleep. 2007;30:401-411 14. Kronfol Z, Nair M, Zhang Q, et al: Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Psychosom Med. 1997;59:42-50 15. Malone JL, Simms TE, Gray GC, et al: Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J AIDS. 1990;3:144-151 16. Paglieroni TG, Holland PV: Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994;34:512-516

TCGR
83122

T-Cell Receptor Gene Rearrangement, PCR, Blood

Clinical Information: The T-cell receptor (TCR) genes (alpha, beta, delta, and gamma) are comprised of numerous, discontinuous coding segments that somatically rearrange to produce heterodimeric cell surface T-cell receptors, either alpha/beta (90%-95% of T cells) or gamma/delta (5%-10% of T cells). With rare exceptions (eg, some neoplastic B-lymphoid proliferations), other cell types retain the germline configuration of the TCR genes without rearrangement. The marked diversity of somatic TCR-gene rearrangements is important for normal immune functions but also serves as a valuable marker to distinguish abnormal T-cell proliferations from reactive processes. A monoclonal expansion of a T-cell population will result in the predominance of a single TCR-gene rearrangement pattern. In contrast, reactive T-cell expansions are polyclonal (or multiclonal), with no single clonotypic population predominating in the population of T cells. These distributive differences in both TCR sequence and genomic rearrangement fragment sizes can be detected by molecular techniques (ie, polymerase chain reaction) and used to determine if a population of T cells shows monoclonal or polyclonal features.

Useful For: Determining whether a T-cell population is polyclonal or monoclonal using blood specimens

Interpretation: An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal T-cell population. In the appropriate clinicopathologic setting, a monoclonal result is associated with a neoplastic proliferation of T cells (see Cautions).

Reference Values:
An interpretive report will be provided.
Positive, negative, or indeterminate for a clonal T-cell population

Clinical References: 1. Liu H, Bench AJ, Bacon CM, et al. A practical strategy for the routine use of BIOMED-2 PCR assays for detection of B- and T-cell clonality in diagnostic haematopathology. Br J Haematol. 2007;138(1):31-43 2. Van Krieken JH, Langerak AW, Macintyre EA, et al. Improved reliability of lymphoma diagnostics via PCR-based clonality testing: report of the BIOMED-2 Concerted Action BHM4-CT98-3936. Leukemia. 2007;21(2):201-206 3. Bruggemann M, White H, Gaulard P, et al. Powerful strategy for polymerase chain reaction-based clonality assessment in T-cell malignancies Report of the BIOMED-2 Concerted Action BHM4 CT98-3936. Leukemia. 2007;21(2):215-221 4. Langerak AW, Groenen PJTA, Bruggemann M, et al. EuroClonality/BIOMED-2 guidelines for interpretation and reporting of Ig/TCR clonality testing in suspected lymphoproliferations. Leukemia. 2012;26(10):2159-2171 5. Davies K, Staniforth J, Haowei Xie, W, et al. Advances in the assessment of T-cell clonality. Diagn Histopathol. 2020;26(9):388-397

TCGBM
31139

T-Cell Receptor Gene Rearrangement, PCR, Bone Marrow

Clinical Information: The T-cell receptor (TCR) genes (alpha, beta, delta, and gamma) are comprised of numerous, discontinuous coding segments that somatically rearrange to produce heterodimeric T-cell surface receptors, either alpha/beta (90%-95% of T cells) or gamma/delta (5%-10% of T cells). With rare exceptions (eg, some neoplastic B-lymphoid proliferations), other cell types retain the germline configuration of the TCR genes without rearrangement. The marked diversity of somatic TCR-gene rearrangements is important for normal immune functions but also serves as a valuable marker to distinguish abnormal T-cell proliferations from reactive processes. A monoclonal expansion of a T-cell population will result in the predominance of a single TCR-gene rearrangement pattern. In contrast, reactive T-cell expansions are polyclonal (or multiclonal), with no single clonotypic population predominating in the population of T cells. These distributive differences in both TCR sequence and genomic rearrangement fragment sizes can be detected by molecular techniques (ie, polymerase chain reaction) and used to determine if a population of T cells shows monoclonal or polyclonal features.

Useful For: Determining whether a T-cell population is polyclonal or monoclonal

Interpretation: An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal T-cell population. In the appropriate clinicopathologic setting, a monoclonal result is associated with a neoplastic proliferation of T cells (see Cautions).

Reference Values:
An interpretive report will be provided.

Positive, negative, or indeterminate for a clonal T-cell population

Clinical References: 1. Liu H, Bench AJ, Bacon CM, et al. A practical strategy for the routine use of BIOMED-2 PCR assays for detection of B- and T-cell clonality in diagnostic haematopathology. Br J Haematol. 2007;138(1):31-43 2. van Krieken JHJM, Langerak AW, Macintyre EA, et al. Improved reliability of lymphoma diagnostics via PCR-based clonality testing: report of the BIOMED-2 Concerted Action BHM4-CT98-3936. Leukemia. 2007;21(2):201-206 3. Bruggermann M, White H, Gaulard P, et al. Powerful strategy for polymerase chain reaction-based clonality assessment in T-cell malignancies Report of the BIOMED-2 Concerted Action BHM4 CT98-3936. Leukemia. 2007;21(2):215-221 4. Langerak AW, Groenen PJTA, Bruggemann M, et al. EuroClonality/BIOMED-2 guidelines for interpretation and reporting of Ig/TCR clonality testing in suspected lymphoproliferations. Leukemia. 2012;26(10):2159-2171. doi:10.1038/leu.2012.246 5. Davies K, Staniforth J, Haowei Xie W, et al.

Advances in the assessment of T-cell clonality. Diag Histopathol. 2020;26(9):388-397

TCGET 802124 T-Cell Receptor Gene Rearrangement, PCR, Tissue

Clinical Information: The T-cell receptor (TCR) genes (alpha, beta, delta, and gamma) are comprised of numerous, discontinuous coding segments that somatically rearrange to produce heterodimeric T-cell surface receptors, either alpha/beta (90%-95% of T cells) or gamma/delta (5%-10% of T cells). With rare exceptions (eg, some neoplastic B-lymphoid proliferations), other cell types retain the germline configuration of the TCR genes without rearrangement. The marked diversity of somatic TCR-gene rearrangements is important for normal immune functions but also serves as a valuable marker to distinguish abnormal T-cell proliferations from reactive processes. A monoclonal expansion of a T-cell population will result in the predominance of a single TCR-gene rearrangement pattern. In contrast, reactive T-cell expansions are polyclonal (or multiclonal), with no single clonotypic population predominating in the population of T cells. These distributive differences in both TCR sequence and genomic rearrangement fragment sizes can be detected by molecular techniques (ie, polymerase chain reaction) and used to determine if a population of T cells shows monoclonal or polyclonal features.

Useful For: Determining whether a T-cell population is polyclonal or monoclonal using paraffin-embedded specimens

Interpretation: An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal T-cell population. In the appropriate clinicopathologic setting, a monoclonal result is associated with a neoplastic proliferation of T cells (see Cautions).

Reference Values:
An interpretive report will be provided.

Positive, negative, or indeterminate for a clonal T-cell population

Clinical References: 1. van Heijst JM, Ceberio I, Lipuma LB, et al. Quantitative assessment of T cell repertoire recovery after hematopoietic stem cell transplantation. Nature Medicine. 2013;19(3):372-378 2. Liu H, Bench AJ, Bacon CM, et al. A practical strategy for the routine use of BIOMED-2 PCR assays for detection of B- and T-cell clonality in diagnostic haematopathology. Br J Haematol. 2007;138(1):31-43 3. Van Krieken JH, Langerak AW, Macintyre EA, et al. Improved reliability of lymphoma diagnostics via PCR-based clonality testing: report of the BIOMED-2 concerted action BHM4-CT98-3936. Leukemia. 2007;21(2):201-206 4. Bruggemann M, White H, Gaulard P, et al. Powerful strategy for polymerase chain reaction-based clonality assessment in T-cell malignancies report of the BIOMED-2 Concerted Action BHM4 CT98-3936. Leukemia. 2007;21(2):215-221 5. Davies K, Staniforth J, Haowei Xie W, et al. Advances in the assessment of T-cell clonality. Diag Histopathol. 2020;26(9):388-397

TCGRV 31140 T-Cell Receptor Gene Rearrangement, PCR, Varies

Clinical Information: The T-cell receptor (TCR) genes (alpha, beta, delta, and gamma) are comprised of numerous, discontinuous coding segments that somatically rearrange to produce heterodimeric cell surface TCR, either alpha/beta (90%-95% of T cells) or gamma/delta (5%-10% of T cells). With rare exceptions (eg, some neoplastic B-lymphoid proliferations), other cell types retain the germline configuration of the TCR genes without rearrangement. The marked diversity of somatic TCR-gene rearrangements is important for normal immune functions but also serves as a valuable marker to distinguish abnormal T-cell proliferations from reactive processes. A monoclonal expansion of a T-cell

population will result in the predominance of a single TCR-gene rearrangement pattern. In contrast, reactive T-cell expansions are polyclonal (or multiclonal), with no single clonotypic population predominating in the population of T cells. These distributive differences in both TCR sequence and genomic rearrangement fragment sizes can be detected by molecular techniques (ie, polymerase chain reaction) and used to determine if a population of T cells shows monoclonal or polyclonal features.

Useful For: Determining whether a T-cell population is polyclonal or monoclonal using body fluid or tissue specimens

Interpretation: An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal T-cell population. In the appropriate clinicopathologic setting, a monoclonal result is associated with a neoplastic proliferation of T cells (see Cautions).

Reference Values:
An interpretive report will be provided.
Positive, negative, or indeterminate for a clonal T-cell population

Clinical References: 1. Liu H, Bench AJ, Bacon CM, et al: A practical strategy for the routine use of BIOMED-2 PCR assays for detection of B- and T-cell clonality in diagnostic haematopathology. Br J Haematol. 2007 Jul;138(1):31-43 2. van Krieken JHJM, Langerak AW, Macintyre EA, et al: Improved reliability of lymphoma diagnostics via PCR-based clonality testing: report of the BIOMED-2 Concerted Action BHM4-CT98-3936. Leukemia. 2007 Feb;21(2):201-206 3. Bruggermann M, White H, Gaulard P, et al: Powerful strategy for polymerase chain reaction-based clonality assessment in T-cell malignancies Report of the BIOMED-2 Concerted Action BHM4 CT98-3936. Leukemia. 2007 Feb;21(2):215-221 4. Langerak AW, Groenen PJTA, Bruggemann M, et al: EuroClonality/BIOMED-2 guidelines for interpretation and reporting of Ig/TCR clonality testing in suspected lymphoproliferations. Leukemia. 2012 Oct;26(10):2159-2171. doi: 10.1038/leu.2012.246 5. Davies K, Staniforth J, Haowei Xie, W, et al: Advances in the assessment of T-cell clonality. Diagn Histopathol. 2020 Sept;26(9):388-397

TCRB
610067

T-Cell Receptor V-Beta Repertoire Analysis, Spectratyping, Blood

Clinical Information: The rearrangement of the T-cell receptor (TCR) through somatic recombination of V (variable), D (diversity), J (joining), and C (constant) regions is a defining event in the development and maturation of a T cell. TCR gene rearrangement takes place in the thymus. During the process of rearrangement, DNA byproducts are generated called T-cell receptor excision circles (TREC) and these are used as markers of T cells that have recently emigrated from the thymus (TRECS / T-Cell Receptor Excision Circles Analysis, Blood). T cells, as part of the adaptive immune system, recognize foreign antigens when they are displayed on the surface of the body's own cells. T cells recognize these foreign antigens as peptides presented in the context of major histocompatibility complex (MHC) molecules through their TCRs. Each TCR exists as 2 different polypeptide chains (heterodimers) called the TCR alpha chain and TCR beta chain, and these are linked by disulfide bonds. The majority of T cells (approximately 90%) in the body express TCRs with alpha and beta chains. A minority of T cells express other T-cell receptors made of different polypeptide chains, gamma and delta. Each T cell has approximately 30,000 identical antigen receptors on its cell surface. A TCR has only one antigen-binding site, in contrast to the B-cell receptor, which has two. TCRs are never secreted and always remain on the cell surface. The alpha and beta chains are encoded by different gene loci (alpha and beta TCR gene locus). The beta chain locus rearranges before the alpha chain and a functional beta chain has to be produced in order for the T cell to form a pre-T-cell receptor. The expression of the rearranged beta chain with an alpha chain precursor suppresses additional gene rearrangement at the TCR beta locus. The TCR alpha chain locus rearrangement can proceed even with production of a functional alpha chain until there is positive selection of the particular T cell. However, it is important to note that each T cell has a single

functional specificity for its TCR. A key concept in understanding the immune response is that there is enormous diversity in the immune system to enable protection against a huge array of pathogens. Since the germline genome is limited in size, diversity is achieved not only by the process of V(D)J recombination but also by junctional (junctions between V-D and D-J segments) deletion of nucleotides and addition of pseudo-random, non-templated nucleotides. In particular, the CDR3 (complementarity determining region 3), which is the most critical determinant of antigenic specificity in T cells (and B cells) is short (between 66-90 nucleotides, approximately 20-30 amino acids) and amenable to assessment of length by fragment length analysis, which provides a size resolution of up to one base pair between different CDR3 regions. It is thought that the CDR3-TCR beta chain repertoire in healthy adults contains somewhere between 3 and 4 million unique sequences.(1) Other reports suggest that the unique TCR repertoire after thymic selection is between 10 to 100 million in humans.(2) There is, however, a bias in TCR selection with overrepresentation of certain TCRs that are widely used in individuals who share the same major histocompatibility types and these are called "public TCRs." Public TCRs generally have fewer random nucleotide additions in their sequence. The TCR V beta repertoire varies significantly between individuals and populations because of 7 frequently occurring inactivating alterations (ie, polymorphisms) in functional gene segments and a large deletion/insertion-related alteration encompassing 2 V beta gene segments. With this latter situation, the TCR Vb 6-2/6-3 and TCR Vb 4-3 genes are frequently deleted from all ethnic groups.(3) It has been reported that the total number of functional TCR V beta gene segments expressed by an individual varies from 42 to 47.(4) Deep sequencing technologies are evolving to analyze this large diversity in the adaptive immune receptors.(5,6) However, deep sequencing of the T-cell and B-cell receptor genes is not yet widely available and is expensive. Flow cytometry-based analysis to assess TCR V beta diversity is available. However, the antibodies are limited and therefore the assay cannot assess the entire TCR V beta repertoire. On the other hand, TCR beta chain repertoire analysis by fragment length analysis (spectratyping) using fluorescent primers to measure CDR3 length variability, while unable to provide the extreme high resolution of deep sequencing, can provide a global "snapshot" of TCR repertoire diversity, which is useful for most clinical applications where this level of assessment is required.(7-14) It is important to note that this method uses polymerase chain reaction to amplify the rearranged variable regions to provide adequate template for sequencing (fragment length analysis), and this can introduce bias due to the more efficient amplification of certain templates compared to others. Despite this limitation, since this assay is not quantitative, it is still able to provide an assessment of diversity by measuring the CDR3 length in various TCR V beta genes, which are organized into 24 families.

Useful For: Assessment of T-cell receptor diversity in various clinical contexts including inborn errors of immunity (formerly primary immunodeficiencies), monitoring immune reconstitution post-hematopoietic stem cell transplantation, and temporal assessment of repertoire changes in autoimmune diseases and viral infections

Interpretation: An interpretive report will be provided with adult and pediatric reference values for the relative contribution of each family to the total repertoire (% diversity ratio). The interpretation will be based on visual analysis of the spectratype (polyclonal, oligoclonal, or monoclonal) for each family as well as assessment of the number of peaks (numerical value not reported), and diversity ratio (DR) (reported value). Information on the distribution of peaks, eg, Gaussian vs non-Gaussian, will also be included in the report, where appropriate. Internal analytical and quality controls will be assessed to determine the suitability of reporting a patient result. Correlation with the clinical context will be made when possible, based on clinical history provided in the patient information sheet, which should be provided with the patient sample.

Reference Values:
References values will be provided in the patient report.

Clinical References: 1. Robins HS, Campregher PV, Srivastava SK, et al: Comprehensive assessment of T-cell receptor beta-chain diversity in alphabeta T cells. Blood. 2009;114:4099-4107 2. Arstila TP, Casrouge A, Baron V, et al: A direct estimate of the human alpha-beta T cell receptor

diversity. Science. 1999;958-961 3. Brennan RM, Petersen J, Neller MA: The impact of a large and frequent deletion in the human TCR beta locus on antiviral immunity. J Immunol. 2012;188:2742-2748 4. Mackelprang R, Carlson CS, Subrahmanyan L, et al: Sequence variation in the human T-cell receptor loci. Immunol Rev. 2002;190:26-39 5. Warren EH, Matsen IV FA, Chou J: High-throughput sequencing of B- and T-lymphocyte antigen receptors in hematology. Blood. 2013;122:19-22 6. Robins H: Immunosequencing: applications of immune repertoire deep sequencing. Curr Opin Immunol. 2013;25:646-652 7. Gorski J, Yassai M, Zhu X, et al: Circulating T cell repertoire complexity in normal individuals and bone marrow recipients analyzed by CDR3 spectratyping. J Immunol. 1994;152:5109-5119 8. Memon SA, Sportes C, Flomerfelt FA, et al: Quantitative analysis of T cell receptor diversity in clinical samples of human peripheral blood. J Immunol Methods. 2012;375:84-92 9. van Heijst JMJ, Ceberio I, Lipuma LB, et al: Quantitative assessment of T cell repertoire recovery after hematopoietic stem cell transplantation. Nature Medicine. 2013;19:372-378 10. Wada T, Schurman SH, Garabedian EK, et al: Analysis of T-cell repertoire diversity in Wiskott-Aldrich syndrome. Blood. 2005;106:3895-3897 11. Pirovano S, Mazzolari E, Pasic S, et al: Impaired thymic output and restricted T-cell repertoire in two infants with immunodeficiency and early-onset generalized dermatitis. Immunol Letters. 2003;86:93-97 12. Villa A, Notarangelo LD, Roifman CM: Omenn syndrome: inflammation in leaky severe combined immunodeficiency. J Allergy Clin Immunol. 2008;122:1082-1086 13. Sullivan KE: The clinical, immunological and molecular spectrum of chromosome 22q11.2 deletion syndrome and DiGeorge syndrome. Curr Opin Allergy Clin Immunol. 2004;4:505-512 14. Markert ML, Devlin BH, McCarthy EA: Thymus transplantation. Clin Immunol. 2010;135:236-246

TCP
89319

T-Cell Subsets, Naive, Memory, and Activated, Blood

Clinical Information: T cells, after completing development and initial differentiation in the thymus, enter the periphery as naive T cells. Naive T cells undergo further differentiation into effector and memory T cells in the peripheral lymphoid organs after recognizing specific antigenic peptides in the context of major histocompatibility (MHC) molecules, through the antigen-specific T-cell receptor. In addition to the cognate signal of the peptide-MHC complex interaction (the term cognate refers to 2 biological molecules that normally interact), T cells require additional costimulatory signals to complete T-cell activation. Naive T cells circulate continuously through the lymph nodes and, on recognition of specific antigen, undergo activation. Due to their antigen-inexperienced state, naive T cells require activation by more potent antigen-presenting cells, such as dendritic cells. Naive T cells can survive in circulation for prolonged periods of time and are very important in contributing to T-cell repertoire diversity. They proliferate in response to interleukin-2 as a consequence of their response to antigen through recognition of peptide-MHC costimulation. These expanded antigen-specific T cells undergo further differentiation into effector cells. The differentiation of naive CD8 T cells into cytotoxic effectors capable of killing target T cells loaded with endogenous peptides on MHC class I molecules may require additional costimulatory signals from CD4 T cells. Naive CD4 T cells also differentiate into different effector subsets such as Th1, Th2, and Th17, which produce specific cytokines.(1) T cells can be subdivided into naive and memory subsets based on the expression of cell-surface markers, such as CD45RA and CD45RO among others. It was initially thought that the presence of cell-surface CD45RA indicated the naive subset, while the presence of CD45RO indicated memory subsets. It has now been shown that multiple, rather than single, markers are required to distinguish these subsets.(2) Lanzavecchia and Sallusto proposed a model where naive T cells expressing CD45RA and CCR7 lose CD45RA expression on recognition of antigen.(3) The surface markers for identifying naive T-cell subsets include CD45RA, CD62L (L-selectin), and CD27.(4,5) Memory T cells are antigen-experienced cells that are present in greater numbers than antigen-specific precursors and can respond more efficiently and rapidly to a specific antigen. Memory T cells can maintain their populations independent of antigen by homeostatic proliferation in response to cytokines. While there are subcategories of memory T cells based on effector function and cell surface and cytolytic molecule expression, the 2 main categories of memory T cells are central memory T cells (Tcm) and effector memory T cells (Tem).(1,6) Tcm express the CD45RO molecule along with CD62L (L-selectin) and CCR7 and are present mainly in lymphoid tissue.(6,7) They can respond to antigens through rapid proliferation and expansion and differentiation

into Tem. By themselves, Tcm are not directly effective in effector cytolytic function. Unlike Tcm, Tem express only CD45RO (not CD62L and CCR7).(6) As the name suggests, Tem have remarkable effector function, though they do not proliferate well. Tem are present throughout the circulation in peripheral tissues providing immune surveillance. Memory T cells are particularly important for maintenance of immune competence since they are associated with a rapid and effective response to pathogens. Therefore, depletion of this compartment has more immediate significance than the depletion of naive T cells. Activation of human T cells is critical for the optimal and appropriate performance of T-cell functions within the adaptive immune response. Activated naive T cells undergo proliferation, as well as subsequent differentiation into effector T cells, and are capable of producing cytokines that can modulate the immune response in a variety of ways.(8) There are several markers associated with T-cell activation, but those most commonly used include CD25 (IL-25R)(8) and MHC class II.(9) Additionally, the expression of the costimulatory molecule CD28 augments the T-cell activation response.(10) The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day.(11) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(12-14) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(11) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening,(15) and during summer compared to winter.(16) These data therefore indicate that timing and consistency in the timing of blood collection are critical when serially monitoring patients for lymphocyte subsets.

Useful For: Determining the presence of naive, memory, and activated T cells in various clinical contexts including autoimmune diseases, immunodeficiency states, T-cell recovery post-hematopoietic stem cell transplant, DiGeorge syndrome, and as a measure for T-cell immune competence Naive T-cells results can be used as a surrogate marker for thymic-derived T-cell reconstitution, when used in conjunction with assessment of T-cell receptor excision circles (TRECS / T-Cell Receptor Excision Circles Analysis, Blood) Assessing a patient's relative risk for infections Evaluating patients with cellular or combined primary immunodeficiencies Evaluating T-cell reconstitution after hematopoietic stem cell transplant, chemotherapy, biological therapy, immunosuppression, or immunomodulator therapy Evaluating patients with autoimmune diseases Evaluating patients who are HIV-positive for naive and memory subsets Evaluating T-cell immune competence (presence of memory and activated T cells) in patients with recurrent infections

Interpretation: Absence or reduction of naive T cells with or without T-cell lymphopenia indicates absent or impaired T-cell reconstitution or thymic output. Reduction in activated T cells can also indicate a reduced T-cell immune competent state. Increases in naive T cells with corresponding decreases in the memory T-cell compartment indicates a failure of further differentiation and effector function or selective loss of memory T cells and an increased risk for infection.

Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References: 1. Bettelli E, Oukka M, Kuchroo VK. T(H)-17 cells in the circle of immunity and autoimmunity. Nat Immunol. 2007;8(4):345-350 2. De Rosa SC, Herzenberg LA, Herzenberg LA, Roederer M. 11-color, 13-parameter flow cytometry: identification of human naive T-cells by phenotype, function, and T-cell receptor diversity. Nat Med. 2001;7(2):245-248 3. Sallusto F, Lenig D, Forster R, Lipp M, Lanzavecchia A. Two subsets of memory T-lymphocytes with distinct homing potentials and effector functions. Nature. 1999;401(6754):708-712 4. Picker LJ, Treer JR, Ferguson-Darnell B, Collins PA, Buck D, Terstappen LW. Control of lymphocyte recirculation in man. I. Differential regulation of the peripheral lymph node homing receptor L-selectin on T-cells during the

virgin to memory cell transition. J Immunol. 1993;150(3):1105-1121 5. Morimoto C, Schlossman SF. P. Rambotti lecture. Human naive and memory T-cells revisited: New markers (CD31 and CD27) that help define CD4+ T-cell subsets. Clin Exp Rheumatol. 1993;11(3):241-247 6. LaRosa DF, Orange JS. Lymphocytes. J Allergy Clin Immunol. 2008;121(2 Suppl):S364-369 7. Foster AE, Marangolo M, Sartor MM, et al. Human CD62L-memory T-cells are less responsive to alloantigen stimulation than CD62L+ naive T-cells: potential for adoptive immunotherapy and allodepletion. Blood. 2004;104(8):2403-2409 8. Brenchley JM, Douek DC, Ambrozal DR, Chatterji M, Betts MR, Davis LS, Koup RA. Expansion of activated human naive T-cells preceded effector function. Clin Exp Immunol. 2002;130(3):431-440 9. Holling TM, van der Stoep N, Quinten E, van den Elsen PJ. Activated human T-cells accomplish MHC class II expression through T-cell specific occupation of class II transactivator promoter III. J Immunol. 2002;168(2):763-770 10. Thompson CB, Lindsten T, Ledbetter JA, et al. CD28 activation pathway regulates the production of multiple T-cell-derived lymphokines/cytokines. Proc Natl Acad Sci USA. 1989;86(4):1333-1337 11. Carmichael KF, Abayomi A. Analysis of diurnal variation of lymphocyte subsets in healthy subjects and its implication in HIV monitoring and treatment. 15th Intl Conference on AIDS, Bangkok, Thailand, 2004, Abstract B11052 12. Dimitrov S, Benedict C, Heutling D, Westermann J, Born J, Lange T: Cortisol and epinephrine control opposing circadian rhythms in T cell subsets. Blood. 2009;113(21):5134-5143 13. Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating antigen presenting cells regulated by sleep. Sleep. 2007;30(4):401-411 14. Kronfol Z, Nair M, Zhang Q, Hill EE, Brown MB. Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Psychosom Med. 1997;59(1):42-50 15. Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS. Sources of variability in repeated T-helper lymphocyte counts from HIV 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J Acquir Immune Defic Syndr (1988). 1990;3:144-151 16. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994;34(6):512-516 17. Delmonte OM, Fleisher TA. Flow cytometry: Surface markers and beyond. J Allergy Clin Immunol. 2019;143(2):528-537 18. Knight V, Heimall JR, Chong H, et al. A toolkit and framework for optimal laboratory evaluation of individuals with suspected primary immunodeficiency. J Allergy Clin Immunol Pract. 2021;9(9):3293-3307.e6

TREGS
89318

T-Cell Subsets, Regulatory (Tregs), Blood

Clinical Information: Regulatory T cells (Tregs) are a population of CD4+ T cells with a unique role in the immune response. Tregs are crucial in suppressing aberrant pathological immune responses in autoimmune diseases, transplantation, and graft-vs-host disease after allogeneic hematopoietic stem cell transplantation.(1) Tregs are activated through the specific T-cell receptor, but their effector function is nonspecific, and they regulate the local inflammatory response through cell-to-cell contact and cytokine secretion.(2) Tregs secrete interleukin (IL)-9, IL-10, and transforming growth factor-beta 1 (TGF-beta 1), which aid in the mediation of immunosuppressive activity. Chief characteristics of the Treg population are surface expression of the CD25 protein (IL-2Ra) and the intracellular presence of the transcription factor FOXP3. The IL-7 receptor (CD127) is downregulated on FOXP3+CD4+CD25+ T cells and provides an alternative cell-surface marker to FOXP3 for detecting natural Tregs (CD4+CD25+CD127lo).(2) Natural Tregs account for 5% to 10% of the total CD4 T-cell population and are derived from thymic precursors.(3) Since CD25 is also expressed on activated T cells, the concomitant use of CD127 permits the differentiation of Tregs from activated T cells.(4) Natural Tregs express the memory marker CD45RO and have limited ability to proliferate. However, within the CD4+CD25+Treg population, there is a subset of Tregs that express the CD45 isoform generally associated with naive T cells (CD45RA), and this subset has been called natural naive (Nn) Tregs. Nn Tregs are most prominent in young adults and decrease with age along with the rest of the naive CD4 T-cell population.(5) Like other naive T cells, Nn Tregs have high proliferative capacity, as well as the suppressor activity of other Treg subsets. Evidence suggests that Nn Tregs also have a thymic ancestry and are the precursors of the natural Tregs (that are of the memory, antigen-experienced phenotype) and appear to be composed of T cells with self-reactive T-cell receptors.(5) Other subsets of Tregs include the T-helper 3 (Th3) cells, which secrete high levels of TGF-beta 1 and can be induced by oral administration of antigen, and regulatory T-class 1 (Tr1) cells, which

secrete interferon-gamma and IL-10.(5) These Treg subsets are most likely induced in the periphery and are responsible for peripheral tolerance to self-antigens. The suppressive activity of Th3 and Tr1 cells are related to the cytokines they produce, TGF-beta 1 and IL-10, respectively. The absence of Tregs as a result of variants in the FOXP3 gene causes a primary immunodeficiency called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked inheritance).(6) Patients with IPEX have a complex manifestation of symptoms including severe watery diarrhea due to significant villous atrophy and lymphocytic infiltration of bowel mucosa, early-onset autoimmune endocrinopathies involving the pancreas or thyroid, and a dermatitic (eczematous) rash. In addition, there are other autoimmune manifestations including autoimmune cytopenias and autoimmune hepatitis. Kidney disease is quite common in these patients. Finally, these patients also have a significant predisposition to infections including sepsis, pneumonia, meningitis, and osteomyelitis.(6) Decreased FOXP3+CD4+CD25+Tregs have been reported in other inborn errors of immunity.(7) There is an expansion of Nn Tregs in patients with monoclonal gammopathy of undetermined significance and multiple myeloma, likely as a response to the process of malignant transformation.(8) Expansion of Tregs has also been reported in other neoplasias including B-cell chronic lymphocytic leukemia, Hodgkin disease, and solid tumors. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day.(9) Circadian variations in circulating T-cell counts have been shown to negatively correlate with plasma cortisol concentration.(10-12) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(10) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening,(13) and during summer compared to winter.(14) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Evaluating patients with clinical features of IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked inheritance) and other primary immunodeficiencies, autoimmune diseases, allergy and asthma, and graft-vs-host disease post-hematopoietic stem cell transplantation

Interpretation: The lack of regulatory T cells (Tregs) is associated with variants in the FOXP3 gene. Low Tregs are also seen in the context of other inborn errors of immunity. Reduced Nn Tregs and natural Tregs are likely to predispose to autoimmunity, while reductions in Th3/Tr1 cells may impair oral and peripheral tolerance, also facilitating the development of autoimmunity. The presence of expanded naive Tregs may indicate a process of malignant transformation, if other clinical features of malignant disease are present. Increased Tregs in donor stem cell allografts have been associated with a reduced incidence of graft-versus-host disease (ie, mediating a protective effect) after allogeneic stem cell transplantation.

Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References: 1. Sakaguchi S, Sakaguchi N, Shimizu J, et al. Immunologic tolerance maintained by CD25+CD4+ regulatory T cells: their common role in controlling autoimmunity, tumor immunity, and transplantation tolerance. Immunol Rev. 2001;182:18-32 2. Liu W, Putnam AL, Xu-Yu Z, et al. CD127 expression inversely correlates with FOXP3 and suppressive function of human CD4+ Treg cells. J Exp Med. 2006;203(7):1701-1711 3. Seddiki N, Santner-Nanan B, Tangye SG, et al. Persistence of naive CD45RA+ regulatory T-cells in adult life. Blood. 2006;107(7):2830-2838 4. Seddiki N, Santner-Nanan B, Martinson J, et al. Expression of interleukin (IL)-2 and IL-7 receptors discriminates between human regulatory and activated T-cells. J Exp Med. 2006;203(7):1693-1700 5. Valmori D, Merlo A, Souleimanian NE, Hesdorffer CS, Ayyoub M. A peripheral circulating compartment of natural naive CD4 Tregs. J Clin Invest. 2005;115(7):1953-1962 6. Torgerson TR, Ochs

HD. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked: forkhead box protein 3 mutations and lack of regulatory T-cells. J Allergy Clin Immunol. 2007;120(4):744-750 7. Wobma H, Janssen E. Expanding IPEX: Inborn errors of regulatory T cells. Rheum Dis Clin North Am. 2023;49(4):825-840. doi:10.1016/j.rdc.2023.06.0098. Beyer M, Kochanek M, Giese T, et al. In vivo peripheral expansion of naive CD4+CD25high FOXP3 + regulatory T cells in patients with multiple myeloma. Blood. 2006;107(10):3940-3949 9. Carmichael KF, Abayomi A. Analysis of diurnal variation of lymphocyte subsets in healthy subjects and its implication in HIV monitoring and treatment. 15th Intl Conference on AIDS, Bangkok, Thailand, 2004, Abstract B11052 10. Dimitrov S, Benedict C, Heutling D, Westermann J, Born J, Lange T. Cortisol and epinephrine control opposing circadian rhythms in T cell subsets. Blood. 2009;113(21):5134-5143 11. Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating human antigen presenting cells regulated by sleep. Sleep. 2007;30(4):401-411 12. Kronfol Z, Nair M, Zhang Q, Hill EE, Brown MB. Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. Psychosom Med. 1997;59(1):42-50 13. Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS. Sources of variability in repeated T-helper lymphocyte counts from human immunodeficiency virus type 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J Acquir Immune Defic Syndr (1988). 1990;3(2):144-151 14. Paglieroni TG, Holland PV. Circannual variation in lymphocyte subsets, revisited. Transfusion. 1994;34(6):512-516 15. Gambineri E, Ciullini Mannurita S, Hagin D, et al. Clinical, immunological, and molecular heterogeneity of 173 patients with the phenotype of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. Front Immunol. 2018;9:2411 16. Park JH, Lee KH, Jeon B, et al. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome: A systematic review. Autoimmun Rev. 2020;19(6):102526 17. Delmonte OM, Fleisher TA. Flow cytometry: Surface markers and beyond. J Allergy Clin Immunol. 2019;143(2):528-537 18. Knight V, Heimall JR, Chong H, et al. A toolkit and framework for optimal laboratory evaluation of individuals with suspected primary immunodeficiency. J Allergy Clin Immunol Pract. 2021;9(9):3293-3307.e6

CYTH1
622036

T-Helper Cell Type 1 Cytokine Panel, Plasma

Clinical Information:

Useful For: Assessment of plasma cytokine levels to understand the etiology of autoimmune and proinflammatory conditions when used in conjunction with clinical information and other laboratory testing

Interpretation: Elevated cytokine concentrations could be consistent with the presence of infection or other inflammatory process.

Reference Values:

TNF:
<18 years: Not established
> or =18 years: <10.0 pg/mL

IFN-gamma:
<18 years: Not established
> or =18 years: <60.0 pg/mL

IL-2:
<18 years: Not established
> or =18 years: <60.0 pg/mL

IL-2 receptor alpha soluble:

<18 years: Not established
> or =18 years: < or =959 pg/mL

IL-12p70:
<18 years: Not established
> or =18 years: <200 pg/mL

Clinical References: 1. Cerrillo E, Moret I, Iborra M, et al. A nomogram combining fecal calprotectin levels and plasma cytokine profiles for individual prediction of postoperative Crohn's disease recurrence. Inflamm Bowel Dis. 2019;25(10):1681-1691. doi:10.1093/ibd/izz053 2. Li S, Hao X, Gong Y, et al. Effect of shenling baizhu powder on the serum TH1 cytokines of elderly patients with ulcerative colitis complicated by bloody purulent stool. Am J Transl Res. 2021;13(8):9701-9707 3. Abdelrahman AH, Salama, II, Salama SI, et al. Role of some serum biomarkers in the early detection of diabetic cardiomyopathy. Future Sci OA. 2021;7(5):FSO682. doi:10.2144/fsoa-2020-0184 4. Weng L, Chen Y, Liang T, et al. Biomarkers of interstitial lung disease associated with primary Sjogren's syndrome. Eur J Med Res. 2022;27(1):199. doi:10.1186/s40001-022-00828-3 5. Popova V, Geneva-Popova M, Kraev K, Batalov A. Assessment of TNF-alpha expression in unstable atherosclerotic plaques, serum IL-6 and TNF-alpha levels in patients with acute coronary syndrome and rheumatoid arthritis. Rheumatol Int. 2022;42(9):1589-1596. doi:10.1007/s00296-022-05113-4 6. Li L, Chen B, Zhao H, Wang G. Bone changes and curative effect of infliximab in patients with ankylosing spondylitis. J Musculoskelet Neuronal Interact. 2020;20(3):437-443 7. Zhao S, Liu Y, Zhou C, et al. Prediction model of delayed graft function based on clinical characteristics combined with serum IL-2 levels. BMC Nephrol. 2022;23(1):284. doi:10.1186/s12882-022-02908-2 8. Ye Q, Shao WX, Xu XJ, Yang YZ. The clinical application value of cytokines in treating infectious diseases. PLoS One. 2014;9(6):e98745. doi:10.1371/journal.pone.0098745 9. Wang Q, Wang C, Yang M, Li X, Cui J, Wang C. Diagnostic efficacy of serum cytokines and chemokines in patients with candidemia and bacteremia. Cytokine. 2020;130:155081. doi:10.1016/j.cyto.2020.155081

TLBLF
65413

T-Lymphoblastic Leukemia/Lymphoma, FISH, Tissue

Clinical Information: T-lymphoblastic lymphoma (T-LBL) is the non-leukemic form of T-acute lymphoblastic leukemia (T-ALL). In the United States, the incidence of ALL is roughly 6000 new cases per year, or approximately 1 in 50,000. ALL accounts for approximately 70% of all childhood leukemia cases (ages 0 to 19 years), making it the most common childhood cancer. Approximately 85% of pediatric ALL cases are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). T-ALL is more common in adolescents than younger children and accounts for 25% of adult ALL. When occurring as a primary lymphoblastic lymphoma, approximately 90% are T-cell lineage versus only 10% B-cell lineage. T-LBL characteristically presents in adolescents and young adults as a mediastinal mass with or without concurrent bone marrow involvement. It is not uncommon that the only sample available with T-LBL involvement is a paraffin-embedded mediastinal or lymph node biopsy specimen. Specific genetic abnormalities can be identified in the majority of T-ALL/LBL cases, although many of the classic abnormalities are "cryptic" by conventional chromosome studies and must be identified by fluorescence in situ hybridization (FISH) studies and are associated with various prognoses. One predictive marker, amplification of the ABL1 gene region, has been identified in 5% of T-ALL/LBL, and these patients may be responsive to targeted tyrosine kinase inhibitors. A combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients to characterize the T-ALL/LBL clone for prognostic genetic subgroups.

Useful For: Detecting recurrent common chromosome abnormalities associated with T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) using client specified probes Identifying and tracking known chromosome abnormalities in patients with T-ALL and monitoring response to therapy

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. A positive result is not diagnostic for T-lymphoblastic lymphoma (T-LBL) but may provide relevant prognostic information. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References: WHO Classification of Tumours Editorial Board, eds. Haematolymphoid tumours. 5th ed. IARC Press; 2024. WHO Classification of Tumours, Volume 11

TPIT
607889

T-PIT Immunostain, Technical Component Only

Clinical Information: T-box transcription factor (T-PIT) is the transcription factor of functioning and silent corticotroph adenomas and is useful for the diagnosis of corticotroph adenoma and null cell adenoma. T-PIT may be included as part of a panel along with transcription factors SF-1 and Pit-1 to identify null cell adenomas (all negative).

Useful For: Diagnosis of corticotroph, silent corticotroph, and null cell adenomas of the pituitary

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Jastania RA, Alsaad KO, Al-Shraim M, Kovacs K, Asa SL. Double adenomas of the pituitary: transcription factors Pit-1, T-pit, and SF-1 identify cytogenesis and differentiation. Endocr Pathol. 2005;16(3):187-194 2. Casar-Borota O, Bollerslev J, Ponten F. Immunohistochemistry for transcription factor T-Pit as a tool in diagnostics of corticotroph pituitary tumours. Pituitary. 2018;21(4):443 3. Sjostedt E, Bollerslev J, Mulder J, Lindskog C, Ponten F, Casar-Borota O. A specific antibody to detect transcription factor T-Pit: a reliable marker of corticotroph cell differentiation and a tool to improve the classification of pituitary neuroendocrine tumours. Acta Neuropathol. 2017;134(4):675-677 4. Drummond J, Roncaroli F, Grossman AB, Korbonits M. Clinical and pathological aspects of silent pituitary adenomas. J Clin Endocrinol Metab. 2019;104(7):2473-2489 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

T3FR
621321

T3 (Triiodothyronine), Free, Serum

Clinical Information: Normally T3 (triiodothyronine) circulates tightly bound to thyroxine-binding globulin and albumin. Only 0.3% of the total T3 is unbound (free); the free fraction is the active form. In hyperthyroidism, both T4 (thyroxine, tetraiodothyronine) and T3 levels (total and free) are usually elevated, but in a small subset of hyperthyroid patients (T3 toxicosis), only T3 is elevated. Generally, free T3 (FT3) measurement is not necessary since total T3 will suffice. However, FT3 levels may be required to evaluate clinically euthyroid patients who have an altered distribution of binding proteins (eg, pregnancy, dysalbuminemia).

Useful For: A second- or third-level test of thyroid function Confirmation of hyperthyroidism, supplementing the T4 (tetraiodothyronine), sensitive thyrotropin, and total T3 assays Evaluating clinically

euthyroid patients who have an altered distribution of binding proteins

Interpretation: Elevated free T3 (triiodothyronine) values are associated with thyrotoxicosis or excess thyroid hormone replacement.

Reference Values:
Pediatric
0-1 month: 2.7-8.5 pg/mL
1-<12 months: 3.4-5.6 pg/mL
1-<14 years: 3.0-5.1 pg/mL
14-<19 years: 3.3-5.3 pg/mL

Adult (> or =19 years): 2.0-4.4 pg/mL

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html.

Clinical References: 1. Peyro Saint Paul L, Debruyne D, Bernard D, Mock DM, Defer GL. Pharmacokinetics and pharmacodynamics of MD1003 (high-dose biotin) in the treatment of progressive multiple sclerosis. Expert Opin Drug Metab Toxicol. 2016;12(3):327-344 2. Grimsey P, Frey N, Bendig G, et al. Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. J Pharmacokinet Pharmacodyn. 2017;2(4):247-256 3. Lee SY, Pearce EN. Hyperthyroidism: A Review. JAMA. 2023;330(15):1472-1483. doi:10.1001/jama.2023.19052 4. Freedman DB, Halsall D, Marhsall WJ and Ellervik C. Thyroid diseases. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1572-1616

RT3
9405

T3 (Triiodothyronine), Reverse, Serum

Clinical Information: Reverse triiodothyronine (rT3) differs from triiodothyronine (T3) in the positions of the iodine atoms attached to the aromatic rings. The majority of rT3 found in the circulation is formed by peripheral deiodination (removal of an iodine atom) of T4 (thyroxine). rT3 is believed to be metabolically inactive. The rT3 level tends to follow the T4 level: low in hypothyroidism and high in hyperthyroidism. Additionally, increased levels of rT3 have been observed in starvation, anorexia nervosa, severe trauma and hemorrhagic shock, hepatic dysfunction, postoperative states, severe infection, and in burn patients (ie, sick euthyroid syndrome). This appears to be the result of a switchover in deiodination functions with the conversion of T4 to rT3 being favored over the production of T3.

Useful For: Aiding in the diagnosis of the sick euthyroid syndrome

Interpretation: In hospitalized or sick patients with low triiodothyronine (T3) values, elevated reverse triiodothyronine (rT3) values are consistent with sick euthyroid syndrome. Also, the finding on an elevated rT3 level in a critically ill patient helps exclude a diagnosis of hypothyroidism. The rT3 is high in patients on medications such as propylthiouracil, ipodate, propranolol, amiodarone, dexamethasone, and the anesthetic agent halothane. Dilantin decreases rT3 due to the displacement from thyroxine-binding globulin, which causes increased rT3 clearance. To convert from ng/dL to nmol/L, multiply the ng/dL result by 0.01536.

Reference Values:
10-24 ng/dL

Clinical References: 1. Bowerbank SL, Carlin MG, Dean JR. A direct comparison of liquid chromatography-mass spectrometry with clinical routine testing immunoassay methods for the detection and quantification of thyroid hormones in blood serum. Anal Bioanal Chem. 2019;411(13):2839-2853 2. Moore WT, Eastman RC: Diagnostic Endocrinology. Mosby; 1990:182-183

T3
8613

T3 (Triiodothyronine), Total, Serum

Clinical Information: Thyroid hormones regulate numerous developmental, metabolic, and neural activities throughout the body. The thyroid gland synthesizes 2 hormones. The 2 main hormones secreted by the thyroid gland are thyroxine (T4), which contains 4 atoms of iodine, and triiodothyronine (T3). T3 production in the thyroid gland constitutes approximately 20% of the total T3; the rest is generated by the conversion (deiodination) of T4 to T3. T3 is also produced by conversion (deiodination) of T4 in peripheral tissues. Circulating levels of T4 are much greater than T3 levels, but T3 is biologically the most metabolically active hormone (3-4 times more potent than T4), although its effect is briefer due to its shorter half-life compared to T4. Thyroid hormones circulate primarily bound to carrier proteins (eg, thyroid-binding globulin [TBG], prealbumin, and albumin), whereas only a small fraction circulates unbound (free). Only the free forms are metabolically active. While both T3 and T4 are bound to TBG, T3 is bound less firmly than T4. Total T3 consists of both the bound and unbound fractions. In hyperthyroidism, both T4 and T3 levels are usually elevated, but in a small subset of hyperthyroid patients, only T3 is elevated (T3 toxicosis). In hypothyroidism, T4 and T3 levels are decreased. T3 levels are frequently low in sick or hospitalized euthyroid patients.

Useful For: Second-order testing for hyperthyroidism in patients with low thyroid-stimulating hormone values and normal thyroxine levels Diagnosing triiodothyronine (T3) toxicosis This test is not useful for general screening of the population without clinical suspicion of hyperthyroidism.

Interpretation: Triiodothyronine (T3) values above 200 ng/dL in adults or over age-related cutoffs in children are consistent with hyperthyroidism or increased thyroid hormone-binding proteins. Abnormal levels (high or low) of thyroid hormone-binding proteins (primarily albumin and thyroid-binding globulin) may cause abnormal T3 concentrations in euthyroid patients.

Reference Values:

Pediatric
0-5 days: 73-288 ng/dL
6 days-2 months: 80-275 ng/dL
3-11 months: 86-265 ng/dL
1-5 years: 92-248 ng/dL
6-10 years: 93-231 ng/dL
11-19 years: 91-218 ng/dL

Adult (> or =20 years): 80-200 ng/dL

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Peyro Saint Paul L, Debruyne D, Bernard D, Mock DM, Defer GL. Pharmacokinetics and pharmacodynamics of MD1003 (high-dose biotin) in the treatment of progressive multiple sclerosis. Expert Opin Drug Metab Toxicol. 2016;12(3):327-344 2. Grimsey P, Frey N, Bendig G, et al. Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. J Pharmacokinet Pharmacodyn. 2017;2(4):247-256. doi:10.4155/ipk-2017-0013 3. Hay ID, Klee GG. Linking medical needs and performance goals: clinical and laboratory perspectives on thyroid disease. Clin Chem. 1993;39(7):1519-1524 4. Klee GG. Clinical

usage recommendations and analytic performance goals for total and free triiodothyronine measurements. Clin Chem. 1996;42(1):155-159 5. Ellervik C, Halsall D, Nygaard B. Thyroid disorders. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 57

FRT4D
8859

T4 (Thyroxine), Free, Dialysis, Serum

Clinical Information: Thyroxine (T4) and triiodothyronine (T3) are the 2 biologically active thyroid hormones. T4 makes up more than 80% of circulating thyroid hormones. Following secretion by the thyroid gland, approximately 70% of circulating T4 and T3 are bound to thyroid-binding globulin (TBG), while 10% to 20% each are bound to transthyretin (TTR) and albumin, respectively. Less than 0.1% circulates as free T4 (FT4) or free T3 (FT3). FT4 and FT3 enter and leave cells freely by diffusion. Only the free hormones are biologically active, but bound and free fractions are in equilibrium. Equilibrium with TTR and albumin is rapid. By contrast, TBG binds thyroid hormones very tightly and equilibrium dissociation is slow. Biologically, TBG-bound thyroid hormone serves as a hormone reservoir, and T4 serves as a prohormone for T3. Within cells, T4 is either converted to T3, which is about 5 times as potent as T4, or reverse T3, which is biologically inactive. Ultimately, T3, and to a much lesser degree T4, bind to the nuclear thyroid hormone receptor, altering gene expression patterns in a tissue-specific fashion. Under normal physiologic conditions, FT4 and FT3 exert direct and indirect negative feedback on pituitary thyrotropin (TSH) levels, the major hormone regulating thyroid gland activity. This results in tight regulation of thyroid hormone production and constant levels of FT4 and FT3 independent of the binding protein concentration. Measurement of FT4 and FT3, in conjunction with TSH measurement, therefore, represents the best method to determine thyroid function status. It also allows determination of whether hyperthyroidism (increased FT4) or hypothyroidism (low FT4) are primary (most cases; TSH altered in the opposite direction as FT4) or secondary/tertiary (hypothalamic/pituitary origin; TSH altered in the same direction as FT4). By contrast, total T4 and T3 levels can vary widely as a response to changes in binding protein levels, without any change in free thyroid hormone levels and, hence, actual thyroid function status. FT4 is usually measured by automated analog immunoassays. In most instances, this will result in accurate results. However, abnormal types or quantities of binding proteins found in some patients and most often related to other illnesses or drug treatments, may interfere in the accurate measurement of FT4 by analog immunoassays. These problems can be overcome by measuring FT4 by equilibrium dialysis, free from interfering proteins.

Useful For: Determining thyroid status of sick, hospitalized patients Determining thyroid status of patients in whom abnormal binding proteins have been identified Possibly useful in pediatric patients

Interpretation: All free hormone assays should be combined with thyrotropin measurements. Free thyroxine (FT4) levels below 0.8 ng/dL indicate possible hypothyroidism. FT4 levels above 2.0 ng/dL indicates possible hyperthyroidism. Neonates can have significantly higher FT4 levels. The hypothalamic-pituitary-thyroid axis can take several days or, sometimes, weeks to mature.

Reference Values:
0.8-2.0 ng/dL
Reference values apply to all ages.

Clinical References: 1. De Brabandere VI, Hou P, Stockl D, Thienpont LM, De Leenheer AP. Isotope dilution-liquid chromatography/electrospray ionization-tandem mass spectrometry for the determination of serum thyroxine as a potential reference method. Rapid Commun Mass Spectrom. 1998;12(16):1099-1103 2. Jain R, Uy HL. Increase in serum free thyroxine levels related to intravenous heparin treatment. Ann Intern Med. 1996;124(1 Pt 1):74-75 3. Stockigt JR. Free thyroid hormone measurement. A critical appraisal. Endocrinol Metab Clin North Am. 2001;30(2):265-289 4. Sakai H,

Nagao H, Sakurai M, et al. Correlation between serum levels of 3,3',5'-triiodothyronine and thyroid hormones measured by liquid chromatography-tandem mass spectrometry and immunoassay [published correction appears in PLoS One. 2016;11(7):e0159169]. PLoS One. 2015;10(10):e0138864.doi:10.1371/journal.pone.0138864 5. Kahric-Janicic N, Soldin SJ, Soldin OP, West T, Gu J, Jonklaas J. Tandem mass spectrometry improves the accuracy of free thyroxine measurements during pregnancy. Thyroid. 2007;17(4):303-311.doi:10.1089/thy.2006.0303

FRT4
8725

T4 (Thyroxine), Free, Serum

Clinical Information: Free thyroxine (FT4) comprises a small fraction of total thyroxine. FT4 is available to the tissues and is, therefore, the metabolically active fraction. Elevations in FT4 cause hyperthyroidism, while decreases cause hypothyroidism.

Useful For: Evaluating suspected thyroid function disorders using free thyroxine measured together with thyroid-stimulating hormone

Interpretation: Elevated values suggest hyperthyroidism or exogenous thyroxine. Decreased values suggest hypothyroidism. Free thyroxine (FT4) works well to correct total T4 values for thyroxine-binding globulin alterations but may give misleading values when abnormal binding proteins are present or the patient has other major illnesses (euthyroid sick syndrome).

Reference Values:

Pediatric
0-5 days: 0.9-2.5 ng/dL
6 days-2 months: 0.9-2.2 ng/dL
3-11 months: 0.9-2.0 ng/dL
1-5 years: 1.0-1.8 ng/dL
6-10 years: 1.0-1.7 ng/dL
11-19 years: 1.0-1.6 ng/dL

Adult (> or =20 years): 0.9-1.7 ng/dL

For SI unit Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Melmed S, Polonsky KS, Larsen PR, Kronenberg H. Williams Textbook of Endocrinology. 12th ed. Saunders Company; 2011:348-414 2. Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023

T4FT4
36108

T4 (Thyroxine), Total and Free, Serum

Clinical Information: Total Thyroxine: Thyroxine (T4) is synthesized in the thyroid gland. T4 is metabolized to triiodothyronine (T3) peripherally by deiodination. T4 is considered a reservoir or prohormone for T3, the biologically most active thyroid hormone. About 0.05% of circulating T4 is in the free, ie, unbound, portion. The remainder is bound to thyroxine-binding globulin), prealbumin, and albumin. The hypothalamus secretes thyrotropin-releasing hormone, which stimulates the pituitary to release thyrotropin, formerly thyroid-stimulating hormone (TSH). TSH stimulates the thyroid to secrete T4. T4 is partially converted peripherally to T3. High amounts of T4 and T3 (mostly from peripheral conversion of T4) cause hyperthyroidism. T4 and T3 cause positive feedback to the pituitary and hypothalamus with resultant suppression or stimulation of the thyroid gland as follows: decrease of TSH if T3 or T4 is high (hyperthyroidism) and increase of TSH if T3 or T4 is low (hypothyroidism). Measurement of total T4 gives a reliable reflection of clinical thyroid status in the absence of protein

binding abnormalities. However, changes in binding proteins can occur that affect the level of total T4 but leave the level of unbound hormone unchanged. Free Thyroxine: Free thyroxine comprises a small fraction of total thyroxine. The free T4 (FT4) is available to the tissues and is, therefore, the metabolically active fraction. Elevations in FT4 cause hyperthyroidism, while decreases cause hypothyroidism.

Useful For: Assessing thyroid function when thyroid function disorders are suspected

Reference Values:

Clinical References: 1. Peyro Saint Paul L, Debruyne D, Bernard D, Mock DM, Defer GL: Pharmacokinetics and pharmacodynamics of MD1003 (high-dose biotin) in the treatment of progressive multiple sclerosis. Expert Opin Drug Metab Toxicol. 2016;12(3):327-344 2. Grimsey P, Frey N, Bendig G, et al: Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. J Pharmacokinet Pharmacodyn. 2017 Sept;2(4):247-256. doi: 10.4155/ipk-2017-0013 3. Melmed S, Polonsky KS, Larsen PR, et al: Williams Textbook of Endocrinology. 12th ed. Elsevier Saunders; 2011:348-414

T4
8724

T4 (Thyroxine), Total Only, Serum

Clinical Information: Thyroxine (T4) is synthesized in the thyroid gland. T4 is metabolized to triiodothyronine (T3) peripherally by deiodination. T4 is considered a reservoir or prohormone for T3, the biologically most active thyroid hormone. About 0.05% of circulating T4 is in the free, ie, unbound, portion. The remainder is bound to thyroxine-binding globulin, prealbumin, and albumin. The hypothalamus secretes thyrotropin-releasing hormone, which stimulates the pituitary to release thyrotropin (previously thyroid-stimulating hormone: TSH). TSH stimulates the thyroid to secrete T4. T4 is partially converted peripherally to T3. High amounts of T4 and T3 (mostly from peripheral conversion of T4) cause hyperthyroidism. T4 and T3 cause positive feedback to the pituitary and hypothalamus with resultant suppression or stimulation of the thyroid gland as follows: decrease of TSH if T3 or T4 is high (hyperthyroidism) and increase of TSH if T3 or T4 is low (hypothyroidism). Measurement of total T4 gives a reliable reflection of clinical thyroid status in the absence of protein-binding abnormalities and non-thyroidal illness. However, changes in binding proteins can occur that affect the level of total T4 but leave the level of unbound hormone unchanged.

Useful For: Monitoring treatment with synthetic hormones (synthetic T3 [triiodothyronine] will cause a low total T4 [thyroxine]) Monitoring treatment of hyperthyroidism with thiouracil and other anti-thyroid drugs Index of thyroid function when the thyroxine-binding globulin is normal and non-thyroidal illness is not present

Interpretation: Values of more than 11.7 mcg/dL in adults or more than the age-related cutoffs in children are seen in hyperthyroidism and in patients with acute thyroiditis. Values below 4.5 mcg/dL in adults or below the age-related cutoffs in children are seen in hypothyroidism, myxedema, cretinism, chronic thyroiditis, and occasionally, subacute thyroiditis. Increased total T4 (thyroxine) is seen in pregnancy and patients who are on estrogen medication. These patients have increased total T4 levels due to increased thyroxine-binding globulin (TBG) levels. Decreased total T4 is seen in patients on treatment with anabolic steroids or nephrosis (decreased TBG levels). A thyrotropin-releasing hormone stimulation test may be required for certain cases of hyperthyroidism. Clinical findings are necessary to determine if thyrotropin, TBG, or free T4 testing is needed.

Reference Values:

Clinical References:

FFT4F
91548

T4, Free, Direct Dialysis

Reference Values:

Age	Reference Range	Unit of Measure
(Adult)		
Adult (Males and Females)	0.9-2.2	ng/dL
(Pediatric)		
Prematures, 25-30 weeks Birth-7 days	0.5-3.3	ng/dL
Prematures, 31-36 weeks Birth-7 days	1.3-4.7	ng/dL
Cord Blood, >37 weeks	1.2-2.2	ng/dL
Birth-4 days	2.2-5.3	ng/dL
2 months to 2 years	1.2-2.5	ng/dL
3 to 17 years	1.0-2.4	ng/dL
(Pregnancy)		
First Trimester	0.9-2.0	ng/dL
Second Trimester	0.8-1.5	ng/dL
Third Trimester	0.8-1.7	ng/dL

TAKRO
35145

Tacrolimus, Blood

Clinical Information: Tacrolimus is a macrolide antibiotic derived from the fungus Streptomyces tsukubaensis. Like cyclosporine, tacrolimus inhibits calcineurin to suppress T cells. Tacrolimus is metabolized by cytochrome P450 (CYP) 3A4; thus, its concentrations are affected by drugs that inhibit (calcium channel blockers, antifungal agents, some antibiotics, grapefruit juice) or induce (anticonvulsants, rifampin) this enzyme. Tacrolimus has a narrow therapeutic range, and adverse effects are common, particularly at high doses and concentrations, making therapeutic drug monitoring essential. Since 90% of tacrolimus is in the cellular components of blood, especially erythrocytes, whole blood is the preferred specimen for analysis of trough concentrations. Target steady-state concentrations vary depending on clinical protocol, the presence or risk of rejection, time from transplant, type of allograft, concomitant immunosuppression, and side effects (mainly nephrotoxicity). Optimal trough blood concentrations are generally between 5.0 and 15.0 ng/mL. Higher levels are often sought immediately after transplant, but as organ function stabilizes at about 4 weeks from transplant, doses are generally reduced in stable patients for most solid organ transplants. Trough concentrations should be maintained below 20 ng/mL.

Useful For: Monitoring whole blood tacrolimus concentration during therapy, particularly in individuals coadministered cytochrome P450 (CYP) 3A4 substrates, inhibitors, or inducers Adjusting dose to optimize immunosuppression while minimizing toxicity Evaluating patient compliance

Interpretation: Most individuals display optimal response to tacrolimus with trough whole blood

levels of 5.0 to 15.0 ng/mL. Preferred therapeutic ranges may vary by transplant type, protocol, and comedications. Therapeutic ranges are based on specimen collected at trough (ie, immediately before a scheduled dose). Higher results will be obtained when the blood is drawn at other times. The assay is specific for tacrolimus; it does not cross-react with cyclosporine, cyclosporine metabolites, sirolimus, sirolimus metabolites, or tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry are approximately 30% less than by immunoassay.

Reference Values:
5.0-15.0 ng/mL (Trough)

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.

Clinical References: 1. Kahan BD, Keown P, Levy GA, Johnston A. Therapeutic drug monitoring of immunosuppressant drugs in clinical practice. Clin Ther. 2002;24(3):330-350 2. Scott LJ, McKeage K, Keam SJ, Plosker GL. Tacrolimus: a further update of its use in the management of organ transplantation. Drugs. 2003;63(12):1247-1297 3. Milone MC, Shaw LM: Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

TACPK
88157

Tacrolimus, Peak, Blood

Clinical Information: Tacrolimus (Prograf) is a macrolide antibiotic derived from the fungus Streptomyces tsukubaensis. Like cyclosporine, tacrolimus inhibits calcineurin to suppress T cells. Tacrolimus is metabolized by cytochrome P450 (CYP) 3A4; thus, its concentration is affected by drugs that inhibit (calcium channel blockers, antifungal agents, some antibiotics, grapefruit juice) or induce (anticonvulsants, rifampin) this enzyme. Tacrolimus has a narrow therapeutic range, and adverse effects are common, particularly at high doses and concentrations, making therapeutic drug monitoring essential. Since 90% of tacrolimus is in the cellular components of blood, especially erythrocytes, whole blood is the preferred specimen for analysis of trough concentrations. Target steady-state concentrations vary depending on clinical protocol, the presence or risk of rejection, time from transplant, type of allograft, concomitant immunosuppression, and side effects (mainly nephrotoxicity). Optimal trough blood concentrations are generally between 5.0 and 15.0 ng/mL. Higher levels are often sought immediately after transplant, but as organ function stabilizes at about 4 weeks from transplant, doses are generally reduced in stable patients for most solid organ transplants. Trough concentrations should be maintained below 20 ng/mL. Optimal postdose sampling strategies and blood concentrations have not been well established for tacrolimus. A study of 54 liver transplant patients suggested that most individuals have tacrolimus blood concentrations ranging between 5.0 and 30.0 ng/mL in specimens collected 1 to 4 hours after dosing, although some patients showed slightly higher blood concentrations 1-hour postdose.

Useful For: Assessment of postdosing (peak) blood tacrolimus concentrations

Interpretation: This test measures postdose levels of tacrolimus. Established reference ranges reflect trough measurement and are not applicable to specimens collected after dosing. No reference ranges or standard sampling protocols have been established for postdosing tacrolimus levels, but a limited study of liver transplant recipients suggests most patients will show postdose tacrolimus levels ranging from 5.0 to 30.0 ng/mL when collected 1 to 4 hours after dosing. The narrow therapeutic window and high individual pharmacokinetic variability of tacrolimus make regulation of dose by blood concentrations essential. Since 90% of the drug is in the cellular components of blood, especially erythrocytes, whole

blood, rather than plasma, concentrations are measured and correlate better with efficacy and toxicity. This assay is specific for tacrolimus; it does not cross-react with cyclosporine, cyclosporine metabolites, sirolimus, sirolimus metabolites, or tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry are approximately 30% less than by immunoassay.

Reference Values:
5.0-30.0 ng/mL

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time posttransplant. Results should be interpreted in conjunction with this clinical information and any physical signs or symptoms of rejection or toxicity.

Clinical References: 1. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453 2. Kahan BD, Keown P, Levy GA, Johnston A. Therapeutic drug monitoring of immunosuppressant drugs in clinical practice. Clin Ther. 2002;24(3):330-350 3. Scott LJ, McKeage K, Keam SJ, Plosker GL. Tacrolimus: a further update of its use in the management of organ transplantation. Drugs. 2003;63(12):1247-1297

TAPEN
62594

Tapentadol and Metabolite, Random, Urine

Clinical Information: Tapentadol, a centrally acting opioid analgesic, is used in the treatment of moderate to severe acute and chronic pain and for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults (extended-release formulation only). Tapentadol acts as an opiate agonist through its binding to mu-opioid receptors and through the inhibition of norepinephrine reuptake. About 97% of the parent drug is metabolized. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. Tapentadol and its metabolites (N-desmethyltapentadol and hydroxyl-tapentadol) are excreted almost exclusively via the kidneys, and approximately 70% of the drug is excreted in urine in the conjugated form. The metabolites of tapentadol have no analgesic activity. The half-life of tapentadol is approximately 4 hours. Opioid analgesics have high abuse potential and the regular use of tapentadol may result in physical dependence and tolerance. Tapentadol is a schedule II-controlled substance with abuse liability similar to other opioid agonists.

Useful For: Monitoring of compliance utilizing tapentadol Detection and confirmation of the illicit use of tapentadol This test is not intended for use in employment-related testing.

Interpretation: The presence of tapentadol or N-desmethyltapentadol levels of 25 ng/mL or higher is a strong indicator that the patient has used tapentadol.

Reference Values:
Negative (Positive result is reported with a quantitative result.)

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Tapentadol: 25 ng/mL
N-desmethyltapentadol: 25ng/mL; reported qualitatively (Present or Negative)

Clinical References: 1. Tapentadol. In: Merative Micromedex. Merative; Accessed February 09, 2024. Available at: www.micromedexsolutions.com/ 2. Jutkiewicz EM, Traynor JR. Opioid analgesics. In: Brunton LL, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 14th ed. McGraw-Hill Education; 2023 3. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:454-454

FIOCA
57944

Tapioca IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >=50 Very Strong Positive

Reference Values:
<0.35 kU/L

TABSU
604267

Targeted Benzodiazepine Screen, Random, Urine

Clinical Information: Benzodiazepines represent a large family of medications used to treat a wide range of disorders from anxiety to seizures, and they are also used in pain management. With a high risk for abuse/diversion, professional practice guidelines recommend compliance monitoring for these medications using urine drug tests. However, traditional benzodiazepine immunoassays suffer from a lack of cross-reactivity with all the benzodiazepines, so many compliant patients taking either clonazepam (Klonopin) or lorazepam (Ativan) may screen negative by immunoassay but are positive when confirmatory testing is done. The new targeted benzodiazepine screening test provides a more sensitive and specific test to check for compliance to all the commonly prescribed benzodiazepines and looks for both the parent drug and its metabolites in the urine.

Useful For: Qualitatively (present vs not detected) identifying 27 benzodiazepine compounds (parent drug and metabolites) in urine to help determine compliance or identify illicit benzodiazepine drug use This test is not intended for employment-related testing.

Interpretation: If a benzodiazepine or its corresponding metabolites is identified (present), it indicates that the patient has used the respective benzodiazepine in the recent past. The absence of expected benzodiazepines or their metabolites may indicate noncompliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, diluted or adulterated urine, or limitations of testing. The concentration of the drug must be greater than or equal to the cutoff to be reported as present. If a specific drug concentration is required, the laboratory must be contacted within 2 weeks of specimen collection/testing to request quantification by a second analytical technique at an additional charge.

Reference Values:
Only orderable as part of profile. For more information see:
-CSMPU / Controlled Substance Monitoring Panel, Random, Urine
-ADMPU / Addiction Medicine Profile with Reflex, 22 Drug Classes, High Resolution Mass Spectrometry and Immunoassay Screen, Random, Urine
-CSMEU / Controlled Substance Monitoring Enhanced Profile with Reflex, 21 Drug Classes, High Resolution Mass Spectrometry and Immunoassay Screen, Random, Urine
-CSMTU / Controlled Substance Monitoring Targeted Profile, 17 Drug Classes, Mass Spectrometry, Random, Urine
-TBSU / Targeted Benzodiazepine Screen, Random, Urine

Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Alprazolam: 10 ng/mL
Alpha-hydroxyalprazolam: 10 ng/mL
Alpha-hydroxyalprazolam glucuronide: 50 ng/mL
Chlordiazepoxide: 10 ng/mL

Clobazam: 10 ng/mL
N-desmethylclobazam: 200 ng/mL
Clonazepam: 10 ng/mL
7-Aminoclonazepam: 10 ng/mL
Diazepam: 10 ng/mL
Nordiazepam: 10 ng/mL
Flunitrazepam: 10 ng/mL
7-Aminoflunitrazepam: 10 ng/mL
Flurazepam: 10 ng/mL
2-Hydroxy ethyl flurazepam: 10 ng/mL
Lorazepam: 10 ng/mL
Lorazepam glucuronide: 50 ng/mL
Midazolam: 10 ng/mL
Alpha-hydroxy midazolam: 10 ng/mL
Oxazepam: 10 ng/mL
Oxazepam glucuronide: 50 ng/mL
Prazepam: 10 ng/mL
Temazepam: 10 ng/mL
Temazepam glucuronide: 50 ng/mL
Triazolam: 10 ng/mL
Alpha-hydroxy triazolam: 10 ng/mL
Zolpidem: 10 ng/mL
Zolpidem phenyl-4-carboxylic acid: 10 ng/mL

Clinical References: 1. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline-Using clinical laboratory tests to monitor drug therapy in pain management patients. J Appl Lab Med. 2018;2(4):489-526 2. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

TBSU
604262

Targeted Benzodiazepine Screen, Random, Urine

Clinical Information: Benzodiazepines represent a large family of medications used to treat a wide range of disorders from anxiety to seizures, and they are also used in pain management. With a high risk for abuse and diversion, professional practice guidelines recommend compliance monitoring for these medications using urine drug tests. However, traditional benzodiazepine immunoassays suffer from a lack of cross-reactivity with all the benzodiazepines, so many compliant patients taking either clonazepam (Klonopin) or lorazepam (Ativan) may screen negative by immunoassay but are positive when confirmatory testing is done. The new targeted benzodiazepine screening test provides a more sensitive and specific test to check for compliance to all the commonly prescribed benzodiazepines and looks for both the parent drug and its metabolites in the urine.

Useful For: Determining compliance or identifying illicit benzodiazepine drug use This test is not intended for employment-related testing.

Interpretation: If a benzodiazepine or its corresponding metabolites is identified (present), it indicates that the patient has used the respective benzodiazepine in the recent past. The absence of expected benzodiazepines or their metabolites may indicate noncompliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, diluted or adulterated urine, or limitations of testing. The concentration of the drug must be greater than or equal to the cutoff to be reported as present. If a specific drug concentration is required, the laboratory must be contacted within 2 weeks of specimen collection/testing to request quantification by a second analytical technique at an additional

charge.

Reference Values:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Alprazolam: 10 ng/mL
Alpha-hydroxyalprazolam: 10 ng/mL
Alpha-hydroxyalprazolam glucuronide: 50 ng/mL
Chlordiazepoxide: 10 ng/mL
Clobazam: 10 ng/mL
N-Desmethylclobazam: 200 ng/mL
Clonazepam: 10 ng/mL
7-Aminoclonazepam: 10 ng/mL
Diazepam: 10 ng/mL
Nordiazepam: 10 ng/mL
Flunitrazepam: 10 ng/mL
7-Aminoflunitrazepam: 10 ng/mL
Flurazepam: 10 ng/mL
2-Hydroxy ethyl flurazepam: 10 ng/mL
Lorazepam: 10 ng/mL
Lorazepam glucuronide: 50 ng/mL
Midazolam: 10 ng/mL
Alpha-hydroxy midazolam: 10 ng/mL
Oxazepam: 10 ng/mL
Oxazepam glucuronide: 50 ng/mL
Prazepam: 10 ng/mL
Temazepam: 10 ng/mL
Temazepam glucuronide: 50 ng/mL
Triazolam: 10 ng/mL
Alpha-hydroxy triazolam: 10 ng/mL
Zolpidem: 10 ng/mL
Zolpidem phenyl-4-carboxylic acid: 10 ng/mL

Clinical References: 1. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline-Using clinical laboratory tests to monitor drug therapy in pain management patients. J Appl Lab Med. 2018;2(4):489-526 2. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

TOPSU
65059

Targeted Opioid Screen, Random, Urine

Clinical Information: Opioids are a large class of medications commonly used to relieve acute and chronic pain or help manage opioid abuse and dependence. Medications that fall into this class include buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, and others. Opioids work by binding to the opioid receptors that are found in the brain, spinal cord, gastrointestinal tract, and other organs. Common side effects of opioids include drowsiness, confusion, nausea, constipation, and, in severe cases, respiratory depression. These are dose dependent and vary with tolerance. These medications can also produce physical and psychological dependence and have a high risk for abuse and diversion, which is one of the main reasons many professional practice guidelines recommend compliance testing in patients prescribed these medications. Opioids are readily absorbed from the gastrointestinal tract, nasal mucosa,

lungs, and after subcutaneous or intermuscular injection. Opioids are primarily excreted from the kidney in both free and conjugated forms. This assay does not hydrolyze the urine sample and looks for both parent drugs and metabolites (including glucuronide forms). The detection window for most opioids in urine is approximately 1 to 3 days with longer detection times for some compounds (ie, methadone).

Useful For: Qualitatively (present vs not detected) identifying 33 opioid compounds (parent drug and metabolites) in urine to help determine compliance or identify illicit opioid drug use This test is not intended for use in employment-related testing.

Interpretation: If an opioid or its corresponding metabolites is identified (present), it indicates that the patient has used the respective opioid in the recent past. The absence of expected opioids or their metabolites may indicate noncompliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, diluted or adulterated urine, or limitations of testing. The concentration of the drug must be greater than or equal to the cutoff to be reported as present. If a specific drug concentration is required, the laboratory must be contacted within 2 weeks of specimen collection/testing to request quantification by a second analytical technique at an additional charge.

Reference Values:

Only orderable as part of profile. For more information see:
-CSMPU / Controlled Substance Monitoring Panel, Random, Urine
-ADMPU / Addiction Medicine Profile with Reflex, 22 Drug Classes, High Resolution Mass Spectrometry and Immunoassay Screen, Random, Urine
-CSMEU / Controlled Substance Monitoring Enhanced Profile with Reflex, 21 Drug Classes, High Resolution Mass Spectrometry and Immunoassay Screen, Random, Urine
-CSMTU / Controlled Substance Monitoring Targeted Profile, 17 Drug Classes, Mass Spectrometry, Random, Urine
-TOSU / Targeted Opioid Screen, Random, Urine

Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Codeine: 25 ng/mL
Codeine-6-beta-glucuronide: 100 ng/mL
Morphine: 25 ng/mL
Morphine-6-beta-glucuronide: 100 ng/mL
6-Monoacetylmorphine: 25 ng/mL
Hydrocodone: 25 ng/mL
Norhydrocodone: 25 ng/mL
Dihydrocodeine: 25 ng/mL
Hydromorphone: 25 ng/mL
Hydromorphone-3-beta-glucuronide: 100 ng/mL
Oxycodone: 25 ng/mL
Noroxycodone: 25 ng/mL
Oxymorphone: 25 ng/mL
Oxymorphone-3-beta-glucuronide: 100 ng/mL
Noroxymorphone: 25 ng/mL
Fentanyl: 2 ng/mL
Norfentanyl: 2 ng/mL
Meperidine: 25 ng/mL
Normeperidine: 25 ng/mL
Naloxone: 25 ng/mL
Naloxone-3-beta-glucuronide: 100 ng/mL
Methadone: 25 ng/mL
2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine: 25 ng/mL

Propoxyphene: 25 ng/mL
Norpropoxyphene: 25 ng/mL
Tramadol: 25 ng/mL
O-desmethyltramadol: 25 ng/mL
Tapentadol: 25 ng/mL
N-desmethyltapentadol: 50 ng/mL
Tapentadol-beta-glucuronide: 100 ng/mL
Buprenorphine: 5 ng/mL
Norbuprenorphine: 5 ng/mL
Norbuprenorphine glucuronide: 20 ng/mL

Clinical References: 1. Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill; 2006:chap 21 2. Rovine T, Ferrero CL, American Pain Society. Chronic Pain in America: Roadblocks to Relief. Roper Starch Worldwide, Inc; 1999. Updated October 2, 2001. Accessed December 13, 2024. Available at http://accurateclinic.com/wp-content/uploads/2016/04/Chronic-Pain-In-America-Roadblocks-To-Relief-1999.pdf 3. Magnani B, Kwong T. Urine drug testing for pain management. Clin Lab Med. 2012;32(32):379-390. doi:10.1016/j.cll.2012.07.001 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 5. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive Summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline-using clinical laboratory tests to monitor drug therapy in pain management patients. J Appl Lab Med. 2018;2(4):489-526

TOSU
604261

Targeted Opioid Screen, Random, Urine

Clinical Information: Opioids are a large class of medications commonly used to relieve acute and chronic pain or help manage opioid abuse and dependence. Medications that fall into this class include buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, and others. Opioids work by binding to the opioid receptors that are found in the brain, spinal cord, gastrointestinal tract, and other organs. Common side effects of opioids include drowsiness, confusion, nausea, constipation, and, in severe cases, respiratory depression. These are dose dependent and vary with tolerance. These medications can also produce physical and psychological dependence and have a high risk for abuse and diversion, which is one of the main reasons many professional practice guidelines recommend compliance testing in patients prescribed these medications. Opioids are readily absorbed from the gastrointestinal tract, nasal mucosa, lungs, and after subcutaneous or intermuscular injection. Opioids are primarily excreted from the kidney in both free and conjugated forms. This assay does not hydrolyze the urine sample and looks for both parent drugs and metabolites (including glucuronide forms). The detection window for most opioids in urine is approximately 1 to 3 days with longer detection times for some compounds (ie, methadone).

Useful For: Determining compliance or identifying illicit opioid drug use using urine specimens This test is not intended for employment-related testing.

Interpretation: If an opioid or its corresponding metabolites is identified (present), it indicates that the patient has used the respective opioid in the recent past. The absence of expected opioids or their metabolites may indicate noncompliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, diluted or adulterated urine, or limitations of testing. The concentration of the drug must be greater than or equal to the cutoff to be reported as present. If a specific drug concentration is required, the laboratory must be contacted within 2 weeks of specimen collection/testing to request quantification by a second analytical technique at an additional charge.

Reference Values:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Codeine: 25 ng/mL
Codeine-6-beta-glucuronide: 100 ng/mL
Morphine: 25 ng/mL
Morphine-6-beta-glucuronide: 100 ng/mL
6-monoacetylmorphine: 25 ng/mL
Hydrocodone: 25 ng/mL
Norhydrocodone: 25 ng/mL
Dihydrocodeine: 25 ng/mL
Hydromorphone: 25 ng/mL
Hydromorphone-3-beta-glucuronide: 100 ng/mL
Oxycodone: 25 ng/mL
Noroxycodone: 25 ng/mL
Oxymorphone: 25 ng/mL
Oxymorphone-3-beta-glucuronide: 100 ng/mL
Noroxymorphone: 25 ng/mL
Fentanyl: 2 ng/mL
Norfentanyl: 2 ng/mL
Meperidine: 25 ng/mL
Normeperidine: 25 ng/mL
Naloxone: 25 ng/mL
Naloxone-3-beta-glucuronide: 100 ng/mL
Methadone: 25 ng/mL
2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP): 25 ng/mL
Propoxyphene: 25 ng/mL
Norpropoxyphene: 25 ng/mL
Tramadol: 25 ng/mL
O-desmethyltramadol: 25 ng/mL
Tapentadol: 25 ng/mL
N-desmethyltapentadol: 50 ng/mL
Tapentadol-beta-glucuronide: 100 ng/mL
Buprenorphine: 5 ng/mL
Norbuprenorphine: 5 ng/mL
Norbuprenorphine glucuronide: 20 ng/mL

Clinical References: 1. Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill; 2006:chap 21 2. Rovine T, Ferrero CL, American Pain Society. Chronic Pain in America: Roadblocks to Relief. Roper Starch Worldwide, Inc; 1999. Updated October 2, 2001. Accessed December 13, 2024. Available at http://accurateclinic.com/wp-content/uploads/2016/04/Chronic-Pain-In-America-Roadblocks-To-Relief-1999.pdf 3. Magnani B, Kwong T. Urine drug testing for pain management. Clin Lab Med. 2012;32(32):379-390 4. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. St Louis, MO: Elsevier; 2023:chap 43 5. Jannetto PJ, Bratanow NC, Clark WA, et al. Executive Summary: American Association of Clinical Chemistry Laboratory Medicine Practice Guideline-using clinical laboratory tests to monitor drug therapy in pain management patients. J Appl Lab Med. 2018;2(4):489-526

TSTIM 610273 Targeted Stimulant Screen, Random, Urine

Clinical Information: Stimulants are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Amphetamine and methamphetamine are also prescription drugs used in the treatment of narcolepsy and attention-deficit disorder/attention-deficit hyperactivity disorder (ADHD). Methylphenidate is another stimulant used to treat ADHD. Phentermine is indicated for the management of obesity. All other amphetamines (eg, methylenedioxymethamphetamine: MDMA) are Drug Enforcement Administration scheduled Class I compounds. Due to their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis.

Useful For: Aiding in the determination of compliance or identify illicit stimulant drug use This test is not intended for use in employment-related testing.

Interpretation: If a stimulant or its corresponding metabolite is identified (present), it indicates that the patient has used the respective stimulant in the recent past (typically 1-3 days). The absence of the expected stimulant or its metabolites may indicate noncompliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, diluted or adulterated urine, or limitations of testing. The concentration of the drug must be greater than or equal to the cutoff to be reported as present. If a specific drug concentration is required, the laboratory must be contacted within 2 weeks of specimen collection/testing to request quantification by a second analytical technique at an additional charge.

Reference Values:

Only orderable as part of profile. For more information see:
-CSMPU / Controlled Substance Monitoring Panel, Random, Urine
-ADMPU / Addiction Medicine Profile with Reflex, 22 Drug Classes, High Resolution Mass Spectrometry and Immunoassay Screen, Random, Urine
-CSMEU / Controlled Substance Monitoring Enhanced Profile with Reflex, 21 Drug Classes, High Resolution Mass Spectrometry and Immunoassay Screen, Random, Urine
-CSMTU / Controlled Substance Monitoring Targeted Profile, 17 Drug Classes, Mass Spectrometry, Random, Urine
-TSPU / Targeted Stimulant Screen, Random, Urine

Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Methamphetamine: 100 ng/mL
Amphetamine: 100 ng/mL
3,4-Methylenedioxymethamphetamine (MDMA): 100 ng/mL
3,4-Methylenedioxy-N-ethylamphetamine (MDEA): 100 ng/mL
3,4-Methylenedioxyamphetamine (MDA): 100 ng/mL
Ephedrine: 100 ng/mL
Pseudoephedrine: 100 ng/mL
Phentermine: 100 ng/mL
Phencyclidine (PCP): 20 ng/mL
Methylphenidate: 20 ng/mL
Ritalinic acid: 100 ng/mL

Clinical References:

TSPU
610272

Targeted Stimulant Screen, Random, Urine

Clinical Information: Stimulants are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Amphetamine and methamphetamine are also prescription drugs used in the treatment of narcolepsy and attention-deficit disorder/attention-deficit hyperactivity disorder (ADHD). Methylphenidate is another stimulant used to treat ADHD. Phentermine is indicated for the management of obesity. All other amphetamines (eg, methylenedioxymethamphetamine: MDMA) are Drug Enforcement Administration scheduled Class I compounds. Due to their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis.

Useful For: Determining compliance or identifying illicit stimulant drug use This test is not intended for employment-related testing.

Interpretation: If a stimulant or its corresponding metabolite is identified (present), it indicates that the patient has used the respective stimulant in the recent past (typically 1-3 days). The absence of the expected stimulant or its metabolites may indicate noncompliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, diluted or adulterated urine, or limitations of testing. The concentration of the drug must be greater than or equal to the cutoff to be reported as present. If a specific drug concentration is required, the laboratory must be contacted within 2 weeks of specimen collection/testing to request quantification by a second analytical technique at an additional charge.

Reference Values:
Not detected (Positive results are reported with qualitative "Present" results)

Cutoff concentrations:
Methamphetamine: 100 ng/mL
Amphetamines: 100 ng/mL
3,4-Methylenedioxymethamphetamine (MDMA): 100 ng/mL
3,4-Methylenedioxy-N-ethylamphetamine (MDEA): 100 ng/mL
3,4-Methylenedioxyamphetamine (MDA): 100 ng/mL
Ephedrine: 100 ng/mL
Pseudoephedrine: 100 ng/mL
Phentermine: 100 ng/mL
Phencyclidine (PCP): 20 ng/mL
Methylphenidate: 20 ng/mL
Ritalinic acid: 100 ng/mL

Clinical References:

TARR
82486

Tarragon, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by

respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to taragon Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

TRAP
70570

Tartrate-Resistant Acid Phosphatase (TRAP) Immunostain, Technical Component Only

Clinical Information: Tartrate-resistant acid phosphatase (TRAP) is a basic, iron-binding protein found within the cytoplasmic granules of cells of hairy cell leukemia. TRAP can be useful in distinguishing hairy cell leukemia from other types of B-cell lymphomas. Caution should be used since other types of lymphoma can also be positive, such as marginal zone lymphoma, but usually their staining is less intense. Normal mast cells also express TRAP.

Useful For: Classification of leukemias and lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic

evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Dunphy CH. Reaction patterns of TRAP and DBA.44 in hairy cell leukemia, hairy cell variant, and nodal and extranodal marginal zone B-cell lymphomas. Appl Immunohistochem Mol Morphol. 2008;16(2):135-139 2. Hoyer JD, Li CY, Yam LT, Hanson CA, Kurtin PJ. Immunohistochemical demonstration of acid phosphatase isoenzyme 5 (tartrate-resistant) in paraffin sections of hairy cell leukemia and other hematologic disorders. Am J Clin Pathol. 1997;108(3):308-315 3. Janckila AJ, Cardwell EM, Yam LT, Li CY. Hairy cell identification by immunohistochemistry of tartrate-resistant acid phosphatase. Blood. 1995;85(10):2839-2844 4. Janckila AJ, Slone SP, Lear SC, Martin A, Yam LT. Tartrate-resistant acid phosphatase as an immunohistochemical marker for inflammatory macrophages. Am J Clin Pathol. 2007;127(4):556-566 5. Sherman MJ, Hanson CA, Hoyer JD. An assessment of the usefulness of immunohistochemical stains in the diagnosis of hairy cell leukemia. Am J Clin Pathol. 2011;136(3):390-399 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TAU3
70628

TAU 3 Immunostain, Technical Component Only

Clinical Information: The Tau 3 antibody stains microtubule-associated proteins in the brain that are associated with diseases of the central nervous system, especially neurodegenerative disorders.

Useful For: Diagnosis of neurodegenerative disorders

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. de Silva R, Lashley T, Ravesz T, et al. Detecting tau isoforms in archival cases. Acta Neuropathol (Berl). 2004;107(2):181-182 2. de Silva R, Lashley T, Strand C, et al. An immunohistochemical study of cases of sporadic and inherited frontotemporal lobar degeneration using 3R- and 4R-specific tau monoclonal antibodies. Acta Neuropathol (Berl). 2006;111(4):329-340 3. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TAU4
70627

TAU 4 Immunostain, Technical Component Only

Clinical Information: The Tau 4 antibody stains microtubule-associated proteins in the brain that are associated with diseases of the central nervous system, especially neurodegenerative disorders.

Useful For: Diagnosis of neurodegenerative disorders

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. de Silva R, Lashley T, Revesz T, Lees A, Powers JM. Detecting tau isoforms in archival cases. Acta Neuropathol. 2004;107(2):181-182 2. de Silva R, Lashley T, Strand C, et al. An immunohistochemical study of cases of sporadic and inherited frontotemporal lobar degeneration using 3R- and 4R-specific tau monoclonal antibodies. Acta Neuropathol. 2006;111(4):329-340 3. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TAUI
70558

TAU Immunostain, Technical Component Only

Clinical Information: Tau proteins are microtubule-associated proteins that regulate the dynamics of the microtubule network and are especially involved in the axonal transport and neuronal plasticity. Antibodies to Tau proteins stain the tangles of microtubules associated with Alzheimer cytoskeletal pathology, neurofibrillary tangles, neuropil threads, and neuritic ("senile") plaques. Tau has become important in the analysis of a wide variety of neurodegenerative disorders, including Alzheimer disease, Pick disease, corticobasal degeneration, supranuclear palsy, multisystem atrophy, as well as a recently recognized category of disorders known as tauopathies.

Useful For: Analysis of neurodegenerative disorders

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Bigio EH. Making the diagnosis of frontotemporal lobar degeneration. Arch Pathol Lab Med. 2013;137(3):314-325 2. Smith C, Graham DI, Murray LS, Nicoll JA. Tau immunohistochemistry in acute brain injury. Neuropathol Appl Neurobiol. 2003;29(5):496-502 3. Tokuda T, Ikeda S, Yanagisawa N, Ihara Y, Glenner GG. Re-examination of ex-boxers' brains using immunohistochemistry with antibodies to amyloid beta-protein and tau protein. Acta Neuropathol. 1991;82(4):280-285 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HEXAZ
35454

Tay-Sachs Disease, HEXA Gene, Full Gene Analysis, Varies

Clinical Information: Tay-Sachs disease (TSD) is an inherited lysosomal storage disease caused by a deficiency of the enzyme beta-hexosaminidase A. It is characterized by accumulation of GM2 gangliosides in cells of the brain and central nervous system. The HEXA gene encodes the alpha subunit of beta-hexosaminidase A and mutations in this gene cause TSD. TSD occurs in approximately 1 in 200,000 live births with a carrier frequency of 1 in 250 to 1 in 300 in the general population. The carrier frequency for this disease in individuals of Ashkenazi Jewish ancestry is 1 in 31. The classic form of TSD becomes apparent in infancy when mild motor weakness is noted along with impaired visual acuity and the presence of a "startle response." Other manifestations include progressive neurodegeneration, seizures, and blindness, leading to total incapacitation and death. The subacute and adult-onset types of TSD are characterized by later ages of onset and a broad spectrum of disease symptoms and severity. TSD is inherited in an autosomal recessive manner. Several common mutations in the HEXA gene account for 92% of disease-causing mutations in the Ashkenazi Jewish population. Testing for these mutations is available as a panel, TSDP / Tay-Sachs Disease, Mutation Analysis, HEXA. In non-Ashkenazi Jewish individuals, the detection rate for the common mutations is

significantly decreased. Sequencing of the entire HEXA gene detects less common disease-causing mutations. The recommended first-tier test for TSD carrier screening and diagnosis in all patients is a biochemical test that measures hexosaminidase A activity in white blood cells, NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes.

Useful For: Second-tier test for confirming a biochemical diagnosis of Tay-Sachs disease (TSD) Carrier testing of individuals with a family history of TSD but an affected individual is not available for testing or disease-causing mutations have not been identified Testing individuals with enzyme activity consistent with carrier status but negative molecular testing by a panel of common mutations

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424 2. Gravel RA, Kaback MM, Proia RL, et al: The GM2 gangliosidosis. In The Metabolic and Molecular Bases of Inherited Disease. Eigth edition. Edited by CR Scriver, AL Beaudet, WS Sly, et al. New York, McGraw-Hill Book Company, 2001, pp 3827-3876 3. ACOG Committee on Genetics: ACOG Committee Opinion #318; Screening for Tay-Sachs disease. Obstet Gynecol 2005;106(4):893-894

FGTEA
57684

Tea IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

TEA
82625

Tea, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to tea Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

TELDP
619886

Telomere Biology Disorders Gene Panel, Varies

Clinical Information: Telomeres are highly specialized structures composed of TTAGGG nucleotide repeats and proteins that protect chromosome ends. Under normal circumstances, telomeres shorten with every cycle of DNA replication. Telomerase is an enzyme complex that can extend the length of the telomere, thus helping to slow the shortening process. Telomerase is most active in highly proliferative tissues, such as lymphocytes, skin, intestine, and bone marrow. Telomere biology disorders (TBD) include a complex group of syndromes characterized by abnormally short telomeres. Telomere length analysis in leukocyte subsets is usually performed by flow fluorescent in situ hybridization. The severity of TBD syndromes is variable, and they may present in children or adults. Symptoms of TBD include bone marrow failure, pulmonary fibrosis, liver disease, gastrointestinal disease, and mucocutaneous abnormalities. The prevalence of cancer in the short telomere syndromes is increased. These cancers are mainly hematological malignancies, such as myelodysplastic syndrome and acute myelogenous leukemia, although some solid tumor prevalence is also increased (eg, oral squamous cell carcinoma). Recognition and diagnosis of underlying TBD is important, as it can help guide treatment decisions. Dyskeratosis congenita (DC) was the first TBD to be described. The subsets of DC include classic DC, Hoyeraal Hreidarsson syndrome (HHS), Revesz syndrome, DC-like conditions, Coats plus

syndrome, and isolated subtypes. Patients with the classic forms of DC are usually diagnosed in childhood with a triad of mucocutaneous features, including dysplastic nails, anomalies of skin pigmentation, and oral leukoplakia. Other features may include bone marrow failure, gastrointestinal disease, liver disease, pulmonary fibrosis, a predisposition to certain cancers, and other medical problems. Alternatively, some patients may have one of the 3 classic features of classic DC along with a hypocellular bone marrow. These patients all have very short telomeres (<1% percentile of age) in leukocytes. Patients with HHS have the features of classic DC but additionally have cerebellar hypoplasia, neurological conditions, and severe immunodeficiency. They can also have low T-cell numbers with severe B and natural killer (NK) cell lymphopenia (T+/-B- NK-) reminiscent of severe combined immunodeficiency. In Revesz syndrome, patients have bilateral exudative retinopathy along with other features of DC. Coats plus syndrome is also characterized by bilateral exudative retinopathy in addition to gastrointestinal problems and other symptoms. When a TBD manifests in adulthood, the presentation can be variable according to the severity of the telomere length defect relative to age. A broad umbrella of clinical features could include bone marrow failure, pulmonary fibrosis, liver disease not otherwise classified, myelodysplastic syndrome, acute myeloid leukemia, or early onset of malignancies within the DC grouping. A classification of DC-like may be applied for patients who do not meet the diagnostic criteria of DC but have several features reminiscent of the disease. This could include presence of bone marrow failure, developmental delay, familial history of pulmonary fibrosis, and no other clear diagnosis. The TBD can be inherited in a variety of patterns, including X-linked recessive, autosomal dominant, and autosomal recessive. Approximately 60% to 80% of patients with TBD have variants in the genes evaluated by this panel. In autosomal dominant DC, phenotypes may present at a younger age and more severely in successive generations (genetic anticipation). The genetic anticipation is mediated by the shortened telomeres that are inherited together with the disease-causing variant. It is increasingly recognized that TBD also include syndromes characterized by abnormally long telomeres. Telomere length is controlled, and like short telomeres, long telomeres also have consequences, mainly increased risk of cancers. The genetic basis of these short and long telomere syndromes may be linked to different disease-causing variants in the same genes. Loss-of-function variants in TERT lead to short telomere syndromes as described earlier, whereas gain-of-function variants lead to increased telomere length and autosomal dominant familial melanoma. Similarly, disease-causing variants in ACD and TINF2 have been described to cause both long and short telomers. Long telomeres caused by these variants lead to increased cancer risk (familial melanoma and thyroid cancer).

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of a telomere biology disorder Establishing a diagnosis of a telomere biology disorder, allowing for appropriate management and surveillance for disease features based on the gene and/or variant involved Identifying disease-causing variants within genes known to be associated with increased risk for telomere defects, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided

Clinical References: 1. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Podlevsky JD, Bley CJ, Omana RV, Qi X, Chen JJL. The telomerase database. Nucleic Acids Res. 2008;36(Database issue):D339-343. doi:10.1093/nar/gkm700 3. Armanios M. The role of telomeres in human disease. Annu Rev Genomics Hum Genet. 2022 Aug;23:363-381. doi:10.1146/annurev-genom-010422-091101 4. Bluteau O, Sebert M, Leblanc T, et al: A landscape of germ line mutations in a cohort of inherited bone marrow failure patients. Blood. 2018 Feb 15;131(7):717-732. doi: 10.1182/blood-2017-09-806489 5. Lai TP, Wright WE, Shay

JW: Comparison of telomere length measurement methods. Philos Trans R Soc Lond B Biol Sci. 2018 Mar 5;373(1741):20160451. doi: 10.1098/rstb.2016.0451 6. Niewisch MR, Savage SA: An update on the biology and management of dyskeratosis congenita and related telomere biology disorders. Expert Rev Hematol. 2019;12(12):1037-1052. doi:10.1080/17474086.2019.1662720 7. Grill S, Nandakumar J. Molecular mechanisms of telomere biology disorders. J Biol Chem. 2021;296:100064. doi:10.1074/jbc.REV120.014017

FFTEM
80763

Temazepam (Restoril), Serum

Reference Values:
Reference Range: 50 - 1000 ng/mL

TDT
70563

Terminal Deoxynucleotidyl Transferase (TdT) Immunostain, Technical Component Only

Clinical Information: Terminal deoxynucleotidyl transferase (TdT) is a nuclear enzyme that adds individual nucleotides to the termini of DNA strands without the use of a DNA template. TdT is expressed normally in cortical thymocytes, immature hematopoietic stem cells, and B and T lymphoblasts. Diagnostically, TdT positivity can be helpful in confirming a diagnosis of lymphoblastic lymphoma or leukemia. Acute myeloid leukemias can also express TdT.

Useful For: Classification of leukemias or lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

TERTD
618208

TERT Promoter Mutation Analysis, Droplet Digital PCR, Tumor

Clinical Information: The TERT gene encodes the catalytic subunit of telomerase, an enzyme complex that regulates telomere length. Mutations in the TERT promoter, primarily involving mutational hotspot positions c.-124 (also known as C228) and c.-146 (also known as C250), increase telomerase activity allowing tumor cells to overcome cellular senescence. In central nervous system (CNS) tumors, TERT promoter mutations are a diagnostic and grading molecular biomarker in diffuse gliomas and meningioma. TERT promoter mutations are observed in other CNS tumor types and are not seen in CNS reactive non-neoplastic processes. TERT promoter mutations are also a molecular biomarker in non-CNS tumors, including hepatocellular tumors, melanoma, myxoid liposarcoma, thyroid carcinoma and urothelial carcinoma.

Useful For: Identifying specific mutations within the TERT promoter that assist in tumor diagnosis/classification

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board: Central nervous system tumours. 5th ed. World Health Organization; 2021. WHO Classification of Tumours, Vol. 6 2. Killela PJ, Reitman ZJ, Jiao Y, et al. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. Proc Natl Acad Sci USA. 2013;110(15):6021-6026 3. Koelsche C, Sahm F, Capper D, et al. Distribution of TERT promoter mutations in pediatric and adult tumors of the nervous system. Acta Neuropathol. 2013;126(6):907-915 4. Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med. 2015;372(26):2499-2508 5. Cancer Genome Atlas Research Network, Brat DJ, Verhaak RG, et al. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med. 2015;372(26):2481-2498 6. Huang FW, Hodis E, Xu MJ, et al. Highly recurrent TERT promoter mutations in human melanoma. Science. 2013;339(6122):957-959 7. Schulze K, Imbeaud S, Letouze E, et al. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. Nat Genet. 2015;47(5):505-511

FFTFT
75751

Testosterone, Free (Dialysis) and Total, MS

Useful For: Helpful in assessing testicular function in prepubescent hypogonadal males and in managing hirsutism and virilization in females

Reference Values:

TESTOSTERONE, TOTAL, MS Age	Males (ng/dL)	Females (ng/dL)
Cord blood	17-61	16-44
1-10 days	< or =187	< or =24
11-30 days	Not established	Not established
1-2 months	72-344	< or =17
3-4 months	< or =201	< or =12
5-6 months	< or =59	< or =13
7-11 months	< or =16	< or =11
1-5 years	< or =5	< or =8
6-7 years	< or =25	< or =20
8-10 years	< or =42	< or =35
11 years	< or =260	< or =40
12-13 years	< or =420	< or =40
14-17 years	< or =1000	< or =40
> or = 18 years	250-1100	2-45
TESTOSTERONE, FREE Age	Males (pg/mL)	Females (pg/mL)
0-4 years	Not established	Not established
5-9 years		0.2-5.0

10-13 years	0.7-52.0	0.1-7.4
14-17 years	18.0-111.0	0.5-3.9
18-69 years	35.0-155.0	0.1-6.4
70-89 years	30.0-135.0	0.2-3.7
>89 years	Not established	Not established

FFBTT
75934

Testosterone, Free, Bioavailable, and Total, MS

Clinical Information: This test is helpful in assessing testicular function in males and managing hirsutism, virilization in females.

Reference Values:
See Laboratory Report

TTBS
80065

Testosterone, Total and Bioavailable, Serum

Clinical Information: Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In female patients, its main role is as an estrogen precursor. In both sexes, it also exerts anabolic effects and influences behavior. In men, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone, with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH) and, to a lesser degree, inhibins and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which, in men, also is called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free hormone. Historically, only free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligo-amenorrhea, or infertility. Mild-to-moderate testosterone elevations are usually asymptomatic in male patients but can cause distressing symptoms in female patients. The exact causes for mild-to-moderate elevations in testosterone often remain obscure. Common causes of pronounced elevations of testosterone include genetic conditions (eg, congenital adrenal hyperplasia), adrenal, testicular, and ovarian tumors, and abuse of testosterone or gonadotrophins by athletes. Decreased testosterone in female individuals causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In male patients, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In men, there also is a gradual, modest but progressive, decline in testosterone production starting between the 4th and 6th decade of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone-deficient women. However, severe hypogonadism, consequent to aging, alone is rare. Measurement of total testosterone (TTST / Testosterone, Total, Mass Spectrometry, Serum) is often

sufficient for diagnosis, particularly if it is combined with measurements of LH and follicle-stimulating hormone (LH / Luteinizing Hormone [LH], Serum and FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particularly if abnormalities in SHBG (SHBG1 / Sex Hormone-Binding Globulin, Serum) function or levels are present. Additional measurements of bioavailable or free testosterone (TGRP / Testosterone, Total and Free, Serum) are recommended in this situation. While both bioavailable and free testosterone can be used for the same indications, determination of bioavailable testosterone levels may be superior to free testosterone measurement in most situations.

Useful For: Recommended second-level test for suspected increases or decreases in physiologically active testosterone: -Assessment of androgen status in cases with suspected or known sex hormone-binding globulin binding abnormalities -Assessment of functional circulating testosterone in early pubertal boys and older men -Assessment of functional circulating testosterone in women with symptoms or signs of hyperandrogenism but normal total testosterone levels -Monitoring testosterone therapy or antiandrogen therapy

Interpretation: Total testosterone and general interpretation of testosterone abnormalities: In male patients: Decreased testosterone levels indicate partial or complete hypogonadism. In hypogonadism, serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: -Genetic causes (eg, Klinefelter syndrome, XXY males) -Developmental causes (eg, testicular maldescent) -Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) -Infections (eg, mumps) -Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) -Metabolic disorders (eg, hemochromatosis, liver failure) -Orchidectomy Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal," LH/FSH levels. Causes include: -Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmann syndrome, congenital hypopituitarism) -Pituitary or hypothalamic tumors -Hyperprolactinemia of any cause -Malnutrition -Excessive exercise -Cranial irradiation -Head trauma -Medical or recreational drugs (eg, estrogens, gonadotropin releasing hormone [GnRH] analogs, cannabis) Increased testosterone levels: -In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further work-up is necessary to determine the cause of precocious puberty. -In men, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50%. Monitoring testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH. When undergoing testosterone replacement therapy, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below. Evidence shows that lowering testosterone levels to less than 20?ng/dL improves patient survival and delays disease progression. In female patients: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: -Congenital adrenal hyperplasia: Non-classical (mild) variants may not present in childhood but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors, such as 17-hydroxyprogesterone (OHPG / 17-Hydroxyprogesterone, Serum), are elevated, often to a greater degree than testosterone. - Prepubertal girls: Analogous to boys, but at lower levels, increased levels of testosterone are seen in precocious puberty. -Ovarian or adrenal neoplasms: High estrogen values also may be observed and LH and FSH are low or "normal." Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values above 200 ng/dL. -Polycystic ovarian syndrome: Hirsutism, acne, menstrual disturbances, insulin resistance, and, frequently, obesity form part of this syndrome. Total testosterone levels may be normal or mildly elevated and uncommonly exceed 200 ng/dL. Monitoring testosterone replacement therapy: The only evidence-based indication for testosterone for women is for hypoactive sexual desire disorder/dysfunction. There are insufficient data for using

testosterone for any other symptom/condition or for disease prevention. If it is used, then levels should always be kept within the normal range for females. Bioavailable or free testosterone levels should also be monitored to avoid overtreatment. Monitoring antiandrogen therapy: Antiandrogen therapy is most frequently employed in the management of mild-to-moderate idiopathic female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable or free testosterone (TGRP / Testosterone, Total and Free, Serum) also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical end points and the primary treatment end point is the clinical response. Testosterone, Total and Bioavailable: Usually, bioavailable and free testosterone levels parallel the total testosterone levels. However, a number of conditions and medications are known to increase or decrease the sex hormone-binding globulin (SHBG) concentration, which may cause total testosterone concentration to change without necessarily influencing the bioavailable or free testosterone concentration, or vice versa: -Treatment with corticosteroids and sex steroids (particularly oral conjugated estrogen) can result in changes in SHBG levels and availability of sex-steroid binding sites on SHBG. This may make diagnosis of subtle testosterone abnormalities difficult. -Inherited abnormalities in SHBG binding -Liver disease and severe systemic illness -In pubertal boys and adult men, mild decreases of total testosterone without LH abnormalities can be associated with delayed puberty or mild hypogonadism. In this case, either bioavailable or free testosterone measurements are better indicators of mild hypogonadism than determination of total testosterone levels. -In polycystic ovarian syndrome and related conditions, there is often significant insulin resistance, which is associated with low SHBG levels. Consequently, bioavailable or free testosterone levels may be more significantly elevated. Either bioavailable or free testosterone (TGRP / Testosterone, Total and Free, Serum) should be used as supplemental tests to total testosterone in the above situations. The correlation coefficient between bioavailable and free testosterone (by equilibrium dialysis) is 0.9606. However, bioavailable testosterone is usually the preferred test, as it more closely reflects total bioactive testosterone, particularly in older men. Men at this age have elevated SHBG levels and may also have varying albumin levels due to coexisting illnesses.

Reference Values:

TESTOSTERONE, TOTAL:
Males
0-5 months: 75-400 ng/dL
6 months-9 years: <7-20 ng/dL
10-11 years: <7-130 ng/dL
12-13 years: <7-800 ng/dL
14 years: <7-1,200 ng/dL
15-16 years: 100-1,200 ng/dL
17-18 years: 300-1,200 ng/dL
> or =19 years: 240-950 ng/dL
Tanner Stages*
I (prepubertal): <7-20
II: 8-66
III: 26-800
IV: 85-1,200
V (young adult): 300-950

Females
0-5 months: 20-80 ng/dL
6 months-9 years: <7-20 ng/dL
10-11 years: <7-44 ng/dL
12-16 years: <7-75 ng/dL
17-18 years: 20-75 ng/dL
> or =19 years: 8-60 ng/dL
Tanner Stages*

I (prepubertal): <7-20
II: <7-47
III: 17-75
IV: 20-75
V (young adult): 12-60

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

TESTOSTERONE, BIOAVAILABLE:
Males
< or =19 years: Not established
20-29 years: 83-257 ng/dL
30-39 years: 72-235 ng/dL
40-49 years: 61-213 ng/dL
50-59 years: 50-190 ng/dL
60-69 years: 40-168 ng/dL
> or =70 years: Not established

Females (non-oophorectomized)
< or =19 years: not established
20-50 years (on oral estrogen): 0.80-4.0 ng/dL
20-50 years (not on oral estrogen): 0.80-10 ng/dL
>50 years: Not established

Clinical References: 1. Manni A, Pardridge WM, Cefalu W, et al. Bioavailability of albumin-bound testosterone. J Clin Endocrinol Metab. 1985;61(4):705-710 2. New MI, Josso N. Disorders of gonadal differentiation and congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. 1988;17(2):339-366 3. Dumesic DA. Hyperandrogenic Anovulation: A New View of Polycystic Ovary Syndrome. Postgraduate Obstetrics and Gynecology. Vol 15, No.13, June 1995 4. Morley JE, Perry HM 3rd. Androgen deficiency in aging men: role of testosterone replacement therapy. J Lab Clin Med. 2000;135(5):370-378. doi:10.1067/mlc.2000.106455 5. Sizonenko PC, Paunier L. Hormonal changes in puberty III: Correlation of plasma dehydroepiandrosterone, testosterone, FSH, and LH with stages of puberty and bone age in normal boys and girls and in patients with Addison's disease or hypogonadism or with premature or late adrenarche. J Clin Endocrinol Metab. 1975;41(5):894-904. doi:10.1210/jcem-41-5-894 6. Goudas VT, Dumesic DA. Polycystic ovary syndrome. Endocrinol Metab Clin North Am. 1997;26(4):893-912. doi:10.1016/s0889-8529(05)70286-3 7. Braunstein GD. Androgen insufficiency in women: summary of critical issues. Fertil Steril. 2002;77 Suppl 4:S94-S99. doi:10.1016/s0015-0282(02)02962-x 8. Juul A, Skakkebaek NE. Androgens and the ageing male. Hum Reprod Update. 2002;8(5):423-433. doi:10.1093/humupd/8.5.423 9. Hackbarth JS, Hoyne JB, Grebe SK, Singh RJ. Accuracy of calculated free testosterone differs between equations and depends on gender and SHBG concentration. Steroids. 2011;76(1-2):48-55. doi:10.1016/j.steroids.2010.08.008 10. Goldman AL, Bhasin S, Wu FCW, Krishna M, Matsumoto AM, Jasuja R. A reappraisal of testosterone's binding in circulation: Physiological and clinical implications. Endocr Rev. 2017;38(4):302-324. doi:10.1210/er.2017-00025 11. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and Management of Testosterone Deficiency: AUA Guideline. J Urol. 2018;200(2):423-432 12. Trost L. Update to the Testosterone Guideline. J Urol. 2024;211(4):608-610 13. Al-Sharefi A, Quinton R. Current National and International Guidelines for the Management of Male Hypogonadism: Helping Clinicians to Navigate Variation in Diagnostic Criteria and Treatment Recommendations. Endocrinol Metab (Seoul). 2020;35(3):526-540. doi:10.3803/EnM.2020.760 14. Davis SR, Baber R, Panay N, et al. Global Consensus Position Statement on the Use of Testosterone Therapy for Women. J Clin Endocrinol Metab.

2019;104(10):4660-4666. doi:10.1210/jc.2019-01603 15. Martin KA, Anderson RR, Chang RJ, et al. Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(4):1233-1257. doi:10.1210/jc.2018-00241 16. Crawford ED, Heidenreich A, Lawrentschuk N, et al. Androgen-targeted therapy in men with prostate cancer: evolving practice and future considerations. Prostate Cancer Prostatic Dis. 2019;22(1):24-38

TTST
8533

Testosterone, Total, Mass Spectrometry, Serum

Clinical Information: Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In female patients, its main role is as an estrogen precursor. In both sexes, it exerts anabolic effects and influences behavior. In men, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone with minor contributions by the adrenal glands and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH) and, to a lesser degree, inhibins and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which, in men, is also called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free hormone. Historically, only free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG-bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligomenorrhea, or infertility. Mild-to-moderate testosterone elevations are usually asymptomatic in male patients but can cause distressing symptoms in female patients. The exact cause for mild-to-moderate elevations of testosterone often remains obscure. Common causes of pronounced elevations include genetic conditions (eg, congenital adrenal hyperplasia), adrenal, testicular, and ovarian tumors, and abuse of testosterone or gonadotrophins by athletes. Decreased testosterone in female patients causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In male patients, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In men, there also is a gradual modest but progressive decline in testosterone production starting between the fourth and sixth decade of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone-deficient women. However, severe hypogonadism, consequent to aging alone, is rare. Measurement of total testosterone is often sufficient for diagnosis, particularly if it is combined with measurements of LH and follicle-stimulating hormone (LH / Luteinizing Hormone [LH], Serum and FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particularly if abnormalities in SHBG (SHBG1 / Sex Hormone-Binding Globulin, Serum) function or levels are present. Additional measurements of bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone Total and Free, Serum) are recommended in this situation. For more information see Steroid Pathways

Useful For: Evaluating men with symptoms or signs of possible hypogonadism, such as loss of libido, erectile dysfunction, gynecomastia, osteoporosis, or infertility Evaluating boys with delayed or precocious puberty Monitoring testosterone replacement therapy Monitoring antiandrogen therapy (eg, used in prostate cancer, precocious puberty, treatment of idiopathic hirsutism, male-to-female transgender disorders, etc.) Evaluating women with hirsutism, virilization, and oligoamenorrhea Evaluating women with symptoms or signs of possible testosterone deficiency Evaluating infants with ambiguous genitalia or virilization Diagnosing androgen-secreting tumors

Interpretation: In male patients: Decreased testosterone levels indicate partial or complete hypogonadism. In hypogonadism, serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: -Genetic causes (eg, Klinefelter syndrome, XXY males) -Developmental causes (eg, testicular maldescent) -Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) -Infections (eg, mumps) -Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) -Metabolic disorders (eg, hemochromatosis, liver failure) -Orchidectomy Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal" LH/FSH levels. Causes include: -Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmann syndrome, congenital hypopituitarism) -Pituitary or hypothalamic tumors -Hyperprolactinemia of any cause -Malnutrition -Excessive exercise -Cranial irradiation -Head trauma -Medical or recreational drugs (eg, estrogens, gonadotropin releasing hormone [GnRH] analogs, cannabis) Increased testosterone levels: -In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further workup is necessary to determine the cause of precocious puberty. -In men, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50%. Monitoring testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH. When undergoing testosterone replacement therapy, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below. Evidence shows that lowering testosterone levels to less than 20?ng/dL improves patient survival and delays disease progression. In female patients: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: -Congenital adrenal hyperplasia: Non-classical (mild) variants may not present in childhood, but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors, such as 17-hydroxyprogesterone (OHPG / 17-Hydroxyprogesterone, Serum), are elevated, often to a greater degree than testosterone. -Prepubertal girls: Analogous to boys, but at lower levels, increased levels of testosterone are seen in precocious puberty. -Ovarian or adrenal neoplasms: High estrogen values also may be observed and LH and FSH are low or "normal." Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values above 200 ng/dL. -Polycystic ovarian syndrome. Hirsutism, acne, menstrual disturbances, insulin resistance and, frequently, obesity form part of this syndrome: Total testosterone levels may be normal or mildly elevated and uncommonly exceed 200 ng/dL. Monitoring testosterone replacement therapy: The only evidence-based indication for testosterone for women is for hypoactive sexual desire disorder/dysfunction. There are insufficient data for using testosterone for any other symptom/condition or for disease prevention. If it is used, then levels should be kept within the normal range for females at all times. Bioavailable or free testosterone levels should also be monitored to avoid overtreatment. Monitoring antiandrogen therapy: Antiandrogen therapy is most commonly employed in the management of mild-to-moderate idiopathic female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable or free testosterone should also be monitored to ensure treatment adequacy; see TTFB / Testosterone, Total, Bioavailable, and Free, Serum. However, there are no universally agreed biochemical endpoints and the primary treatment end point is the clinical response.

TTIGS
36667

Tetanus Toxoid IgG Antibody, Serum

Clinical Information: Tetanus results from contamination of wounds or lacerations with Clostridium tetani spores from the environment. The spores germinate to actively replicating bacterial cells localized within the wound and produce the heat-labile toxin tetanospasmin. Tetanospasmin attaches to peripheral nerve endings and travels to the central nervous system where it blocks inhibitory impulses to motor neurons and leads to severe, spastic muscle contractions, a classic characteristic of tetanus. The disease is preventable by vaccination with tetanus toxoid (formaldehyde-treated tetanospasmin), which stimulates development of antitetanus toxoid antibodies. In the United States, tetanus toxoid is administered to children as part of the combined diphtheria, tetanus, and acellular pertussis (TDaP) vaccine. Two to 3

weeks following vaccination, a patient's immunological response may be assessed by measuring the total antitetanus toxoid IgG antibody level in serum. An absence of antibody formation postvaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs.

Useful For: Assessing antibody response to the tetanus toxoid vaccine, which should be performed at least 3 weeks after immunization Aiding in the evaluation of immunodeficiency This test should not be used to diagnose tetanus infection.

Interpretation: Results greater than or equal to 0.01 suggest a vaccine response. A tetanus toxoid booster should be strongly considered for patients with anti-tetanus toxoid IgG values between 0.01 and 0.5 IU/mL. Some cases of tetanus, usually mild, have occasionally been observed in patients with a measurable serum level of 0.01 to 1.0 IU/mL.

Reference Values:
Vaccinated: Positive (> or =0.01 IU/mL)
Unvaccinated: Negative (<0.01 IU/mL)

Clinical References: 1. Boland Birch T, Bleck TP. Tetanus (Clostridium tetani). In Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2948-2953 2. Gergen PJ, McQuillan GM, Kiely M, et al. A population-based serologic survey of immunity to tetanus in the United States. N Engl J Med. 1995;332(12):761-766 3. Bjorkholm B, Wahl M, Granstrom M, Hagberg L. Immune status and booster effects of low doses of tetanus toxoid in Swedish medical personnel. Scand J Infect Dis. 1994;26(4):471-475 4. Ramsay ME, Corbel MJ, Redhead K, et al. Persistence of antibody after accelerated immunization with diptheria/tetanus/pertussis vaccine. BMJ. 1991;302(6791):1489-1491 5. Rubin RL, Tang FL, Chan EK, et al. IgG subclasses of anti-tetanus toxoid antibodies in adult and newborn normal subjects and in patients with systemic lupus erythematosus, Sjogren's syndrome, and drug-induced autoimmunity. J Immunol. 1986;137(8):2522-2527 6. Simonsen O, Bentzon MW, Heron I. ELISA for the routine determination of antitoxic immunity to tetanus. J Biol Stand. 1986;14(3):231-239

FFTEN 57102 Tetrahydrobiopterin and Neopterin Profile (BH4, N)

Clinical Information: CSF Neopterin/Tetrahydrobiopterin (NC03) is useful for diagnosis of certain disorders of neurotransmitter metabolism. This testing may also be used for assessment of Variants of Uncertain Significance (VUS) identified during genetic testing (e.g. Next Generation Sequencing or Capillary Sequencing Testing). CLINICAL Tetrahydrobiopterin (BH4) serves as a cofactor for the hydroxylation of phenylalanine and in the biosynthesis of biogenic amines. Deficiency of BH4 may occur as a result of mutations causing a reduction in one of the three biosynthetic enzymes, guanosine triphosphate cyclohydrolase, 6-pyruvoyl-tetrahydropterin synthase, sepiapterin reductase, or the two regenerating enzymes, pterin-4-carbinolamine dehydratase, and dihydropteridine reductase. Defects in BH4 metabolism can result in hyperphenylalaninemia and deficiency of the neurotransmitters dopamine and serotonin. Changes in CSF neopterin may also occur in deficiency of the BH4 synthesis pathway. Disorders of BH4 metabolism are characterized by a wide range of symptoms that may include developmental delay, mental disability, behavioral disturbances, dystonia, Parkinsonian symptoms, gait disturbances, speech delay, psychomotor retardation and ptosis.

Reference Values:

TGOGF
621841

TGFBR3 (1p22), OGA (10q24) Rearrangement, FISH, Tissue

Clinical Information: Chromosomal rearrangement involving the OGA (previously MGEA5) gene or the TGFBR3 gene have recently been associated with both pleomorphic hyalinizing angiectatic tumor of soft parts and hemosiderotic fibrolipomatous tumor. Either one or both rearrangements may be present and support a diagnosis in the proper clinical and pathologic context. Rearrangement of one or both genes may be present in other neoplastic processes and is not diagnostic in isolation. These rearrangements are unusual in that they do not result specific RNA transcript products and therefore are often not detectable through many next-generation sequencing approaches but can typically be detected by fluorescence in situ hybridization testing.

Useful For: Supporting the diagnosis of pleomorphic hyalinizing angiectatic tumor, or hemosiderotic fibrolipomatous tumors associated with rearrangement of the OGA and/or TGFBR3 gene when used in conjunction with an anatomic pathology consultation

Interpretation: The result is considered positive when the percent of cells with separation of the OGA and/or TGFBR3 FISH probes with an abnormality exceeds the normal cutoff for the OGA and/or TGFBR3 FISH probe set. A positive result suggests rearrangement of the OGA and/or TGFBR3 gene and likely reflects OGA and/or TGFBR3 fusion with a partner gene. The significance of this finding is dependent on the clinical and pathologic features. The result is considered negative when the percent of cells with separation of the OGA and/or TGFBR3 FISH probes does not exceed the normal cutoff for the OGA or TGFBR3 FISH probe set. A negative result does not exclude the presence of a OGA or TGFBR3 rearrangement. Rearrangement of the OGA or TGFBR3 gene may be present in other neoplastic processes.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. WHO Classification of Tumours Editorial Board. Soft Tissue and Bone Tumours. 5th ed. IARC; 2020. WHO Classification of Tumours Series. Vol. 3, 280-283 2. Zreik RT, Carter JM, Sukov WR, et al. TGFBR3 and MGEA5 rearrangements are much more common in 'hybrid' hemosiderotic fibrolipomatous tumor-myxoinflammatory fibroblastic sarcomas than in classical myxoinflammatory fibroblastic sarcomas: a morphological and fluorescence in situ hybridization study. Hum Pathol. 2016;53:14-24

THEV1
608085

Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum

Clinical Information: This consultative study is primarily designed for the evaluation of microcytosis but also has the ability to test for the detection of almost all known hemoglobin disorders in an economical manner. Because this can include multiple tests for alpha thalassemias, beta thalassemias, delta-beta thalassemia, hereditary persistence of fetal hemoglobin (HPFH), and for all known hemoglobin (Hb) variants, an expert in these disorders can guide testing to explain the clinical question or reported complete blood cell count values. This evaluation is particularly useful for complete classification of compound combinations of Hb S with alpha or beta thalassemia, Hb E/beta-0-thalassemia, and many other complex alpha and beta thalassemia disorders. Since iron deficiency can mimic thalassemias, ferritin levels are measured to evaluate this possibility if a serum sample is received. Hb disorders include those

associated with thalassemias (decreased protein quantity) and Hb variants (abnormal protein production). Many are clinically harmless, and others cause symptoms, including microcytosis, sickling disorders, hemolysis, erythrocytosis, cyanosis/hypoxia, long-standing or familial anemia, compensated or episodic anemia, and increased methemoglobin or sulfhemoglobin results. Hb disorders can show patterns of either autosomal recessive or autosomal dominant inheritance. The thalassemias are a group of disorders of Hb synthesis. Normal adult Hb consists of 2 alpha-globin chains (encoded by 2 pairs of alpha-globin genes, each pair located on chromosome 16), and 2 beta-globin chains (encoded by 2 beta-globin genes, each located on chromosome 11). Thalassemia syndromes result from an underproduction of 1 or 2 types of globin chains and are characterized by the type (alpha, beta, delta, gamma) and magnitude of underproduction (number of defective genes) and the severity of clinical symptoms (minor, intermedia, major). The severity of the clinical and hematologic effects is directly related to the imbalance of alpha-like to beta-like chains. The most common form of thalassemia is alpha thalassemia. Alpha thalassemia usually involves deletion of entire alpha genes and varies in severity depending on the number of alpha chains deleted (or rendered nonfunctional). Alpha thalassemia trait usually results from the deletion of 2 alpha genes. The most common form of Hb H disease, results from dysfunction of 3 alpha chains, and shows a variable phenotype with most showing moderate anemia. The deletion of all 4 alpha genes (Barts hydrops fetalis) is incompatible with life without significant medical intervention. Nondeletional alpha thalassemia alterations can also result in either thalassemia trait or Hb H disease and are less common than deletional forms. Conversely, most beta thalassemia alterations are due to single nucleotide substitutions that can occur anywhere in the beta-globin gene. Large deletions of the beta-globin gene complex can result in elevations in Hb F, such as HPFH or delta-beta thalassemia. While the presence of a single beta-gene variants (beta thalassemia trait) results primarily in red blood cells microcytosis, cases with 2 beta-gene abnormalities show a wide range in clinical severity, and many cases require molecular testing to understand the phenotype.

Useful For: Evaluation of microcytosis Extensive and economical diagnosis and classification of hemoglobinopathies or thalassemia, including complex disorders Diagnosis of hereditary persistence of hemoglobin

Interpretation: A hematopathologist expert in these disorders evaluates the case, appropriate tests are performed, and an interpretive report is issued.

Reference Values:
Definitive results and an interpretive report will be provided.

Clinical References: 1. Hoyer JD, Hoffman DR. The thalassemia and hemoglobinopathy syndromes. In: McClatchey KD, Amin HM, Curry JL, eds. Clinical Laboratory Medicine. 2nd ed. Lippencott Williams and Wilkins; 2002:866-892 2. Brancaleoni V, Di Pierro E, Motta I, Cappellini MD. Laboratory diagnosis of thalassemia. Int J Lab Hematol. 2016;38 Suppl 1:32-40 3. Hartveld C. State of the art and new developments in molecular diagnostics for hemoglobinopathies in multiethnic societies. Int J Lab Hematol. 2014;36:1-12

THEV0 608092 Thalassemia Summary Interpretation, Blood

Clinical Information: Some hemoglobin disorders can be very complex and involve abnormalities of the alpha, beta, delta, and gamma genes. These abnormalities can be due to, not only point variants, but also deletions within 1 or more globin genes. Multiple genetic variants can be seen in the same patient, and molecular testing is necessary to fully evaluate such cases. A summary interpretation that incorporates all the testing performed is beneficial to the ordering physician.

Useful For: Incorporating and summarizing subsequent molecular results into an overall interpretation for the THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum

Interpretation: An interpretive report will be provided that summarizes all testing as well as any pertinent clinical information.

Reference Values:
Only orderable as a reflex. For more information see THEV1 / Thalassemia and Hemoglobinopathy Evaluation, Blood and Serum.

An interpretive report will be provided.

Clinical References: 1. OMIM. 141800 Hemoglobin-alpha locus 1; HBA1. Updated September 15, 2023. Accessed November 18, 2024. Available at www.omim.org/entry/141800?search=141800&highlight=141800 2. OMIM. 141900 Hemoglobin-beta locus; HBB. Updated September 15, 2023. Accessed November 18, 2024. Available at www.omim.org/entry/141900?search=141900&highlight=141900 3. Kipp BR, Roellinger SE, Lundquist PA, Highsmith WE, Dawson DB. Development and clinical implementation of a combination deletion PCR and multiplex ligation-dependent probe amplification assay for detecting deletions involving the human alpha-globin gene cluster. J Mol Diagn. 2011;13(5):549-557 doi:10.1016/j.jmoldx.2011.04.001 4. Thom CS, Dickson CF, Gell DA, Weiss MJ. Hemoglobin variants: biochemical properties and clinical correlates. Cold Spring Harb Perspect Med. 2013;3(3):a011858 5. Harteveld CL, Higgs DR. Alpha-thalassemia. Orphanet J Rare Dis. 2010;5:13 6. Thein SL. The molecular basis of beta-thalassemia. Cold Spring Harb Persepct Med. 2013;3(5):a011700 7. Hein MS, Oliveira JL, Swanson KC, et al. Large deletions involving the beta globin gene complex: genotype-phenotype correlation of 119 cases. Blood. 2015;126(23):3374

TLU
8603

Thallium, 24 Hour, Urine

Clinical Information: Thallium is odorless, tasteless, and found in trace amounts in the earth's crust. It is used in the manufacturing of electronic devices, switches, and closures. It has previously been used in rodenticides. The greatest exposure can occur from eating food (eg, fruits and vegetables) since it's easily taken up by plants through the roots. Cigarette smoking is also a source of exposure. Accidental ingestion may lead to vomiting, diarrhea, and leg pains, followed by a severe and sometimes fatal sensorimotor polyneuropathy. Peripheral neuropathy may occur within 1 week of exposure, while hair loss begins and continues for several weeks. Gastrointestinal symptoms, including pain, diarrhea, and constipation have also been reported in acute ingestion, along with myalgias, pleuritic chest pain, insomnia, optic neuritis, hypertension, cardiac abnormalities, Mees lines, and liver injury. Most thallium is excreted in the urine, can be found within an hour after exposure, and can be detected as long as two months after exposure.

Useful For: Detecting toxic thallium exposure in 24-hour urine collections

Interpretation: Patients exposed to high doses of thallium (>1 g) present clinically with alopecia, peripheral neuropathy, seizures, and kidney failure. Exposed patients can have urine output greater than 10 mcg/day. The long-term consequences of such an exposure are poor.

Reference Values:
0-17 years: Not established
> or =18 years: <2 mcg/24 hours

Clinical References: 1. Bank WJ, Pleasure DE, Suzuki K, Nigro M, Katz R. Thallium poisoning. Arch Neurol. 1972;26(5):456-464 2. Pelclova D, Urban P, Ridson P, et al. Two-year follow-up of two patients after severe thallium intoxication. Hum Exp Toxicol. 2009;28(5):263-272 3. Zhao G, Ding M, Zhang B, et al. Clinical manifestations and management of acute thallium poisoning. Eur Neurol. 2008;60(6):292-297 4. Agency for Toxic Substances and Disease Registry: Toxicological profile for

thallium. US Department of Health and Human Services; October 2024. Accessed December 26,2024. Available at www.atsdr.cdc.gov/ToxProfiles/tp54.pdf 5. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 44

TLB
8149

Thallium, Blood

Clinical Information: Thallium is odorless, tasteless and found in trace amounts in the earth's crust. It is used in the manufacturing of electronic devices, switches, and closures. It had previously been used in rodenticides. The greatest exposure can occur from eating food (eg, fruits and vegetables) since it's easily taken up by plants through the roots. Cigarette smoking is also a source of exposure. Accidental ingestion may lead to vomiting, diarrhea, and leg pains, followed by a severe and sometimes fatal sensorimotor polyneuropathy. Peripheral neuropathy may occur within 1 week of exposure, while hair loss begins and continues for several weeks. Gastrointestinal symptoms, including pain, diarrhea, and constipation have also been reported in acute ingestion, along with myalgias, pleuritic chest pain, insomnia, optic neuritis, hypertension, cardiac abnormalities, Mees lines, and liver injury. Most thallium is excreted in the urine, can be found within an hour after exposure, and can be detected as long as two months after exposure.

Useful For: Detecting toxic exposure in whole blood specimens

Interpretation: Normal thallium blood concentrations are less than 1 ng/mL. Significant exposure is associated with thallium concentrations in blood greater than 10 ng/mL and as high as 50 ng/mL. The long-term sequelae from such an exposure is poor. Patients exposed to high doses of thallium (>1 g) present clinically with alopecia (hair loss), peripheral neuropathy, seizures, and kidney failure

Reference Values:
0-17 years: Not established
> or =18 years: <2 ng/mL

Clinical References: 1. Pelcloval D, Urbanl, P, Ridsonl P, et al. Two-year follow-up of two patients after severe thallium intoxication. Hum Exper Toxicol. 2009;28:263-272 2. Zhao G, Ding M, Zhang B, et al. Clinical manifestations and management of acute thallium poisoning. Eur Neurol. 2008;60:292-297 3. Agency for Toxic Substances and Disease Registry: Toxicological profile for thallium. US Department of Health and Human Services; July 1992. Available at www.atsdr.cdc.gov/ToxProfiles/tp54.pdf 4. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:455.e55

TLUCR
615255

Thallium/Creatinine Ratio, Random, Urine

Clinical Information: Thallium is odorless, tasteless, and found in trace amounts in the earth's crust. It is used in the manufacturing of electronic devices, switches, and closures. It had previously been used in rodenticides. The greatest exposure can occur from eating food (eg, fruits and vegetables) since its easily taken up by plants through the roots. Cigarette smoking is also a source of exposure. Accidental ingestion may lead to vomiting, diarrhea, and leg pains, followed by a severe and sometimes fatal sensorimotor polyneuropathy. Peripheral neuropathy may occur within 1 week of exposure, while hair loss begins and continues for several weeks. Gastrointestinal symptoms, including pain, diarrhea, and constipation have also been reported in acute ingestion, along with myalgias, pleuritic chest pain, insomnia, optic neuritis, hypertension, cardiac abnormalities, Mees lines, and liver injury. Most thallium is excreted in the urine, can be found within an hour after exposure, and can be detected as long as two months after exposure.

Useful For: Detecting toxic thallium exposure in random urine specimens

Interpretation: Patients exposed to high doses of thallium (>1 g) present with alopecia, peripheral neuropathy, and seizures, and kidney failure. Normal daily thallium excretion is less than 1 mcg/day. Exposed patients can have urine thallium excretion greater than 10 mcg/day. The long-term consequences of such an exposure are poor.

Reference Values:
THALLIUM:
0-17 years: Not established
> or =18 years: <2 mcg/g creatinine

CREATININE:
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years of age.

Clinical References: 1. Bank WJ, Pleasure DE, Suzuki K, Nigro M, Katz R. Thallium poisoning. Arch Neurol. 1972;26(5):456-464. doi:10.1001/archneur.1972.00490110090009 2. Pelclova D, Urban P, Ridson P, et al. Two-year follow-up of two patients after severe thallium intoxication. Hum Exp Toxicol. 2009;28(5):263-272. doi:10.1177/0960327109106487 3. Zhao G, Ding M, Zhang B, et al. Clinical manifestations and management of acute thallium poisoning. Eur Neurol. 2008;60(6):292-297. doi:10.1159/000157883 4. Strathmann FG, Blum LM. Toxic elements. In: Rifai N, Chiu RWK, Young I, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:455.e55 5. Campanella B, Colombaioni L, Benedetti E, et al. Toxicity of thallium at low doses: A review. Int J Environ Res Public Health. 2019;16(23):4732. doi:10.3390/ijerph16234732

FHCCF
75831

THC Confirmation, MS, SP

Interpretation: Assay threshold: 1.0 ng/mL

Reference Values:
Negative
Units: ng/mL

FMARX
75832

THC, MS, WB/SP Rfx

Reference Values:
Only orderable as a reflex from FMARI

THEO
8661

Theophylline, Serum

Clinical Information: Theophylline and its congener, aminophylline, are used to relax smooth muscles of the bronchial airways and pulmonary blood vessels to relieve and prevent symptoms of asthma and bronchospasm. Theophylline is typically administered orally at a dose of 400 mg/day or 6 mg/kg, whichever is lower, or intravenously as aminophylline at 0.4 mg/kg/hour. Oral dosage may be increased at 200 mg increments to a maximum of 900 mg/day, or 13 mg/kg if the steady-state blood concentration is within the therapeutic range of 8.0 to 20.0 mcg/mL. Theophylline has a half-life of approximately 4 hours in children and adult smokers, and 8.7 hours in nonsmoking adults. The volume of distribution is approximately 0.5 L/kg, and the drug is approximately 40% protein bound. Theophylline exhibits zero-

order clearance kinetics like phenytoin, small increases in dose yield disproportionately large increases in blood concentration. Coadministration of cimetidine and erythromycin will significantly inhibit theophylline clearance, requiring dosage reduction. Other drugs such as allopurinol, ciprofloxacin, oral contraceptives, and propranolol inhibit theophylline clearance to a lesser degree. Smoking induces the synthesis of cytochrome P448, the antipyrine-dependent cytochrome, which significantly increases the rate of metabolism of theophylline. Drugs such as phenobarbital, phenytoin, carbamazepine, and rifampin slightly increase the rate at which the drug is cleared. Theophylline exhibits rather severe toxicity that is proportional to blood level.

Useful For: Assessing and adjusting theophylline dosage for optimal therapeutic level Assessing theophylline toxicity

Interpretation: Response to theophylline is directly proportional to the serum level. Patients usually receive the best response when the serum level is above 8.0 mcg/mL, with minimal toxicity experienced as long as the level is less than or equal to 20.0 mcg/mL.

Reference Values:
Therapeutic:
Bronchodilation: 8.0-20.0 mcg/mL
Neonatal apnea (< or =4 weeks old): 6.0-13.0 mcg/mL
Critical value: >20.0 mcg/mL

Clinical References: 1. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453.e9 2. Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. McGraw-Hill; 2018

TDP
42356

Thiamine (Vitamin B1), Whole Blood

Clinical Information: Thiamine (vitamin B1, thiamin) is an essential vitamin required for carbohydrate metabolism, brain function, and peripheral nerve myelination. Thiamine is obtained from the diet. Body stores are limited, and deficiencies can develop quickly. The total thiamine pool in the average adult is about 30 mg. An intake of 0.5 mg per 1000 kcal per day is needed to maintain this pool. Due to its relatively short storage time, marginal deficiency can occur within 10 days and more severe deficiency within 21 days if intake is restricted. Approximately 80% of all chronic alcoholics are thiamine deficient due to poor nutrition. However, deficiency also can occur in individuals who are older adults, have chronic gastrointestinal problems, have marked anorexia, are on cancer treatment, or are receiving diuretic therapy. The signs and symptoms of mild-to-moderate thiamine deficiency are nonspecific and may include poor sleep, malaise, weight loss, irritability, and confusion. Newborns breastfed from deficient mothers may develop dyspnea and cyanosis; diarrhea, vomiting, and aphonia may follow. Moderate deficiency can affect intellectual performance and well-being, despite a lack of apparent clinical symptoms. Severe deficiency causes congestive heart failure (wet beriberi), peripheral neuropathy (dry beriberi), Wernicke encephalopathy (a medical emergency that can progress to coma and death), and Korsakoff syndrome (an often irreversible memory loss and dementia that can follow). Rapid treatment of Wernicke encephalopathy with thiamine can prevent Korsakoff syndrome. Symptoms of dry beriberi include poor appetite, fatigue, and peripheral neuritis. Symptoms of wet beriberi include cardiac failure and edema. Patients with Wernicke encephalopathy present with behavior change (confusion, delirium, apathy), diplopia (often sixth nerve palsies), and ataxia. A late stage, in which the patients may develop an irreversible amnestic confabulatory state, is referred to as the Wernicke-Korsakoff syndrome. The response to thiamine therapy in deficient patients is usually rapid. Thiamine deficiency is a treatable, yet underdiagnosed, disorder in the United States. A heightened level of awareness of the possibility of thiamine deficiency is necessary to identify,

intervene, and prevent thiamine deficiency's dire consequences. It appears that no conditions are directly attributable to thiamine excess and that thiamine administration is safe except in extremely rare cases of anaphylaxis from intravenous thiamin. Whole blood thiamine testing is superior to currently available alternative tests for assessing thiamine status. Serum or plasma thiamine testing suffers from poor sensitivity and specificity, and less than 10% of blood thiamine is contained in plasma. Transketolase determination, once considered the most reliable means of assessing thiamine status, is now considered an inadequate method. The transketolase method is an indirect assessment. Since transketolase activity requires thiamin, decreased transketolase activity is presumed to be due to the decrease of thiamin. However, the test is somewhat nonspecific, as other factors may decrease transketolase activity. Transketolase is less sensitive than liquid chromatography-tandem mass spectrometry), has poor precision, and specimen stability concerns.

Useful For: Assessment of thiamine deficiency Measuring thiamine levels in patients with behavioral changes, eye signs, gait disturbances, delirium, and encephalopathy; or in patients with questionable nutritional status, especially those who appear at risk and who also are being given insulin for hyperglycemia

Interpretation: Values for thiamine diphosphate of less than 70 nmol/L are suggestive of thiamine deficiency.

Reference Values:
70-180 nmol/L

Clinical References: 1. Naidoo DP, Bramdev A, Cooper K. Wernicke's encephalopathy and alcohol-related disease. Postgrad Med J. 1991;67(793);978-981 2. Herve C, Beyne P, Letteron PH, Delacoux E. Comparison of erythrocyte transketolase activity with thiamin and thiamin phosphate ester levels in chronic alcoholic patients. Clin Chim Acta. 1995;234(1-2):91-100 3. Majumdar SK, Shaw GK, O'Gorman P, et al. Blood vitamin status (B1, B2, B6, folic acid, and B12) in patients with alcohol liver disease. Int J Vitam Nutr Res. 1982;52:266-271 4. Ball GFM. Vitamins: Their role in the human body. Blackwell Publishing; 2004:273-288 5. Brin M. Erythrocyte as a biopsy tissue for functional evaluation of thiamin adequacy. JAMA. 1964;187:762-766 6. Roberts NB, Taylor A. Sodi R. Vitamins and trace elements. In: Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:639-718 7. Sodi R. Vitamins and trace elements. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:417

DTHPV
70336

ThinPrep Diagnostic with Human Papillomavirus (HPV) Reflex, Varies

Clinical Information: Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic) stages, to carcinoma in situ, and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. Follow-up of the cervical Papanicolaou (Pap) abnormality atypical squamous cells of undetermined significance (ASCUS) is costly and frustrating to patients and clinicians because a large percentage of these patients have normal colposcopic and biopsy findings. Yet, a significant percentage (10%-15%) will have an underlying high-grade squamous intraepithelial lesion (HSIL). The majority (>99%) of cervical epithelial neoplasms are the result of human papillomavirus (HPV) infection. High-risk HPV (HR-HPV) types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) can result in both low-grade squamous intraepithelial lesions and HSIL, as well as invasive carcinomas. Patients with HSIL have a greater risk for progression to carcinoma. In the setting of an abnormal Pap result, the presence of HR-HPV types in cervical specimens identifies a subgroup of patients with a greater likelihood of having a HSIL. If the patient has been previously diagnosed with an abnormal Pap result or is at high risk, consider I the diagnostic test rather than the screen; order STHPV / ThinPrep Screen with Human Papillomavirus (HPV) Reflex, Varies. Persistent

infection with HPV is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN).(1-3) The presence of HPV has been implicated in more than 99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high-risk for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.(4-6) Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. DNA testing by polymerase chain reaction has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may: 1. Increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years old and older with normal cytology 2. Reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing ASCUS Recent data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 or HPV-18 positive women is 11.4% (95% CI 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women.(7) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16 and 18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 or HPV-18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.(4)

Useful For: Management and triage of patients aged 21 years or older with abnormal Papanicolaou (Pap) results Diagnostic test for detection of human papillomavirus (HPV) high-risk genotypes associated with the development of cervical cancer Results can be used as an aid in triaging women with abnormal Pap smear results Individual genotyping of HPV-16 or HPV-18 if present Results of HPV-16 and HPV-18 genotyping can be used as an aid in triaging women with positive high-risk HPV (HR-HPV) but negative Pap smear results

Interpretation:

Reference Values:

ThinPrep PAPANICOLAOU:

Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

Note: Abnormal results will be reviewed by a pathologist at an additional charge.

HUMAN PAPILLOMAVIRUS (HPV):
Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Clinical References: 1. Solomon D, Schiffman M, Tarone R, ALTS Study group: Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. J Natl Cancer Inst. 2001 Feb 2 ;93:293-299 2. Soloman D, Davey D, Kurman R, et al: The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002 Apr 24;287(16):2114-2119 3. Wright TC, Cox JT, Massad LS, et al: 2001 Consensus guidelines for the management of women with cervical cytological abnormalities. JAMA. 2002;287:2120-2129 4. Saslow D, Solomon D, Lawson HW, et al: American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer. J Low Genit Tract Dis. 2012;16(3):175-204 5. Walboomers JM, Jacobs MV, Manos MM, et al: Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999 Sep;189(1):12-19 6. de Sanjose S, Quint WG, Alemany L, et al: Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010 Nov;11(11):1048-1056 7. Wright TC, Stoler MH, Sharma A, et al: Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV positive, cytology-negative results. Am J Clin Pathol. 2011 Oct;136(4):578-586 8. Solomon D: Forward. In: Nayar R, Wilbur DC, eds. The Bethesda System for Reporting Cervical Cytology: Definitions, Criteria, and Explanatory Notes. 3rd ed. Springer; 2015 9. Massad LS, Einstein MH, Huh WK, et al: 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2013 April;17(5 Suppl 1):S1-S27 10. Sherman ME, Lorincz A, Scott DR, et al: Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. J Nat Cancer Inst. 2003 January;95(1):46-52

TPRPD
70333

ThinPrep Diagnostic, Varies

Clinical Information: The ThinPrep Pap test is an alternative preparation method for the cervical Pap screening test. The method utilizes a liquid-based technique that replaces the direct smear method of the conventional Pap screen. This method is one of several technologies developed to improve visualization of cellular material by reducing smearing trauma, air drying artifact, and obscuring blood and inflammation. In addition, variability in smearing technique is eliminated as the majority of processing and preparation is performed in the laboratory under controlled conditions. Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic) stages, to carcinoma in situ, and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. Follow-up of the cervical Pap abnormality atypical squamous cells of undetermined significance is costly and frustrating to patients and clinicians because a large percentage of these patients have normal colposcopic and biopsy findings. Yet, a significant percentage (10%-15%) will have an underlying high-grade squamous intraepithelial lesion.

Useful For: Detecting cervical carcinoma or intraepithelial lesions when screening women for possible cervical neoplasia

Interpretation: Standard reporting, as defined by the Bethesda System is utilized.(1)

Reference Values:
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.
Note: Abnormal results will be reviewed by a pathologist at an additional charge.

Clinical References: 1. Nayar R, Wilbur DC, eds The Bethesda System for Reporting Cervical Cytology: Definitions, Criteria, and Explanatory Notes. 3rd ed. Springer; 2015 2. Austin RM, Ramzey I: Increased detection of epithelial cell abnormalities by liquid-based gynecologic cytology preparations. A

review of accumulated data. Acta Cytol. 1998 Feb;42(1):178-184 3. Guidos BJ, Selvaggi SM: Use of the ThinPrep Pap test in clinical practice. Diagn Cytopathol. 1999 Feb;20(2):70-73 4. Kurman RJ, Solomon D: The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses: Definitions, Criteria, and Explanatory Notes for Terminology and Specimen Adequacy. Springer-Verlag; 1994 5. Gay JD, Donaldson LD, Goellner JR: False-negative results in cervical cytologic studies. Acta Cytol. 1985 Nov-Dec;29(6):1043-1046 6. Saslow D, Solomon D, Lawson HW, et al: American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. J Low Genit Tract Dis. 2012 Jul;16(3):175-204

STHPV 70335 ThinPrep Screen with Human Papillomavirus (HPV) Reflex, Varies

Clinical Information: Squamous cell carcinoma of the cervix is believed to develop in progressive stages, from normal through precancerous (dysplastic) stages to carcinoma in situ and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. Follow-up of the cervical Pap abnormality atypical squamous cells of undetermined significance (ASCUS) is costly and frustrating to patients and clinicians because a large percentage of these patients have normal colposcopic and biopsy findings. Yet, a significant percentage (10%-15%) will have an underlying high-grade squamous intraepithelial lesion (HSIL). The majority (>99%) of cervical epithelial neoplasms are the result of human papillomavirus (HPV) infection. High-risk HPV (HR-HPV) types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) can result in low-grade squamous intraepithelial lesions and HSIL, as well as invasive carcinomas. Patients with HSIL have a greater risk for progression to carcinoma. In the setting of an abnormal Pap result, the presence of HR-HPV types in cervical specimens identifies a subgroup of patients with a greater likelihood of having a HSIL. If the patient has been previously diagnosed with an abnormal Pap result or is at high risk, consider ordering the diagnostic test: DTHPV / ThinPrep Diagnostic with Human Papillomavirus (HPV) Reflex, Varies rather than this screen. Persistent infection with HPV is the principal cause of cervical cancer and its precursor, cervical intraepithelial neoplasia (CIN).(1-3) The presence of HPV has been implicated in greater than 99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high-risk for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.(4-6) Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. Infection with any HPV type can produce CIN, although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has dramatically decreased the death rates due to cervical cancer in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy, and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper

implementation of nucleic acid testing for HPV may: 1, Increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology 2.Reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing ASCUS. Recent data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 or HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women.(7) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.(4)

Useful For: Managing and triaging of patients, aged 21 years or older, with abnormal Pap results Screening for detection of high-risk (HR) human papillomavirus (HPV) genotypes associated with the development of cervical cancer Aids in triaging women with abnormal Pap smear results Individual genotyping of HPV-16 and HPV-18 if present Aids in triaging women with positive HR-HPV but negative Pap smear results

Interpretation: Cytology: Standard reporting, as defined by the Bethesda System, is utilized. Human papillomavirus: A positive result indicates the presence of human papillomavirus (HPV) DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance Pap smear result and who are positive for high-risk HPV (HR-HPV), consider referral for colposcopy if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 or HPV-18, consider referral for colposcopy if clinically indicated. For women aged 30 years and older with a negative Pap smear and positive HR-HPV test result but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

Reference Values:

ThinPrep PAPANICOLAOU

Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.
Note: Abnormal results will be reviewed by a pathologist at an additional charge.

HUMAN PAPILLOMAVIRUS (HPV)

Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Clinical References: 1. Solomon D, Schiffman M, Tarone R: Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. J Natl Cancer Inst. 2001 Feb;93(4):293-299 2. Soloman D, Davey D, Kurman R, et al: The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002 Apr;287(16):2114-2119 3. Wright TC Jr, Cox JT, Massad LS, et al: 2001 consensus guidelines for the management of women with cervical cytological abnormalities. JAMA 2002 Apr;287(16):2120-2129 4. Saslow D, Solomon D, Lawson HW, et al: American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin. 2012 May-Jun;62(3):147-72 5. Walboomers JM, Jacobs MV, Manos MM, et al: Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999 Sep;189(1):12-19 6. de Sanjose S, Quint WG, Alemany L, et al: Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010 Nov;11(11):1048-1056 7. Wright TC Jr, Stoler MH, Sharma A, et al: Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV positive, cytology-negative results. Am J Clin Pathol. 2011 Oct;136(4):578-586 8. Massad LS, Einstein MH, Huh

WK, et al: 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2013 Apr;17(5 Suppl 1):S1-S27 9. Sherman ME, Lorincz AT, Scott DR, et al: Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. J Nat Cancer Inst, 2003 Jan;95(1):46-52

TPRPS 70332 ThinPrep Screen, Varies

Clinical Information: The ThinPrep Pap test is an alternative preparation method for the cervical Pap screening test. The method utilizes a liquid-based technique that replaces the direct smear method of the conventional Pap screen. This method is one of several technologies developed to improve visualization of cellular material by reducing smearing trauma, air-drying artifact, and obscuring blood and inflammation. In addition, variability in smearing technique is eliminated as the majority of processing and preparation is performed in the laboratory under controlled conditions. Squamous cell carcinoma of the cervix is believed to develop in progressive stages, from normal through precancerous (dysplastic) stages to carcinoma in situ and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. Follow-up of the cervical Pap abnormality atypical squamous cells of undetermined significance is costly and frustrating to patients and clinicians because a large percentage of these patients have normal colposcopic and biopsy findings. Yet, a significant percentage (10%-15%) will have an underlying high-grade squamous intraepithelial lesion.

Useful For: Screening for cervical carcinoma or intraepithelial lesions

Interpretation: Standard reporting, as defined by the Bethesda System is utilized.(1)

Reference Values:
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.
Note: Abnormal results will be reviewed by a pathologist at an additional charge.

Clinical References: 1. Nayer R, Wilbur DC, eds: The Bethesda System for Reporting Cervical Cytology: Definitions, Criteria, and Explanatory Notes. 3rd edition. Springer; 2015 2. Austin RM, Ramzey I: Increased detection of epithelial cell abnormalities by liquid-based gynecologic cytology preparations. A review of accumulated data. Acta Cytol. 1998 Jan-Feb;42(1):178-184 3. Guidos BJ, Selvaggi SM: Use of the ThinPrep Pap test in clinical practice. Diagn Cytopathol. 1999 Feb;20(2):70-73 4. Kurman RJ, Soloman D, eds: The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses: Definitions, Criteria, and Explanatory Notes for Terminology and Specimen Adequacy. Springer-Verlag; 1994 5. Gay JD, Donaldson LD, Goellner JR: False-negative results in cervical cytologic studies. Acta Cytol. 1985 Nov-Dec;29:1043-1046 6. Saslow D, Solomon D, Lawson HW, et al: American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin. 2012 May-Jun;16(3):175-204

DTPCO 70338 ThinPrep with Human Papillomavirus (HPV) Co-Test-Diagnostic, Varies

Clinical Information: The majority (>99%) of cervical epithelial neoplasms are the result of human papillomavirus (HPV) infection. High-risk HPV (HR-HPV) types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) can result in both low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL), as well as invasive carcinoma.(1,2) Patients with both negative cytology and negative HPV have been shown to be at extremely low risk for cervical neoplasia.(1,2) For women 30 years and older who have received a negative Pap smear test and

concurrent negative HPV results, the American Cancer Society (ACS) and American College of Obstetricians and Gynecologists (ACOG) recommendations for cervical screening state that physicians may lengthen the screening interval to 3 years when using the combined tests. Patients deemed to be at high risk by the clinician should still be screened more frequently. The presence of HR-HPV types in cervical specimens identifies a subgroup of patients with a greater likelihood of having a high-grade squamous intraepithelial lesion. Current guidelines for follow-up of a cytology-negative/HPV-positive patient recommend repeat HPV testing in 12 months.(2) Persistent infection with HPV is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN).(1-3) The presence of HPV has been implicated in more than 99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.(4-6) Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy, and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. DNA testing by polymerase chain reaction has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance). Recent data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and HPV-18 positive women is 11.4% (95% CI 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women.(7) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16 and 18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 or HPV-18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.(4)

Useful For: Detection and diagnosis of cervical carcinoma or intraepithelial lesions and the presence or absence of high-risk human papillomavirus (HR-HPV) in women over age 30 at risk for cervical neoplasia Detecting high-risk HPV genotypes associated with the development of cervical cancer Aids in triaging women with abnormal Pap smear results Individual genotyping of HPV-16 or HPV-18 if present Aids in triaging women with positive HR-HPV 16 and 18, but negative Pap smear results

Interpretation: Cytology: Standard reporting, as defined by the Bethesda System is utilized. Human papillomavirus (HPV): A positive result indicates the presence of HPV DNA due to 1 or more of the

following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk HPV (HR-HPV), consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result, but who are positive for HPV-16 or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

Reference Values:

ThinPrep PAPANICOLAOU
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

HUMAN PAPILLOMAVIRUS (HPV)
Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Clinical References: 1. Lorincz AT, Richart RM: Human papillomavirus DNA testing as an adjunct to cytology in cervical screening programs. Arch Pathol Lab Med. 2003 Aug;127(8):959-968 2. Wright TC Jr, Schiffman M: Adding a test for human papillomavirus DNA to cervical-cancer screening. N Engl J Med. 2003 Feb 6;348(6):489-490 3. Solomon D, Davey D, Kurman R, et al: The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002 Apr 24;287(16):2114-2119 4. Saslow D, Solomon D, Lawson HW, et al: American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. J Low Genit Tract Dis. 2012 Jul;16(3):175-204 5. Walboomers JM, Jacobs MV, Manos MM, et al: Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999 Sep;189(1):12-19 6. de Sanjose S, Quint WG, Alemany L, et al: Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010 Nov;11(11):1048-1056 7. Wright TC Jr, Stoler MH, Sharma A, Zhang G, Behrens C, Wright TL: Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV positive, cytology-negative results. Am J Clin Pathol. 2011 Oct;136(4):578-586 8. Massad LS, Einstein MH, Huh WK, et al: 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2013 Apr;17(5 Suppl 1):S1-S27 9. Sherman ME, Lorincz AT, Scott DR, et al: Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. J Nat Cancer Inst. 2003 Jan 1;95(1):46-52

CTPCO
616073

ThinPrep with Human Papillomavirus (HPV) Co-Test-Screen with p16/Ki67 Dual Stain Reflex, Varies

Clinical Information: The majority (>99%) of cervical epithelial neoplasms are the result of human papillomavirus (HPV) infection. High-risk (HR) HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) can result in both low-grade squamous intraepithelial lesions and high-grade squamous intraepithelial lesions, as well as invasive carcinomas.(1,2) Patients with both a negative cytology and negative HPV have been shown to be at extremely low risk for cervical neoplasia.(1,2) For women 30 years and older who have received a negative Pap test and concurrent negative HPV result, the American Cancer Society and American College of Obstetricians and Gynecologists recommendations for cervical screening state that physicians may lengthen the screening interval to 3 years when using the combined test. Patients deemed to be high risk by the clinician should be screened more frequently. The presence of HR-HPV types in cervical specimens identifies a subgroup of patients with a greater likelihood of having a high-grade squamous intraepithelial lesion. Current guidelines for follow-up of a cytology-negative/HPV-positive patient recommend repeat HPV testing in 12 months.(2) Persistent infection with HPV is the principal cause of cervical cancer and its precursor, cervical

intraepithelial neoplasia (CIN).(1-3) The presence of HPV has been implicated in more than 99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.(4-6) Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN, although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Papanicolaou (Pap) smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists, and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy, and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by polymerase chain reaction has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may: 1. Increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women aged 30 years and older with normal cytology 2. Reduce the need for unnecessary colposcopy and treatment in patients aged 21 years and older with cytology results showing atypical squamous cells of undetermined significance Recent data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in women who are HPV-16 and HPV-18 positive is 11.4% (95% CI 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in women who are HR-HPV negative.(7) Based in part on these data, the American Society for Colposcopy and Cervical Pathology now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 or HPV-18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.(4) The IMPACT trial evaluated the performance of the CINtec PLUS Cytology test as a triage test to stratify women aged 25 to 65 years who are cobas 4800 HPV positive in primary HPV cervical cancer screening for referral to colposcopy, and the performance of the CINtec PLUS Cytology test as a triage test to stratify women aged 30 to 65 years who are cobas 4800 HPV positive with NILM (negative for intraepithelial lesion or malignancy) Pap cytology in adjunctive cervical cytology and HPV screening for referral to colposcopy.(8) It is the responsibility of the physicians and other healthcare professionals or the US guidelines to provide guidance as to whether women with positive CINtec PLUS Cytology results should be referred to colposcopy, and what type of follow-up should be recommended for women who test negative for the CINtec PLUS.

Useful For: Screening for cervical carcinoma or intraepithelial lesions and the presence or absence of high-risk human papillomavirus (HR-HPV) when screening women aged 30 to 65 years for possible cervical neoplasia Aiding in triaging women with abnormal Papanicolaou (Pap) smear results Aiding in triaging women with positive HR-HPV but negative Pap smear results Aiding in triaging women aged 30 to 65 years with NILM (negative for intraepithelial lesion or malignancy) and 12 other HR-HPV positive test results using the cobas 4800 HPV Test in adjunctive cervical cytology and HR-HPV screening, to

determine the need for referral to colposcopy

Interpretation: Standard reporting, as defined by the Bethesda System is utilized. Human papillomavirus (HPV): A positive result indicates the presence of HPV DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. CINtec PLUS Cytology: If no cervical epithelial cells show simultaneous brown cytoplasmic immunostaining and red nuclear immunostaining, the CINtec PLUS Cytology test result is considered negative. For patients with a Papanicolaou (Pap) smear result of atypical squamous cells of undetermined significance and who are positive for high-risk HPV (HR-HPV), consider referral for colposcopy if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 or HPV-18, consider referral for colposcopy if clinically indicated. For women aged 30 to 65 years with a negative Pap smear, positive HR-HPV test result, but negative HPV-16 and HPV-18 and CINtec Plus positive, consider referral for colposcopy if clinically indicated For women aged 30 to 65 years with a negative Pap smear, positive HR-HPV test result, but negative HPV-16 and HPV-18 and CINtec Plus negative, consider repeat testing by both cytology and a HR-HPV test in 12 months.

Reference Values:

ThinPrep PAPANICOLAOU
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

HUMAN PAPILLOMAVIRUS (HPV)
Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

CINtec PLUS Cytology, Immunocytochemical dual stain for p16/Ki-67 has been performed.
Result: Negative

Clinical References: 1. Lorincz AT, Richart RM. Human papillomavirus DNA testing as an adjunct to cytology in cervical screening programs. Arch Pathol Lab Med. 2003;127(8):959-968 2. Wright TC Jr, Schiffman M. Adding a test for human papillomavirus DNA to cervical-cancer screening. N Engl J Med. 2003;348(6):489-490 3. Nayar R, Wilbur DC, eds. The Bethesda System for Reporting Cervical Cytology: Definitions, Criteria, and Explanatory Notes. 3rd ed. Springer International Publishing; 2015 4. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. J Low Genit Tract Dis. 2012;16(3):175-204 5. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12-19 6. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11(11):1048-1056 7. Wright TC Jr, Stoler MH, Sharma A, et al. Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV+, cytology-negative results. Am J Clin Pathol 2011;136(4):578-586 8. Package insert: CINtec PLUS Cytology. Roche Diagnostics; version 1018621US Rev D, 06/2024 9. Massad LS, Einstein MH, Huh WK, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors [published correction appears in J Low Genit Tract Dis. 2013 Jul;17(3):367]. J Low Genit Tract Dis. 2013;17(5 Suppl 1):S1-S27 10. Sherman ME, Lorincz AT, Scott DR, et al. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. J Natl Cancer Inst. 2003;95(1):46-52 11. Clarke MA, Cheung LC, Castle PE, et al. Five-year risk of cervical precancer following p16/Ki-67 dual-stain triage of HPV-positive women. JAMA Oncol. 2019;5(2):181-186. doi:10.1001/jamaoncol.2018.4270 12. Wentzensen N, Clarke MA, Bremer R, et al. Clinical evaluation of human papillomavirus screening with p16/Ki-67 dual stain triage in a large organized cervical cancer screening program [published correction appears in JAMA Intern Med. 2019 Jul 1;179(7):1007. doi:10.1001/jamainternmed.2019.2636.]. JAMA Intern Med. 2019;179(7):881-888. doi:10.1001/jamainternmed.2019.0306 13. Wright TC Jr, Stoler MH, Ranger-Moore J, et al. Clinical validation of p16/Ki-67 dual-stained cytology triage of HPV-positive women:

STPCO
70337

ThinPrep with Human Papillomavirus (HPV) Co-Test-Screen, Varies

Clinical Information: The majority (>99%) of cervical epithelial neoplasms are the result of human papillomavirus (HPV) infection. High-risk HPV (HR-HPV) types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) can result in both low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL), as well as invasive carcinomas.(1,2) Patients with both a negative cytology and negative HPV have been shown to be at extremely low risk for cervical neoplasia.(1,2) For women 30 years old and older who have received a negative Pap test and concurrent negative HPV result, the American Cancer Society and American College of Obstetricians and Gynecologists recommendations for cervical screening state that physicians may lengthen the screening interval to 3 years when using the combined test. Patients deemed to be high risk by the clinician should still be screened more frequently. The presence of HR-HPV types in cervical specimens identifies a subgroup of patients with a greater likelihood of having a HSIL. Current guidelines for follow-up of a cytology-negative/HPV-positive patient recommend repeat HPV testing in 12 months.(2) Persistent infection with HPV is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN).(1-3) The presence of HPV has been implicated in more than 99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.(4-6) Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists, and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy, and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. DNA testing by polymerase chain reaction has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may: 1. Increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology 2. Reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance Recent data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and HPV-18 positive women is 11.4% (95% CI 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women.(7) Based in part on these data, the American Society for Colposcopy and Cervical Pathology now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology.

Women who are found to be positive for HPV-16 or HPV-18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.(4)

Useful For: Screening for cervical carcinoma or intraepithelial lesions and the presence or absence of high-risk human papillomavirus (HR-HPV) when screening women over the age of 30 for possible cervical neoplasia Detection of high-risk HPV genotypes associated with the development of cervical cancer Aids in triaging women with abnormal Pap smear results Individual genotyping of HPV-16 or HPV-18 if present Aids in triaging women with positive HR-HPV but negative Pap smear results

Interpretation: Cytology: Standard reporting, as defined by the Bethesda System is utilized. Human papillomavirus (HPV): A positive result indicates the presence of HPV DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance Pap smear result and who are positive for high-risk HPV (HR-HPV), consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

Reference Values:

ThinPrep PAPANICOLAOU
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

HUMAN PAPILLOMAVIRUS (HPV)
Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Clinical References: 1. Lorincz AT, Richart RM: Human papillomavirus DNA testing as an adjunct to cytology in cervical screening programs. Arch Pathol Lab Med. 2003 Aug;127(8):959-968 2. Wright TC, Jr, Schiffman M: Adding a test for human papillomavirus DNA to cervical-cancer screening. N Engl J Med. 2003 Feb 6;348(6):489-490 3. Soloman D, Davey D, Kurman R, et al: The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002 Apr;287(16):2114-2119 4. Saslow D, Solomon D, Lawson HW, et al: American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer. J Low Genit Tract Dis. 2012 Jul;16(3):175-204 5. Walboomers JM, Jacobs MV, Manos MM, et al: Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999 Sep;189(1):12-19 6. de Sanjose S, Quint WG, Alemany L, et al: Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010 Nov;11(11):1048-1056 7. Wright TC Jr, Stoler MH, Sharma A, et al: Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV positive, cytology-negative results. Am J Clin Pathol. 2011 Oct;136(4):578-586 8. Massad LS, Einstein MH, Huh WK, et al: 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2013 Apr;17(5 Suppl 1):S1-S27 9. Sherman ME, Lorincz A, Scott DR, et al: Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. J Nat Cancer Inst. 2003 Jan 1;95(1):46-52

FFTIO
57708

Thiocyanate, Serum

Reference Values:

Toxic Thiocyanate concentrations: Greater than 10 mg/dL

THIO
65381

Thiopurine Metabolites, Whole Blood

Clinical Information: This test is primarily used to verify compliance, optimize therapy, and identify elevated metabolite concentrations that may result in toxicity after initiation of thiopurine drug therapy for the treatment of inflammatory bowel disease. Recommended time points for monitoring include: 4 weeks after starting treatment to verify patient compliance and look for early risk of toxicity; 12 to 16 weeks after starting therapy when 6-thioguanine nucleotides have reached steady-state; and annually.(1) It may also be ordered in patients who do not respond to therapy as expected or as needed for dose changes, flare-ups, signs of toxicity, or suspicion of noncompliance. The test will measure 6-methylmercaptopurine and 6-thioguanine nucleotides in erythrocytes.

Useful For: Aids physicians in dose adjustments, minimizing dose-dependent toxicity, and monitoring compliance of thiopurine drug therapy

Interpretation: Target 6-thioguanine concentrations are 235 to 450 pmol/8x10(8) red blood cell (RBC) with lower levels suggesting suboptimal dosing and higher levels associated with increased risk of myelotoxicity and leukopenia. High 6-methylmercaptopurine levels (greater than 5700 pmol/8x10[8] RBC) suggest an increased risk for hepatotoxicity and potentially "thiopurine hypermethylation."

Reference Values:
6-Thioguanine Nucleotides (6-TGN): 235-450 pmol/8x10(8) red blood cell (RBC)
6-Methylmercaptopurine (6-MMP): Less than or equal to 5700 pmol/8x10(8) RBC

Clinical References: 1. Goel RM, Blaker P, Mentzer A, Fong SCM, Marinaki AM, Sanderson JD. Optimizing the use of thiopurines in inflammatory bowel disease. Ther Adv Chronic Dis. 2015;6(3):138-146 2. Shipkova M, Armstrong VM, Wieland E, Oellerich M. Differences in nucleotide hydrolysis contribute to the differences between erythrocyte 6-thioguanine nucleotide concentrations determined by two widely used methods. Clin Chem. 2003:49(2):260-268 3. Boulieu R, Dervieux T. High-performance liquid chromatographic determination of methyl 6-mercaptopurine nucleotides (Me6-MPN) in red blood cells: analysis of Me6-MPN per se or Me6-MPN derivative? J Chromatogr B Biomed Sci Appl. 1999;730(2):273-276 4. Kirchherr H, Shipkova M, von Ahsen N. Improved method for therapeutic drug monitoring of 6-thioguanine nucleotides and 6-methylmercaptopurine in whole-blood by LC/MSMS using isotope-labeled internal standards. Ther Drug Monit. 2013:35(3):313-321

TPNUQ
610062

Thiopurine Methyltransferase (TPMT) and Nudix Hydrolase (NUDT15) Genotyping, Varies

Clinical Information: The thiopurine drugs are purine antimetabolites that are useful in the treatment of acute lymphoblastic leukemia, autoimmune disorders (eg, Crohn disease, rheumatoid arthritis), and organ transplant recipients. The thiopurine drugs, 6-mercaptopurine, 6-thioguanine, and azathioprine are prodrugs that require intracellular activation to 6-thioguanine nucleotides (6-TGN). This activation is catalyzed by multiple enzymes. The cytotoxic effects of thiopurine drugs are achieved mainly through incorporation of 6-TGN into DNA and RNA. The pathway that leads to synthesis of active cytotoxic 6-TGN is in competition with inactivation pathways catalyzed by thiopurine methyltransferase (TPMT). Evaluation of this pathway is important because the level of 6-TGN measured in red blood cells have been correlated with both thiopurine therapeutic efficacy and toxicity such as myelosuppression. TPMT activity is inherited as a monogenic codominant trait, and variable TPMT activity is associated with TPMT genetic variants. The distribution of TPMT activity in red blood cells is trimodal in the population of people with European ancestry, with approximately 0.3% having deficient (undetectable) TPMT activity, 11% low (intermediate) activity, and 89% normal TPMT activity. The allele for normal TPMT activity (wild type) has been designated TPMT*1. Four TPMT alleles, comprised of a combination of 3 different single-nucleotide variants, account for the majority of inactivating alleles in some ancestral populations,

including Europeans: TPMT*2, TPMT*3A, and TPMT*3C. Less frequently occurring TPMT alleles including TPMT*4, TPMT*5, TPMT*8, and TPMT*12 also have been implicated as deficiency alleles. If no TPMT variant alleles are detected by this assay, the most likely genotype is that of TPMT*1/*1, although the presence of other rarer alleles cannot be excluded. Nudix hydrolase (NUDT15) is thought to dephosphorylate the active metabolites of thiopurines, TGTP, and TdGTP, which prevents their incorporation into DNA and decreases their cytotoxic effects. Genetic variants in NUDT15 that decrease this activity are strongly associated with thiopurine-related myelosuppression. NUDT15 deficiency is most common among East Asian (22.6%), South Asian (13.6%), and Native American populations (12.5%-21.2%). Studies in other populations are ongoing. This test evaluates variants associated with NUDT15*2, NUDT15*3, NUDT15*4, and NUDT15 *5. If no NUDT15 variant alleles are detected by this assay, the most likely genotype is that of NUDT15*1/*1, although the presence of other rarer alleles cannot be excluded. Individuals with variants in both TPMT and NUDT15 have been identified and were significantly more sensitive to mercaptopurine than individuals heterozygous for a variant in only one gene. Integration of both TPMT and NUDT15 testing may allow for more accurate prediction of thiopurine-related toxicity risk to guide dosing, particularly among patients from diverse populations. Table 1. TPMT Enzyme Activity of Individual Star Alleles TPMT allele cDNA nucleotide change (NM_000367.4) Amino acid change Effect on enzyme metabolism *1 None (wild type) None (wild type) Normal function *2 c.238G>C p.Ala80Pro (p.A80P) No activity *3A c.460G>A and c.719A>G p.Ala154Thr (p.A154T) and p.Tyr240Cys (p.Y240C) No activity *3B c.460G>A p.Ala154Thr (p.A154T) No activity *3C c.719A>G p.Tyr240Cys (p.Y240C) No activity *4 c.626-1G>A Not applicable, splice site No activity *5 c.146T>C p.Leu49Ser (p.L49S) No activity *8 c.644G>A p.Arg215His (p.R215H) Reduced activity *12 c.374C>T p.Ser125Leu (p.S125L) Reduced activity Table 2. NUDT15 Enzyme Activity of Individual Star Alleles NUDT15 allele cDNA nucleotide change (NM_018283.3) Amino acid change Effect on enzyme metabolism *1 None (wild type) None (wild type) Normal activity *2 or *3 c.415C>T p.Arg139Cys (p.R139C) No activity *4 c.416G>A p.Arg139His (p.R139H) No activity *5 c.52G>A p.Val18Ile (p.V18I) No activity The US Food and Drug Administration, the Clinical Pharmacogenetics Implementation Consortium, and some professional societies recommend consideration of TPMT and NUDT15 genotype testing or TPMT enzyme activity testing along with NUDT15 genotype testing prior to the initiation of therapy with thiopurine drugs. There is substantial evidence linking TPMT and NUDT15 genotypes to phenotypic variability. Dose adjustments based upon TPMT and NUDT15 genotypes have reduced thiopurine-induced adverse effects without compromising desired antitumor and immunosuppressive therapeutic effects in several clinical settings. Genotyping is not impacted by other medications known to inhibit TPMT activity. Complementary clinical testing is available to measure TPMT enzymatic activity in erythrocytes (TPMT3 / Thiopurine Methyltransferase Activity Profile, Erythrocytes) if the clinician wants to check for lower TPMT enzyme activity, regardless of cause. Testing for TPMT enzyme activity is not impacted by variants in NUDT15.

Useful For: Predicting potential for toxicity to thiopurine drugs (6-mercaptopurine, 6-thioguanine, and azathioprine)

Interpretation: The TPMT genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the TPMT Nomenclature Committee.(1) NUDT15 genotype and associated star alleles are as described by Moriyama et al.(2) and catalogued in the Pharmacogene Variation Consortium (www.pharmvar.org). For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. TPMT nomenclature committee (TPMT Alleles): Table of TPMT Alleles. Linkoping University; Updated November 2022. Accessed March 19, 2025. Available at

https://liu.se/en/research/tpmt-nomenclature-committee 2. Moriyama T, Nishii R, Perez-Andreu V, et al. NUDT15 polymorphisms alter thiopurine metabolism and hematopoietic toxicity. Nat Genet. 2016;48(4):367-373. doi:10.1038/ng.3508 3. Appell ML, Berg J, Duley J, et al. Nomenclature for alleles of the thiopurine methyltransferase gene. Pharmacogenet Genomics. 2013;23(4):242-248. doi:10.1097/FPC.0b013e32835f1cc0 4. Nguyen CM, Mendes MA, Ma JD. Thiopurine methyltransferase (TPMT) genotyping to predict myelosuppression risk. PLoS Curr. 2011;3:RRN1236. doi:10.1371/currents.RRN1236 5. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-1105. doi:10.1002/cpt.1304 6. Weinshilboum R. Thiopurine pharmacogenetics: clinical and molecular studies of thiopurine methyltransferase. Drug Metab Dispos. 2001;29(4 Pt 2):601-605 7. Zaza G, Cheok M, Krynetskaia N, et al. Thiopurine pathway. Pharmacogenet Genomics. 2010;20(9):573-574. doi:10.1097/FPC.0b013e328334338f 8. Sterner RM, Hall PL, Matern D, Black JL, Moyer AM. Genotype and Phenotype Correlation of the TPMT*8 Allele in Thiopurine Metabolism. J Mol Diagn. 2024;26(11):988-994. doi:10.1016/j.jmoldx.2024.07.005 9. Pratt VM, Cavallari LH, Fulmer ML, et al. TPMT and NUDT15 Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, and Pharmacogenomics Knowledgebase. J Mol Diagn. 2022;24(10):1051-1063. doi:10.1016/j.jmoldx.2022.06.007

TPMT3
65188

Thiopurine Methyltransferase Activity Profile, Erythrocytes

Clinical Information: Thiopurine methyltransferase (TPMT) deficiency is a condition in which patients treated with standard doses of azathioprine (AZA, Imuran), 6-mercaptopurine (6-MP, Purinethol), or 6-thioguanine (6-TG, Thioguanine Tabloid) may develop life-threatening myelosuppression or severe hematopoietic toxicity. The metabolic conversion of AZA, 6-MP, or 6-TG to purine nucleotides and the subsequent incorporation of these nucleotides into DNA play an important role in both the therapeutic efficacy and toxicity of these drugs. A competitive catabolic route for the metabolism of thiopurines is catalyzed by the TPMT enzyme, which inactivates them by thiomethylation. A balance must be established between these competing metabolic pathways so that sufficient amounts of drug are converted to the nucleotide to act as an antimetabolite and antimetabolite levels do not become so high as to cause potentially lethal bone marrow suppression. TPMT deficiency is an autosomal recessive condition with an incidence of approximately 1 in 300 individuals homozygous for deleterious variants in the TPMT gene; about 10% of the population are heterozygous carriers of TPMT variants. Adverse effects of AZA, 6-MP, or 6-TG administration can be observed in individuals who are either homozygous or heterozygous for TPMT deficiency. TPMT hyperactivity is also a known phenotype. Individuals who are hypermetabolizers have therapeutic resistance to thiopurine drugs and therefore, cannot achieve therapeutic levels. If an individual with TPMT hyperactivity is treated with higher and higher doses of thiopurine drugs, they may develop severe hepatotoxicity. Therefore, treatment with alternative medications is recommended for hypermetabolizers. As such, knowing a patient's TPMT status prior to treatment with AZA, 6-MP, or 6-TG is important for purposes of calculating safe drug dosages for therapy.

Useful For: Detection of individuals with low thiopurine methyltransferase (TPMT) activity who are at risk for excessive myelosuppression or severe hematopoietic toxicity when taking thiopurine drugs Detection of individuals with hyperactive TPMT activity who have therapeutic resistance to thiopurine drugs and may develop hepatotoxicity if treated with these drugs

Interpretation: This assay is used to detect individuals with low and intermediate thiopurine methyltransferase (TPMT) activity who may be at risk for myelosuppression when exposed to standard doses of thiopurines, including azathioprine (Imuran), 6-mercaptopurine (Purinethol), or 6-thioguanine (Thioguanine Tabloid). TPMT is the primary metabolic route for inactivation of thiopurine drugs in the

bone marrow. When TPMT activity is low, it is predicted that proportionately more 6-mercaptopurine can be converted into the cytotoxic 6-thioguanine nucleotides that accumulate in the bone marrow causing excessive toxicity. This test can also detect TMPT hyperactivity. Individuals who are hypermetabolizers cannot achieve therapeutic levels as they have therapeutic resistance to thiopurine drugs. Severe hepatotoxicity may develop if an individual with TPMT hyperactivity is treated with higher and higher doses of thiopurine drugs. The activity of TPMT is measured by 3 different substrates. Reports include the quantitative activity level of TPMT for each of 3 different substrates and an interpretation of these results. When abnormal results are detected, a detailed interpretation is given, including an overview of results and suggestion as to whether patient has TPMT deficiency or hyperactivity, as well as discussion of treatment considerations. TPMT phenotype testing does not replace the need for clinical monitoring of patients treated with thiopurine drugs. Genotype for TPMT cannot be inferred from TPMT activity (phenotype). Phenotype testing should not be requested for patients currently treated with thiopurine drugs. TPMT activity is measured in red blood cells. If a patient has had a blood transfusion within 60 days of testing, the patient's true enzyme activity may not be accurately reflected.

Reference Values:

6-Methylmercaptopurine (normal): 3.00-6.66 nmol/mL/hour
6-Methylmercaptopurine riboside (normal): 5.04-9.57 nmol/mL/hour
6-Methylthioguanine riboside (normal): 2.70-5.84 nmol/mL/hour

Clinical References: 1. Relling MV, Gardner EE, Sandborn WJ, et al. Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. Clin Pharmacol Ther. 2011;89(3):387-391 2. Lennard L. Implementation of TPMT testing. Br J Clin Pharmacol. 2014;77(4):704-714 3. Schedel J, Godde A, Schutz E, et al. Impact of thiopurine methyltransferase activity and 6-thioguanine nucleotide concentrations in patients with chronic inflammatory diseases. Ann N Y Acad Sci. 2006;1069:477-491 4. Zhou S. Clinical pharmacogenomics of thiopurine S-methyltransferase. Curr Clin Pharmacol. 2006;1(1):119-128 5. Asadov C, Aliyeva G, Mustafayeva K. Thiopurine S-methyltransferase as a pharmacogenetic biomarker: Significance of testing and review of major methods. Cardiovasc Hematol Agents Med Chem. 2017;15(1):23-30

FSULU
75890

Thiosulfate, Urine

Reference Values:

Reporting limit determined each analysis

Creatinine (mg/L)
U.S. Population (10th-90th percentiles, median)

All participants:
335 - 2370 mg/L, median: 1180 (n=22,245)

Males:
495 - 2540 mg/L, median: 1370 (n=10, 610)

Females:
273 - 2170 mg/L, median: 994 (n=11,635)

Thiosulfate (mcg/mL)
Generally less than 9.2 mcg/mL (based on a median creatinine concentration of 1.18 g/L

Thiosulfate (Creatinine corrected) (mcg/g Creat)
Generally less than 7.8 mg/g creatinine

FFTHI
91126

Thiothixene (Navane)

Reference Values:
Reference Range: 10.0 - 30.0 ng/mL

TTSC
602184

Thrombin Time (Bovine), Plasma

Clinical Information: Prolonged clotting times may be associated with a wide variety of coagulation abnormalities including: -Deficiency or functional abnormality (congenital or acquired) of many of the coagulation proteins -Deficiency or functional abnormality of platelets -Specific factor inhibitors -Acute disseminated intravascular coagulation -Exogenous anticoagulants (eg, heparin, warfarin) The prothrombin time and activated partial thromboplastin time are first-order tests for coagulation abnormalities and are prolonged in many disorders. A battery of coagulation tests is often required to determine the cause of prolonged clotting times. Thrombin catalyzes the transformation of fibrinogen to fibrin (by cleaving fibrinopeptides A and B), which is followed by polymerization of fibrin to form a clot. The thrombin time (TT) test measures the time of clot formation when thrombin is added to citrated plasma. The phospholipid-dependent procoagulant enzyme cascades (intrinsic, extrinsic, and "common" pathway) are bypassed by the addition of exogenous thrombin. Therefore, the TT mainly reflects functions and interactions of solution-phase exogenous thrombin and endogenous fibrinogen.

Useful For: Detecting or excluding the presence of heparin or heparin-like anticoagulants (which act by enhancing antithrombin's inhibition of thrombin and other procoagulant enzymes) when used in conjunction with the reptilase time (RT) in evaluating unexplained prolonged clotting times Identifying the cause of a prolonged prothrombin time, activated partial thromboplastin time, or dilute Russell viper venom time when used in conjunction with the RT and fibrinogen assay

Interpretation: Prolongation of the thrombin time (TT) is consistent with the presence of heparin-like anticoagulants, hypofibrinogenemia, dysfibrinogenemia, fibrin degradation products, and antibody inhibitors of thrombin. An immeasurably prolonged TT is usually the result of heparin in the specimen or, rarely, the presence of thrombin antibodies or afibrinogenemia. When the TT test is performed with diluted bovine thrombin to achieve a normal plasma clotting time of about 20 seconds, the TT is capable of detecting unfractionated heparin at a concentration of 0.05 units/mL of heparin. Other tests useful in interpreting the significance of prolongation of the TT include: reptilase time (RT), human thrombin time, clottable fibrinogen assay, and the fibrin D-dimer assay. These tests are available as components of coagulation profile test panels. As seen in the following table, RT can help distinguish among the various causes of a prolonged TT. Thrombin time Reptilase time Causes Remarks Prolonged Prolonged Hypo- or afibrinogenemia Ascertain by determination of fibrinogen Prolonged Prolonged Dysfibrinogenemia Ascertain by specific assay Prolonged Normal Heparin or inhibitor of thrombin Differentiate by human TT and/or heparin assays Prolonged Prolonged Fibrin(ogen) split products (FSP) Ascertain by FSP or D-dimer assay Note: Rare congenital dysfibrinogenemias associated with venous thromboembolism (eg, fibrinogen Bordeaux) may demonstrate normal thrombin and reptilase times and normal Clauss fibrinogen levels.

Reference Values:
15.8-24.9 seconds

Clinical References: 1. Koepke JA: Coagulation testing systems. In: Practical Laboratory Hematology. Churchill Livingston; 1991 2. Corriveau DM, Fritsma G: Hemostasis and Thrombosis in the Clinical Laboratory. JB Lippincott Company; 1988 3. Galanakis DK: Plasma thrombin time and related tests. In: Williams Hematology. 5th ed. McGraw-Hill Book Company; 1995:L91-L93 4. Greaves M, Preston FE: Approach to the bleeding patient. In: Colman RW, Hirsh J, Marder VJ, et al. eds. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. 4th ed. JB Lippincott Company; 2001:783-837 5.

Turgeon TL, ed: Clinical Hematology. 6th ed. Wolkers Kluer and Co; 2018

FFTAC
75672

Thrombin-Antithrombin Complex

Clinical Information:

Reference Values:
<4.3 ng/mL
Pre-analytical conditions such as a difficult draw may spuriously increase test results.

AATHI
603184

Thrombophilia Profile Interpretation

Clinical Information: Thrombophilia is defined as an acquired or familial disorder associated with thrombosis. The clinical presentation of an underlying thrombophilia predominantly includes venous thromboembolism (deep vein thrombosis, pulmonary embolism, superficial vein thrombosis). Other manifestations that have been linked to thrombophilia include recurrent miscarriage and complications of pregnancy (eg, severe preeclampsia, abruptio placentae, intrauterine growth restriction, stillbirth). The current thrombophilia does not predict for arterial thrombosis. Demographic or environmental exposures that compound the risk of venous thromboembolism among persons with a thrombophilia include increasing age, male gender, obesity, surgery, trauma, hospitalization for medical illness, malignant neoplasm, prolonged immobility during travel (eg, prolonged airplane travel), oral contraceptive use, estrogen therapy (both oral and transdermal), tamoxifen and raloxifene therapy, and infertility drugs. Central venous catheters and transvenous pacemaker wires increase the risk for upper extremity deep vein thrombosis; this risk is unrelated to thrombophilia. Inherited thrombophilias include: -Deficiency due to reduced plasma protein level or dysfunctional protein of: -Antithrombin -Protein C -Protein S -Dysfibrinogenemias (rare) -Activated protein C resistance due to the factor V R506Q (Leiden) mutation -Prothrombin G20210A mutation Acquired thrombophilias include a lupus-like anticoagulant (antiphospholipid antibodies) and disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF). DIC/ICF may cause thrombotic as well as hemorrhagic events. Positive tests for DIC/ICF can also occur as consequences of thrombosis. Acquired deficiencies of fibrinogen, protein C, protein S, and antithrombin may be found in conjunction with liver disease (they are produced by the liver) or DIC/ICF and are of uncertain significance with respect to thrombosis risk. Acquired deficiencies of protein C and protein S are also found in patients with liver disease who are being treated with oral anticoagulants (eg, warfarin, Coumadin), since both of these proteins are dependent upon the action of vitamin K for normal function. Acquired protein S deficiency also occurs in thrombotic thrombocytopenic purpura, pregnancy or estrogen therapy, nephrotic syndrome, and sickle cell anemia. In acute illness, the level of acute-phase reactants rise (including C4b binding protein, which binds and inactivates protein S in the plasma) and the portion of bound protein S also rises leaving a lower proportion of free protein S. The significance of acquired protein S deficiency with respect to thrombosis risk is unknown.

Useful For: Interpretation of testing performed as part of a profile to evaluate patients with thrombosis or hypercoagulability states including detecting a lupus-like anticoagulant; dysfibrinogenemia; disseminated intravascular coagulation/intravascular coagulation and fibrinolysis, detecting a deficiency of antithrombin, protein C, or protein S, detecting activated protein C resistance (and the factor V R506Q [Leiden] mutation if indicated), and detecting the prothrombin G20210A mutation

Interpretation: An interpretive report will be provided when testing is completed, noting a presence or absence of thrombophilia.

Reference Values:
Only orderable as part of a profile. For more information see AATHR / Thrombophilia Profile, Plasma.

An interpretive report will be provided.

Clinical References: 1. Pengo V, Tripodi A, Reber G, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2009;7(10):1737-1740 2. Keeling D, Mackie I, Moore GW, et al. Guidelines on the investigation and management of antiphospholipid syndrome. Br J Haemotol. 2012;157(1):47-58 3. Clinical and Laboratory Standards Institute (CLSI). Laboratory Testing for the Lupus Anticoagulant; Approved Guideline. CLSI document H60-A., Clinical Laboratory Standards Institute, 2014

AATHR
603304

Thrombophilia Profile, Plasma and Whole Blood

Clinical Information: Thrombophilia is defined as an acquired or familial disorder associated with thrombosis. The clinical presentation of an underlying thrombophilia predominantly includes venous thromboembolism (deep vein thrombosis, pulmonary embolism, superficial vein thrombosis). Other manifestations that have been linked to thrombophilia include recurrent miscarriage and complications of pregnancy (eg, severe preeclampsia, abruptio placentae, intrauterine growth restriction, stillbirth). Thrombophilia does not predict arterial thrombosis. Demographic or environmental exposures that compound the risk of venous thromboembolism among persons with a thrombophilia include increasing age, male gender, obesity, surgery, trauma, hospitalization for medical illness, malignant neoplasm, prolonged immobility during travel (eg, prolonged airplane travel), oral contraceptive use, estrogen therapy (both oral and transdermal), tamoxifen and raloxifene therapy, and infertility drugs. Central venous catheters and transvenous pacemaker wires increase the risk for upper extremity deep vein thrombosis; this risk is unrelated to thrombophilia. Inherited thrombophilias include: -Deficiency due to reduced plasma protein level or dysfunctional protein of: -Antithrombin -Protein C -Protein S -Dysfibrinogenemias (rare) -Activated protein C resistance due to the factor V Leiden variant (F5 c.1601G>A; p.Arg534Gln, historically known as R506Q) -Prothrombin F2 c.*97G>A variant (historically known as G20210A) Acquired thrombophilias include a lupus-like anticoagulant (antiphospholipid antibodies) and disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF). DIC/ICF may cause thrombotic as well as hemorrhagic events. Positive tests for DIC/ICF can also occur as consequences of thrombosis. Acquired deficiencies of fibrinogen, protein C, protein S, and antithrombin may be found in conjunction with liver disease (they are produced by the liver) or DIC/ICF and are of uncertain significance with respect to thrombosis risk. Acquired deficiencies of protein C and protein S are also found in patients with liver disease who are being treated with oral anticoagulants (eg, warfarin, Coumadin), since both proteins are dependent upon the action of vitamin K for normal function. Acquired protein S deficiency also occurs in thrombotic thrombocytopenic purpura, pregnancy or estrogen therapy, nephrotic syndrome, and sickle cell anemia. In acute illness, the levels of acute-phase reactants rise (including C4b binding protein, which binds and inactivates protein S in the plasma), and the portion of bound protein S also rises, leaving a lower proportion of free protein S. The significance of acquired protein S deficiency with respect to thrombosis risk is unknown.

Useful For: Evaluating patients with thrombosis or hypercoagulability states Detecting a lupus-like anticoagulant; dysfibrinogenemia; disseminated intravascular coagulation/intravascular coagulation and fibrinolysis Detecting a deficiency of antithrombin, protein C, or protein S Detecting activated protein C resistance (and the factor V Leiden [p.Arg534Gln, historically known as R506Q] variant if indicated) Detecting the prothrombin F2 c.*97G>A variant (historically known as G20210A)

Interpretation: An interpretive report will be provided when testing is completed, noting the presence or absence of thrombophilia.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Pengo V, Tripodi A, Reber G, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2009(10):1737-1740. doi:10.1111/j.1538-7836.2009.03555.x 2. Keeling D, Mackie I, Moore GW, Greer IA, Greaves M, British Committee for Standards in Haematology: Guidelines on the investigation and management of antiphospholipid syndrome. Br J Haemotol. 2012;157(1):47-58. doi:10.1111/j.1365-2141.2012.09037.x 3. Clinical and Laboratory Standards Institute (CLSI). Laboratory Testing for the Lupus Anticoagulant; Approved Guideline. CLSI document H60-A. CLSI; 04/2014 4. Favaloro EJ and Lippi G. eds. Hemostasis and Thrombosis, Methods and Protocols. Humana Press; 2017

FFTPO
57822

Thrombopoietin (TPO)

Reference Values:
7 – 99 pg/mL

GNTHR
619271

Thrombosis Disorders, Comprehensive Gene Panel, Next-Generation Sequencing, Varies

Clinical Information: Thrombophilia is defined as an acquired or familial disorder associated with thrombosis. The clinical presentation of an underlying thrombophilia predominantly includes venous thromboembolism (deep vein thrombosis, pulmonary embolism, superficial vein thrombosis). Other manifestations linked to thrombophilia include recurrent miscarriage and complications of pregnancy (eg, severe preeclampsia, abruptio placentae, intrauterine growth restriction, and stillbirth). Determination of a hereditary thrombosis disorder contributing to thrombotic events in an individual or family can be useful for prognosis and risk assessment. Identification of an alteration that is known or suspected to cause disease can also be useful for determining the risk for thrombosis for family members. This panel evaluates 16 genes associated with a variety of hereditary thrombosis disorders, including thrombotic thrombocytopenic purpura; thrombophilia due to thrombin defect; thrombophilia due to activated protein C resistance; fibrinogen deficiencies (afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia, and hypodysfibrinogenemia); histidine-rich glycoprotein deficiency; paroxysmal nocturnal hemoglobinuria (somatic); familial hyperfibrinolysis; plasminogen deficiency and dysplasminogenemia; protein C deficiency; purpura fulminans; protein S deficiency; antithrombin deficiency; heparin cofactor 2 deficiency; and thrombomodulin deficiency. The risk for developing thrombosis associated with these syndromes varies. For example, the relative risk (95% CI) for the incidence of a first-lifetime venous thromboembolism event associated with antithrombin deficiency is 17.5 (9.1-33.8), protein C deficiency is 11.3 (5.7-22.3), and protein S deficiency is 32.4 (16.7-62.9).(2) Several of the genes on this panel have established thrombosis risk or expert group guidelines.(1-6) Indications for testing include, but are not limited to: -Individuals with venous thromboembolism (VTE) under the age of 50, recurrent and/or spontaneous VTE, or VTE at an unusual site (eg, hepatic, mesenteric, portal, cerebral veins) -Individuals with a strong family history of thrombosis or pulmonary embolism -Individuals with warfarin-induced skin necrosis or neonatal purpura fulminans -Individuals whose personal or family history indicates coinheritance of multiple hereditary thrombosis

Useful For: Evaluating hereditary thrombosis in patients with a personal or family history suggestive of a hereditary thrombosis disorder Confirming a hereditary thrombosis disorder diagnosis with the identification of a known or suspected pathogenic alteration in one or more of 16 genes associated with a variety of hereditary thrombosis disorders Determining the disease-causing alterations within one or

more of these 16 genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of a thrombosis disorder Identifying the causative alteration for genetic counseling purposes Prognosis and risk assessment based on the genotype-phenotype correlations Carrier testing for close family members of an individual with a hereditary thrombosis disorder diagnosis This test is not intended for prenatal diagnosis.

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Arachchillage DJ, Mackillop L, Chandratheva A, Motawani J, MacCallum P, Laffan M: Thrombophilia testing: A British Society for Haematology guideline. Brit J Haematol. 2022 Aug;198(3):443-458 2. Pruthi RK: Optimal utilization of thrombophilia testing. Int J Lab Hematol. 2017 May;39(s1):104-110 3. Middeldorp S: Inherited thrombophilia: a double-edged sword. Hematol-Am Soc Hematol Educ Program. 2016 Dec 2;1:1-9 4. Tregouet DA, Morange PE: What is currently known about the genetics of venous thromboembolism at the dawn of next generation sequencing technologies. Br J Haematol. 2018 Feb;180(3):335-345 5. International Society on Thrombosis and Haemostasis: Bleeding Thrombotic and Platelet Disorder TIER1 genes. ISTH; 2018. Updated July 2022. Accessed October 6, 2022. Available at: www.isth.org/page/GinTh_GeneLists 6. Megy K, Downes K, Simeoni I, et al: Curated disease-causing genes for bleeding, thrombotic, and platelet disorders: Communication from the SSC of the ISTH. J Thromb Haemost. 2019 Aug;17(8):1253-1260 7. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

THSIF
605244

Thrombospondin Type 1 Domain Containing 7A (THSD7A), Immunofluorescence

Clinical Information: Thrombospondin type 1 domain-containing 7A (THSD7A) is a target antigen in membranous nephropathy (MN) and is detected in approximately 3% to 5% of non- phospholipase A2 receptor (PLA2R)-associated MN patients. Differentiating THSD7A-associated MN from PLA2R-associated MN is critical as approximately 20% of patients with THSD7A-associated MN have solid malignancy suggesting that THSD7A-associated MN is more likely to be secondary to malignancy than PLA2R-associated MN.

Useful For: Diagnosis of thrombospondin type 1 domain-containing 7A (THSD7A)-associated membranous nephropathy

Interpretation: Staining is interpreted and reported as negative or positive.

Clinical References: 1. Hoxha E, Beck Jr LH, Wiech T et al. An indirect immunofluorescence method facilitates detection of thrombospondin type 1 domain-containing 7A-specific antibodies in membranous nephropathy. J Am Soc Nephrol. 2017;28:520-531 2. Larsen CP, Cossey LN, Bech LH. THSD7A staining of membranous glomerulopathy in clinical practice reveals cases with dual autoantibody positivity. Mod Pathol. 2016;29:421-426 3. Sharma SG, Larsen CP: Tissue staining for THSD7A in glomeruli correlates with serum antibodies in primary membranous nephropathy: a clinicopathological study. Mod Pathol. 2018;31(4):616-622

THSD7
607079

Thrombospondin Type-1 Domain-Containing 7A Antibodies, Serum

Clinical Information: Recently, autoantibodies against phospholipase A2 receptor (PLA2R) in the kidney were determined to be the major target antigen for patients with idiopathic/primary membranous nephropathy (MN).(1) Approximately 70% of patients with primary MN circulate anti-PLA2R antibodies, and in the remaining 30% (who are PLA2R-negative), anti-thrombospondin type-1 domain-containing 7A (THSD7A) was shown to have approximately a 10% prevalence (or about 3% of all primary MN patients).(2) Mouse podocytes express THSD7A and introduction of anti-THSD7A autoantibodies induces MN in murine models. Mouse podocytes do not express PLA2R so exogenous administration of anti-PLA2R does not recapitulate membranous nephropathy in mice.(3) Additionally, THSD7A has been described as a potential tumor antigen and, thus, it has been suggested that THSD7A-positive patients merit a thorough cancer screening.(4)

Useful For: Distinguishing primary from secondary membranous nephropathy cases with antibodies against THSD7A

Interpretation: Therapy outcome can be monitored by measuring the antibody titer. A titer increase, decrease, or disappearance generally precedes a change in clinical status. Thus, the determination of the antibody titer has a high predictive value with respect to clinical remission, relapse, or risk assessment after kidney transplantation.

Reference Values:
Negative

Clinical References: 1. Beck LH Jr, Bonegio RG, Lambeau G, et al: M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;361:11-21. doi: 10.1056/NEJMoa0810457 2. Tomas NM, Beck LH Jr, Meyer-Schwesinger C, et al: Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med. 2014;371:2277-2287.doi: 10.1056/NEJMoa1409354 3. Tomas NM, Hoxha E, Reinicke AT, et al: Autoantibodies against thrombospondin type 1 domain-containing 7A induce membranous nephropathy. J Clin Invest. 2016;126(7):2519-2532. doi: 10.1172/JCI85265 4. Stahl PR, Hoxha E, Wiech T, Schroder C, Simon R, Stahl RA: THSD7A expression in human cancer. Genes Chromosomes Cancer. 2017;56:314-327. doi: 10.1002/gcc.22440

THYM
82606

Thyme, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to thyme Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or

anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

TGAB
84382

Thyroglobulin Antibody, Serum

Clinical Information: Thyroglobulin autoantibodies bind thyroglobulin (Tg), a major thyroid-specific protein. Tg plays a crucial role in thyroid hormone synthesis, storage, and release. Tg is not secreted into the systemic circulation under normal circumstances. However, follicular destruction through inflammation (thyroiditis and autoimmune hypothyroidism), hemorrhage (nodular goiter), or rapid disordered growth of thyroid tissue, as may be observed in Graves disease or follicular cell-derived thyroid neoplasms, can result in leakage of Tg into the blood stream. This results in the formation of autoantibodies to Tg (anti-Tg) in some individuals. The same processes also may result in exposure of other "hidden" thyroid antigens to the immune system, resulting in the formation of autoantibodies to other thyroid antigens, in particular thyroid peroxidase (TPO) (anti-TPO). Since anti-Tg and anti-TPO autoantibodies are observed most frequently in autoimmune thyroiditis (Hashimoto disease), they were originally considered to be of possible pathogenic significance in this disorder. However, the consensus opinion today is that they are merely disease markers. It is felt that the presence of competent immune cells at the site of thyroid tissue destruction in autoimmune thyroiditis simply predisposes the patient to form autoantibodies to hidden thyroid antigens. In individuals with autoimmune hypothyroidism, 30% to 50% will have detectable anti-Tg autoantibodies, while 50% to 90% will have detectable anti-TPO autoantibodies. In Graves disease, both types of autoantibodies are observed at approximately half these rates. The presence of anti-Tg, which occurs in 15% to 30% of thyroid cancer patients, could result in

misleading Tg results. In immunometric assays, the presence of thyroid antibody can lead to false-low measurement, whereas it might lead to false-high results in competitive assays.

Useful For: As an adjunct in the diagnosis of autoimmune thyroid diseases: Hashimoto disease, postpartum thyroiditis, neonatal hypothyroidism, and Graves disease

Interpretation: Diagnosis of Autoimmune Thyroid Disease: Measurements of antithyroperoxidase (anti-TPO) have higher sensitivity and equal specificity to antithyroglobulin (anti-Tg) measurements in the diagnosis of autoimmune thyroid disease. Anti-Tg levels should, therefore, only be measured if anti-TPO measurements are negative but clinical suspicion of autoimmune thyroid disease is high. Detection of significant titers of anti-Tg or anti-TPO autoantibodies is supportive evidence for a diagnosis of Graves disease in patients with thyrotoxicosis. However, measurement of the pathogenic antithyrotropin receptor antibodies by binding assay (THYRO / Thyrotropin Receptor Antibody, Serum) or bioassay (TSI / Thyroid-Stimulating Immunoglobulin, Serum) is the preferred method of confirming Graves disease in atypical cases and under special clinical circumstances. Positive thyroid autoantibody levels in patients with high-normal or slightly elevated serum thyrotropin levels predict the future development of more profound hypothyroidism. Patients with postpartum thyroiditis with persistently elevated thyroid autoantibody levels have an increased likelihood of permanent hypothyroidism. In cases of neonatal hypothyroidism, the detection of anti-TPO or anti-Tg in the infant suggests transplacental antibody transfer, particularly if the mother has a history of autoimmune thyroiditis or detectable thyroid autoantibodies. The neonatal hypothyroidism is likely to be transient in these cases.

Reference Values:
<4.0 IU/mL
Reference values apply to all ages.

Clinical References: 1 Sapin P, d'Herbomez M, Gasser F, Meyer L, Schlienger JL: Increased sensitivity of a new assay for anti-thyroglobulin antibody detection in patients with autoimmune thyroid disease. Clin Biochem. 2003 Nov;36(8):611-616. doi: 10.1016/s0009-9120(03)00114-0 2. Saravanan P, Dayan CM: Thyroid autoantibodies. Endocrinol Metab Clin North Am. 2001 June;30(2):315-337 3. Baloch Z, Carayon P, Conte-Devolx B, et al: Laboratory Medicine Practice Guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease Thyroid. 2003 Jan;13(1):3-126 4. Soh SB, Aw TC: Laboratory testing in thyroid conditions - Pitfalls and clinical utility. Ann Lab Med. 2019 Jan;39(1):3-14. doi: 10.3343/alm.2019.39.1.3 5. Spencer C, Fatemi S: Thyroglobulin antibody (TgAb) methods - Strengths, pitfalls and clinical utility for monitoring TgAb-positive patients with differentiated thyroid cancer. Best Pract Res Clin Endocrinol Metab. 2013 Oct;27(5):701-712. doi: 10.1016/j.beem.2013.07.003 6. Netzel BC, Grebe SK, Carranza Leon BG, et al: Thyroglobulin (Tg) testing revisited: Tg assays, TgAb assays, and correlation of results with clinical outcomes. J Clin Endocrinol Metab. 2015 Aug;100(8):E1074-83. doi: 10.1210/jc.2015-1967 7. Algeciras-Schimnich A: Thyroglobulin measurement in the management of patients with differentiated thyroid cancer. Crit Rev Clin Lab Sci. 2018 May;55(3):205-218. doi: 10.1080/10408363.2018.1450830 8. Netzel BC, Grebe SK, Algeciras-Schimnich A: Usefulness of a thyroglobulin liquid chromatography-tandem mass spectrometry assay for evaluation of suspected heterophile interference. Clin Chem. 2014 Jul;60(7):1016-1018. doi: 10.1373/clinchem.2014.224816 9. Wassner AJ, Della Vecchia M, Jarolim P, Feldman HA, Huang SA: Prevalence and significance of thyroglobulin antibodies in pediatric thyroid cancer. J Clin Endocrinol Metab. 2017 Sep 1;102(9):3146-3153. doi: 10.1210/jc.2017-00286 10. Frohlich E, Wahl R: Thyroid autoimmunity: Role of anti-thyroid antibodies in thyroid and extra-thyroidal diseases. Front Immunol. 2017 May 9;8:521. doi: 10.3389/fimmu.2017.00521

TGABI
610071

Thyroglobulin Antibody, Serum

Clinical Information: Serum thyroglobulin (Tg) measurements are used in the follow-up of

differentiated follicular cell-derived thyroid carcinoma. Because Tg is thyroid specific, serum Tg concentrations should be undetectable or very low after the thyroid gland is removed during treatment for thyroid cancer. Most often Tg is measured by immunometric assays, as they are widely available in automated high-throughput instruments, have shorter turnaround times, and have functional sensitivities of 0.1 mcg/L or less. However, these immunoassays may be affected by the presence of both anti-thyroglobulin antibody (TgAb) and heterophile antibody interferences. The presence of TgAb might cause falsely low/undetectable Tg that can mask disease; whereas heterophile antibodies might cause falsely high Tg that can be mistaken for residual or recurrent disease. Some patients, due to exposure to animal antigens, have developed heterophile antibodies, such as human anti-mouse antibodies, that can interfere with immunoassay testing by binding to the animal antibodies used in immunoassays. In some sandwich immunoassays, including those for Tg, the presence of heterophile antibodies in the patient's sample might lead to a false-positive result. Although rare, false-negative results due to heterophile interference have also been reported in the literature. Manufacturers often add blocking agents to their reagents, but occasionally, patient samples containing heterophile antibodies are incompletely blocked and exhibit heterophile antibody interference. Subsequent reporting of erroneous results can have adverse effects on patient management, especially with tumor marker assays. Dilution of the specimen prior to assay performance often yields unexpected nonlinear results in the presence of interfering substances, such as heterophile antibodies or TgAb. Heterophile blocking tube treatment is also utilized for troubleshooting samples that exhibit potential heterophile interference. Finally, assessment of an analyte such as Tg with an alternative assay will often lead to apparent discrepant results in the presence of heterophile antibodies or TgAb interference. Measurement of Tg by liquid chromatography tandem mass spectrometry (Tg-MS) has been introduced as a method for accurate Tg quantitation in the presence of TgAb and heterophile antibodies. Tg-MS assays are based on peptide quantitation after tryptic digestion and immunocapture of Tg-specific peptides. The advantage of trypsin digestion is that all proteins are cleaved, including both TgAb and heterophile antibodies, thus eliminating them as interferences.

Useful For: Initial testing as a part of evaluating suspected interference from heterophile antibodies causing a falsely elevated thyroglobulin result

Interpretation: Anti-thyroglobulin (Tg) antibodies (Ab) may interfere with the measurement of Tg. TgAb should be measured in conjunction with every measurement of serum Tg to rule out potential interference. Anti-TgAb greater or equal to 1.8 IU/mL are likely to cause interference in the Tg immunoassay. In the Beckman Access Tg immunoassay utilized in this interference evaluation, the presence of TgAb is most likely to cause a reduction in measured Tg concentrations. Measurement of Tg by mass spectrometry is not affected by the presence of TgAb.

Reference Values:
Only orderable as part of profile. For more information see IETG / Interference Evaluation Heterophile, Thyroglobulin Tumor Marker, Serum.

<1.8 IU/mL
Reference values apply to all ages.

Clinical References: 1. Barbesino G, Algeciras-Schimnich A, Bornhorst JA. False positives in thyroglobulin determinations due to the presence of heterophile antibodies: an underrecognized and consequential clinical problem. Endocr Pract. 2021;27(5):396-400. doi:10.1016/j.eprac.2020.10.011 2. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-1214 3. Netzel BC, Grebe SKG, Algeciras-Schimnich A. Usefulness of a thyroglobulin liquid chromatography-tandem mass spectrometry assay for evaluation of suspected heterophile interference. Clin Chem. 2014;60(7):1016-1018 4. Algeciras-Schimnich A. Thyroglobulin measurement in the management of patients with differentiated thyroid cancer. Crit Rev Clin Lab Sci. 2018;55(3):205-218 5. Ward G, Simpson A, Boscato L, Hickman PE. The investigation of interferences

in immunoassay. Clin Biochem. 2017;50(18):1306-1311

THYR
70565

Thyroglobulin Immunostain, Technical Component Only

Clinical Information: Thyroglobulin is a glycoprotein product of thyroid epithelial cells, which is then complexed with iodine before being secreted as thyroid hormone in the blood. In normal thyroid, thyroglobulin staining is seen at the apical surface of thyrocytes and within the colloid in the center of thyroid follicles. The thyroglobulin antibody is useful in classifying poorly differentiated or metastatic thyroid carcinomas.

Useful For: Classification of thyroid carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Albores-Saavedra J, Nadji M, Civantos F, Morales AR. Thyroglobulin in carcinoma of the thyroid: an immunohistochemical study. Hum Pathol. 1983;14(1):62-66 2. Bejarano PA, Nikiforov YE, Swenson ES, Biddinger PW. Thyroid transcription factor-1, thyroglobulin, cytokeratin 7, and cytokeratin 20 in thyroid neoplasm. Appl Immunohistochem Mol Morphol. 2000;8(3):189-194 3. Rosai J. Immunohistochemical markers of thyroid tumors: significance and diagnostic applications. Tumor. 2003;89(5):517-519 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TGMS
62749

Thyroglobulin Mass Spectrometry, Serum

Clinical Information: Thyroglobulin (Tg) is a highly thyroid-specific large homodimeric glycoprotein (approximately 660 kDa). It contains 8% to 10% of carbohydrates and iodine. Thyroxine (T4) and triiodothyronine (T3) are synthesized on Tg within the lumen of thyroid follicles. For T4 and T3 release, Tg is reabsorbed into thyrocytes and proteolytically degraded, liberating T4 and T3 for secretion. Small amounts of intact Tg are secreted alongside T4 and T3 and are detectable in the serum of healthy individuals, with levels roughly paralleling thyroid size (0.5-1.0 ng/mL Tg per gram thyroid tissue, depending on thyrotropin [TSH] level). In situations of disordered thyroid growth (eg, goiter), increased thyroid activity (eg, Graves disease), or glandular destruction (eg, thyroiditis), larger amounts of Tg may be released into the circulation. Clinically, the main use of serum Tg measurements is in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is highly organ-specific, serum Tg concentrations should be undetectable, or very low, after the thyroid gland is removed during primary treatment for thyroid cancer. Current clinical guidelines consider a serum Tg of more than 1 ng/mL in an athyrotic individual as suspicious of possible residual or recurrent disease. To improve diagnostic accuracy, it is recommended this measurement be initially obtained after TSH stimulation, either following thyroid hormone withdrawal, or after injection of recombinant human TSH. Most patients will have a relatively low risk of recurrence and thereafter, will only require unstimulated Tg measurement. If unstimulated (on thyroxine) serum Tg measurements are less than 0.1 to 0.2 ng/mL, the risk of disease is below 1%. Patients with higher Tg levels, who have no demonstrable remnant of thyroid tissue, might require additional testing, such as additional stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg above 2 ng/mL is considered suspicious. There are 3 situations, when serum Tg measurement may be misleading: 1. Remnant thyroid tissue (see above, 0.5-1 ng/mL Tg per gram) 2. Antithyroglobulin autoantibodies (TgAb), which occur

in 15% to 30% of thyroid cancer patients, can lead to false-low measurement in immunometric assays (most commonly used); in competitive assays they may cause false-high results. 3. Heterophile antibodies (HAb), which are antibodies that are capable of interacting with the antibodies used in immunoassays, usually resulting in false-high measurements. Depending on the assay and the patient population, this can lead to erroneously high results in 0.1% to 3.0% of patients. Traditionally, there have been no reliable means to obtain accurate Tg measurements in patients with TgAb or HAb. However trypsin digestion of serum proteins, which cuts both antibodies and Tg into predictable fragments, has allowed accurate quantification of Tg in samples with antibody interferences through measurement of Tg-specific tryptic peptides by mass spectrometry.

Useful For: Accurate measurement of serum thyroglobulin (Tg) in patients with known or suspected antithyroglobulin autoantibodies (TgAb) or heterophile antibodies (HAb) Reflex testing of samples with previously unknown TgAb status that prove TgAb positive during immunoassay testing Assisting in the differential diagnosis of early phase silent thyroiditis versus Graves disease in patients without thyroid cancer (the mass spectrometry-based method would only be ordered if these patients have TgAb or HAb)

TGII
610072

Thyroglobulin, Interference Interpretation

Clinical Information: Serum thyroglobulin (Tg) measurements are used in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is thyroid-specific, serum Tg concentrations should be undetectable, or very low, after the thyroid gland is removed during treatment for thyroid cancer. Most often Tg is measured by immunometric assays as they are widely available in automated high-throughput instruments, have shorter turnaround times, and have functional sensitivities of 0.1 mcg/L or less. However, these immunoassays may be affected by the presence of both anti-thyroglobulin antibody (TgAb) and heterophile antibody interferences. The presence of TgAb might cause falsely low/undetectable Tg that can mask disease; whereas heterophile antibodies might cause falsely high Tg that can be mistaken for residual or recurrent disease. Some patients, due to exposure to animal antigens, have developed heterophile antibodies, such as human anti-mouse antibodies, that can interfere with immunoassay testing by binding to the animal antibodies used in immunoassays. In some sandwich immunoassays, including those for Tg, the presence of heterophile antibodies in the patient's sample might lead to a false-positive result. Although rare, false-negative assay results due to heterophile interference have also been reported in the literature. Manufacturers often add blocking agents to their reagents, but, occasionally, patient samples containing heterophile antibodies are incompletely blocked and exhibit heterophile antibody interference. Subsequent reporting of erroneous results can have adverse effects on patient management, especially with tumor marker assays. Dilution of the specimen prior to assay performance often yields unexpected nonlinear results in the presence of interfering substances such as heterophile antibodies and/or TgAb. Heterophile blocking tube treatment is also utilized for troubleshooting samples that exhibit potential heterophile interference. Finally, assessment of an analyte such as Tg with an alternative assay will often lead to apparent discrepant results in the presence of heterophile antibodies and/or TgAb interference. Measurement of Tg by liquid chromatography tandem mass spectrometry (Tg-MS) has been introduced as a method for accurate Tg quantitation in the presence of TgAb and heterophile antibodies. Tg-MS assays are based on peptide quantitation after tryptic digestion and immunocapture of Tg-specific peptides. The advantage of trypsin digestion is that all proteins are cleaved, including both TgAb and heterophile antibodies, thus eliminating them as interferences.

Useful For: Interpretation for the evaluation of suspected interference from heterophile antibodies causing a falsely elevated thyroglobulin result

Interpretation:

Reference Values:
Only orderable as part of profile. For more information see IETG / Interference Evaluation Heterophile, Thyroglobulin Tumor Marker, Serum.

An interpretive report will be provided.

Clinical References: 1. Barbesino G, Algeciras-Schimnich A, Bornhorst JA. False positives in thyroglobulin determinations due to the presence of heterophile antibodies: an underrecognized and consequential clinical problem. Endocr Pract. 2021;27(5):396-400. doi:10.1016/j.eprac.2020.10.011 2. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-1214 3. Netzel BC, Grebe SKG, Algeciras-Schimnich A. Usefulness of a thyroglobulin liquid chromatography-tandem mass spectrometry assay for evaluation of suspected heterophile interference. Clin Chem. 2014;60(7):1016-1018 4. Algeciras-Schimnich A. Thyroglobulin measurement in the management of patients with differentiated thyroid cancer. Crit Rev Clin Lab Sci. 2018;55(3):205-218 5. Ward G, Simpson A, Boscato L, Hickman PE. The investigation of interferences in immunoassay. Clin Biochem. 2017;50(18):1306-1311

HTGR
62936

Thyroglobulin, Tumor Marker Reflex, Serum

Clinical Information: Thyroglobulin (Tg) is a thyroid-specific glycoprotein (approximately 660 kDa) that serves as the source for thyroxine (T4) and triiodothyronine (T3) production within the lumen of thyroid follicles. For T4 and T3 release, Tg is reabsorbed into thyrocytes and proteolytically degraded, liberating T4 and T3 for secretion. Small amounts of intact Tg are secreted alongside T4 and T3 and are detectable in the serum of healthy individuals with levels roughly paralleling thyroid size (0.5-1.0 ng/mL Tg per gram thyroid tissue, depending on thyrotropin [TSH] level). In situations of disordered thyroid growth (eg, goiter), increased thyroid activity (eg, Graves disease), or glandular destruction (eg, thyroiditis), larger amounts of Tg may be released into the circulation. Clinically, the main use of serum Tg measurements is in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is thyroid-specific, serum Tg concentrations should be undetectable or very low after the thyroid gland is removed during treatment for thyroid cancer. Current clinical guidelines consider a serum Tg concentration above 1 ng/mL in an athyrotic individual as suspicious of possible residual or recurrent disease. To improve diagnostic accuracy, it is recommended this measurement be initially obtained after TSH stimulation, either following thyroid hormone withdrawal or after injection of recombinant human TSH. Most patients will have a relatively low risk of recurrence and thereafter will only require unstimulated Tg measurement. If unstimulated (on thyroxine) serum Tg measurements are less than 0.1 to 0.2 ng/mL, the risk of disease is below 1%. Patients with higher Tg levels, who have no demonstrable remnant of thyroid tissue, might require additional testing, such as additional stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg above 2 ng/mL is considered suspicious. The presence of anti-thyroglobulin autoantibodies (TgAb), which occur in 15% to 30% of patients with thyroid cancer, could lead to misleading Tg results. In immunometric assays, the presence of TgAb can lead to falsely low measurement, whereas it might lead to falsely high results in competitive assays. Traditionally, there have been no reliable means to obtain accurate Tg measurements in patients with TgAb. However, recently, trypsin digestion of serum proteins, which cuts both antibodies and Tg into predictable fragments, has allowed accurate quantification of Tg in samples with antibody interferences through measurement of Tg-specific tryptic peptides by mass spectrometry.

Useful For: Reporting of accurate thyroglobulin results, depending on the antithyroglobulin antibodies status of the patient Accurate measurement of serum thyroglobulin in patients with known or suspected antithyroglobulin autoantibodies or possible heterophile antibodies

Interpretation: Current guidelines recommend measurement of thyroglobulin (Tg) using a sensitive immunoassay (limit of quantification less than 1 ng/mL); for measurements of unstimulated Tg, the detection limit should be in the 0.1 to 0.2 ng/mL range. In all cases, serum anti-thyroglobulin autoantibodies (TgAb) should also be measured, preferably with a method that allows detection of low concentrations of TgAb. If TgAb are detected, the laboratory report should alert the ordering provider to the possibility of falsely low Tg results. If the apparent Tg concentration is below 1.0 ng/mL, the sample

should be remeasured by liquid chromatography tandem mass spectrometry (LC-MS/MS). This will allow confident detection of Tg in the presence of TgAb down to 0.2 ng/mL (risk of residual/recurrent disease <1%-3%). Samples from patients with Tg concentrations above 1.0 ng/mL might not require Tg measurement by mass spectrometry because current guidelines suggest further work-up may be necessary above this threshold. However, the positive predictive value for residual/recurrent disease is modest when Tg is just above this threshold (3%-25%) in athyrotic patients. Above 10 ng/mL, the risk of residual/recurrent disease is at least 25%, with many studies showing 60% to above 90% risks. In selected patients, it might also be useful to test TgAb positive samples by mass spectrometry, even if the Tg concentration is above 1.0 ng/mL but has not yet passed the 10 ng/mL threshold. These considerations are even more relevant in patients with a known thyroid remnant of a few grams, who may always have serum Tg concentrations of 1.0 to 10 ng/mL, owing to remnant Tg secretion, regardless of the presence or absence of residual/recurrent cancer. It has been determined that the presence of TgAb in serum can lead to underestimation of Tg concentration by immunometric methods. When TgAb are present in samples with detectable Tg, the Tg values may be underestimated by up to 60% in immunoassays. In addition, some specimens containing TgAb, which are negative for Tg by immunoassay, tested positive by LC-MS/MS. Therefore, measuring of Tg by LC-MS/MS is the preferred method in TgAb positive patients. Thyroglobulin by Immunoassay and Mass Spectrometry: Thyroglobulin (Tg) reference intervals are for patients with an intact thyroid and not for patients who have had surgery for thyroid cancer. Tg reference intervals in patients that have undergone thyroidectomy or any treatment for follicular thyroid cancer are dependent on the residual mass of the thyroid tissue after surgery. Tg results, regardless of concentration, should not be interpreted as absolute evidence for the presence or absence of papillary or follicular thyroid cancer. This result needs to be interpreted in the context of the clinical evaluation.

Reference Values:

THYROGLOBULIN ANTIBODY
<1.8 IU/mL

THYROGLOBULIN, TUMOR MARKER
< or =33 ng/mL

Clinical References: 1. Grebe SKG. Diagnosis and management of thyroid carcinoma: A focus on serum thyroglobulin. Expert Rev Endocrinol Metab. 2009;4(1):25-43. doi:10.1586/17446651.4.1.25 2. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer; Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-1214. doi:10.1089/thy.2009.0110 3. Pacini F, Catagana MG, Brilli L, Pentheroudakis G; on behalf of the ESMO Guidelines Working Group: Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v214-9. doi:10.1093/annonc/mdq190 4. National Comprehensive Cancer Network (NCCN) guidelines for treatment of cancer by site: version 4.2024: Thyroid Carcinoma. Accessed October 3, 2024. Available at www.nccn.org/professionals/physician_gls/default.aspx#site 5. Tuttle RM. Differentiated thyroid cancer: Role of serum thyroglobulin. In: Cooper DS, Ross DS, Mulder JE, eds. Updated June 27, 2023. Accessed October 3, 2024. Available at: www.uptodate.com/contents/differentiated-thyroid-cancer-role-of-serum-thyroglobulin

TFNAB
607714

Thyroglobulin, Tumor Marker, Fine-Needle Aspiration Biopsy Needle Wash

Clinical Information: Thyroglobulin (Tg) is a 660,000 Da glycoprotein produced exclusively by the follicular cells of the thyroid. Given the tissue specificity of Tg production, measurement of serum concentrations in athyrotic patients enables detection of persistence, recurrence, or metastasis of differentiated thyroid carcinoma. In addition, Tg measurement in biopsy specimens of nonthyroidal

tissues may assist in confirming and localizing metastatic disease. In papillary thyroid carcinoma (PTC), which accounts for greater than 80% of all thyroid cancer cases, most metastatic disease occurs in loco-regional lymph nodes in the neck, which are easily examined by ultrasound. Most suspicious nodes undergo ultrasonography-guided fine-needle aspiration biopsy (FNAB) for cytology examination to determine a diagnosis. Unfortunately, in up to 20% of cases, inadequate cellularity or nonrepresentative sampling precludes the diagnosis. Measurement of Tg in FNAB washes from lymph nodes suspected of metastatic PTC is used as an adjunct to cytology examination after ultrasonography-guided FNAB in situations where cytology is inconclusive. One of the advantages of the measurement of Tg in FNAB washes is that a dedicated needle pass is not necessary for analysis. Most often, the washout is performed by rinsing the FNAB needle with a small volume of saline immediately after the cellular component of the biopsy has been expelled for cytological examination. The diagnostic performance of Tg in FNAB washouts often allows for the accurate diagnosis of cases in which cytology is nondiagnostic. A meta-analysis of 24 studies and 2865 lymph nodes reported a pooled sensitivity of 95% and specificity of 94% for detection of metastatic PTC. The diagnostic performance of Tg in FNAB washes is superior in athyrotic patients. In studies that included patients with the thyroid gland, the sensitivity was 86.2% and specificity was 90.2%. Including only patients after thyroidectomy showed improved performance with a sensitivity of 96.9% and specificity of 94.1%. In an in-house study, a Tg cut-off of 1 ng/mL for FNAB-needle wash specimens provided 100% sensitivity and 96.2% specificity for the detection of metastatic thyroid carcinoma in lymph nodes from athyrotic patients. The diagnostic performance of Tg at the 1-ng/mL cut-off compared favorably with cytology (95.1% overall agreement) and allowed accurate diagnosis in 18 of the 19 cases in which cytology was nondiagnostic or not performed. A number of professional guidelines recommend the measurement of Tg in FNAB washouts from lymph nodes in cases of inadequate cytology or cases with conflicting cytological and ultrasound evaluations. Interpretation of Tg concentrations in FNAB needle washes from tissues other than lymph nodes is not well defined and needs to be considered on a case-by-case basis. The most established use is to determine the tissue origin of a thyroid mass/nodule or other neck mass/nodule that is suspected to be thyroid derived. This can be accomplished by measuring Tg, calcitonin and parathyroid hormone in the lesion. Measurement of Tg in thyroid bed tissue in patients, who underwent total thyroidectomy and radioactive iodine ablation, is a relatively frequent application of Tg testing and may differentiate scar tissue from residual normal thyroid tissue. Occasionally lesions in other organs might be biopsied to determine by Tg measurement if they are thyroid derived, if cytology/histology is not informative.

Useful For: Confirming or excluding metastases in enlarged or ultrasonographically suspicious lymph nodes from athyrotic individuals treated for differentiated thyroid cancer in conjunction with cytologic analysis Confirming or excluding the presence of thyroid tissue in the biopsied area from athyrotic individuals treated for differentiated thyroid cancer in conjunction with cytologic analysis This test is not useful for screening asymptomatic individuals for neoplastic disease.

Interpretation: Lymph Nodes: In athyrotic patients with a history of differentiated thyroid carcinoma, thyroglobulin (Tg) concentration greater than 1.0 ng/mL in the fine-needle aspiration biopsy (FNAB) needle wash suggests the presence of metastatic differentiated follicular cell-derived thyroid carcinoma in the biopsied area. Tg measurements yield reliable results in most cases with nondiagnostic cytology and are approximately equal in diagnostic accuracy to cytological examinations that are deemed sufficient for diagnosis. Non-lymph nodes: When measuring Tg in FNAB needle washes from thyroid bed tissue after total thyroidectomy and radioactive iodine ablation to differentiate thyroid versus scar tissue, an undetectable Tg concentration is consistent with the absence of thyroid-derived tissue (including thyroid carcinoma) at the site biopsied. Detectable Tg concentration is consistent with the presence of thyroid-derived tissue, but it is not indicative of the presence of malignancy. Measurement of Tg in FNAB needle washes from a thyroid nodule may be used to distinguish parathyroid versus follicular cell derived and C-cell derived thyroid tissue but cannot identify a malignant process in the nodule. For all other biopsied sites, eg, lung, kidney, liver, brain, bone, and various other sites, absence of measurable Tg in FNAB needle washes is consistent with the absence of thyroid-derived tissue (including thyroid carcinoma) at the site biopsied. A detectable Tg concentration

is consistent of the presence of thyroid-derived tissue, but it is not necessarily indicative of the presence of malignancy.

Reference Values:

Lymph node: < or =1.0 ng/mL

This cutoff has been validated for total needle wash volumes of < or =1.5 mL of normal saline. If wash volumes are substantially larger, a lower cutoff might apply.

Non-lymph node: An interpretive report will be provided.

Clinical References: 1. Grani G, Fumarola A: Thyroglobulin in lymph node fine-needle aspiration washout: a systematic review and meta-analysis of diagnostic accuracy. J Clin Endocrinol Metab. 2014 Jun;99(6):1970-1982 2. Snozek CLH, Chambers EP, Reading CC, et al: Serum thyroglobulin, high-resolution ultrasound, and lymph node thyroglobulin in diagnosis of differentiated thyroid carcinoma nodal metastases. J Clin Endocrinol Metab. 2007 Nov;92(11):4278-4281 3. Algeciras-Schimnich A: Thyroglobulin measurement in the management of patients with differentiated thyroid cancer. Crit Rev Clin Lab Sci. 2018 May;55(3):205-218

HTG2
62800

Thyroglobulin, Tumor Marker, Serum

Clinical Information: Thyroglobulin (Tg) is a thyroid-specific glycoprotein (approximately 660 kDa) that serves as the source for thyroxine (T4) and triiodothyronine (T3) production within the lumen of thyroid follicles. For T4 and T3 release, Tg is reabsorbed into thyrocytes and proteolytically degraded, liberating T4 and T3 for secretion. Small amounts of intact Tg are secreted alongside T4 and T3 and are detectable in the serum of healthy individuals with levels roughly paralleling thyroid size (0.5-1.0 ng/mL Tg per gram thyroid tissue, depending on thyroid-stimulating hormone [TSH] level). In situations of disordered thyroid growth (eg, goiter), increased thyroid activity (eg, Graves disease), or glandular destruction (eg, thyroiditis), larger amounts of Tg may be released into the circulation. Clinically, the main use of serum Tg measurements is in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is thyroid-specific, serum Tg concentrations should be undetectable or very low after the thyroid gland is removed during treatment for thyroid cancer. Current clinical guidelines consider a serum Tg concentrations above 1 ng/mL in an athyrotic individual as suspicious of possible residual or recurrent disease. To improve diagnostic accuracy, it is recommended this measurement be initially obtained after TSH stimulation, either following thyroid hormone withdrawal or after injection of recombinant human TSH. Most patients will have a relatively low risk of recurrence and will thereafter only require unstimulated Tg measurement. If unstimulated (on thyroxine) serum Tg measurements are less than 0.1 to 0.2 ng/mL, the risk of disease is below 1%. Patients with higher Tg levels who have no demonstrable remnant of thyroid tissue might require additional testing, such as further stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg above 2 ng/mL is considered suspicious. The presence of antithyroglobulin autoantibodies (TgAb), which occur in 15% to 30% of patients with thyroid cancer, could lead to misleading Tg results. In immunometric assays, the presence of TgAb can lead to falsely low results, whereas it might lead to falsely high results in competitive assays. Traditionally, there have been no reliable means to obtain accurate Tg measurements in patients with TgAb. However, recently trypsin digestion of serum proteins, which cuts both antibodies and Tg into predictable fragments, has allowed accurate quantification of Tg in samples with antibody interferences through measurement of Tg by mass spectrometry. See TGMS / Thyroglobulin Mass Spectrometry, Serum for accurate analysis of patients who are known to be TgAb positive. If TgAb status is unknown, see HTGR / Thyroglobulin, Tumor Marker Reflex, Serum. When HTGR is ordered, TgAb testing is performed first. If TgAb is negative (<1.8 IU/mL), Tg is assayed by immunoassay (sensitive down to 0.1 ng/mL). If TgAb is positive, Tg is assayed by mass spectrometry (sensitive down to 0.2 ng/mL).

Useful For: Follow-up of patients with differentiated thyroid cancers after thyroidectomy and

radioactive iodine ablation

Interpretation: Current guidelines recommend measurement of thyroglobulin (Tg) with a sensitive immunoassay (limit of quantification <1.0 ng/mL); for measurements of unstimulated Tg, the detection limit should be in the 0.1 to 0.2 ng/mL range. In all cases, serum thyroglobulin autoantibodies (TgAb) should also be measured, preferably with a method that allows detection of low concentrations of TgAb. If TgAb are detected, the laboratory report should alert the ordering provider to the possibility of falsely low Tg results if using an immunometric assay. If the apparent Tg concentration is below 1.0 ng/mL, the sample should be remeasured by mass spectrometry. This will allow accurate detection of Tg, in the presence of TgAb, down to 0.2 ng/mL (risk of residual/recurrent disease <1%-3%). Samples from patients with Tg concentrations above 1.0 ng/mL might not require Tg measurement by mass spectrometry because current guidelines suggest further workup might be necessary above this threshold. However, the positive predictive value for residual/recurrent disease is modest when Tg is just above this threshold (3%-25%) in athyrotic patients. Above 10 ng/mL, the risk of residual/recurrent disease is at least 25%, with many studies showing 60% to above 90% risks. In selected patients, therefore, it might also be useful to test TgAb positive samples by mass spectrometry, even if the Tg concentration is above 1.0 ng/mL but not above the 10 ng/mL threshold. These considerations are even more relevant in patients with a known thyroid remnant of a few grams, who may always have serum Tg concentrations of 1.0 to 10 ng/mL, owing to remnant Tg secretion, regardless of the presence or absence of residual/recurrent cancer. It has been determined that the presence of antithyroglobulin autoantibodies (TgAb) in serum can lead to underestimation of Tg concentration by immunometric methods. When TgAb are present in samples with detectable Tg, the Tg values may be underestimated by up to 60% in immunoassays. In addition, approximately 20% of specimens containing TgAb, which are negative for Tg by immunoassay, tested positive by liquid chromatography tandem mass spectrometry. Therefore, measuring Tg by mass spectrometry is the preferred method in TgAb positive patients. Thyroglobulin reference intervals are for patients with an intact thyroid and not for patients who have had surgery for thyroid cancer. Tg reference intervals in patients that have undergone thyroidectomy or any treatment for follicular thyroid cancer are dependent on the residual mass of the thyroid tissue after surgery. Tg results, regardless of concentration, should not be interpreted as absolute evidence for the presence or absence of papillary or follicular thyroid cancer. This result needs to be interpreted in the context of the clinical evaluation.

Reference Values:

Thyroglobulin Tumor Marker
< or =33 ng/mL

Thyroglobulin Antibody:
<1.8 IU/mL
Reference values apply to all ages.

Clinical References: 1. Grebe SKG. Diagnosis and management of thyroid carcinoma: a focus on serum thyroglobulin. Exp Rev Endocrinol Metab. 2009;4(1):25-43. doi:10.1586/17446651.4.1.25 2. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-1214. doi:10.1089/thy.2009.0110 3. Pacini F, Catagana MG, Brilli L, et al. Thyroid cancer. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v214-9. doi:10.1093/annonc/mdq190 4. National Comprehensive Cancer Network (NCCN) guidelines for treatment of cancer by site: version 4.2024: Thyroid Carcinoma. Accessed January 22, 2025. Available at www.nccn.org/professionals/physician_gls/default.aspx#site 5. Tuttle, RM: Serum thyroglobulin in the management of differentiated thyroid cancer. Updated June 27, 2023. Accessed January 22, 2025. Available at www.uptodate.com/contents/differentiated-thyroid-cancer-role-of-serum-thyroglobulin

TGQN
610070

Thyroglobulin, Tumor Marker, Serum

Clinical Information: Serum thyroglobulin (Tg) measurements are used in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is thyroid specific, serum Tg concentrations should be undetectable or very low after the thyroid gland is removed during treatment for thyroid cancer. Most often Tg is measured by immunometric assays as they are widely available in automated high-throughput instruments, have shorter turnaround times, and have functional sensitivities of 0.1 mcg/L or less. However, these immunoassays may be affected by the presence of both anti-thyroglobulin antibody (TgAb) and heterophile antibody interferences. The presence of TgAb might cause falsely low/undetectable Tg that can mask disease; whereas heterophile antibodies might cause falsely high Tg that can be mistaken for residual or recurrent disease. Some patients, due to exposure to animal antigens, have developed heterophile antibodies, such as human anti-mouse antibodies, that can interfere with immunoassay testing by binding to the animal antibodies used in immunoassays. In some sandwich immunoassays, including those for Tg, the presence of heterophile antibodies in the patient's sample might lead to a false-positive result. Although rare, false-negative assay results due to heterophile interference have also been reported in the literature. Manufacturers often add blocking agents to their reagents, but occasionally, patient samples containing heterophile antibodies are incompletely blocked and exhibit heterophile antibody interference. Subsequent reporting of erroneous results can have adverse effects on patient management, especially with tumor marker assays. Dilution of the specimen prior to assay performance often yields unexpected nonlinear results in the presence of interfering substances such as heterophile antibodies and/or TgAb. Heterophile blocking tube treatment is also utilized for troubleshooting samples that exhibit potential heterophile interference. Finally, assessment of an analyte such as Tg with an alternative assay will often lead to apparent discrepant results in the presence of heterophile antibodies and/or TgAb interference. Measurement of Tg by liquid chromatography tandem mass spectrometry (Tg-MS) has been introduced as a method for accurate Tg quantitation in the presence of TgAb and heterophile antibodies. Tg-MS assays are based on peptide quantitation after tryptic digestion and immunocapture of Tg-specific peptides. The advantage of trypsin digestion is that all proteins are cleaved, including both TgAb and heterophile antibodies, thus eliminating them as interferences.

Useful For: Quantitative thyroglobulin measurement as a part of evaluating suspected interference from heterophile antibodies causing a falsely elevated thyroglobulin result

Interpretation:

Reference Values:
Only orderable as part of profile. For more information see IETG / Interference Evaluation Heterophile, Thyroglobulin Tumor Marker, Serum.

< or =33 ng/mL

Clinical References: 1. Barbesino G, Algeciras-Schimnich A, Bornhorst JA. False positives in thyroglobulin determinations due to the presence of heterophile antibodies: an underrecognized and consequential clinical problem. Endocr Pract. 2021;27(5):396-400. doi:10.1016/j.eprac.2020.10.011 2. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-1214 3. Netzel BC, Grebe SKG, Algeciras-Schimnich A. Usefulness of a thyroglobulin liquid chromatography-tandem mass spectrometry assay for evaluation of suspected heterophile interference. Clin Chem. 2014;60(7):1016-1018 4. Algeciras-Schimnich A. Thyroglobulin measurement in the management of patients with differentiated thyroid cancer. Crit Rev Clin Lab Sci. 2018;55(3):205-218 5. Ward G, Simpson A, Boscato L, Hickman PE. The investigation of interferences in immunoassay. Clin Biochem. 2017;50(18):1306-1311

TAB
82041

Thyroid Autoantibodies Profile, Serum

Clinical Information: TGAB: Thyroglobulin autoantibodies bind thyroglobulin (Tg), a major thyroid-specific protein. Tg plays a crucial role in thyroid hormone synthesis, storage, and release. Tg is not secreted into the systemic circulation under normal circumstances. However, follicular destruction through inflammation (thyroiditis and autoimmune hypothyroidism), hemorrhage (nodular goiter), or rapid disordered growth of thyroid tissue, as may be observed in Graves disease or follicular cell-derived thyroid neoplasms, can result in leakage of Tg into the blood stream. This results in the formation of autoantibodies to Tg (anti-Tg) in some individuals. The same processes also may result in exposure of other "hidden" thyroid antigens to the immune system, resulting in the formation of autoantibodies to other thyroid antigens, in particular thyroid peroxidase (TPO) (anti-TPO). Since anti-Tg and anti-TPO autoantibodies are observed most frequently in autoimmune thyroiditis (Hashimoto disease), they were originally considered to be of possible pathogenic significance in this disorder. However, the consensus opinion today is that they are merely disease markers. It is felt that the presence of competent immune cells at the site of thyroid tissue destruction in autoimmune thyroiditis simply predisposes the patient to form autoantibodies to hidden thyroid antigens. In individuals with autoimmune hypothyroidism, 30% to 50% will have detectable anti-Tg autoantibodies, while 50% to 90% will have detectable anti-TPO autoantibodies. In Graves disease, both types of autoantibodies are observed at approximately half these rates. The presence of anti-Tg, which occurs in 15% to 30% of thyroid cancer patients, could result in misleading Tg results. In immunometric assays, the presence of thyroid antibody can lead to false-low measurement; whereas it might lead to false-high results in competitive assays. TPO: Thyroperoxidase (TPO) is an enzyme involved in thyroid hormone synthesis, catalyzing the oxidation of iodide on tyrosine residues in thyroglobulin for the synthesis of triiodothyronine and thyroxine (tetraiodothyronine). TPO is a membrane-associated hemo-glycoprotein expressed only in thyrocytes and is one of the most important thyroid gland antigens. Disorders of the thyroid gland are frequently caused by autoimmune mechanisms with the production of autoantibodies. Anti-TPO antibodies activate complement and are thought to be significantly involved in thyroid dysfunction and the pathogenesis of hypothyroidism. The determination of TPO antibody levels is the most sensitive test for detecting autoimmune thyroid disease (eg, Hashimoto thyroiditis, idiopathic myxedema, and Graves disease), and detectable concentrations of anti-TPO antibodies are observed in most patients with these disorders. The highest TPO antibody levels are observed in patients suffering from Hashimoto thyroiditis. In this disease, the prevalence of TPO antibodies is about 90% of cases, confirming the autoimmune origin of the disease. These autoantibodies also frequently occur (60%-80%) in the course of Graves disease. In patients with subclinical hypothyroidism, the presence of TPO antibodies is associated with an increased risk of developing overt hypothyroidism. Many clinical endocrinologists use the TPO antibody test as a diagnostic tool in deciding whether to treat a patient with subclinical hypothyroidism, and Mayo Clinic Laboratories endorses this practice. For more information, see Thyroid Function Ordering Algorithm.

Useful For: As an adjunct in the diagnosis of autoimmune thyroid diseases: Hashimoto disease, postpartum thyroiditis, neonatal hypothyroidism, and Graves disease Differentiating thyroid autoimmune disorders from nonautoimmune goiter or hypothyroidism As a diagnostic tool in deciding whether to treat a patient who has subclinical hypothyroidism

Interpretation: Diagnosis of Autoimmune Thyroid Disease: Measurements of antithyroperoxidase (TPO) have higher sensitivity and equal specificity to antithyroglobulin (anti-Tg) measurements in the diagnosis of autoimmune thyroid disease. Anti-Tg levels should, therefore, only be measured if anti-TPO measurements are negative, but clinical suspicion of autoimmune thyroid disease is high. Detection of significant titers of anti-Tg or anti-TPO autoantibodies is supportive evidence for a diagnosis of Graves disease in patients with thyrotoxicosis. However, measurement of the pathogenic antithyrotropin (anti-thyroid stimulating hormone)) receptor antibodies by binding assay (THYRO / Thyrotropin Receptor Antibody, Serum) or bioassay (TSI / Thyroid-Stimulating Immunoglobulin, Serum) is the preferred method of confirming Graves disease in atypical cases and under special clinical circumstances. Positive thyroid autoantibody levels in patients with high-normal or slightly elevated

serum thyrotropin levels predict the future development of more profound hypothyroidism. Patients with postpartum thyroiditis with persistently elevated thyroid autoantibody levels have an increased likelihood of permanent hypothyroidism. In cases of neonatal hypothyroidism, the detection of anti-TPO or anti-Tg in the infant suggests transplacental antibody transfer, particularly if the mother has a history of autoimmune thyroiditis or detectable thyroid autoantibodies. The neonatal hypothyroidism is likely to be transient in these cases. In patients with subclinical hypothyroidism, the presence of thyroperoxidase (TPO) antibodies predicts a higher risk of developing overt hypothyroidism, 4.3% per year versus 2.1% per year in antibody-negative individuals. Furthermore, it raises the concern that such patients may be at increased risk of developing other autoimmune diseases, such as adrenal insufficiency and type 1 diabetes. The frequency of detectable anti-TPO observed in nonimmune thyroid disease is similar to the 10% to 12% observed in a healthy population with normal thyroid function. There is a good association between the presence of autoantibodies against TPO and histological thyroiditis. However, in view of the extensive regenerative capacity of the thyroid under the influence of thyrotropin, chronic thyroid disease may be present for years before the clinical manifestation of hypothyroidism becomes evident, if ever.

Reference Values:

THYROGLOBULIN ANTIBODY
<4.0 IU/mL
Reference values apply to all ages.

THYROPEROXIDASE ANTIBODIES
<9.0 IU/mL
Reference values apply to all ages.

Clinical References: 1 Sapin P, d'Herbomez M, Gasser F, Meyer L, Schlienger JL: Increased sensitivity of a new assay for anti-thyroglobulin antibody detection in patients with autoimmune thyroid disease. Clin Biochem. 2003 Nov;36(8):611-616. doi: 10.1016/s0009-9120(03)00114-0 2. Saravanan P, Dayan CM: Thyroid autoantibodies. Endocrinol Metab Clin North Am. 2001 June;30(2):315-337 3. Baloch Z, Carayon P, Conte-Devolx B, et al: Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease Thyroid 2003 Jan;13(1):3-126 4. Algeciras-Schimnich A: Thyroglobulin measurement in the management of patients with differentiated thyroid cancer. Crit Rev Clin Lab Sci. 2018 May;55(3):205-218. doi: 10.1080/10408363.2018.1450830 5. Frohlich E, Wahl R: Thyroid autoimmunity: Role of anti-thyroid antibodies in thyroid and extra-thyroidal diseases. Front Immunol. 2017 May 9;8:521. doi: 10.3389/fimmu.2017.00521 6. Feldt-Rasmussen U: Analytical and clinical performance goals for testing autoantibodies to thyroperoxidase, thyroglobulin, and thyrotropin receptor. Clin Chem. 1996 Jan;42(1):160-163 7. Gharib H, Tuttle RM, Baskin HJ, et al: Consensus Statement #1: Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. Thyroid. 2005 Jan;15(1):24-28. doi: 10.1089/thy.2005.15.24 8. Freedman DB, Halsall D, Marshall WJ, Ellervik C: Thyroid disorders. In: Rifai N, Horvath AR, Wittwer CT: eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1572-1616

THSCM
83633

Thyroid Function Cascade, Serum

Clinical Information: This test utilizes a cascaded testing approach to efficiently evaluate and monitor functional thyroid status. The cascade begins with thyrotropin (TSH, formerly thyroid-stimulating hormone) as a screening assay. In patients with an intact pituitary-thyroid axis, TSH provides a physiologic indicator of the functional level of thyroid hormone activity. Increased TSH indicates inadequate thyroid hormone, and suppressed TSH indicates excess thyroid hormone. Transient TSH abnormalities may be found in seriously ill, hospitalized patients, so this is not the ideal setting to assess thyroid function. However, even in these patients, TSH works better than total T4 (thyroxine, an alternative screening test). When TSH is normal, no additional testing will be necessary. However, when the TSH result is abnormal, appropriate follow-up tests will automatically be performed. If TSH is below

0.3 mIU/L or above 4.2 mIU/L, free T4 is performed. The supplemental measurement of free T4 in patients with abnormal TSH measurements allows one to better assess the severity of the changes. Serum T3 (triiodothyronine) levels often are depressed in sick and hospitalized patients, caused in part by the biochemical shift to the production of reverse T3. Therefore, T3 generally is not a reliable predictor of hypothyroidism. However, in a small subset of hyperthyroid patients, hyperthyroidism may be caused by overproduction of T3 (T3 toxicosis). To help diagnose and monitor this subgroup, T3 is measured on all specimens with suppressed TSH and normal free T4 concentrations. Detectable concentrations of antithyroperoxidase (anti-TPO) antibodies are observed in patients with autoimmune thyroiditis and may cause the destruction of thyroid tissue, eventually resulting in hypothyroidism. Anti-TPO antibodies are measured in all specimens with elevated TSH concentrations. For more information, see Thyroid Function Ordering Algorithm.

Useful For: Screening for a diagnosis of thyroid disease

Interpretation: In primary hypothyroidism, thyrotropin (TSH, formerly thyroid-stimulating hormone) levels will be elevated. In primary hyperthyroidism, TSH levels will be low. The ability to quantitate circulating levels of TSH is important in evaluating thyroid function. It is especially useful in the differential diagnosis of primary (thyroid) from secondary (pituitary) and tertiary (hypothalamus) hypothyroidism. In primary hypothyroidism, TSH levels are significantly elevated, while in secondary and tertiary hypothyroidism, TSH levels are low or normal. Elevated or low TSH in the context of normal free thyroxine is often referred to as subclinical hypo- or hyperthyroidism, respectively. Thyrotropin-releasing hormone (TRH) stimulation differentiates all types of hypothyroidism by observing the change in patient TSH levels in response to TRH. Typically, the TSH response to TRH stimulation is exaggerated in cases of primary hypothyroidism, absent in secondary hypothyroidism, and delayed in tertiary hypothyroidism. Most individuals with primary hyperthyroidism have TSH suppression and do not respond to TRH stimulation test with an increase in TSH over their basal value. Sick, hospitalized patients may have falsely low or transiently elevated TSH.

Reference Values:

0-5 days: 0.7-15.2 mIU/L
6 days-2 months: 0.7-11.0 mIU/L
3-11 months: 0.7-8.4 mIU/L
1-5 years: 0.7-6.0 mIU/L
6-10 years: 0.6-4.8 mIU/L
11-19 years: 0.5-4.3 mIU/L
> or =20 years: 0.3-4.2 mIU/L

Clinical References: 1. Peyro Saint Paul L, Debruyne D, Bernard D, Mock DM, Defer GL: Pharmacokinetics and pharmacodynamics of MD1003 (high-dose biotin) in the treatment of progressive multiple sclerosis. Expert Opin Drug Metab Toxicol. 2016;12(3):327-344. doi:10.1517/17425255.2016.1136288 2. Grimsey P, Frey N, Bendig G, et al: Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. J Pharmacokinet Pharmacodyn. 2017;2(4):247-256. doi:10.4155/ipk-2017-0013 3. Package insert: TSH Reagent. Roche Diagnostics; V2, 03/2020 4. Fatourechi V, Lankarani M, Schryver PG, Vanness DJ, Long KH, Klee GG: Factors influencing clinical decisions to initiate thyroxine therapy for patients with mildly increased serum thyrotropin (5.1-10.0 mIU/L). Mayo Clin Proc. 2003;78(5):554-560. doi:10.4065/78.5.554 5. Wilson JD, Foster D, Kronenburg HM, et al: Williams Textbook of Endocrinology. 9th ed. WB Saunders Company; 1998 6. Melmed S, Polonsky KS, Larsen PR, et al: Williams Textbook of Endocrinology. 12th ed. Elsevier Saunders Company; 2011:348-414 7. Heil W, Ehrhardt V: Reference Intervals for Adults and Children 2008. 9th ed. Roche Diagnostics; 09/2009

TTF8G
70575

Thyroid Transcription Factor (8G7G3/1) Immunostain, Technical Component Only

Clinical Information: Thyroid transcription factor 1 (TTF1) is a nuclear protein expressed in thyroid follicular cells, type II pneumocytes, and a subset of bronchial cells. Given its relative specificity for cells of thyroid or lung origin, this immunostain is often included in a panel to identify the primary site for carcinomas of unknown origin.

Useful For: Identification of thyroid or lung cells as the primary tumor site in carcinomas of unknown origin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Comperat E, Zhang F, Perrotin C, et al. Variable sensitivity and specificity of TTF-1 antibodies in lung metastatic adenocarcinoma of colorectal origin. Mod Pathol. 2005;18:1371-1376 2. Penman D, Downie I, Roberts F. Positive immunostaining for thyroid transcription factor-1 in primary and metastatic colonic adenocarcinoma: a note of caution. J Clin Pathol. 2006;59:663-664 3. Katoh R, Kawaoi A, Miyagi E, et al. Thyroid transcription factor-1 in normal, hyperplastic, and neoplastic follicular thyroid cells examined by immunohistochemistry and nonradioactive in situ hybridization. Mod Pathol. 2000;13(5):570-576 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TTFSP
70576

Thyroid Transcription Factor (SPT24) Immunostain, Technical Component Only

Clinical Information: Thyroid transcription factor 1 (TTF1) is a nuclear protein expressed in thyroid follicular cells, type II pneumocytes, and a subset of bronchial cells. Given its relative specificity for cells of thyroid or lung origin, this immunostain is often included in a panel to identify the primary site for carcinomas of unknown origin.

Useful For: Part of a panel of immunostains to identify the primary site for carcinomas of unknown origin

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Bejarano PA, Nikiforov YE, Swenson ES, Biddinger PW. Thyroid transcription factor-1, thyroglobulin, cytokeratin 7, and cytokeratin 20 in thyroid neoplasms. Appl Immunohistochem Mol Morphol. 2000;8(3):189-194 2. Comperat E, Zhang F, Perrotin C, et al. Variable sensitivity and specificity of TTF-1 antibodies in lung metastatic adenocarcinoma of colorectal origin. Mod Pathol. 2005;18(10):1371-1376 3. Folpe AL, Gown AM, Lamps LW, et al. Thyroid transcription factor-1: immunohistochemical evaluation in pulmonary neuroendocrine tumors. Mod Pathol. 1999;12(1):5-8 4. Matoso A, Singh K, Jacob R, et al. Comparison of thyroid transcription factor-1

expression by 2 monoclonal antibodies in pulmonary and nonpulmonary primary tumors. Appl Immunohistochem Mol Morphol. 2010;18(2):142-149 5. Yatabe Y, Mitsudomi T, Takahashi T. TTF-1 expression in pulmonary adenocarcinomas. Am J Surg Pathol. 2002;26(6):767-773 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TTFK5
70489

Thyroid Transcription Factor 1 (TTF1) (SPT24) and Keratin 5 (KRT5) Immunostain, Technical Component Only

Clinical Information: Thyroid transcription factor 1 (TTF1) is a nuclear protein (detected by the chromogen 3,3'-diaminobenzidine) expressed in thyroid follicular cells, type II pneumocytes, and a subset of bronchial cells. Keratin 5 is a type II cytokeratin (detected by the chromogen fast red) that dimerizes with the type I cytokeratin 14 forming intermediate filaments in the basal layer of the epidermis. Keratin 5 is useful for differentiating squamous cell carcinoma (KRT5 positive) from pulmonary adenocarcinomas (KRT5 negative). This immunostain is often included in a panel to identify the primary site for carcinomas of unknown origin.

Useful For: Thyroid transcription factor 1aids in the classification of carcinomas of unknown origin Keratin 5 aids in the identification of squamous cell carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Kargi A, Gurel D, Tuna B. The diagnostic value of TTF-1, CK 5/6, and p63 immunostaining in classification of lung carcinomas. Appl Immunohistochem Mol Morphol. 2007;15(4):415-420 2. Whithaus K, Fukuoka J, Prihoda TJ, Jagirdar J. Evaluation of napsin A, cytokeratin 5/6, p63, and thyroid transcription factor 1 in adenocarcinoma versus squamous cell carcinoma of the lung. Arch Pathol Lab Med. 2012;136(2):155-162 3. Sterlacci W, Savic S, Schmid T, et al. Tissue-sparing application of the newly proposed IASLC/ATS/ERS classification of adenocarcinoma of the lung shows practical diagnostic and prognostic impact. Am J Clin Pathol. 2012;137(6):946-956 4. Tran L, Mattsson JS, Nodin B, et al. Various antibody clones of napsin A, thyroid transcription factor 1, and p40 and comparisons with cytokeratin 5 and p63 in histopathologic diagnostics of non-small cell lung carcinoma. Appl Immunohistochem Mol Morphol. 2016;24(9):648-659 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TSH
70574

Thyroid-Stimulating Hormone (TSH), Beta Immunostain, Technical Component Only

Clinical Information: Thyroid-stimulating hormone (TSH) stimulates thyroid growth and production of thyroid hormones. TSH-producing cells constitute approximately 5% of the cells of the normal anterior pituitary. Antibodies to TSH are used in a panel to subclassify pituitary adenomas.

Useful For: Part of a panel of immunostains used in the classification of pituitary adenomas

Interpretation: This test does not include pathologist interpretation, only technical performance of

the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Molitch ME. Diagnosis and Treatment of Pituitary Adenomas: A Review. JAMA. 2017;317(5):516-524. doi:10.1001/jama.2016.19699 2. Mete O, Gomez-Hernandez K, Kucharczyk W, et al. Silent subtype 3 pituitary adenomas are not always silent and represent poorly differentiated monomorphous plurihormonal Pit-1 lineage adenomas. Mod Pathol. 2016;29(2):131-142. doi:10.1038/modpathol.2015.151 3. Cossu G, Daniel RT, Pierzchala K, et al. Thyrotropin-secreting pituitary adenomas: a systematic review and meta-analysis of postoperative outcomes and management. Pituitary. 2019;22(1):79-88. doi:10.1007/s11102-018-0921-3 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

STSH
8939

Thyroid-Stimulating Hormone-Sensitive (s-TSH), Serum

Clinical Information: Thyrotropin (TSH, formerly thyroid-stimulating hormone) is a glycoprotein hormone consisting of 2 subunits. The alpha subunit is similar to those of follicle-stimulating hormone, human chorionic gonadotropin, and luteinizing hormone. The beta subunit is different from those of the other glycoprotein hormones and confers its biochemical specificity. TSH is synthesized and secreted by the anterior pituitary in response to a negative feedback mechanism involving concentrations of free triiodothyronine and free thyroxine. Additionally, the hypothalamic tripeptide, thyrotropin-releasing hormone, directly stimulates TSH production. TSH interacts with specific cell receptors on the thyroid cell surface and gives rise to 2 main actions. First, it stimulates cell reproduction and hypertrophy. Second, it stimulates the thyroid gland to synthesize and secrete triiodothyronine and thyroxine. Serum TSH concentrations exhibit a diurnal variation with the peak occurring during the night and the nadir occurring between 10 a.m. and 4 p.m. This biological variation does not influence the interpretation of the test result since most clinical TSH measurements are performed on ambulatory patients between 8 a.m. and 6 p.m. When hypothalamic-pituitary function is normal, a log/linear inverse relationship between serum TSH and free thyroxine exists. See Thyroid Function Ordering Algorithm in Special Instructions.

Useful For: Screening for thyroid dysfunction and detecting mild (subclinical), as well as overt, primary hypo- or hyperthyroidism in ambulatory patients Monitoring patients on thyroid replacement therapy Confirmation of thyrotropin (TSH, formerly thyroid-stimulating hormone) suppression in thyroid cancer patients on thyroxine suppression therapy Prediction of thyrotropin-releasing hormone-stimulated TSH response

Interpretation: In primary hypothyroidism, thyrotropin (TSH, formerly thyroid-stimulating hormone) levels will be elevated. In primary hyperthyroidism, TSH levels will be low. The ability to quantitate circulating levels of TSH is important in evaluating thyroid function. It is especially useful in the differential diagnosis of primary (thyroid) from secondary (pituitary) and tertiary (hypothalamus) hypothyroidism. In primary hypothyroidism, TSH levels are significantly elevated, while in secondary and tertiary hypothyroidism, TSH levels are low or normal. Elevated or low TSH in the context of normal free thyroxine is often referred to as subclinical hypo- or hyperthyroidism, respectively. Thyrotropin-releasing hormone (TRH) stimulation differentiates all types of hypothyroidism by observing the change in patient TSH levels in response to TRH. Typically, the TSH response to TRH stimulation is exaggerated in cases of primary hypothyroidism, absent in secondary hypothyroidism, and delayed in tertiary hypothyroidism. Most individuals with primary hyperthyroidism have TSH suppression and do not respond to TRH stimulation with an increase in TSH over their basal value. Sick, hospitalized patients may have falsely low or transiently elevated TSH.

Reference Values:
0-5 days: 0.7-15.2 mIU/L
6 days-2 months: 0.7-11.0 mIU/L
3-11 months: 0.7-8.4 mIU/L
1-5 years: 0.7-6.0 mIU/L
6-10 years: 0.6-4.8 mIU/L
11-19 years: 0.5-4.3 mIU/L
> or =20 years: 0.3-4.2 mIU/L

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

TSI
8634

Thyroid-Stimulating Immunoglobulin, Serum

Clinical Information: Autoimmune thyroid disease is characterized by the presence of autoantibodies against various thyroid components, namely the thyrotropin (formerly thyroid-stimulating hormone: TSH) receptor (TSHR), thyroid-peroxidase (TPO), and thyroglobulin (Tg), as well as an inflammatory cellular infiltrate of variable severity within the gland. Among the autoantibodies found in autoimmune thyroid disease, TSHR autoantibodies are most closely associated with disease pathogenesis. All forms of autoimmune thyrotoxicosis (Graves disease, hashitoxicosis, neonatal thyrotoxicosis) are caused by the production of TSHR-stimulating autoantibodies. The role of the TPO and Tg autoantibodies in either autoimmune thyrotoxicosis or autoimmune hypothyroidism is less well established; they may merely represent epiphenomena. Detectable concentrations of anti-TPO antibodies are observed in most patients with autoimmune thyroid disease (eg, Hashimoto thyroiditis, idiopathic myxedema, and Graves disease). Autoantibodies that bind and transactivate the TSHR lead to stimulation of the thyroid gland independent of the normal feedback-regulated TSH stimulation. These TSHR autoantibodies also are known as long-acting thyroid-stimulator or thyroid-stimulating immunoglobulins (TSI). Some patients with Graves disease also have TSHR-blocking antibodies, which do not transactivate the TSHR. The balance between TSI and TSHR-blocking antibodies, as well as their individual titers, are felt to be determinants of Graves disease severity. At least 20% of patients with autoimmune hypothyroidism also have evidence either of TSHR-blocking antibodies or, less commonly, TSI. TSHR autoantibodies may be found before autoimmune thyrotoxicosis becomes biochemically or clinically manifest. Since none of the treatments for Graves disease aim at the underlying disease process, but rather ablate thyroid tissue or block thyroid hormone synthesis, TSI may persist after apparent cure. TSI are IgG antibodies and can, therefore, cross the placental barrier causing neonatal thyrotoxicosis. First-order tests for autoimmune thyroid disease include TPO / Thyroperoxidase Antibodies, Serum (most suited for suspected cases of autoimmune hypothyroidism) and THYRO / Thyrotropin Receptor Antibody, Serum. Thyrotropin receptor antibody (TSHR-antibody) is a binding assay that detects both TSI and TSHR-blocking autoantibodies; it can be used instead of this TSI assay for most applications, as long as the results are interpreted in the clinical context. The TSHR-antibody test has a shorter turnaround time than the TSI assay, is less expensive, and if interpreted within the clinical context, has excellent correlation with the TSI assay. Specific detection of TSI is accomplished by this second-order bioassay.

Useful For: Second-order testing for autoimmune thyroid disease, including: -Differential diagnosis of etiology of thyrotoxicosis in patients with ambiguous clinical signs or contraindicated (eg, pregnant or breast-feeding) or indeterminate thyroid radioisotope scans -Diagnosis of clinically suspected Graves disease (eg, extrathyroidal manifestations of Graves disease: endocrine exophthalmos, pretibial myxedema, thyroid acropachy) but normal thyroid function tests -Determining the risk of neonatal thyrotoxicosis in a fetus of a pregnant female with active or past Graves disease -Differential diagnosis of gestational thyrotoxicosis versus first-trimester manifestation or recurrence of Graves disease -Assessing the risk of Graves disease relapse after antithyroid drug treatment A combination of TSI / Thyroid-Stimulating Immunoglobulin, Serum and THYRO / Thyrotropin Receptor Antibody, Serum is useful as an adjunct in the diagnosis of unusual cases of hypothyroidism (eg, Hashitoxicosis).

Interpretation: The sensitivity and specificity of an elevated thyroid-stimulating immunoglobulins (TSI) index for Graves disease diagnosis depends on whether patients have clinically active, untreated disease or disease treated with antithyroid drugs. Using a TSI index of 1.3 as the cutoff level in newly diagnosed, untreated patients, the sensitivity and specificity are higher than 90%. For a higher cutoff of 1.8, specificity approaches 100%, but sensitivity decreases somewhat. In patients with inactive or treated Graves disease the specificity is similar, while sensitivity is lower, ranging from 50% to 80%. Significant neonatal thyrotoxicosis is likely if a pregnant woman with a history of Graves disease has a TSI index above 3.9 during the last trimester, regardless of her remission status. Lesser elevations are only occasionally associated with neonatal thyrotoxicosis. This is particularly relevant for women who have previously undergone thyroid-ablative therapy or are on active antithyroid drug treatment and therefore, no longer display biochemical or clinical evidence of thyrotoxicosis. Gestational thyrotoxicosis, which is believed to be due to a combination of human chorionic gonadotropin cross-reactivity on the thyrotropin receptor (TSHR) and transient changes in thyroid hormone protein binding, is not associated with an elevated TSI index. Finding an elevated TSI index in this setting suggests underlying Graves disease. An elevated TSI index at the conclusion of a course of anti-thyroid drug treatment is highly predictive of relapse of Graves disease. However, the converse, a normal TSI index, is not predictive of prolonged remission. In patients with thyroid function tests that fluctuate between hypo- and hyperthyroidism or vice versa, a clearly elevated TSHR-antibody level (>25%) and a simultaneous TSI index that is normal or only minimally elevated (1.3-1.8) suggest a diagnosis of possible Hashitoxicosis.

Reference Values:

< or =1.3 TSI index

Reference values apply to all ages.

Clinical References: 1. Grebe SKG. Thyroid disease. In: King RA, Rotter JI, Motulsky AG, eds. The Genetic Basis of Common Diseases. 2nd ed. Oxford University Press; 2002:397-430 2. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26(10):1343-1421. doi:10.1089/thy.2016.0229 3. Kahaly GJ, Bartalena L, Hegedus L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018;7(4):167-186 4. Lytton SD, Schluter A, Banga PJ. Functional diagnostics for thyrotropin hormone receptor autoantibodies: bioassays prevail over binding assays. Front Biosci (Landmark Ed). 2018;23(11):2028-2043 5. De Leo S, Pearce EN. Autoimmune thyroid disease during pregnancy. Lancet Diabetes Endocrinol. 2018;6(7):575-586 6. Stan MN, Algeciras-Schimnich A, Murthy V, Thapa P, Araki N. Diagnostic utility of a new assay for thyroid stimulating immunoglobulins in Graves' disease and thyroid eye disease. Thyroid. 2022;32(2):170-176. doi:10.1089/thy.2021.0299

TPO
81765

Thyroperoxidase Antibodies, Serum

Clinical Information: Thyroperoxidase (TPO) is an enzyme involved in thyroid hormone synthesis, catalyzing the oxidation of iodide on tyrosine residues in thyroglobulin for the synthesis of triiodothyronine and thyroxine (tetraiodothyronine). TPO is a membrane-associated hemo-glycoprotein expressed only in thyrocytes and is one of the most important thyroid gland antigens. Disorders of the thyroid gland are frequently caused by autoimmune mechanisms with the production of autoantibodies. Anti-TPO antibodies activate complement and are thought to be significantly involved in thyroid dysfunction and the pathogenesis of hypothyroidism. The determination of TPO antibody levels is the most sensitive test for detecting autoimmune thyroid disease (eg, Hashimoto thyroiditis, idiopathic myxedema, and Graves disease), and detectable concentrations of anti-TPO antibodies are observed in most patients with these disorders. The highest TPO antibody levels are observed in patients suffering from Hashimoto thyroiditis. In this disease, the prevalence of TPO antibodies is about 90% of cases, confirming the autoimmune origin of the disease. These autoantibodies also frequently occur (60%-80%) in the course of Graves disease. In patients with subclinical hypothyroidism, the presence of TPO antibodies is associated with an increased risk of developing overt hypothyroidism. Many clinical

endocrinologists use the TPO antibody test as a diagnostic tool in deciding whether to treat a patient with subclinical hypothyroidism, and Mayo Clinic Laboratories endorses this practice. For more information, see Thyroid Function Ordering Algorithm.

Useful For: Aiding in the diagnosis of thyroid autoimmune disorders Differentiating thyroid autoimmune disorders from nonautoimmune goiter or hypothyroidism As a diagnostic tool in deciding whether to treat a patient who has subclinical hypothyroidism

Interpretation: Values above 9.0 IU/mL generally are associated with autoimmune thyroiditis, but elevations are also seen in other autoimmune diseases. In patients with subclinical hypothyroidism, the presence of thyroperoxidase (TPO) antibodies predicts a higher risk of developing overt hypothyroidism, 4.3% per year versus 2.1% per year in antibody-negative individuals. Furthermore, it raises the concern that such patients may be at increased risk of developing other autoimmune diseases, such as adrenal insufficiency and type 1 diabetes. The frequency of detectable anti-TPO observed in nonimmune thyroid disease is similar to the 10% to 12% observed in a healthy population with normal thyroid function. There is a good association between the presence of autoantibodies against TPO and histological thyroiditis. However, in view of the extensive regenerative capacity of the thyroid under the influence of thyrotropin, chronic thyroid disease may be present for years before the clinical manifestation of hypothyroidism becomes evident, if ever.

Reference Values:
<9.0 IU/mL
Reference values apply to all ages.

Clinical References: 1. Feldt-Rasmussen U: Analytical and clinical performance goals for testing autoantibodies to thyroperoxidase, thyroglobulin, and thyrotropin receptor. Clin Chem. 1996 Jan;42(1):160-163 2. Gharib H, Tuttle RM, Baskin HJ, et al: Consensus Statement #1: Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. Thyroid. 2005 Jan;15(1):24-28. doi: 10.1089/thy.2005.15.24 3. Freedman DB, Halsall D, Marshall WJ, Ellervik C: Thyroid disorders. In: Rifai N, Horvath AR, Wittwer CT: eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1572-1616

THYRO
81797

Thyrotropin Receptor Antibody, Serum

Clinical Information: Autoimmune thyroid disease is characterized by the presence of autoantibodies against various thyroid components, namely the thyrotropin receptor, thyroid peroxidase, and thyroglobulin, as well as by an inflammatory cellular infiltrate of variable severity within the gland. Among the autoantibodies found in autoimmune thyroid disease, thyrotropin receptor autoantibodies (TRAb) are most closely associated with disease pathogenesis. All forms of autoimmune thyrotoxicosis (Graves disease [GD], Hashitoxicosis, neonatal thyrotoxicosis) are caused by the production of stimulating TRAb. These autoantibodies, also known as long-acting-thyroid-stimulators or thyroid-stimulating immunoglobulins (TSI), bind to the receptor and transactivate it, leading to stimulation of the thyroid gland independent of the normal feedback-regulated thyrotropin stimulation. Some patients with GD also have TRAb that do not transactivate the thyrotropin receptor. The balance between stimulating and blocking antibodies, as well as their individual titers, is felt to be a determinant of GD severity. Some patients with autoimmune hypothyroidism also have evidence of either blocking TRAb or, rarely, TSI. Thyrotropin receptor autoantibodies may be detected before autoimmune thyrotoxicosis becomes biochemically or clinically manifest. Since none of the treatments for GD are aimed at the underlying disease process but rather ablate thyroid tissue or block thyroid hormone synthesis, TSI may persist after apparent clinical cure. This is of particular relevance for pregnant women with a history of GD treated with thyroid-ablative therapy. Some of these women may continue to produce TSI. Since

TSI are IgG antibodies, they can cross the placental barrier causing neonatal thyrotoxicosis. While the gold standard for thyroid-stimulating immunoglobulins is the bioassay (see TSI / Thyroid-Stimulating Immunoglobulin, Serum), the TRAb test has a shorter turnaround time, less analytical variability, and is less expensive.

Useful For: Recommended first-line test for detection of thyrotropin receptor antibodies Differential diagnosis of etiology of thyrotoxicosis in patients with ambiguous clinical findings and/or contraindicated (eg, pregnant or breast-feeding) or nondiagnostic thyroid radioisotope scans Diagnosing clinically suspected Graves disease (GD) (eg, extrathyroidal manifestation of GD include endocrine exophthalmos, pretibial myxedema, thyroid acropachy) in patients with normal thyroid function tests Determining the risk of neonatal thyrotoxicosis in a fetus of a pregnant female with active or past active GD Differential diagnosis of gestational thyrotoxicosis versus first trimester manifestation or recurrence of GD Assessing the risk of GD relapse after antithyroid drug treatment

Interpretation: The sensitivity and specificity of an elevated thyrotropin receptor antibody (TRAb) test for Graves disease (GD) diagnosis depends on whether patients have disease treated with antithyroid drugs or clinically active, untreated disease. Based on a study that included specimens from 436 apparently healthy individuals, 210 patients with thyroid diseases without diagnosis of GD, and 102 patients with untreated GD, a decision limit of 1.75 IU/L showed a sensitivity of 97% and a specificity of 99% for detection of GD.(1) In healthy individuals and in patients with thyroid disease without diagnosis of GD, the upper limit of antithyrotropin receptor values are 1.22 IU/L and 1.58 IU/L, respectively (97.5th percentiles). A Mayo study of 115 patients, including 42 patients with GD, showed a sensitivity of 95% and a specificity of 97% for detection of GD at a decision limit of 1.75 IU/L. Assessment of TRAb status is particularly relevant in women who have undergone thyroid ablative therapy or are on active antithyroid treatment and, therefore, no longer display biochemical or clinical evidence of thyrotoxicosis. Significant neonatal thyrotoxicosis is likely if a pregnant woman with a history of GD has TRAb concentrations of more than 3.25 IU/L during the last trimester, regardless of her clinical remission status. Lesser elevations are only occasionally associated with neonatal thyrotoxicosis. Gestational thyrotoxicosis, which is believed to be due to a combination of human chorionic gonadotropin cross-reactivity on the thyrotropin receptor and transient changes in thyroid hormone protein binding, is only very rarely associated with an elevated TRAb test. Finding an elevated test result in this setting usually suggests underlying GD. An elevated TRAb test at the conclusion of a course of antithyroid drug treatment is highly predictive of relapse of GD. However, the converse, a normal TRAb test, is not predictive of prolonged remission.

Reference Values:
< or =1.75 IU/L

Clinical References: 1. Schott M, Hermsen D, Broecker-Preuss M, et al. Clinical value of the first automated TSH receptor autoantibody assay for the diagnosis of Graves disease: an international multicentre trial. Clin Endocrinol (Oxf). 2009;71(4):566-573 2. Hermsen D, Broecker-Preuss M, Casati M, et al. Technical evaluation of the first fully automated assay for the detection of TSH receptor autoantibodies. Clin Chim Acta. 2009;401(1-2):84-89 3. Diana T, Olivo PD, Kahaly GJ. Thyrotropin receptor blocking antibodies. Horm Metab Res. 2018;50(12):853-862 4. Kotwal A, Stan M. Thyrotropin receptor antibodies-an overview. Ophthalmic Plast Reconstr Surg. 2018; 34(4S Supple 1)S20-S27

TBGI
9263

Thyroxine-Binding Globulin (TBG), Serum

Clinical Information: Thyroxine binding globulin (TBG) is the high-affinity serum binding protein for thyroxine and triiodothyronine. Normally, the thyroid adjusts to changing concentrations of TBG by producing more, or less, thyroid hormone to maintain a constant level of metabolically important free hormone. Elevated TBG levels are associated with influences such as pregnancy, genetic predisposition,

oral contraceptives, and estrogen therapy. TBG levels can decrease with androgenic or anabolic steroids, large doses of glucocorticoids, hypoproteinemic states, liver disease, nephrotic syndrome, and congenital TBG variants.

Useful For: Cases in which total thyroid hormone levels do not correlate with the thyrometabolic status, most commonly with pregnancy or the use of contraceptive steroids

Interpretation: A change in thyroxine-binding globulin (TBG) concentration may be of hereditary, pathophysiologic, or pharmacologic origin. The TBG concentration indicates whether an abnormally high or low total thyroid hormone concentration is offset by a parallel increase or decrease in TBG concentration. In TBG deficiency, one may find euthyroid patients with extremely low total thyroxine (T4) values. Conversely, patients with high TBG levels may be clinically euthyroid with high serum total T4 values. Twenty-four specimens obtained during various stages of pregnancy yielded results ranging from 27 to 66 mcg/mL with a median of 43 mcg/mL. The literature suggests 47 to 59 mcg/mL as the range of TBG values expected during the third trimester of pregnancy.

Reference Values:
Males: 12-26 mcg/mL
Females: 11-27 mcg/mL

For International System of Units (SI) conversion for Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Burtis CA, Ashwood ER, Bruns DE eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 4th ed. Elsevier; 2006:2053-2095 2. Wenzel KW: Pharmacological interference with in vitro tests of thyroid function. Metabolism. 1981;30:717-732 3. Mimoto MS, Refetoff S. Clinical recognition and evaluation of patients with inherited serum thyroid hormone-binding protein mutations. J Endocrinol Invest. 2020;43(1):31-41. doi: 10.1007/s40618-019-01084-9 4. Pappa T, Ferrara AM, Refetoff S. Inherited defects of thyroxine-binding proteins. Best Pract Res Clin Endocrinol Metab. 2015;29(5):735-747

T4BPE
38507

Thyroxine-Binding Protein Electrophoresis, Serum

Clinical Information: Normally, almost all thyroxine (99.5%) is bound to thyroxine-binding globulin, prealbumin, and albumin. Deficiencies and aberrant forms of these binding proteins can occur, causing difficulties interpreting thyroid function test results. Such abnormalities may be identified by thyroxine-binding protein electrophoresis.

Useful For: Explaining unusual thyroxine (T4), free T4, and thyroxine-binding globulin test results that do not correlate with the patient's clinical presentation Detecting the presence of aberrant thyroxine-binding proteins, such as abnormal forms of albumin and prealbumin Detecting selective deficiency of one of the thyroxine-binding proteins Detecting antibodies to T4 An adjunct to the diagnosis of patients with high T4 concentration due to peripheral hormone resistance by ruling out thyroxine-binding abnormalities

Interpretation: An interpretive comment will be provided based on the total thyroxine concentration and the thyroxine-binding protein profile observed in the electrophoresis.

Reference Values:
THYROXINE-BINDING PROTEIN ELECTROPHORESIS:
10.3-24.9 mcg T4/dL bound to thyroxine-binding globulin
11.5-34.1 mcg T4/dL bound to albumin

48.8-70.4 mcg T4/dL bound to prealbumin

T4 (THYROXINE), TOTAL ONLY:
Pediatric:
0-5 days: 5.0-18.5 mcg/dL
6 days-2 months: 5.4-17.0 mcg/dL
3-11 months: 5.7-16.0 mcg/dL
1-5 years: 6.0-14.7 mcg/dL
6-10 years: 6.0-13.8 mcg/dL
11-19 years: 5.9-13.2 mcg/dL

Adult (> or =20 years): 4.5-11.7 mcg/dL

For SI unit Reference Values, see www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Hay ID, Klee GG. Thyroid dysfunction. Endocrinol Metab Clin North Am. 1988;17(3):473-509 2. Bartalena L, Robbins J. Thyroid hormone transport proteins. Clin Lab Med. 1993;13(3):583-598 3. Mimoto MS, Refetoff S. Clinical recognition and evaluation of patients with inherited serum thyroid hormone-binding protein mutations. J Endocrinol Invest. 2020;43(1):31-41. doi:10.1007/s40618-019-01084-9 4. Pappa T, Ferrara AM, Refetoff S. Inherited defects of thyroxine-binding proteins. Best Pract Res Clin Endocrinol Metab. 2015;29(5):735-747

FGTIA
75019

Tiagabine (Gabitril), Serum

Reference Values:
Report Limit: 5.0 ng/mL
Reference Range: <235.0 ng/mL

Therapeutic and toxic ranges have not been established.

Peak concentrations are expected at 45 minutes post dose; steady state is generally attained within 2 days.

Observed tiagabine concentrations in clinical trials (30 – 56 mg/day): <1 – 234 ng/mL.

Measured tiagabine concentrations, post marketing (95% confidence interval): 0 – 440 ng/mL.

Note: The 95% confidence interval for tiagabine concentrations determined by MEDTOX Laboratories will be updated periodically as more information becomes available.

STICK
602733

Tick-Borne Antibodies, Modified 2-Tier, ELISA, Serum

Clinical Information: In North America, ticks are the primary vectors of infectious diseases.(1) Worldwide, ticks rank second only to mosquitoes in disease transmission. In the United States, tick-borne diseases include Lyme disease, Rocky Mountain spotted fever, human monocytic and granulocytic ehrlichiosis, babesiosis, tularemia, relapsing fever, and Colorado tick fever. Symptoms of the various tick-vectored diseases range from mild to life-threatening and significantly overlap. Early symptoms, which include fever, aches, and malaise, do not aid in distinguishing the various diseases. Because early treatment can minimize or eliminate the risk of severe disease, early detection is essential, yet patients may not have developed distinctive symptoms to help in the differential diagnosis. A tick-borne panel can assist in identifying the pathogen, allowing treatment to be initiated. For information on the specific

diseases, see the individual test IDs.

Useful For: Evaluation of the most common tick-borne diseases found in the United States, including Lyme disease, human monocytic and granulocytic ehrlichiosis, and babesiosis using the modified 2-tier testing algorithm approach Evaluation of patients with a history of, or suspected, tick exposure who are presenting with fever, myalgia, headache, nausea, and other nonspecific symptoms Sero-epidemiological surveys of the prevalence of the infection in certain populations Diagnosis of Lyme disease

Interpretation: Anaplasma phagocytophilum: A positive immunofluorescence assay (titer > or =1:64) suggests current or previous infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology although antibody levels decline significantly during the year following infection. Ehrlichia chaffeensis: A positive immunofluorescence assay (titer > or =1:64) suggests current or previous infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology although antibody levels decline significantly during the year following infection. Babesia microti: A positive result of an indirect fluorescent antibody test (titer > or =1:64) suggests current or previous infection with Babesia microti. In general, the higher the titer, the more likely it is that the patient has an active infection. Patients with documented infections have usually had titers ranging from 1:320 to 1:2560. Lyme disease: Negative: Negative for antibodies to Borrelia (Borreliella) species causing Lyme disease. Negative results may occur in patients recently infected (< or =14 days) with Borrelia burgdorferi. If recent infection is suspected, repeat testing on a new sample collected in 7 to 14 days is recommended. Equivocal or Positive: Not diagnostic. Supplemental testing in accordance with the modified two-tiered testing algorithm for Lyme disease has been ordered by reflex.

Reference Values:

Anaplasma phagocytophilum ANTIBODY, IgG
<1:64
Reference values apply to all ages.

Ehrlichia chaffeensis (HME) ANTIBODY, IgG
<1:64
Reference values apply to all ages.

Babesia microti IgG ANTIBODIES
<1:64
Reference values apply to all ages.

LYME ANTIBODY
Negative
Reference values apply to all ages.

Clinical References:

TICKS
83265

Tick-Borne Disease Antibodies Panel, Serum

Clinical Information: In North America, ticks are the primary vectors of infectious diseases.(1) Worldwide, ticks rank second only to mosquitoes in disease transmission. In the United States, tickborne diseases include Lyme disease, Rocky Mountain spotted fever, human monocytic and granulocytic ehrlichiosis, babesiosis, tularemia, relapsing fever, and Colorado tick fever. Symptoms of

the various tick-vectored diseases range from mild to life-threatening and significantly overlap. Early symptoms, which include fever, aches, and malaise, do not aid in distinguishing the various diseases. Because early treatment can minimize or eliminate the risk of severe disease, early detection is essential, yet patients may not have developed distinctive symptoms to help in the differential diagnosis. A tickborne panel can assist in identifying the pathogen, allowing treatment to be initiated. For information on the specific diseases, see the individual test IDs.

Useful For: Evaluation of the most common tick-borne diseases found in the United States, including Lyme disease, human monocytic and granulocytic ehrlichiosis, and babesiosis Evaluation of patients with a history of, or suspected, tick exposure who are presenting with fever, myalgia, headache, nausea, and other nonspecific symptoms Seroepidemiological surveys of the prevalence of the infection in certain populations

Interpretation: Ehrlichia chaffeensis: A positive immunofluorescence assay result (titer > or =1:64) suggests current or previous infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology result although antibody levels decline significantly during the year following infection. Anaplasma phagocytophilum: A positive immunofluorescence assay result (titer > or =1:64) suggests current or previous infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology result although antibody levels decline significantly during the year following infection. Babesia microti: A positive result of an indirect fluorescent antibody test (titer > or =1:64) suggests current or previous infection with Babesia microti. In general, the higher the titer, the more likely it is that the patient has an active infection. Patients with documented infections have usually had titers ranging from 1:320 to 1:2560. Lyme disease: Negative: No evidence of antibodies to Borrelia burgdorferi detected. False-negative results may occur in recently infected patients (< or =2 weeks) due to low or undetectable antibody levels to B burgdorferi. If recent exposure is suspected, a second sample should be collected and tested in 2 to 4 weeks. Equivocal or Positive: Not diagnostic. Supplemental testing by immunoblot has been ordered by reflex.

Reference Values:

Ehrlichia chaffeensis (HME) ANTIBODY, IgG
<1:64
Reference values apply to all ages.

Anaplasma phagocytophilum ANTIBODY, IgG
<1:64
Reference values apply to all ages.

Babesia microti IgG ANTIBODIES
<1:64
Reference values apply to all ages.

LYME DISEASE SEROLOGY
Negative
Reference values apply to all ages.

Clinical References: 1. Centers for Disease Control and Prevention (CDC), Division of Vector-Borne Diseases. Tickborne Diseases of the United States: A Reference Manual for Healthcare Providers. 6th ed. US Department of Health and Human Services; 2022. Accessed September 29, 2022. Available at www.cdc.gov/ticks/tickbornediseases/TickborneDiseases-P.pdf 2. Diaz JH. Ticks, including tick paralysis. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:3505-3526

TIKLB
618311

Tick-Borne Panel, Molecular Detection, PCR, Blood

Clinical Information: In North America, ticks are the primary vectors of infectious diseases and rank second only to mosquitoes in disease transmission worldwide. In the United States, tick-borne diseases include Lyme disease, Rocky Mountain spotted fever, human monocytic ehrlichiosis, human granulocytic anaplasmosis, babesiosis, tularemia, relapsing fever, Colorado tick fever, and Borrelia miyamotoi infection.(1) Several of these diseases are transmitted by the same tick, and coinfections are occasionally seen. In particular, Ixodes species ticks are capable of transmitting the causative agents of Lyme disease (Borrelia burgdorferi and Borrelia mayonii), anaplasmosis (Anaplasma phagocytophilum), and babesiosis (Babesia species). These diseases are prevalent throughout the Northeastern and upper Midwestern states and parts of the Pacific Northwest. Symptoms of the various tick-vectored diseases range from mild to life-threatening. Early symptoms, which include fever, aches, and malaise, do not aid in distinguishing the various diseases. Because early treatment can minimize or eliminate the risk of severe disease, early detection is essential, yet patients may not have developed distinctive symptoms to help in the differential diagnosis. A rapid tick-borne polymerase chain reaction panel can assist in identifying the pathogen, allowing treatment to be initiated. While Lyme disease due to B burgdorferi is best detected through 2-tiered serologic testing, acute ehrlichiosis, anaplasmosis, babesiosis, and B miyamotoi infection are best detected using molecular amplification assays. This tick-borne panel offers sensitive, specific, and rapid detection of the agents that cause these 4 diseases. For information on the specific diseases, see the individual test information.

Useful For: Evaluating patients with suspected human monocytic ehrlichiosis, human granulocytic anaplasmosis, babesiosis, or Borrelia miyamotoi infection Evaluating patients with a history of, or suspected, tick exposure who are presenting with fever, myalgia, headache, nausea, and other nonspecific symptoms This test should not be used to screen healthy patients.

Interpretation: Borrelia miyamotoi: A positive result indicates the presence of Borrelia miyamotoi DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with symptoms and clinical findings of tick-borne relapsing fever. Ehrlichia/Anaplasma: Positive results indicate presence of specific DNA from Ehrlichia chaffeensis, Ehrlichia ewingii, Ehrlichia muris eauclairensis, or Anaplasma phagocytophilum and support the diagnosis of ehrlichiosis or anaplasmosis. Negative results indicate absence of detectable DNA from any of these 4 pathogens in specimens, but it does not exclude the presence of the organism or active or recent disease. Since DNA of E ewingii is indistinguishable from that of Ehrlichia canis by this rapid polymerase chain reaction (PCR) assay, a positive result for E ewingii/canis indicates the presence of DNA from either of these 2 organisms. Babesia: A positive result indicates the presence of Babesia species DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with blood smear microscopy, serological results, and clinical findings. A negative result indicates absence of detectable DNA from Babesia species in the specimen but does not always rule out ongoing babesiosis in a seropositive person since the parasitemia may be present at a very low level or may be sporadic. Other tests to consider in evaluating a patient presenting with an acute febrile illness following tick exposure include serologic tests for Lyme disease (Borrelia burgdorferi) and molecular detection (PCR) for ehrlichiosis/anaplasmosis. For patients past the acute stage of infection, serologic tests for these organisms should be ordered prior to PCR testing.

Reference Values:

BABESIA SPECIES, MOLECULAR DETECTION, PCR
Negative

EHRLICHIA/ANAPLASMA, MOLECULAR DETECTION, PCR
Negative

BORRELIA MIYAMOTOI, MOLECULAR DETECTION, PCR

Negative

Reference values apply to all ages.

Clinical References: Caulfield AJ, Pritt BS. Lyme disease coinfections in the United States. Clin Lab Med. 2015;35(4):827-846

BRBST 620148 Tickborne Bacterial, PCR and Sequencing, Blood

Clinical Information: The target population is patients with suspected, but undiagnosed, tickborne bacterial infection involving normally sterile whole blood. Polymerase chain reaction (PCR) amplification of a portion of the 16S ribosomal RNA gene followed by next-generation sequencing of the amplified product can be used to detect tickborne bacterial nucleic acids in such situations, enabling a diagnosis. Ideal specimens are those that specific tickborne PCR tests or blood culture have not resulted in identifiable causative infectious agents. Due to the complexity of this test, the suspected tickborne disease testing algorithm will reflex to this assay only if specific-PCR tests are negative. The test is designed to identify mono-bacterial or poly-bacterial tickborne infections.

Useful For: Detecting and identifying pathogenic tickborne bacteria infecting normally sterile whole blood Potential detection of bacteria that cause similar illnesses to tickborne infections This test should not be used as first tier test. It should only be used when routine testing is negative. This test is not recommended as a test of cure because nucleic acids may persist for long periods of time after successful treatment.

Interpretation: A positive broad-range polymerase chain reaction (PCR)/sequencing result indicates that tickborne bacterial nucleic acid was detected. A negative sequencing result indicates the absence of detectable bacterial nucleic acids in the specimen but does not rule out false-negative results that may occur due to sampling error, sequence variability underlying the primers, the presence of bacterial nucleic acids in quantities less than the limit of detection of the assay, or inhibition of PCR amplification. If testing shows evidence of PCR inhibition, it will be repeated. If inhibition is again detected, the result will be reported as "PCR inhibition present."

Reference Values:
No tickborne bacterial DNA detected

Clinical References: Kingry L, Sheldon S, Oatman S, et al. Targeted metagenomics for clinical detection and discovery of bacterial tick-borne pathogens. J Clin Microbiol. 2020;58(11):e00147-20. doi:10.1128/JCM.00147-20

TILAP 619510 Tilapia, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to

sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to tilapia Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline / Equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

TIMG
82891

Timothy Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to timothy grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FFTIB
91137

Tin, Blood

Reference Values:
Reference Range: <5.0 ng/mL

Toxic range not established.

FFTIN
91101

Tin, Serum

Reference Values:
Reference Range: <5.0 ng/mL

Toxic range has not been established.

Note: Whole blood is the preferred specimen for monitoring exposure to tin.

TSTGP
83671

Tissue Transglutaminase Antibodies, IgA and IgG Profile, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals.(1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Individuals with family members who have celiac disease are at increased risk of developing the disease.(2) Genetic susceptibility is related to specific human leukocyte antigen (HLA) markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. For this reason, HLA-DQ2 and HLA-DQ8 are considered genetic risk factors for celiac disease and are required, but not sufficient, for the disease process to occur. HLA testing is not required for diagnosis in all cases, but can be useful in situations where histology and serology are discrepant, or for individuals who have started a gluten free diet before evaluation.(3) A definitive diagnosis of celiac disease requires a duodenal biopsy demonstrating villous atrophy.(3) Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, individuals with positive laboratory results may be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm). In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial antibody (EMA), tissue transglutaminase (tTG), and deamidated gliadin antibodies.(4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic test is tTG IgA isotype , in individuals who produce sufficient total IgA. For individuals who are IgA deficient, testing for tTG and deamidated gliadin IgG antibodies is required. A recent multi-cohort international study found that a tTG IgA titer of greater than or equal to 10 times the upper limit of normal (ULN) had a positive predictive value of 95% in an adult population.(5) In addition, several prospective studies have shown that a biopsy free approach to celiac disease diagnosis may be possible in children with a tTG titer greater than or equal to10 times the ULN who meet certain criteria.(6-9) Given this evidence, the American College of Gastroenterology now suggests that a positive tTG IgA result greater than 10 times the upper limit of normal with a positive endomysial antibody in a separate blood sample may be sufficient for a diagnosis of celiac disease in children.(3) The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, concentrations of associated autoantibodies decline, which is sometimes accompanied by reconstitution of the small intestinal villi. In most patients, an improvement in clinical symptoms is observed. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease. See Celiac Disease Diagnostic Testing Algorithm for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm.

Useful For: Evaluating patients suspected of having celiac disease, including patients with

compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disease, positivity for HLA DQ2 and/or DQ8) Screening for dermatitis herpetiformis, in conjunction with endomysial antibody test Monitoring response to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

Interpretation: Positive results for tissue transglutaminase (tTG) IgA or IgG antibodies are consistent with a diagnosis for celiac disease and possibly for dermatitis herpetiformis. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is possible and a small intestinal biopsy should be considered to confirm the diagnosis. Negative results for tTg IgA and IgG antibodies indicate a decreased likelihood of celiac disease. A decrease in the concentration of tTG IgA or IgG may begin after initiation of a gluten-free diet and could indicate a response to therapy.

Reference Values:
tTG ANTIBODY, IgA
<4.0 U/mL (negative)
4.0-10.0 U/mL (weak positive)
>10.0 U/mL (positive)
Reference values apply to all ages.

tTG ANTIBODY, IgG
<6.0 U/mL (negative)
6.0-9.0 U/mL (weak positive)
>9.0 U/mL (positive)
Reference values apply to all ages.

Clinical References: 1. Rubin JE, Crowe SE. Celiac disease. Ann Int Med. 2020;172(1):ITC1-ITC16 2. Lebwohl B, Rubio-Tapia A. Epidemiology, presentation, and diagnosis of celiac disease. Gastroenterology. 2021;160(1):63-75 3. Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease. Am J Gastroenterol. 2023;118(1):59-76 4. Penny HA, Raju SA, Sanders DS. Progress in the serology-based diagnosis and management of adult celiac disease. Exp Rev Gastroenterol Hepatol. 2020;14(3):147-154 5. Penny HA, Raju SA, Lau MS, et.al. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. Gut. 2021;70(5):876-883. doi: 10.1136/gutjnl-2020-320913 6. Ylonen V, Lindfors K., Repo M, et al. Non-Biopsy Serology-Based Diagnosis of Celiac Disease in Adults Is Accurate with Different Commercial Kits and Pre-Test Probabilities. Nutrients. 2020;12(9):2736. doi:10.3390/nu12092736 7. Werkstetter KJ, Korponay-Szabo IR, Popp A, et al. Accuracy in Diagnosis of Celiac Disease Without Biopsies in Clinical Practice. Gastroenterology. 2017;153(4):924-935. doi:10.1053/j.gastro.2017.06.002 8. Wolf J, Petroff D, Richter T, et al. Validation of Antibody-Based Strategies for Diagnosis of Pediatric Celiac Disease Without Biopsy. Gastroenterology. 2017;153(2):410-419.e417. doi:10.1053/j.gastro.2017.04.023 9. Ho SS, Keenan JI, Day AS. Role of serological tests in the diagnosis of coeliac disease in children in New Zealand. J Paediatr Child Health. 2020;56(12):1906-1911. doi:10.1111/jpc.15076

TTGA
82587

Tissue Transglutaminase Antibody, IgA, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals.(1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron

deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Individuals with family members who have celiac disease are at increased risk of developing the disease.(2) Genetic susceptibility is related to specific human leukocyte antigen (HLA) markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. For this reason, HLA-DQ2 and HLA-DQ8 are considered genetic risk factors for celiac disease and are required, but not sufficient, for the disease process to occur. HLA testing is not required for diagnosis in all cases, but can be useful in situations where histology and serology are discrepant, or for individuals who have started a gluten free diet before evaluation.(3) A definitive diagnosis of celiac disease requires a duodenal biopsy demonstrating villous atrophy.(3) Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, individuals with positive laboratory results may be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm). In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial antibody (EMA), tissue transglutaminase (tTG), and deamidated gliadin antibodies.(4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic test is tTG IgA isotype, in individuals who produce sufficient total IgA. For individuals who are IgA deficient, testing for tTG and deamidated gliadin IgG antibodies is required. A recent multi-cohort international study found that a tTG IgA titer of greater than or equal to 10 times the upper limit of normal (ULN) had a positive predictive value of 95% in an adult population.(5) In addition, several prospective studies have shown that a biopsy free approach to celiac disease diagnosis may be possible in children with a tTG titer greater than or equal to10 times the ULN who meet certain criteria.(6-9) Given this evidence, the American College of Gastroenterology now suggests that a positive TTG IgA result greater than 10 times the upper limit of normal with a positive endomysial antibody in a separate blood sample may be sufficient for a diagnosis celiac disease in children.(3) The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, concentrations of associated autoantibodies decline, which is sometimes also accompanied by reconstitution of the small intestinal villi. In most patients, an improvement in clinical symptoms is observed. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease. See Celiac Disease Diagnostic Testing Algorithm for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm.

Useful For: Assessment of tissue transglutaminase IgA antibodies for evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disorder, positivity for HLA DQ2 and/or DQ8) Screening for dermatitis herpetiformis, in conjunction with endomysial antibody test Monitoring response to gluten-free diet in patients with dermatitis herpetiformis and celiac disease.

Interpretation: Positive results for tissue transglutaminase (tTG) IgA antibodies are consistent with a diagnosis for celiac disease and possibly for dermatitis herpetiformis. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is possible and a small intestinal biopsy should be considered to confirm the diagnosis. Negative results for tTG IgA antibodies indicate a decreased

likelihood of celiac disease. A decrease in the concentration of tTG IgA may begin after initiation of a gluten-free diet and could indicate a response to therapy.

Reference Values:

<4.0 U/mL (negative)
4.0-10.0 U/mL (weak positive)
>10.0 U/mL (positive)
Reference values apply to all ages.

Clinical References: 1. Rubin JE, Crowe SE. Celiac disease. Ann Int Med. 2020;172(1):ITC1-ITC16 2. Lebwohl B, Rubio-Tapia A. Epidemiology, presentation, and diagnosis of celiac disease. Gastroenterology. 2021;160(1):63-75 3. Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease. Am J Gastroenterol. 2023;118(1):59-76 4. Penny HA, Raju SA, Sanders DS. Progress in the serology-based diagnosis and management of adult celiac disease. Exp Rev Gastroenterol Hepatol. 2020;14(3):147-154 5. Penny HA, Raju SA, Lau MS, et.al. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. Gut. 2021;70(5):876-883. doi:10.1136/gutjnl-2020-320913 6. Ylonen V, Lindfors K., Repo M, et al. Non-Biopsy Serology-Based Diagnosis of Celiac Disease in Adults Is Accurate with Different Commercial Kits and Pre-Test Probabilities. Nutrients. 2020;12(9):2736. doi:10.3390/nu12092736 7. Werkstetter KJ, Korponay-Szabo IR, Popp A, et al. Accuracy in Diagnosis of Celiac Disease Without Biopsies in Clinical Practice. Gastroenterology. 2017;153(4):924-935. doi:10.1053/j.gastro.2017.06.002 8. Wolf J, Petroff D, Richter T, et al. Validation of Antibody-Based Strategies for Diagnosis of Pediatric Celiac Disease Without Biopsy. Gastroenterology. 2017;153(2):410-419.e417. doi:10.1053/j.gastro.2017.04.023 9. Ho SS, Keenan JI, Day AS. Role of serological tests in the diagnosis of coeliac disease in children in New Zealand. J Paediatr Child Health. 2020;56(12):1906-1911. doi:10.1111/jpc.15076

TTGG
83660

Tissue Transglutaminase Antibody, IgG, Serum

Clinical Information:

Useful For: Individuals with IgA deficiency Evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disorder, positivity for HLA DQ2 and/or DQ8 Screening test for dermatitis herpetiformis, in conjunction with an endomysial antibody test Monitoring response to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

Interpretation: Positive results for tissue transglutaminase (tTG) IgG antibodies are consistent with a diagnosis for celiac disease, particularly in individuals who are IgA deficient. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is possible and a small intestinal biopsy should be considered to confirm the diagnosis. Negative results for tTG IgG antibodies indicate a decreased likelihood of celiac disease. A decrease in the concentration of tTG IgG may begin after initiation of a gluten-free diet and could indicate a response to therapy.

Reference Values:

<6.0 U/mL (negative)
6.0-9.0 U/mL (weak positive)
>9.0 U/mL (positive)
Reference values apply to all ages.

Clinical References: 1. Rubin JE, Crowe SE. Celiac disease. Ann Int Med. 2020;172(1):ITC1-ITC16 2. Lebwohl B, Rubio-Tapia A. Epidemiology, presentation, and diagnosis of

celiac disease. Gastroenterology. 2021;160(1):63-75 3. Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology guidelines update: Diagnosis and management of celiac disease. Am J Gastroenterol. 2023;118(1):59-76. doi:10.14309/ajg.0000000000002075 4. Penny HA, Raju SA, Sanders DS. Progress in the serology-based diagnosis and management of adult celiac disease. Expert Rev Gastroenterol Hepatol. 2020;14(3):147-154 5. Penny HA, Raju SA, Lau MS, et al. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. Gut. 2021;70(5):876-883. doi:10.1136/gutjnl-2020-320913 6. Ylonen V, Lindfors K, Repo M, et al. Non-biopsy serology-based diagnosis of celiac disease in adults is accurate with different commercial kits and pre-test probabilities. Nutrients. 2020;12(9):2736 7. Werkstetter KJ, Korponay-Szabo IR, Popp A, et al. Accuracy in diagnosis of celiac disease without biopsies in clinical practice. Gastroenterology. 2017;153(4):924-935. doi:10.1053/j.gastro.2017.06.002 8. Wolf J, Petroff D, Richter T, et al. Validation of antibody-based strategies for diagnosis of pediatric celiac disease without biopsy. Gastroenterology. 2017;153(2):410-419.e17. doi:10.1053/j.gastro.2017.04.023 9. Ho SS, Keenan JI, Day AS. Role of serological tests in the diagnosis of coeliac disease in children in New Zealand. J Paediatr Child Health. 2020;56(12):1906-1911. doi:10.1111/jpc.15076

TIU24
614613

Titanium, 24 Hour, Urine

Clinical Information: Titanium is the ninth most abundant element in the earth's crust. Its light weight and high strength are useful in alloys for diverse applications. There is no evidence that titanium is an essential element. Due in part to titanium's oxide formation propensity, the element is considered to be nontoxic. Soils, drinking water, and air all contain trace amounts of titanium. The food processing industry uses large quantities of titanium as a food additive; processed foods contain higher levels than are found in most produce and organic foodstuffs. The average daily oral intake through food consumption is 0.1 to 1 mg/day, which accounts for more than 99% of exposure. Gastrointestinal absorption of titanium is low (approximately 3%), and most of the ingested titanium is rapidly excreted in the urine and stool. The total body burden of titanium is usually in the range of 9 to 15 mg, a significant portion of which is contained in the lung. Titanium dust entering the respiratory tract is nonirritating and is almost completely non-fibrogenic in humans. Titanium-containing alloys are used in some artificial joints, prosthetic devices, and implants. Titanium dioxide allows osseointegration between an artificial medical implant and bone. Despite their wide use, exposure to these materials has not been linked to toxicity. In one study, patients monitored up to 36 months following joint replacement with titanium-containing joints showed a statistically significant increase in detectable titanium. While titanium concentrations are not a measure of toxicity, they can be useful in determining whether implant breakdown is occurring.

Useful For: Monitoring exposure and elimination of titanium in a 24-hour urine specimen

Interpretation: Elevated concentrations of urinary titanium have been reported after documented exposures.

Reference Values:
0-17 years: Not established
> or =18 years: <1 mcg/24 h

Clinical References: 1. Rifai N, Horvath AR, Wittwer, CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 6th ed. Elsevier; 2018 2. Barry J, Lavigne M, Vendittoli PA. Evaluation of the method for analyzing chromium, cobalt and titanium ion levels in the blood following hip replacement with a metal-on-metal prosthesis. J Anal Toxicol. 2013;37(2):90-6 3. Sarmiento-Gonzalez, A, et al. High resolution ICP-MS determination of Ti, V, Cr, Co, Ni, and Mo in human blood and urine of patients implanted with a hip or knee prothesis. Anal Bioanal Chem. 2008;391(7):2583-9 4. Kim KT, Eo MY, Nguyen TTH, Kim SM. General review of titanium toxicity. Int J Implant Dent.

2019;5(1):10. Published 2019 Mar 11. doi:10.1186/s40729-019-0162-x 5. Jacobs JJ, Skipor AK, Patterson LM, et al. Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. J Bone Joint Surg Am. 1998;80(10):1447-1458 6. Liu TK, Liu SH, Chang CH, Yang RS. Concentration of metal elements in the blood and urine in the patients with cementless total knee arthroplasty. Tohoku J Exp Med. 1998;185(4):253-262 7. Jin T, M Berlin: Titanium. Nordberg GF, Fowler BA, Nordberg M, Friberg LT, et al, eds. Handbook on the Toxicology of Metals. 3rd ed. Academic Press Amsterdam; 2004:861-870 8. Chao EY, Frassica F, Prichard DJ, Moyer TP. Metal ion release in patients with porous coated megaprostheses. 41st Annual Meeting of the Orthopaedic Research Society, Orlando, Florida, 1995 Feb 13-16

TIWB
614612

Titanium, Blood

Clinical Information: Titanium is the ninth most abundant element in the earth's crust. Its light weight and high strength are useful in alloys for diverse applications. There is no evidence that titanium is an essential element. Due in part to titanium's oxide formation propensity, the element is considered to be nontoxic. Soils, drinking water, and air all contain trace amounts of titanium. The food processing industry uses large quantities of titanium as a food additive; processed foods contain higher levels than are found in most produce and organic food products. The average daily oral intake through food consumption is 0.1 to 1 mg/day, which accounts for more than 99% of exposure. Gastrointestinal absorption of titanium is low (approximately 3%), and the majority of ingested titanium is rapidly excreted in the urine and stool. The total body burden of titanium is usually in the range of 9 to 15 mg, a significant portion of which is contained in the lungs. Titanium dust entering the respiratory tract is nonirritating and is almost completely nonfibrogenic in humans. Titanium-containing alloys are used in some artificial joints, prosthetic devices, and implants. Titanium dioxide allows osseointegration between an artificial medical implant and bone. Despite their wide use, exposure to these materials has not been linked to toxicity. In one study, patients monitored up to 36 months following joint replacement with titanium-containing joints showed a statistically significant increase in detectable titanium. While titanium concentrations are not a measure of toxicity, they are useful in determining whether implant breakdown is occurring. Blood titanium concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Detecting and monitoring titanium exposure and potential implant status in patients with orthopedic implants

Interpretation: Clinically, this test is used to detect and monitor titanium exposure and potential implant status in patients with orthopedic implants. Increased concentrations in blood have been proposed as a marker of component wear.

Reference Values:
0-17 years: Not established
> or =18 years: <2 ng/mL

Clinical References: 1. Rifai N, Horvath AR, Wittwer, CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 6th ed. Elsevier; 2018 2. Barry J, Lavigne M, Vendittoli PA. Evaluation of the method for analyzing chromium, cobalt and titanium ion levels in the blood following hip replacement with a metal-on-metal prosthesis. J Anal Toxicol. 2013;37(2):90-96 3. Sarmiento-Gonzalez A, Marchante-Gayon JM, Tejerina-Lobo JM, Paz-Jimenez J, Sanz-Medel A. High-resolution ICP-MS determination of Ti, V, Cr, Co, Ni, and Mo in human blood and urine of patients implanted with a hip or knee prosthesis. Anal Bioanal Chem. 2008;391(7):2583-2589 4. Chao EY, Frassica F, Prichard DJ, Moyer TP. Metal ion release in patients with porous coated megaprostheses. 41st Annual Meeting of

the Orthopaedic Research Society, Orlando, Florida, 1995 Feb 13-16 5. Jacobs JJ, Skipor AK, Patterson LM, et al. Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. J Bone Joint Surg Am. 1998;80(10):1447-1458 6. Liu TK, Liu SH, Chang CH, Yang RS. Concentration of metal elements in the blood and urine in the patients with cementless total knee arthroplasty. Tohoku J Exp Med. 1998;185(4):253-262 7. Krachler M, Domej W, Irgolic KJ. Concentrations of trace elements in osteoarthritic knee-joint effusions. Biol Trace Elem Res. 2000;75:253-263 8. Swiatkowska I, Martin N, Hart AJ. Blood titanium level as a biomarker of orthopaedic implant wear. J Trace Elem Med Biol. 2019;53:120-128. doi:10.1016/j.jtemb.2019.02.013 9. Yao JJ, Lewallen EA, Thaler R, et al. Challenges in the measurement and interpretation of serum titanium concentrations. Biol Trace Elem Res. 2020;196(1):20-26. doi:10.1007/s12011-019-01891-4 10. Swiatkowska I, Martin NG, Henckel J, Apthorp H, Hamshere J, Hart AJ. Blood and plasma titanium levels associated with well-functioning hip implants. J Trace Elem Med Biol. 2020;57:9-17. doi:10.1016/j.jtemb.2019.09.005 11. Kim KT, Eo MY, Nguyen TTH, Kim SM. General review of titanium toxicity. Int J Implant Dent. 2019;5(1):10. Published 2019 Mar 11. doi:10.1186/s40729-019-0162-x

TIS
89367

Titanium, Serum

Clinical Information: Titanium is the ninth most abundant element in the earth's crust. Multiple oxidation states between 2+ and 4+ allow formation of a variety of compounds. There is no evidence that titanium is an essential element. Due in part to titanium's oxide formation propensity, the element is considered to be nontoxic. Soils, drinking water, and air all contain trace amounts of titanium. The food processing industry uses large quantities of titanium as a food additive; processed foods contain higher levels than are found in most produce and organic foodstuffs. The average daily oral intake through food consumption is 0.1 to 1 mg/day, which accounts for more than 99% of exposure. Gastrointestinal absorption of titanium is low (approximately 3%), and most of the ingested titanium is rapidly excreted in the urine and stool. The total body burden of titanium is usually in the range of 9 to 15 mg, a significant portion of which is contained in the lungs. Titanium dust entering the respiratory tract is nonirritating and is almost completely non-fibrogenic in humans. Titanium-containing alloys are used in some artificial joints, prosthetic devices, and implants. Titanium dioxide allows osseointegration between an artificial medical implant and bone. Despite their wide use, to date, exposure to these materials has not been linked to toxicity. In one study, patients monitored up to 36 months following joint replacement with titanium-containing joints showed a statistically significant increase in detectable serum titanium. While titanium concentrations are not a measure of toxicity, they are useful in determining whether implant breakdown is occurring. Serum titanium concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Monitoring metallic prosthetic implant wear

Interpretation: Prosthesis wear is known to result in increased circulating concentration of metal ions. In the absence of an implant, circulating titanium is below 1 ng/mL. Modest increase (1.0-3.0 ng/mL) in serum titanium concentration is evident with a prosthetic device in good condition. Serum concentrations above 10 ng/mL in a patient with titanium-based implant suggest prosthesis wear. Increased serum titanium concentration in the absence of corroborating clinical information does not independently predict prosthesis wear or failure.

Reference Values:
<2 ng/mL

Clinical References: 1. Rifai N, Horvath AR, Wittwer, CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 6th ed. Elsevier; 2018 2. Chao EY, Frassica F, Prichard DJ, Moyer TP: Metal ion release in patients with porous coated megaprostheses. 41st Annual Meeting of the Orthopaedic Research Society, Orlando, Florida, 1995 Feb 13-16 3. Jacobs JJ, Skipor AK, Patterson LM, et al. Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. J Bone Joint Surg Am. 1998;80(10):1447-1458 4. Liu TK, Liu SH, Chang CH, Yang RS. Concentration of metal elements in the blood and urine in the patients with cementless total knee arthroplasty. Tohoku J Exp Med. 1998;185:253-262 5. Krachler M, Domj W, Irgolic KJ. Concentrations of trace elements in osteoarthritic knee-joint effusions. Biol Trace Elem Res. 2000;75:253-263

TIUCR
614614

Titanium/Creatinine Ratio, Random, Urine

Clinical Information: Titanium is the ninth most abundant element in the earth's crust. Its light weight and high strength are useful in alloys for diverse applications. There is no evidence to date that titanium is an essential element. Due in part to titanium's oxide formation propensity, the element is considered to be nontoxic. Soils, drinking water, and air all contain trace amounts of titanium. The food processing industry uses large quantities of titanium as a food additive; processed foods contain higher levels than are found in most produce and organic food products. The average daily oral intake through food consumption is 0.1 to 1 mg/day, which accounts for more than 99% of exposure. Gastrointestinal absorption of titanium is low (approximately 3%), and most of the ingested titanium is rapidly excreted in the urine and stool. The total body burden of titanium is usually in the range of 9 to 15 mg, a significant portion of which is contained in the lungs. Titanium dust entering the respiratory tract is nonirritating and is almost completely nonfibrogenic in humans. Titanium-containing alloys are used in some artificial joints, prosthetic devices, and implants. Titanium dioxide allows osseointegration between an artificial medical implant and bone. Despite their wide use, exposure to these materials has not been linked to toxicity. In one study, patients monitored up to 36 months following joint replacement with titanium-containing joints showed a statistically significant increase in detectable titanium. While titanium concentrations are not a measure of toxicity, they can be useful in determining whether implant breakdown is occurring.

Useful For: Monitoring exposure and elimination of titanium

Interpretation: Elevated concentrations of urinary titanium have been reported after documented exposures.

Reference Values:
TITANIUM
0-17 years: Not established
> or =18 years: <0.4 mcg/g creatinine

CREATININE
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are less than 18 years of age.

Clinical References: 1. Rifai N, Horvath AR, Wittwer, CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 6th ed. Elsevier; 2018 2. Barry J, Lavigne M, Vendittoli PA. Evaluation of the method for analyzing chromium, cobalt and titanium ion levels in the blood following hip replacement with a metal-on-metal prosthesis. J Anal Toxicol. 2013;37(2):90-6 3. Sarmiento-Gonzalez, A, et al. High resolution ICP-MS determination of Ti, V, Cr, Co, Ni, and Mo in human blood and urine of patients implanted with a hip or knee prothesis. Anal Bioanal Chem. 2008;391(7):2583-9 4. Kim KT, Eo MY, Nguyen TTH, Kim SM. General review of titanium toxicity. Int J Implant Dent. 2019;5(1):10. Published 2019 Mar 11. doi:10.1186/s40729-019-0162-x 5. Jacobs JJ, Skipor AK, Patterson

LM, et al: Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. J Bone Joint Surg Am. 1998;80(10):1447-1458 6. Liu TK, Liu SH, Chang CH, Yang RS. Concentration of metal elements in the blood and urine in the patients with cementless total knee arthroplasty. Tohoku J Exp Med. 1998;185(4):253-262 7. Jin T, M Berlin: Titanium. G Nordberg B Fowler M Nordberg et al. Handbook on the toxicology of metals. 3rd ed 2007 Academic Press Amsterdam 861-870 8. Chao EY, Frassica F, Prichard DJ, Moyer TP. Metal ion release in patients with porous coated megaprostheses. 41st Annual Meeting of the Orthopaedic Research Society, Orlando, Florida, 1995 Feb 13-16

TICU
614615

Titanium/Creatinine Ratio, Urine

Clinical Information: Titanium is the ninth most abundant element in the earth's crust. Its light weight and high strength are useful in alloys for diverse applications. There is no evidence to date that titanium is an essential element. Due in part to titanium's oxide formation propensity, the element is considered to be nontoxic. Soils, drinking water, and air all contain trace amounts of titanium. The food processing industry uses large quantities of titanium as a food additive; processed foods contain higher levels than are found in most produce and organic food products. The average daily oral intake through food consumption is 0.1 to 1 mg/day, which accounts for more than 99% of exposure. Gastrointestinal absorption of titanium is low (approximately 3%), and most of ingested titanium is rapidly excreted in the urine and stool. The total body burden of titanium is usually in the range of 9 to 15 mg, a significant portion of which is contained in the lung. Titanium dust entering the respiratory tract is nonirritating and is almost completely nonfibrogenic in humans. Titanium-containing alloys are used in some artificial joints, prosthetic devices, and implants. Titanium dioxide allows osseointegration between an artificial medical implant and bone. Despite their wide use, exposure to these materials has not been linked to toxicity. In one study, patients monitored up to 36 months following joint replacement with titanium-containing joints showed a statistically significant increase in detectable titanium. While titanium concentrations are not a measure of toxicity, they can be useful in determining whether implant breakdown is occurring.

Useful For: Measurement of titanium concentration as part of a profile to assess exposure and elimination of titanium

Interpretation: Elevated concentrations of urinary titanium have been reported after documented exposures.

Reference Values:
Only orderable as part of a profile. For more information see TIUCR / Titanium/Creatinine Ratio, Random, Urine.

0-17 years: Not established
> or =18 years: <0.4 mcg/g Cr

Clinical References: 1. Rifai N, Horvath AR, Wittwer, CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 6th ed. Elsevier; 2018 2. Barry J, Lavigne M, Vendittoli PA. Evaluation of the method for analyzing chromium, cobalt and titanium ion levels in the blood following hip replacement with a metal-on-metal prosthesis. J Anal Toxicol. 2013;37(2):90-6 3. Sarmiento-Gonzalez, A, et al. High resolution ICP-MS determination of Ti, V, Cr, Co, Ni, and Mo in human blood and urine of patients implanted with a hip or knee prothesis. Anal Bioanal Chem. 2008;391(7):2583-9 4. Kim KT, Eo MY, Nguyen TTH, Kim SM. General review of titanium toxicity. Int J Implant Dent. 2019;5(1):10. Published 2019 Mar 11. doi:10.1186/s40729-019-0162-x 5. Jacobs JJ, Skipor AK, Patterson LM, et al. Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. J Bone Joint Surg Am. 1998;80(10):1447-1458 6. Liu TK,

Liu SH, Chang CH, Yang RS. Concentration of metal elements in the blood and urine in the patients with cementless total knee arthroplasty. Tohoku J Exp Med. 1998;185(4) :253-262 7. Jin T, M Berlin: Titanium. G Nordberg B Fowler M Nordberg et al. Handbook on the toxicology of metals. 3rd ed 2007 Academic Press Amsterdam 861-870 8. Chao EY, Frassica F, Prichard DJ, Moyer TP. Metal ion release in patients with porous coated megaprostheses. 41st Annual Meeting of the Orthopaedic Research Society, Orlando, Florida, 1995 Feb 13-16

TLE1
70567

TLE-1 Immunostain, Technical Component Only

Clinical Information: Transducin-like enhancer of split proteins (TLE-1) associates with chromatin, specifically with histone H3. TLE1 is upregulated in early stages of cell differentiation and may have value in the diagnosis of synovial sarcoma, where it is positive in the majority of the cases. However, this marker is not entirely specific for synovial sarcoma, and results should be interpreted in the context of other clinicopathologic and immunophenotypic features.

Useful For: Aids in the identification of synovial sarcoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Terry J, Saito T, Subramanian S, et al. TLE1 as a diagnostic immunohistochemical marker for synovial sarcoma emerging from gene expression profiling studies. Am J Surg Pathol. 2007;31(2):240-246 2. Baird K, Davis S, Antonescu CR, et al. Gene expression profiling of human sarcomas: insights into sarcoma biology. Can Res. 2005;65:9226-9235 3. Segal NH, Pavlidis P, Antonescu Cr, et al. Classification and subtype prediction of adult soft tissue sarcoma by functional genomics. Am J Pathol. 2003:163:691-700 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TOBPA
37063

Tobramycin, Peak, Serum

Clinical Information: Tobramycin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Enterobacter (all species), Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A tobramycin minimum inhibitory concentration (MIC) of less than 4.0 mcg/mL is considered susceptible for gram-negative bacilli, while a MIC of greater than 8.0 mcg/mL is considered resistant. Toxicities include ototoxicity and nephrotoxicity. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels, renal function, and symptoms consistent with ototoxicity is important. For longer durations of use, audiology and vestibular testing should be considered at baseline and periodically during therapy.

Useful For: Monitoring adequacy of serum concentration during tobramycin therapy

Interpretation: Target peak concentrations depend on the type of infection being treated. Peak levels for most infections using conventional dosing are 3.0 to 12.0 mcg/mL. Prolonged exposure to peak concentrations exceeding 12.0 mcg/mL may lead to toxicity.

Reference Values:
Therapeutic: 3.0-12.0 mcg/mL
Toxic: >12.0 mcg/mL

Clinical References: 1. Hammett-Stabler CA, Johns T: Laboratory guidelines for monitoring of antimicrobial drugs. Clin Chem 1998;44(5):1129-1140 2. Moyer TP: Therapeutic drug monitoring. In Tietz Textbook of Clinical Chemistry. Fourth edition. Edited by CA Burtis, ER Ashwood, Philadelphia, WB Saunders Company, 2006 3. Wilson JW, Estes LL: Mayo Clinic Antimicrobial Therapy Quick Guide. Mayo Clinic Scientific Press and Informa Healthcare USA, 2008

TOBRA
37065

Tobramycin, Random, Serum

Clinical Information: Tobramycin is an antibiotic used to treat life-threatening blood infections by gram-negative bacilli, particularly Citrobacter freundii, Enterobacter (all species), Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia. It is often used in combination with beta-lactam therapy. A tobramycin minimum inhibitory concentration (MIC) of less than 4.0 mcg/mL is considered susceptible for gram-negative bacilli, while a MIC of greater than 8.0 mcg/mL is considered resistant. Toxicities include ototoxicity and nephrotoxicity. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels, renal function, and symptoms consistent with ototoxicity is important. For longer durations of use, audiology and vestibular testing should be considered at baseline and periodically during therapy.

Useful For: Monitoring adequacy of serum concentration during tobramycin therapy This unit code is used whenever a specimen is submitted or collected without collection timing information. The phlebotomist should use this unit code if she or he does not know if this is a peak or trough specimen.

Interpretation: Target peak concentrations depend on the type of infection being treated. Goal trough levels should be below 2.0 mcg/mL. Concentrations refer to conventional (non-pulse) dosing. Prolonged exposure to either peak levels exceeding 12.0 mcg/mL or trough levels exceeding 2.0 mcg/mL may lead to toxicity.

Reference Values:
TOBRAMYCIN, PEAK
Therapeutic: 3.0-12.0 mcg/mL
Toxic: >12.0 mcg/mL

TOBRAMYCIN, TROUGH
Therapeutic: <2.0 mcg/mL
Toxic: >2.0 mcg/mL

Clinical References: 1. Hammett-Stabler CA, Johns T: Laboratory Guidelines for Monitoring of Antimicrobial Drugs. Clin Chem 1998;44(5):1129-1140 2. Moyer TP: Therapeutic drug monitoring. In Tietz Textbook of Clinical Chemistry. Fourth edition. Edited by CA Burtis, ER Ashwood, Philadelphia, WB Saunders Company, 2006 3. Wilson JW, Estes LL: Mayo Clinic Antimicrobial Therapy Quick Guide. Mayo Clinic Scientific Press and Informa Healthcare USA, 2008

TOBTA
37064

Tobramycin, Trough, Serum

Clinical Information: Tobramycin is an antibiotic used to treat life-threatening blood infections by gram-negative bacilli, particularly Citrobacter freundii, Enterobacter (all species), Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia

species. It is often used in combination with beta-lactam therapy. A tobramycin minimum inhibitory concentration (MIC) of less than 4.0 mcg/mL is considered susceptible for gram-negative bacilli, while a MIC of greater than 8.0 mcg/mL is considered resistant. Toxicities include ototoxicity and nephrotoxicity. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels, renal function, and symptoms consistent with ototoxicity is important. For longer durations of use, audiology and vestibular testing should be considered at baseline and periodically during therapy.

Useful For: Monitoring adequate clearance of tobramycin near the end of a dosing cycle

Interpretation: Goal levels depend on the type of infection being treated. Goal trough levels should be below 2.0 mcg/mL for conventional (nonpulse) dosing. Prolonged exposure to trough levels exceeding 2.0 mcg/mL may lead to toxicity.

Reference Values:
Therapeutic: <2.0 mcg/mL
Toxic: >2.0 mcg/mL

Clinical References: 1. Hammett-Stabler CA, Johns T: Laboratory guidelines for monitoring of antimicrobial drugs. Clin Chem 1998;44(5):1129-1140 2. Moyer TP: Therapeutic drug monitoring. In Tietz Textbook of Clinical Chemistry. Fourth edition. Edited by CA Burtis, ER Ashwood, Philadelphia, WB Saunders Company, 2006 3. Wilson JW, Estes LL: Mayo Clinic Antimicrobial Therapy Quick Guide. Mayo Clinic Scientific Press and Informa Healthcare USA, 2008

FHIPP
91121

Toluene as Hippuric Acid, Occupational Exposure, Urine

Reference Values:
Creatinine: >50 mg/cL

Hippuric Acid is a metabolite of toluene and benzyl alcohol.

Normal (unexposed population):
Average 0.8 g/L

Exposed:

Biological Exposure Index (BEI):
1.6 g/g creatinine
(toluene exposure: end of shift)
Toxic:
Not established

FFTLB
91141

Toluene, Occupational Exposure, Blood

Reference Values:
Units: mg/L

Normal (unexposed population): None detected

Exposed:
Biological Exposure Index (BEI): 0.05 mg/L (prior to last shift of workweek)
Biological Tolerance Value (BAT): 1.0 mg/L (end of exposure or end of shift)

Toxic:
Blood levels between 50 and 79 mg/L were found in people who died of acute toluene inhalation.

FMATG
57628

Tomato IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

TOMA
82695

Tomato, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to tomato Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

TOPI
81546

Topiramate, Serum

Clinical Information: Topiramate is a broad spectrum, antiepileptic drug used for various types of seizures, Lennox-Gastaut syndrome (a type of childhood onset epilepsy), and migraine prophylaxis. Topiramate blocks voltage-dependent sodium channels, potentiates gamma-aminobutyric acid (GABA) activity at some of the GABA receptors, and inhibits potentiation of the glutamate receptor and carbonic anhydrase enzyme, which all contribute to its antiepileptic and antimigraine efficacy. In general, topiramate shows favorable pharmacokinetics with good absorption (1-4 hours for the immediate-release formulation), low protein binding, and minimal hepatic metabolism. Elimination is predominantly via the kidney, and it is excreted unchanged in the urine with an elimination half-life of approximately 21 hours. As with other anticonvulsant drugs eliminated by the renal system, patients with impaired kidney function exhibit decreased topiramate clearance and a prolonged elimination half-life. Serum concentrations of other anticonvulsant drugs are not significantly affected by the concurrent administration of topiramate, with the exception of patients on phenytoin whose serum concentrations can increase after the addition of topiramate. Other drug-drug interactions include the coadministration of phenobarbital, phenytoin, or carbamazepine, which can result in decreased topiramate concentrations. In addition, concurrent use of posaconazole and topiramate may result in the elevation of topiramate serum concentrations. Therefore, changes in cotherapy with these medications (phenytoin, carbamazepine, posaconazole, or phenobarbital) may require dose adjustment of topiramate, and therapeutic drug monitoring could assist with this. The most common adverse drug effects associated with topiramate include weight loss, loss of appetite, somnolence, dizziness, coordination problems, memory impairment, and paresthesia.

Useful For: Monitoring serum concentrations of topiramate Assessing compliance Assessing potential toxicity

Interpretation: Most individuals display optimal response to topiramate with serum levels 5.0 to 20.0 mcg/mL when used to control seizures. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimens collected at trough (ie, immediately before the next dose). Toxic levels have not been well established.

Reference Values:
Anticonvulsant: 5.0-20.0 mcg/mL

Clinical References:

TRCHG 61859 ToRCH Profile IgG, Serum

Clinical Information: Toxoplasma gondii: Toxoplasma gondii is an obligate intracellular protozoan parasite capable of infecting a variety of intermediate hosts, including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious.(1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, T gondii can remain latent for the life of the host; the risk for reactivation is highest among individuals who are immunosuppressed. Seroprevalence studies performed in the United States indicate approximately 6.7% of individuals between the ages of 12 and 49 have antibodies to T gondii.(2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most frequently present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals that are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involve the central nervous system.(3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation.(4) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only, and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects. Rubella: Rubella (German or 3-day measles) is a member of the Togavirus family, and humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets, and the incubation period following exposure can range from 12 to 23 days.(5) Infection is generally mild, self-limited, and characterized by a maculopapular rash beginning on the face spreading to the trunk and extremities, fever, malaise, and lymphadenopathy.(6) Primary, in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of gestation. Congenital rubella syndrome is often associated with hearing loss and cardiovascular and ocular defects.(7) The United States 2-dose measles, mumps, rubella (MMR) vaccination program, which calls for vaccination of all children, leads to seroconversion in 95% of children following the first dose.(5) A total of 4 cases of rubella were reported to the Centers for Disease Control and Prevention (CDC) in 2011 without any cases of congenital rubella syndrome.(8) Due to the success of the national vaccination program, rubella is no longer considered endemic in the United States.(9) However, immunity may wane with age as approximately 80% to 90% of adults will show serologic evidence of immunity to rubella. Cytomegalovirus: Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow derived cells.(10) Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise, and lymphadenopathy. Cytomegalovirus is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS, and other immunosuppressed patients due to virus reactivation or from a newly acquired infection.(11,12) Infection in these patient populations can affect almost any organ and lead to multi-organ failure. CMV is also responsible for congenital disease among newborns and is one of the ToRCH infections (toxoplasmosis, other

infections including syphilis, rubella, CMV, and herpes simplex virus [HSV]). Cytomegalovirus seroprevalence increases with age. In the United States, the prevalence of CMV-specific antibodies increases from approximately 36% to over 91% in children between the ages of 6 and 11 years and adults over 80 years old, respectively.(13) Herpes Simplex Virus Types 1 and 2: Herpes simplex virus types 1 and 2 are members of the Herpesviridae family and produce infections that range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using a polymerase chain reaction assay or viral culture. However, in instances of subclinical or unrecognized HSV infection, serologic testing for IgG-class antibodies to type-specific HSV glycoprotein G (gG) may be useful. There are several circumstances in which it may be important to distinguish between infection caused by HSV types 1 and 2.(14) For example, the risk for reactivation is highest for HSV type 2, and the method of antiviral therapy may be different depending on the specific type of HSV causing disease. In addition, the results of HSV type specific IgG testing is sometimes used during pregnancy to identify risks of congenital HSV disease and allow for focused counseling prior to delivery.(15,16)

Useful For: Determining immune status of individuals to the rubella virus following vaccination or prior exposure Indicating past or recent infection with Toxoplasma gondii, cytomegalovirus, or herpes simplex virus (HSV) Distinguishing between infection caused by HSV types 1 and 2, especially in patients with subclinical or unrecognized HSV infection

Interpretation: Toxoplasma gondii: A positive Toxoplasma IgG result is indicative of current or past infection with T gondii. A single positive Toxoplasma IgG result should not be used to diagnose recent infection. Equivocal Toxoplasma IgG results may be due to very low levels of circulating IgG during the acute stage of infection. A second specimen should be submitted for testing if clinically indicated. Individuals with negative Toxoplasma IgG results are presumed to not have had previous exposure to T gondii. However, negative results may be seen in cases of remote exposure with subsequent loss of detectable antibody. Seroconversion from negative to positive IgG is indicative of T gondii infection subsequent to the first negative specimen. Rubella: Positive: The presence of detectable IgG-class antibodies to rubella indicates prior exposure through infection or immunization. Individuals testing positive for IgG-class antibodies to rubella are considered immune. Equivocal: Submit an additional specimen for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: The absence of detectable IgG-class antibodies to rubella suggests no prior exposure to this virus or the lack of a specific immune response to immunization. Cytomegalovirus: Positive cytomegalovirus (CMV) IgG results indicate past or recent CMV infection. These individuals may transmit CMV to susceptible individuals through blood and tissue products. Equivocal CMV IgG results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional specimen for testing if clinically indicated. Individuals with negative CMV IgG results are presumed to not have had prior exposure or infection with CMV and are therefore considered susceptible to primary infection. Herpes Simplex Virus: The presence of IgG-class antibodies to herpes simplex virus (HSV) types 1 or 2 indicates previous exposure and does not necessarily indicate that HSV is the causative agent of an acute illness.

Reference Values:

Toxoplasma ANTIBODY, IgG
Negative

Toxoplasma IgG
< or =9 IU/mL (Negative)
10-11 IU/mL (Equivocal)

> or =12 IU/mL (Positive)

RUBELLA ANTIBODY, IgG
Vaccinated: Positive (> or =1.0 AI)
Unvaccinated: Negative (< or =0.7 AI)

CYTOMEGALOVIRUS
Negative

HERPES SIMPLEX VIRUS (HSV), TYPE 1 AND TYPE 2 ANTIBODIES, IgG
Herpes Simplex Virus (HSV) Type 1, IgG
Negative

Herpes Simplex Virus (HSV) Type 2, IgG
Negative

Clinical References: 1. Tenter AM, Heckeroth AR, Weiss LM. Toxoplasma gondii: from animals to humans. Int J Parasitol. 2000;30(12-13):1217-1258 2. Jones JL, Kruszon-Moran D, Sanders-Lewis K, Wilson M. Toxoplasma gondii infection in the United States, 1999-2004, decline from the prior decade. Am J Trop Med Hyg. 2007;77(3):405-410 3. Luft BJ, Remington JS. Toxoplasmic encephalitis in AIDS. Clin Infect Dis. 1992;15(2):211-222 4. Wong SY, Remington JS. Toxoplasmosis in pregnancy. Clin Infect Dis. 1994;18(6):853-861 5. AAP Committee on Infectious Diseases: Rubella. In: Pickering LK, Baker CJ, Kimberlin DW, eds. Red Book. 2012 Report of the Committee on Infectious Diseases. 29th ed. American Academy of Pediatrics; 2012 6. Best JM. Rubella. Semin Fetal Neonatal Med. 2007;12(3):182-192 7. Duszak RS. Congenital rubella syndrome-major review. Optometry. 2009:80(1):36-43 8. Notifiable Diseases and Mortality Tables. MMWR Morb Mortal Wkly Rep. 2012;61(34):466-479 9. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases: Rubella (German measles, three-day measles). CDC; Updated December 31, 2020. Accessed December 16, 2024. Available at www.cdc.gov/rubella/ 10. Soderberg-Naucler C, Fish KN, Nelson JA. Reactivation of latent human cytomegalovirus by allogeneic stimulation of blood cells from healthy donors. Cell. 1997;91(1):119-126 11. Kusne S, Shapiro R, Fung J. Prevention and treatment of cytomegalovirus infection in organ transplant recipients. Transpl Infect Dis. 1999;1(3):187-203 12. Rubin RH. Importance of CMV in the transplant population. Transpl Infect Dis. 1999;1 Suppl 1:3-7 13. Staras SAS, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1998-1994. Clin Infect Dis. 2006;43(9):1143-1151 14. Ashley RL, Wald A. Genital herpes: review of the epidemic and potential use of type-specific serology. Clin Microbiol Rev. 1999;12(1):1-8 15. Ashley RL, Wu L, Pickering JW, Tu MC, Schnorenberg L. Premarket evaluation of a commercial glycoprotein G-based enzyme immunoassay for herpes simplex virus type-specific antibodies. J Clin Microbiol. 1998;36(1):294-295 16. Brown ZA, Selke S, Zeh J, et al. The acquisition of herpes simplex virus during pregnancy. N Engl J Med. 1997;337(8):509-515 17. Binnicker MJ, Jespersen DJ, Harring JA. Evaluation of three multiplex flow immunoassays compared to an enzyme immunoassay for the detection and differentiation of IgG-class antibodies to herpes simplex virus types 1 and 2. Clin Vaccine Immunol. 2010;17(2):253-257 18. Dioverti MV, Razonable RR. Cytomegalovirus. Microbiol Spectr. 2016;4(4). doi:10.1128/microbiolspec.DMIH2-0022-2015 19. Nath P, Kabir MA, Doust SK, Ray A. Diagnosis of Herpes simplex virus: Laboratory and point-of-care techniques. Infect Dis Rep. 2021;13(2):518-539 20. Notifiable Diseases and Mortality Tables. MMWR Morb Mortal Wkly Rep. 2016;65(3):ND-38 21. Wang ZD, Liu HH, Ma ZX, et al. Toxoplasma gondii infection in immunocompromised patients: A systematic review and meta-analysis. Front Microbiol. 2017;8:389

TIBC
2501

Total Iron Binding Capacity, Serum

Clinical Information:

Useful For: Screening for chronic iron overload diseases, particularly hereditary hemochromatosis

Interpretation: Total iron-binding capacity concentrations are elevated in anemia of chronic disease and iron overload conditions.(1) Total iron-binding capacity concentrations are decreased in iron deficiency, iron deficiency anemia, and iron-refractory iron deficiency anemia.(1)

Reference Values:
Only orderable as part of profile. For more information see SFEC / Iron and Total Iron-Binding Capacity, Serum.

250-400 mcg/dL

Clinical References:

TOXCG
616734

Toxocara Antibody, IgG, Serum

Clinical Information: Toxocariasis is a zoonotic parasitic disease caused by the nematode, Toxocara, of which there are 2 species: Toxocara canis and Toxocara cati. Toxocara eggs are shed in the feces of infected animals and, once in the environment, become infectious within 2 to 4 weeks. Humans are accidental hosts and become infected through ingestion of dirt or contaminated material containing Toxocara eggs. Although uncommon, individuals can also get toxocariasis by eating undercooked or raw meat from infected animals. Upon ingestion, Toxocara eggs hatch and larvae are released, which can penetrate the intestinal wall, travel through the bloodstream, and migrate to a variety of tissues (eg, liver, heart, lungs, brain, muscles, eyes). Although Toxocara larvae do not undergo any further development at these sites, they can cause severe local inflammatory reactions, which are the basis of toxocariasis. While the majority of infected people do not have any symptoms, the 2 primary clinical presentations of toxocariasis are visceral larva migrans (visceral toxocariasis) and ocular larva migrans (ocular toxocariasis). Manifestations of toxocariasis reflect parasitic burden, immune response, and resulting inflammation. Symptoms of larva migrans may be characterized by Loffler syndrome (eg, fever, coughing, wheezing, abdominal pain), hepatomegaly, eosinophilia, or irreversible eye problems. Rarely, larvae migrate to the central nervous system, causing eosinophilic meningoencephalitis or granuloma formation. Larvae can also migrate to and penetrate the eye, resulting in ocular toxocariasis, which may lead to retinal scarring, decreased vision, and leukocoria. A Toxocara seroprevalence study in the United States showed that approximately 5% of the US population is infected with Toxocara. Globally, toxocariasis is found in many countries, and rates of prevalence can be as high as 40%, particularly in tropical regions where eggs remain viable in the soil. Children and adolescents under the age of 20, as well as dog owners, are at higher risk of infection. Diagnosis of Toxocara infections involves obtaining relevant clinical and exposure history and relies on antibody detection to Toxocara species. Eosinophilia may also be present, more commonly in visceral toxocariasis. Stool examination for ova and parasites is not useful since eggs are not excreted by humans, only by domestic animals. Currently, antibody testing is the only means of confirming a clinical diagnosis. The recommended serologic test for toxocariasis is an enzyme-linked immunosorbent assay using larval-stage antigens. However, a measurable titer does not distinguish between current and past Toxocara infection. Laboratory findings should be correlated with clinical history.

Useful For: Aiding in the diagnosis of Toxocara infection

Interpretation: Positive: IgG antibodies to Toxocara species detected, suggesting current or past infection. False-positive results may occur in patients with other helminth infections (eg, Ascaris lumbricoides, Schistosoma species, Strongyloides). Equivocal: Recommend follow-up testing in 10 to 14 days if clinically indicated. Negative: No antibodies to Toxocara species detected.

Reference Values:
Negative

Reference values apply to all ages.

Clinical References: 1. Smith HV. Antibody reactivity in human toxocariasis. In: Lewis JW, Maizels RM, eds. Toxocara and Toxocariasis: Clinical, Epidemiological, and Molecular Perspectives. Institute of Biology and the British Society for Parasitology; 1993:91-109 2. Liu EW, Chastain HM, Shin SH, et al. Seroprevalence of antibodies to Toxocara species in the United States and associated risk factors, 2011-2014. Clin Infect Dis. 2018;66(2):206-212 3. Woodhall DM, Fiore AE. Toxocariasis: a review for pediatricians. J Pediatric Infect Dis Soc. 2014;3(2):154-159

FGGMC
75519

Toxoplasma gondii Antibodies (IgG, IgM), ELISA, CSF

Interpretation: Diagnosis of central nervous system infections can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpreting results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood and contamination via bloody taps.

Reference Values:

Reference Range: IgG:	
	Antibody not detected
0.9-1.09	Equivocal
>or=1.10	Antibody detected
IgM:	
	Antibody not detected
0.80-0.99	Equivocal
>or=1.00	Antibody detected

TOXGP
34972

Toxoplasma gondii Antibody, IgG, Serum

Clinical Information: Toxoplasma gondii is an obligate intracellular protozoan parasite capable of infecting a variety of intermediate hosts, including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious.(1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, T gondii can remain latent for the life of the host; the risk for reactivation is highest among individuals who are immunosuppressed. Seroprevalence studies performed in the United States indicate approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to T gondii.(2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most frequently present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine.

Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involve the central nervous system.(3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation.(4) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only, and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects.

Useful For: Determining whether a patient has had previous exposure to or recent infection with Toxoplasma gondii This test is not useful for diagnosing infection in infants younger than 6 months of age. In that age group, IgG antibodies usually are the result of passive transfer from the mother.

Interpretation: A positive Toxoplasma IgG result is indicative of current or past infection with Toxoplasma gondii. A single positive Toxoplasma IgG result should not be used to diagnose recent infection. Equivocal Toxoplasma IgG results may be due to very low levels of circulating IgG during the acute stage of infection. A second specimen should be submitted for testing if clinically indicated. Individuals with negative Toxoplasma IgG results are presumed to not have had previous exposure to T gondii. However, negative results may be seen in cases of remote exposure with subsequent loss of detectable antibody. Seroconversion from negative to positive IgG is indicative of T gondii infection subsequent to the first negative specimen. Recent or acute infection with T gondii can be evaluated with TXM / Toxoplasma gondii Antibody, IgM, Serum. A suspected diagnosis of acute toxoplasmosis should be confirmed by detection of T gondii DNA by polymerase chain reaction analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX / Toxoplasma gondii, Molecular Detection, PCR, Varies). For additional confirmation of a diagnosis, the US Food and Drug Administration issued a Public Health Advisory (07/25/1997) suggesting that sera found to be positive/equivocal for T gondii IgM antibody be sent to a Toxoplasma reference laboratory.

Reference Values:
Toxoplasma antibody, IgG
Negative

Toxoplasma IgG
< or =9 IU/mL (Negative)
10-11 IU/mL (Equivocal)
> or =12 IU/mL (Positive)
Reference values apply to all ages.

Clinical References: 1. Tenter AM, Heckeroth AR, Weiss LM. Toxoplasma gondii: from animals to humans. Int J Parasitol. 2000;30(12-13):1217-1258 2. Jones JL, Kruszon-Moran D, Sanders-Lewis K, Wilson M. Toxoplasma gondii infection in the United States, 1999-2004, decline from the prior decade. Am J Trop Med Hyg. 2007;77(3):405-410 3. Luft BJ, Remington JS. Toxoplasmic encephalitis in AIDS. Clin Infect Dis. 1992;15(2):211-222 4. Wong SY, Remington JS. Toxoplasmosis in pregnancy. Clin Infect Dis. 1994;18(6):853-861 5. Wang ZD, Liu HH, Ma ZX, et al. Toxoplasma gondii infection in immunocompromised patients: A systematic review and meta-analysis. Front Microbiol. 2017;8:389

TXMGP
39857 **Toxoplasma gondii Antibody, IgM and IgG, Serum**

Clinical Information: Toxoplasma gondii is an obligate intracellular protozoan parasite capable of infecting a variety of intermediate hosts, including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious.(1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, T gondii can remain latent for the life of the host; the risk for reactivation is highest among individuals who are immunosuppressed. Seroprevalence studies performed in the United States indicate approximately 6.7% of individuals between the ages of 12 and 49 have antibodies to T gondii.(2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most frequently present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals that are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involve the central nervous system.(3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation.(4) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only, and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects.

Useful For: Determining whether a patient has had previous exposure to or recent infection with Toxoplasma gondii IgG is not useful for diagnosing infection in infants younger than 6 months of age. IgG antibodies in this age group usually are the result of passive transfer from the mother.

Interpretation: Active toxoplasmosis is suggested by the presence of IgM-class antibodies, but elevated anti-IgM titers may be absent in patients who are immunocompromised. In addition, elevated IgM can persist from an acute infection that may have occurred as long ago as 1 year. A suspected diagnosis of acute toxoplasmosis should be confirmed by detection of Toxoplasma gondii DNA by polymerase chain reaction (PCR) analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX / Toxoplasma gondii, Molecular Detection, PCR, Varies). For confirmation of toxoplasmosis, the US Food and Drug Administration issued a Public Health Advisory (07/25/1997) that recommends sera found to be positive for T gondii IgM antibodies should be sent to a Toxoplasma reference laboratory. A single negative result should not be used to rule-out toxoplasmosis, and repeat testing is recommended for patients at high risk for infection. IgG is only indicative of previous exposure to Toxoplasma (recent or past). A single positive Toxoplasma IgG result should not be used to diagnose recent infection. Seroconversion from negative to positive IgG is indicative of recent T gondii infection.

Reference Values:

Toxoplasma IgM
Negative

Toxoplasma IgG
Negative

Toxoplasma IgG Value
< or =9 IU/mL (Negative)
10-11 IU/mL (Equivocal)
> or =12 IU/mL (Positive)
Reference values apply to all ages.

Clinical References: 1. Tenter AM, Heckeroth AR, Weiss LM. Toxoplasma gondii: from animals to humans. Int J Parasitol. 2000;30(12-13):1217-1258 2. Jones JL, Kruszon-Moran D, Rivera HN, Price C, Wilkins PP. Toxoplasma gondii seroprevalence in the United States 2009-2010 and comparison with the past two decades. Am J Trop Med Hyg. 2014;90(6):1135-1139 3. Luft BJ, Remington JS. Toxoplasmic encephalitis in AIDS. Clin Infect Dis. 1992;15(2):211-222 4. Wong SY, Remington JS. Toxoplasmosis in pregnancy. Clin Infect Dis. 1994;18(6):853-861 5. Wang ZD, Liu HH, Ma ZX, et al. Toxoplasma gondii infection in immunocompromised patients: A systematic review and meta-analysis. Front Microbiol. 2017;8:389

TXM
39856

Toxoplasma gondii Antibody, IgM, Serum

Clinical Information: Toxoplasma gondii is an obligate intracellular protozoan parasite capable of infecting a variety of intermediate hosts, including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious.(1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, T gondii can remain latent for the life of the host; the risk for reactivation is highest among individuals who are immunosuppressed. Seroprevalence studies performed in the United States indicate approximately 6.7% of individuals between the ages of 12 and 49 have antibodies to T gondii.(2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most frequently present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involve the central nervous system.(3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation.(4) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only, and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects.

Useful For: Detecting recent infection with Toxoplasma gondii

Interpretation: Active toxoplasmosis is suggested by the presence of IgM-class antibodies, but elevated anti-IgM titers may be absent in patients who are immunocompromised. In addition, elevated IgM can persist from an acute infection that may have occurred as long ago as 1 year. A suspected diagnosis of acute toxoplasmosis should be confirmed by detection of Toxoplasma gondii DNA by polymerase chain reaction analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX / Toxoplasma gondii, Molecular Detection, PCR, Varies). For confirmation of toxoplasmosis, the US Food and Drug Administration issued a Public Health Advisory (07/25/1997) that recommends sera found to be positive for Toxoplasma gondii IgM antibodies should be sent to a Toxoplasma reference laboratory. A single negative result should not be used to rule out toxoplasmosis, and repeat testing is recommended for patients at high risk for infection.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Tenter AM, Heckeroth AR, Weiss LM. Toxoplasma gondii: from animals to humans. Int J Parasitol. 2000;30(12-13):1217-1258 2. Jones JL, Kruszon-Moran D, Rivera HN, Price C, Wilkins PP. Toxoplasma gondii seroprevalence in the United States 2009-2010 and comparison with the past two decades. Am J Trop Med Hyg. 2014;90(6):1135-1139 3. Luft BJ, Remington JS. Toxoplasmic encephalitis in AIDS. Clin Infect Dis. 1992;15(2):211-222 4. Wong SY, Remington JS. Toxoplasmosis in pregnancy. Clin Infect Dis. 1994;18(6):853-861 5. Wang ZD, Liu HH, Ma ZX, et al. Toxoplasma gondii infection in immunocompromised patients: A systematic review and meta-analysis. Front Microbiol. 2017;8:389

TOXB
62977

Toxoplasma gondii, Molecular Detection, PCR, Blood

Clinical Information: Toxoplasma gondii is an obligate intracellular protozoan parasite that can infect a variety of intermediate hosts, including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious.(1,2) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, T gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 years and 49 years have antibodies to T gondii.(3) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system.(4) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation.(3) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. Most infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects. Detection of T gondii DNA by polymerase chain reaction (PCR) has proven to be a rapid and reliable alternative or supportive method for the diagnosis of toxoplasmosis. When performed on blood, it may detect circulating parasite DNA and thus confirm or support the results of serologic testing. PCR testing on peripheral blood has been used successfully to detect cases of ocular toxoplasmosis (3) as well as invasive disease in allogeneic stem cell recipients.(4,5) However, blood may not be a sensitive specimen for detecting organ specific disease (eg, ocular or cerebral toxoplasmosis). In this case, other specimens (eg, ocular fluid, CSF, fresh tissue) should be considered (order PTOX / Toxoplasma gondii, Molecular Detection, PCR, Varies).

Useful For: Supporting the diagnosis of active toxoplasmosis, particularly in immunocompromised individuals

Interpretation: A positive result indicates presence of DNA from Toxoplasma gondii. Negative results indicate absence of detectable DNA, but do not exclude the presence of organism or active or recent disease.

Reference Values:
Negative

Clinical References: 1. Robert-Gangneux F, Darde M. Epidemiology of and diagnostic strategies for toxoplasmosis. Clin Microbiol Rev. 2012 Apr ;25(2):264-296 2. McAuley JB, Singh K: Toxoplasma, In: Carroll KC, Pfaller MA, eds. Manual of Clinical Microbiology, 12th ed. ASM Press; 2019: chap141. 3. Mattos CCB, Meira CS, Ferreira AIC, et al: Contribution of laboratory methods in diagnosing clinically suspected ocular toxoplasmosis in Brazilian patients. Diagn Microbiol Infec Dis. 2011 Jul;70(3):362-366 4. Martino R, Bretagne S, Einsele H, et al: Early detection of Toxoplasma infection by molecular monitoring of Toxoplasma gondii in peripheral blood samples after allogeneic stem cell transplantation. Clin Infect Dis. 2005 Jan 1;40(1):67-78 5. Fricker-Hidalgo H, Bulabois C, Brenier-Pinchart M, et al: Diagnosis of toxoplasmosis after allogeneic stem cell transplantation: results of DNA detection and serological techniques. Clin Infect Dis. 2009;48:e9-e15

PTOX
81795

Toxoplasma gondii, Molecular Detection, PCR, Varies

Clinical Information: Toxoplasma gondii is an obligate intracellular protozoan parasite that can infect a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces, and these rapidly mature in the soil and become infectious.(1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces containing oocysts or through eating undercooked meat containing viable tissue cysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, T gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 years and 49 years have antibodies to T gondii.(2,3) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS and other individuals with profound immune compromise. These infections are usually due to reactivation of latent infections and commonly involved the central nervous system.(4,5) Transplacental transmission of the parasites resulting in congenital toxoplasmosis most often occurs during primary maternal infection and rarely after reactivation in an immunocompromised pregnant woman. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation. (6,7) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. Most infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects. Serology is the traditional method for diagnosing toxoplasmosis and ascertaining the previous exposure history of the host. However, serology may be unreliable or challenging to interpret in immunocompromised patients and in suspected intrauterine infection. Detection of T gondii DNA by polymerase chain reaction has proven to be a rapid and reliable alternative or supportive method for the diagnosis of toxoplasmosis.

Useful For: Supporting the diagnosis of acute cerebral, ocular, disseminated, or congenital toxoplasmosis This test should not be used to screen healthy patients.

Interpretation: A positive result indicates presence of DNA from Toxoplasma gondii. Negative results indicate absence of detectable DNA but do not exclude the presence of organism or active or recent disease.

Reference Values:
Negative

Clinical References: 1. Robert-Gangneux F, Darde M. Epidemiology of and diagnostic strategies for toxoplasmosis. Clin Microbiol Rev. 2012;25(2):264-296 2. Mattos CCB, Meira CS, Ferreira AIC, et al. Contribution of laboratory methods in diagnosing clinically suspected ocular toxoplasmosis in Brazilian patients. Diagn Microbiol Infec Dis. 2011;70(3):362-366 3. Jones JL, Kruszon-Moran D, Elder S, et al. Toxoplasma gondii infection in the United States, 2011-2014. Am J Trop Med Hyg. 2018;98(2):551-557. doi:10.4269/ajtmh.17-0677 4. Martino R, Bretagne S, Einsele H, et al. Early detection of Toxoplasma infection by molecular monitoring of Toxoplasma gondii in peripheral blood samples after allogeneic stem cell transplantation. Clin Infect Dis. 2005 ;40(1):67-78 5. Elsheikha HM, Marra CM, Zhu XQ. Epidemiology, pathophysiology, diagnosis, and management of cerebral toxoplasmosis. Clin Microbiol Rev. 2020;34(1):e00115-19 6. Fricker-Hidalgo H, Bulabois C, Brenier-Pinchart M, et al. Diagnosis of toxoplasmosis after allogeneic stem cell transplantation: results of DNA detection and serological techniques. Clin Infect Dis. 2009;48:e9-e15 7. Maldonado YA, Read JS. Committee on infectious diseases. Diagnosis, treatment, and prevention of congenital toxoplasmosis in the United States. Pediatrics. 2017;139(2):e20163860. doi:10.1542/peds.2016-3860

TOXO
70569

Toxoplasma Immunostain, Technical Component Only

Clinical Information: Immunohistochemical staining for Toxoplasma gondii can help identify the organisms in the cytoplasm of infected cells. T gondii is a sporozoan that lives as an intracellular parasite in various tissues of vertebrates. T gondii is transmitted via raw or undercooked meat, contaminated soil, or by direct contact. Pregnant women and immunosuppressed patients are at highest risk for infection.

Useful For: Identification of Toxoplasma gondii infection

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Mostafa NES, Abdel Hamed EF, Rashed HES, Mohamed SY, Abdelgawad MS, Elasbali AM. The relationship between toxoplasmosis and different types of human tumors. J Infect Dev Ctries. 2018;12(2):137-141 2. Arnold SJ, Kinney MC, McCormick MS, Dummer S, Scott MA. Disseminated toxoplasmosis. Unusual presentations in the immunocompromised host. Arch Pathol Lab Med. 1997;121(8):869-873 3. Held TK, Kruger D, Switala AR, et al. Diagnosis of toxoplasmosis in bone marrow transplant recipients: comparison of PCR-based results and immunohistochemistry. Bone Marrow Transplant. 2000;25(12):1257-1262 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

CSP53
607599

TP53 Gene Somatic Mutation Pre-Analysis Cell Sorting, Varies

Clinical Information: Patients with chronic lymphocytic leukemia (CLL) have variable disease course influenced by a series of tumor biologic factors. The presence of chromosomal 17p- or TP53 gene variation confers a very poor prognosis to a subset of CLL patients, both at time of initial diagnosis as well as at disease progression, or in the setting of therapeutic resistance. TP53 gene variant status in CLL has emerged as the single most predictive tumor genetic abnormality associated with adverse outcome and poor response to standard immunochemotherapy; however, patients can be managed with alternative therapeutic options.

Useful For: Determination of B-cell content and confirmation the presence of a clonal B-cell population evaluating chronic lymphocytic leukemia patients prior to TP53 variant analysis

Interpretation: Correlation with clinical, histopathologic and additional laboratory findings is required for final interpretation of these results. The final interpretation of results for clinical management of the patient is the responsibility of the managing physician.

Reference Values:
Only orderable as a reflex. For more information see P53CA / Hematologic Neoplasms, TP53 Somatic Mutation, DNA Sequencing Exons 4-9, Varies.

Clinical References: 1. Zenz T, Krober A, Scherer K, et al. Monoallelic TP53 inactivation is associated with poor prognosis in chronic lymphocytic leukemia: results from a detailed genetic characterization with long-term follow-up. Blood. 2008;112(8):3322-3329 2. Lehmann S, Oqawa S, Raynaud SD, et al. Molecular allelokaryotyping of early-stage, untreated chronic lymphocytic leukemia. Cancer. 2008;112(6):1296-1305 3. Rossi D, Cerri M, Deambrogi C, et al. The prognostic value of TP53 mutations in chronic lymphocytic leukemia is independent of Del17p13: implications for overall survival and chemorefractoriness. Clin Cancer Res. 2009;15(3):995-1004 4. Zent CS, Call TG, Hogan WJ, et al. Update on risk-stratified management for chronic lymphocytic leukemia. Leuk Lymphoma. 2006;47(9):1738-1746 5. Hampel PJ, Parikh SA. Chronic lymphocytic leukemia treatment algorithm 2022 [published correction appears in Blood Cancer J. 2022 Dec 22;12(12):172]. Blood Cancer J. 2022;12(11):161. Published 2022 Nov 29. doi:10.1038/s41408-022-00756-9 6. Trbusek M, Smardova J, Malcikova J, et al. Missense mutations located in structural p53 DNA-binding motifs are associated with extremely poor survival in chronic lymphocytic leukemia. J Clin Oncol. 2011;29(19):2703-2708 7. Halldorsdottir AM, Lundin A, Murray F, et al. Impact of TP53 mutation and 17p deletion in mantle cell lymphoma. Leukemia. 2011;25(12):1904-1908 8. Young KH, Leroy K, Moller MB, et al. Structural profiles of TP53 gene mutations predict clinical outcome in diffuse large B-cell lymphoma: an international collaborative study. Blood. 2008;112(8):3088-3098

TP53
616496

TP53 Mutation Analysis, Next-Generation Sequencing, Tumor

Clinical Information: The TP53 gene is a tumor suppressor gene that regulates expression of genes involved in cell cycle arrest, apoptosis, DNA repair, and changes in metabolism. Somatic mutations in the TP53 gene are the most common genetic alteration seen in human cancers, with over 50% of adult human tumors bearing inactivating mutations, insertions, and deletions in the TP53 gene. Somatic mutations in the TP53 gene usually correlate with poor outcome and early recurrence in cancer. In central nervous system (CNS) tumors, TP53 mutations are a diagnostic molecular biomarker for medulloblastoma, SHH-activated tumors, and a supporting molecular biomarker for IDH (isocitrate dehydrogenase)-mutant astrocytoma and choroid plexus carcinoma. The results of this test can be useful for predicting prognosis for breast cancer, cervical cancer, melanoma, and other cancers, and for diagnosis/classification of CNS tumors.

Useful For: Assisting in the clinical management of patients with cancer This test is not intended for the evaluation of patients suspected of having an inherited or germline TP53 cancer syndrome (eg, Li Fraumeni syndrome).

Interpretation: The interpretation of molecular biomarker analysis includes an overview of the results and the associated diagnostic, prognostic, and therapeutic implications.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med. 2016;13(1):3-11. doi:10.28092/j.issn.2095-3941.2016.0004 2. Spurr L, Li M, Alomran N, et al. Systematic pan-cancer analysis of somatic allele frequency. Sci Rep. 2018;8(1):7735. Published 2018 May 16. doi:10.1038/s41598-018-25462-0 3. Robels AI, Jen J, Harris CC. Clinical outcomes of TP53 mutations in cancers. Cold Spring Harb Perspect Med. 2016;6(9):a026294. doi:10.1101/cshperspect.a026294 4. Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2010;2(1): a001008 5. WHO Classification of Tumours Editorial Board: Central nervous system tumours. 5th ed. World Health Organization; 2021. WHO Classification of Tumours. Vol 6.

TRAM 62595 Tramadol and Metabolite, Random, Urine

Clinical Information: Tramadol, a centrally acting opioid analgesic, is utilized in the treatment of moderate to moderately severe pain. Tramadol acts as an opiate agonist through the binding of the parent drug and its O-desmethyl (M1) metabolite to mu-opioid receptors and through the weak inhibition of norepinephrine and serotonin reuptake. The active metabolite, O-desmethyltramadol, is a considerably more potent mu-opioid receptor agonist than its parent drug. In urine, approximately 30% of tramadol is excreted as unchanged drug, while approximately 60% is excreted as metabolites (N- and O-desmethyltramadol). The half-life of tramadol and O-desmethyltramadol is approximately 7 hours.

Useful For: Monitoring of compliance utilizing tramadol Detection and confirmation of the illicit use of tramadol This test is not intended for use in employment-related testing.

Interpretation: The presence of tramadol or O-desmethyltramadol levels of 25 ng/mL or higher is a strong indicator that the patient has used tramadol.

Reference Values:
Negative (Positive results are reported with a quantitative result.)

Cutoff concentrations by liquid chromatography tandem mass spectrometry:
Tramadol: 25 ng/mL
O-desmethyltramadol: 25 ng/mL

Clinical References: 1.Tramadol. In: Merative Micromedex. Merative; Accessed December 13, 2024. Available at: www.micromedexsolutions.com/ 2. Jutkiewicz EM, Traynor JR. Opioid analgesics. In: Brunton LL, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 14th ed. McGraw-Hill Education; 2023 3.Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

TFE3I 70564 Transcription Factor E3 (TFE3) Immunostain, Technical Component Only

Clinical Information: Transcription factor E3 (TFE3) is a member of the microphthalmia transcription factor (MiTF)/TFE family of helix-loop-helix transcription factors. TFE3 overexpression is observed in TFE translocation-associated renal cell carcinoma and alveolar soft part sarcoma.

Useful For: Assessment of transcription factor E3 expression

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Komai Y, Fujiwara M, Fujii Y, et al. Adult Xp11 translocation renal cell carcinoma diagnosed by cytogenetics and immunohistochemistry. Clin Cancer Res. 2009;15(4):1170-1176 2. Vistica DT, Krosky PM, Kenney S, et al. Immunohistochemical discrimination between the ASPL-TFE3 fusion proteins of alveolar soft part sarcoma. J Pediatr Hematol Oncol. 2008;30(1):46-52 3. Argani P, Antonescu CR, Couturier J, et al. PRCC-TFE3 renal carcinomas: morphologic, immunohistochemical, ultrastructural, and molecular analysis of an entity associated with the t(X;1)(p11.2;q21). Am J Surg Pathol .2002;26(12):1553-1566 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TRSF
34623

Transferrin, Serum

Clinical Information: Transferrin is the primary plasma iron transport protein, which binds iron strongly at physiological pH. It is a glycoprotein with an approximate molecular weight of 80 kDa, consisting of a polypeptide strand with two N-glycosidically linked oligosaccharide chains with two homologous binding sites for ferric (Fe 3+) iron serving to keep iron nonreactive in circulation and deliver it to cells with transferrin receptors. The rate of transferrin synthesis in the liver can be altered according to the body's iron requirements and iron reserves. The circulating concentration increases in response to iron deficiency and decreases in response to iron overload. Transferrin concentration also depends on liver function and nutritional status. It also acts as a negative acute phase reactant, decreasing in concentration in the presence of inflammation; however, it has a minor intraindividual biologic variation of 5%. Transferrin is generally only 25% to 30% saturated with iron. Total iron binding capacity (TIBC) can be estimated from transferrin concentration using the molecular weight of the transferrin and accounting that 1 transferrin molecule can bind 2 atoms of iron.(1) The degree of iron saturation is a more useful indicator of functional iron depletion or overload than transferrin concentration alone. Serum iron, TIBC, and percent saturation are widely used for the diagnosis of iron deficiency and hemochromatosis. However, serum ferritin is a much more sensitive and reliable test for demonstration of iron deficiency. Soluble transferrin receptor performs similarly and is unaffected by inflammation. Reticulocyte hemoglobin has also been used as a sensitive early indicator of iron deficiency and anemia.

Useful For: Evaluation of iron overload diseases Evaluation of iron deficiency as a cause of anemia

Interpretation: Transferrin concentrations are elevated in anemia of chronic disease and iron overload conditions.(1) Transferrin concentrations are decreased in iron deficiency, iron deficiency anemia, and iron-refractory iron deficiency anemia.(1)

Reference Values:
200-360 mg/dL

Clinical References: 1. Swinkels DW. Iron metabolism. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 40 2. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet. 2016;387(10021):907-916

FFTRZ
75024

Trazodone (Desyrel)

Reference Values:
Reference Range: 800 - 1600 ng/mL

FHEAV
57949

Tree of Heaven (Ailanthus spp) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

TREE1
81886

Tree Panel #1, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to trees in panel #1 Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive

5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

TREE3
81704

Tree Panel #3, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to tress in panel #3 Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive

6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

TREE4
81705

Tree Panel #4, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to trees in panel #4 Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive

6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FHAL
90119

Triazolam (Halcion)

Reference Values:
Reference Range: 5.0 - 20.0 ng/mL

TRCNG
616733

Trichinella Antibody, IgG, Serum

Clinical Information: Trichinosis is an infection by the nematode parasite, Trichinella spiralis. The infection is acquired by ingestion of larvae in inadequately cooked, contaminated meat, especially pork, bear, and walrus meat. After ingestion, acid-pepsin digestion in the stomach liberates the larvae, which develop into adult worms in the small intestine. After fertilization, the female worm produces larvae that penetrate the mucosa and seed the skeletal muscles via the blood stream. The larvae coil and encyst in muscle fibers, remaining viable for up to several years. Diarrhea is the most common symptom associated with intestinal infection with adult worms. Fever, periorbital swelling, muscle pain and swelling, pulmonary symptoms, and rash develop during systemic invasion by the larvae.

Useful For: As an adjunct in the diagnosis of trichinosis

Interpretation: Positive: Results are suggestive of current or past infection with Trichinella spiralis. Results should be used in conjunction with clinical, epidemiologic and other laboratory tests to diagnose current infection. Borderline: Recommend follow-up testing in 10 to 14 days if clinically indicated Negative: No antibodies to Trichinella spiralis detected. Repeat testing in 2 to 3 weeks if clinically indicated.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Grove DI: Tissue nematodes. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. Vol 2. 4th ed. Churchill Livingstone; 1995:2531-2537 2. Pasternack MS: Myositis and myonecrosis. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:1307-1316

FFTRU
91099

Trichloroacetic Acid, Urine

Reference Values:
Creatinine: >50 mg/dL

Trichloroethane Exposure:
Normal (unexposed population):
None detected

Exposed:
Biological Exposure Index (BEI):
10 mg/L (end of workweek)
Toxic:
Not established

Trichloroethylene Exposure:
Normal (unexposed population):
None detected
Exposed:
Biological Exposure Index (BEI):
100 mg/g creat (end of workweek)

Biological Tolerance Value (BAT):
100 mg/L (end of exposure or end of shift, or after several shifts for long-term exposure)
Toxic:
Not established

Tetrachloroethylene (Perchloroethylene) Exposure:
Normal (unexposed population):
None detected
Exposed:
Biological Exposure Index (BEI):
7.0 mg/L (end of workweek)
Toxic:
Not established

TRVI
82853

Trichoderma viride, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Trichoderma viride Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

MTRNA 61756

Trichomonas vaginalis, Nucleic Acid Amplification, Varies

Clinical Information: Trichomonas vaginalis is a protozoan parasite that commonly infects the genital tract of men and women. It is considered to be the most common nonviral sexually transmitted infection (STI), with an estimated 2.6 million cases documented in 2020 in the United States. Although up to 70% of infected individuals are asymptomatic, infections may be associated with vaginitis, urethritis, and cervicitis in women and urethritis and prostatitis in men. Patients that are infected with T vaginalis have an increased risk of acquiring other STIs, such as HIV, while infections in pregnant women are associated with premature labor, low birth-weight offspring, premature rupture of membranes, and post-hysterectomy/post-abortion infection. Symptoms of T vaginalis overlap considerably with other STIs; therefore, laboratory diagnosis is required for definitive diagnosis. The most frequently used method for detection is microscopic examination of a wet-mount preparation of vaginal secretions. However, this method has only 35% to 80% sensitivity compared with culture. Culture also suffers from relatively low sensitivity (38%-82%) when compared to molecular methods. Culture is technically challenging and takes 5 to 7 days to complete. Molecular methods, such as the Aptima T vaginalis assay, offer high sensitivity and specificity for detection of trichomoniasis. The Aptima test utilizes target capture, transcription-mediated amplification, and hybridization protection assay technologies for detection of T vaginalis ribosomal RNA.

Useful For: Detecting Trichomonas vaginalis in prostatic massage (VB3) fluid or male urethral swabs

TVRNA 61755

Trichomonas vaginalis, Nucleic Acid Amplification, Varies

Clinical Information: Trichomonas vaginalis is a protozoan parasite that commonly infects the genital tract of men and women. It is considered to be the most common nonviral sexually transmitted infection (STI), with an estimated 2.6 million cases documented in 2020 in the United States. Although up to 70% of infected individuals are asymptomatic, infections may be associated with vaginitis, urethritis, and cervicitis in women and urethritis and prostatitis in men. Patients that are infected with T vaginalis have an increased risk of acquiring other STIs, such as HIV, while infections in pregnant women are associated with premature labor, low birth-weight offspring, premature rupture of membranes, and post-hysterectomy/post-abortion infection. Symptoms of T vaginalis overlap considerably with other STIs; therefore, laboratory diagnosis is required for definitive diagnosis. The most frequently used method for

detection is microscopic examination of a wet-mount preparation of vaginal secretions. However, this method has only 35% to 80% sensitivity compared with culture. Culture also suffers from relatively low sensitivity (38%-82%) when compared to molecular methods. Culture is technically challenging and takes 5 to 7 days to complete. Molecular methods, such as the Aptima T vaginalis assay, offer high sensitivity and specificity for detection of trichomoniasis. The Aptima test utilizes target capture, transcription-mediated amplification, and hybridization protection assay technologies for detection of T vaginalis ribosomal RNA.

Useful For: Detecting Trichomonas vaginalis in urine, cervical/endocervical or vaginal specimen types

Interpretation: A positive result indicates the presence of nucleic acid from Trichomonas vaginalis and is strongly supportive of a diagnosis of trichomoniasis. A negative result indicates the absence of nucleic acid from T vaginalis. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of inconclusive indicates that a new specimen should be collected. The predictive value of an assay depends on the prevalence of the disease in any specific population. In settings with a high prevalence of sexually transmitted infections, positive assay results have a high likelihood of being true-positive results. In settings with a low prevalence of sexually transmitted infections, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with infection, positive results should be carefully assessed, and the patient retested by other methods if appropriate.

Reference Values:
Negative

Clinical References: 1. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187 2. Andrea SB, Chapin KC. Comparison of Aptima Trichomonas vaginalis transcription-mediated amplification assay and BD affirm VPIII for detection of T. vaginalis in symptomatic women: performance parameters and epidemiological implications. J Clin Microbiol. 2011;49(3):866-9. doi:10.1128/JCM.02367-10 3. Chernesky M, Jang D, Gilchrist J, et al. Ease and comfort of cervical and vaginal sampling for Chlamydia trachomatis and Trichomonas vaginalis with a new Aptima specimen collection and transportation kit. J Clin Microbiol. 2014;52(2):668-70. doi:10.1128/JCM.02923-13

FFTMV
75554

Trichophyton Mentagrophytes (var interdigitale) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

TCPT
82720

Trichophyton rubrum, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend

upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Trichophyton rubrum Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

TRPS1
616890

Trichorhinophalangeal syndrome type 1 (TRPS1) Immunostain, Technical Component Only

Clinical Information: Trichorhinophalangeal syndrome type 1 (TRPS1) is a novel transcription factor that functions as a regulator for the growth and differentiation of both normal mammary epithelial cells and breast carcinomas. TRPS1 is a specific and sensitive marker for breast carcinoma, particularly triple negative breast cancers. TRPS1 may be useful in diagnosing primary and metastatic breast carcinomas.

Useful For: Identification of breast carcinoma including triple negative breast cancer

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Ai D, Yao J, Yang F, et al: TRPS1: a highly sensitive and specific marker for breast carcinoma, especially for triple-negative breast cancer. Mod Pathol.2021 Apr;34(4):710-719 2. Chang G, Jhamai M, van Weerden W, et al: The TRPS1 transcription factor: androgenic regulation in prostate cancer and high expression in breast cancer. Endocr -Relat Cancer. 2004 Dec; 11(4):815-822 3. Chen J, Litton J, Xiao L, et al: Quantitative immunohistochemical analysis and prognostic significance of TRPS-1, a new GATA transcription factor family member, in breast cancer. Horm Canc. 2010 Feb 1;(1):21-33

TGLBF
606918

Triglycerides, Body Fluid

Clinical Information: Triglyceride concentration in body fluids is correlated to the presence of chylomicrons and can be useful when diagnosing chylous effusion or differentiating from pseudochylous effusion.(1) Chylous effusions are characterized by the presence of chyle which contains chylomicrons circulating through the lymphatic system. Pseudochylous effusions do not have chylomicrons. These fluids have a milky appearance and can be confused with chylous effusions. While chylous effusions often have elevated triglyceride concentrations and decreased cholesterol concentrations, identification of chylomicrons is considered the gold standard for the diagnosis. Pleural fluid: Chylothorax is the name given to pleural effusions containing chylomicrons. They develop when chyle accumulates from disruption of the lymphatic system, often the thoracic duct, caused mainly by malignancy or trauma.(1) Lymph contains chylomicron rich chyle characterized by high concentrations of triglycerides. Pseudochylous effusions are the name given to milky appearing effusions that do not contain lymphatic contents but rather form gradually through the breakdown of cellular lipids in long-standing effusions such as rheumatoid pleuritis, tuberculosis, or myxedema and by definition the effluent contains high concentrations of cholesterol.(2) Differentiation of pseudochylothorax from chylothorax is important as their milky or opalescent appearance is similar, however therapeutic management strategies differ. Peritoneal fluid: Chylous ascites is the name given to peritoneal effusions containing chylomicrons. Obstruction of lymph flow causing leakage from dilated subserosal lymphatics, exudation through the walls of retroperitoneal megalymphatics, and direct leakage of chyle due to a lymphoperitoneal fistula have been proposed as possible mechanisms causing chylous ascites.(3) Elevated triglyceride concentrations have the best correlation with detection of chylomicrons, while cholesterol is not useful at predicting the presence or absence of chylomicrons.

Useful For: Distinguishing between chylous and nonchylous effusions Measurement of triglycerides in body fluids as a surrogate for chylomicrons

Interpretation: Pleural fluid triglyceride concentrations over 110 mg/dL are consistent with a chylous effusion. Triglyceride concentrations below 50 mg/dL are usually not due to chylous effusions.(1) Peritoneal fluid triglyceride concentrations over 187 mg/dL are most consistent with chylous effusion.(3)

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Hooper C, Lee YC, Maskell N; BTS Pleural Guideline Group:

Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65(Suppl2):ii4-17. doi:10.1136/thx.2010.136978 2. Staats BA, Ellefson RD, Budahn LL, et al. The lipoprotein profile of chylous and nonchylous pleural effusions. Mayo Clin Proc. 1980;55(11):700-704 3. Thaler MA, Bietenbeck A, Schulz C, Luppa PB. Establishment of triglyceride cut-off values to detect chylous ascites and pleural effusions. Clin Biochem. 2017;50(3):134-138. doi:10.1016/j.clinbiochem.2016.10.008 4. McGrath EE, Blades Z, Anderson PB. Chylothorax: aetiology, diagnosis, and therapeutic options. Respir Med. 2010;104(1):1-8. doi:10.1016/j.rmed.2009.08.010

TRIGC
606879

Triglycerides, CDC, Serum

Clinical Information: Triglycerides are esters of the trihydric alcohol, glycerol, with 3 long-chain fatty acids. They are partly synthesized in the liver and partly derived from the diet.

Useful For: Measurement of triglycerides as part of lipoprotein profiling

Interpretation: Increased plasma triglyceride levels are indicative of a metabolic abnormality and, along with elevated cholesterol, are considered a risk factor for atherosclerotic disease. Hyperlipidemia may be inherited or be associated with biliary obstruction, diabetes mellitus, nephrotic syndrome, kidney failure, or metabolic disorders related to endocrinopathies. Increased triglycerides may also be associated with alcohol consumption, sedentarism or medication-induced (eg, prednisone). Since cholesterol and triglycerides can vary independently, measurement of both is more meaningful than the measurement of cholesterol only.

Reference Values:
Only orderable as part of a profile. For more information see LMPP / Lipoprotein Metabolism Profile, Serum.

Triglycerides
2-9 years:
Acceptable: <75 mg/dL
Borderline high: 75-99 mg/dL
High: > or =100 mg/dL

10-17 years:
Acceptable: <90 mg/dL
Borderline high: 90-129 mg/dL
High: > or =130 mg/dL

> or =18 years:
Normal: <150 mg/dL
Borderline high: 150-199 mg/dL
High: 200-499 mg/dL
Very high: > or =500 mg/dL

Reference values have not been established for patients younger than 2 years.

Clinical References: 1. Grundy SM, Stone NJ, Bailey AL, et al: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: A report of the american college of cardiology/american heart association task force on clinical practice guidelines. Circulation. 2019;139(25):e1082-e1143. doi:10.1016/j.jacc.2018.11.002 2. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on

integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128 Suppl5(Suppl 5):S213-S256 3. Rosenson RS, Najera SD, Hegele RA. Heterozygous familial hypercholesterolemia presenting as chylomicronemia syndrome. J Clin Lipidol. 2017;11(1):294-296. doi:10.1016/j.jacl.2016.12.005 4. Hopkins PN, Brinton EA, Nanjee MN. Hyperlipoproteinemia type 3: the forgotten phenotype. Curr Atheroscler Rep. 2014;16(9):440. doi:10.1007/s11883-014-0440-2 5. Gotoda T, Shirai K, Ohta T, et al. Diagnosis and management of type I and type V hyperlipoproteinemia. J Atheroscler Thromb. 2012;19(1):1-12 6. Gonzales KM, Donato LJ, Shah P, Simha V. Measurement of apolipoprotein B levels helps in the identification of patients at risk for hypertriglyceridemic pancreatitis. J Clin Lipidol. 2021;15(1):97-103. doi:10.1016/j.jacl.2020.11.010

TRIG1
616665

Triglycerides, Serum

Clinical Information: Triglycerides are oily lipids carried in the blood by lipoproteins. Triglycerides are primarily carried by very low-density lipoprotein (VLDL), chylomicrons, and remnant lipoproteins. Recent evidence supports triglycerides as an independent risk factor for atherosclerotic cardiovascular disease (ASCVD). Several conditions are associated with increased plasma triglycerides, including obesity, pregnancy, physical inactivity, excess alcohol intake, kidney disease, and diabetes. Elevated triglycerides are often associated with reduced high-density lipoprotein cholesterol, insulin resistance, hypertension, fatty liver disease, and increased waist circumference. In addition to cardiovascular risk, elevated triglycerides confer a risk for acute pancreatitis.

Useful For: Managing atherosclerotic cardiovascular disease risk

Interpretation: Maintaining desirable concentrations of lipids lowers atherosclerotic cardiovascular disease (ASCVD) risk. Establishing appropriate treatment strategies and lipid goals require that blood lipid values be considered in context with other risk factors including, age, sex, smoking status, and medical history of hypertension, diabetes, and cardiovascular disease. Triglycerides results of 500 mg/dL and above are severely elevated, increasing the risk of pancreatitis. Triglycerides can be lowered by increasing physical activity, low-fat diet, weight loss, and/or triglyceride lowering pharmaceuticals.

Reference Values:
The National Lipid Association and the National Cholesterol Education Program have set the following guidelines for lipids in a context of cardiovascular risk for adults 18 years old and older:
TRIGLYCERIDES
Normal: <150 mg/dL
Borderline High: 150-199 mg/dL
High: 200-499 mg/dL
Very High: > or =500 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids in a context of cardiovascular risk for children 2 to 17 years old:
TRIGLYCERIDES
2-9 years:
Acceptable: <75 mg/dL
Borderline High: 75-99 mg/dL
High: > or =100 mg/dL
10-17 years:
Acceptable: <90 mg/dL
Borderline High: 90-129 mg/dL
High: > or =130 mg/dL

Reference values have not been established for patients who are younger than 24 months of age.
For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Clinical References: 1. Grundy SM, Stone NJ, Bailey AL, et al: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Jun 18;139(25):e1082-e1143 2. Jacobson TA, Ito MK, Maki KC, et al: National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1-executive summary. J Clin Lipidol. 2014;8(5):473-488. doi: 10.1016/j.jacl.2014.07.007 3. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics. 2011 Dec;128 Suppl 5(Suppl 5):S213-S256. doi: 10.1542/peds.2009-2107C

TMP
80146

Trimethoprim, Serum

Clinical Information: Trimethoprim is coadministered with sulfamethoxazole for prophylaxis or treatment of bacterial infections. These agents are used to treat a variety of infections, including methicillin-resistant Staphylococcus aureus, and for prophylaxis in immunosuppressed patients, such as individuals who are HIV-positive. Trimethoprim has a wide therapeutic index and dose-dependent toxicity. Trimethoprim accumulates in patients with kidney failure. Therapeutic drug monitoring is not commonly performed unless there are concerns about adequate absorption, clearance, or compliance. Accordingly, routine drug monitoring is not indicated in all patients.

Useful For: Monitoring trimethoprim therapy to ensure drug absorption, clearance, or compliance

Interpretation: Most patients will display peak steady-state serum concentrations of more than 2.0 mcg/mL when the specimen is collected at least 1 hour after an oral dose. Target concentrations may be higher depending on the intent of therapy.

Reference Values:
>2.0 mcg/mL (Peak)

Clinical References: 1. Kamme C, Melander A, Nilsson NI. Serum and saliva concentrations of sulfamethoxazole and trimethoprim in adults in children: Relation between saliva concentrations and in vitro activity against nasopharyngeal pathogens. Scand J Infect Dis. 1983;15(1):107-113. doi:10.3109/inf.1983.15.issue-1.18 2. Young T, Oliphant C, Araoyinbo I, Volmink J. Co-trimoxazole prophylaxis in HIV: the evidence. S Afr Med J. 2008;98(4):258-259 3. Avdic E, Cosgrove SE. Management and control strategies for community-associated methicillin-resistant Staphylococcus aureus. Expert Opin Pharmacother. 2008;9(9):1463-1479. doi:10.1517/14656566.9.9.1463 4. Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 13th ed. McGraw-Hill Publishing; 2018

TRMP
64269

Trimipramine, Serum

Clinical Information: Trimipramine is a tricyclic antidepressant with additional anxiety-reducing sedative activity. Daily dosages for adults range from 50 mg to 300 mg and are usually divided into 2 to 3 doses per day. Therapeutic ranges are based on serum samples collected at trough (ie, immediately before the next dose). Peak serum concentrations are typically achieved after 1 to 6 hours post dosage. Common adverse effects include hypotension, tachycardia, constipation, dizziness, somnolence, and blurred vision. Risk of toxicity increases when concentrations exceed 500 ng/mL. Serious adverse effects include coma,

seizures, and QRS prolongation with ventricular dysrhythmias.

Useful For: Monitoring trimipramine concentration during therapy Evaluating potential trimipramine toxicity May aid in evaluating patient compliance

Interpretation: Most individuals display optimal response to trimipramine with serum levels of 150 to 300 ng/mL. Risk of toxicity is increased with trimipramine levels above 500 ng/mL. Some individuals may respond well outside of this range or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimens collected at trough (ie, immediately before the next dose).

Reference Values:
Therapeutic concentration: 150-300 ng/mL
Note: Therapeutic ranges are for specimens collected at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

Clinical References: 1. Wille SM, Cooreman SG, Neels HM, Lambert WE. Relevant issues in the monitoring and the toxicology of antidepressants. Crit Rev Clin Lab Sci. 2008;45(1):25-89 2. Thanacoody HK, Thomas SHL. Antidepressant poisoning. Clin Med (Lond). 2003;3(2):114-118 3. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018;51(1-01):9-62 4. Milone MC, Shaw LM. Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:420-453

TPIC
608424

Triosephosphate Isomerase Enzyme Activity, Blood

Clinical Information: Triosephosphate isomerase (TPI) converts dihydroxyacetone phosphate to glyceraldehyde 3-phosphate during glycolysis. Clinically significant TPI deficiency (OMIM #615512, autosomal recessive) is rare and classically manifests as a severe multisystem disorder with early hemolytic anemia and progressive neurologic impairment in infancy. Other clinical features include motor impairment, diaphragm paralysis, cardiomyopathy and susceptibility to infections. Some cases have isolated hemolytic anemia.

Useful For: Evaluating individuals with chronic nonspherocytic hemolytic anemia Evaluating individuals with early onset neurologic impairment Genetic counseling for families with triosephosphate isomerase deficiency

Interpretation: Clinically significant hemolytic anemias due to triosephosphate isomerase deficiency are associated with activity levels less than 30% of mean normal. Heterozygotes usually show approximately 50% of mean normal activity and are clinically unaffected.

Reference Values:
Only available as part of a profile. For more information see:
-HAEV1 / Hemolytic Anemia Evaluation, Blood
-EEEV1 / Red Blood Cell (RBC) Enzyme Evaluation, Blood

> or =12 months of age: 1033-1363 U/g Hb
Reference values have not been established for patients who are younger than 12 months of age.

Clinical References: 1. Orosz F, Olah J, Ovadi J: Triosephosphate isomerase deficiency: facts and doubts. IUBMB Life. 2006 Dec;58(12):703-715. doi: 10.1080/15216540601115960 2. Fermo E,

Bianchi P, Vercellati C, et al: Triose phosphate isomerase deficiency associated with two novel mutations in TPI gene. Eur J Haematol. 2010 Aug;85(2):170-173. doi: 10.1111/j.1600-0609.2010.01451.x 3. Tanaka KR, Zerez CR: Red cell enzymopathies of the glycolytic pathway. Semin Hematol. 1990;27:165 4. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia-pathophysiology, clinical aspects, and laboratory diagnosis. Int J Lab Hematol. 2014;36(3):388-397

TPI1
607458

Triosephosphate Isomerase Enzyme Activity, Blood

Clinical Information: Triosephosphate isomerase (TPI) converts dihydroxyacetone phosphate to glyceraldehyde 3-phosphate during glycolysis. Clinically significant TPI deficiency (OMIM #615512, autosomal recessive) is rare and classically manifests as a severe multisystem disorder with early hemolytic anemia and progressive neurologic impairment in infancy. Other clinical features include motor impairment, diaphragm paralysis, cardiomyopathy, and susceptibility to infections. Some cases have isolated hemolytic anemia.

Useful For: Evaluating individuals with chronic nonspherocytic hemolytic anemia Evaluating individuals with early onset neurologic impairment Genetic counseling for families with triosephosphate isomerase deficiency

Interpretation: Clinically significant hemolytic anemias due to triosephosphate isomerase deficiency are associated with activity levels below 30% of mean normal. Heterozygotes usually show approximately 50% of mean normal activity and are clinically unaffected.

Reference Values:
> or =12 months: 1033-1363 U/g Hb
Reference values have not been established for patients who are less than12 months of age.

Clinical References: 1. Orosz F, Olah J, Ovadi J. Triosephosphate isomerase deficiency: facts and doubts. IUBMB Life. 2006;58(12):703-715 2. Fermo E, Bianchi P, Vercellati C, et al. Triose phosphate isomerase deficiency associated with two novel mutations in TPI gene. Eur J Haematol. 2010;85(2):170-173 3. Tanaka KR, Zerez CR. Red cell enzymopathies of the glycolytic pathway. Semin Hematol. 1990;27:165-185 4. Koralkova P, van Solinge WW, van Wijk R. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia-pathophysiology, clinical aspects, and laboratory diagnosis. Int J Lab Hematol. 2014;36:388-397

T46CS
616449

Tripartite Motif-Containing Protein 46 (TRIM46) IgG, Cell Binding Assay, Serum

Clinical Information: Tripartite motif-containing protein 46 (TRIM46)-IgG is a marker of an autoimmune neurological disorder commonly associated with underlying malignancy. Patients commonly present with cerebellar ataxia and neoplasms frequently of neuroendocrine lineage.

Useful For: Detecting tripartite motif-containing protein 46 (TRIM46)-IgG by cell-binding assay using serum specimens Evaluation of an autoimmune/paraneoplastic neurological syndrome among patients presenting with cerebellar ataxia, encephalitis, or encephalomyelitis.

Interpretation: A positive result is consistent with a tripartite motif-containing protein 46 (TRIM46)-IgG associated autoimmune disease of the central nervous system. A paraneoplastic cause should be considered.

Reference Values:
Only orderable as a reflex. For more information see:
ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum

Negative

Clinical References:

T46CC 616450 Tripartite Motif-Containing Protein 46 (TRIM46) IgG, Cell Binding Assay, Spinal Fluid

Clinical Information: Tripartite motif-containing protein 46 (TRIM46)-IgG is a marker of an autoimmune neurological disorder commonly associated with underlying malignancy. Patients commonly present with cerebellar ataxia and neoplasms frequently of neuroendocrine lineage.

Useful For: Detecting tripartite motif-containing protein 46 (TRIM46)-IgG by cell-binding assay using cerebrospinal fluid specimens Evaluation of an autoimmune/paraneoplastic neurological syndrome among patients presenting with cerebellar ataxia, encephalitis, or encephalomyelitis

Interpretation: A positive result is consistent with a tripartite motif-containing protein 46 (TRIM46)-IgG associated autoimmune disease of the central nervous system. A paraneoplastic cause should be considered.

Reference Values:
Only orderable as a reflex. For more information see:
ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

Negative

Clinical References:

T46TS 616447 Tripartite Motif-Containing Protein 46 (TRIM46) IgG, Tissue Immunofluorescence Titer, Serum

Clinical Information: Tripartite motif-containing protein 46 (TRIM46-IgG) is a marker of an autoimmune neurological disorder commonly associated with underlying malignancy. Patients commonly present with cerebellar ataxia and neoplasms frequently of neuroendocrine lineage.

Useful For: Reporting an end titer result for tripartite motif-containing protein 46 (TRIM46)-IgG in serum specimens Evaluation of an autoimmune/paraneoplastic neurological syndrome among patients presenting with cerebellar ataxia, encephalitis, or encephalomyelitis.

Interpretation: A positive result is consistent with a tripartite motif-containing protein 46 (TRIM46-IgG) associated autoimmune disease of the central nervous system. A paraneoplastic cause should be considered.

Reference Values:
Only orderable as a reflex. For more information see:
ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Serum
DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum

<1:240

Clinical References: 1. van Coevorden-Hameete MH, van Beuningen SFB, Perrenoud M, et al. Antibodies to TRIM46 are associated with paraneoplastic neurological syndromes. Ann Clin Tran Neurol. 2017;4(9):680-686. doi:10.1002/acn3.396 2. Shams'ili S, de Leeuw B, Hulsenboom E, Jaarsma D, Smitt PS. A new paraneoplastic encephalomyelitis autoantibody reactive with the axon initial segment. Neurosci Lett. 2009;467(2):169-172. doi:10.1016/j.neulet.2009.10.031 3. Valencia-Sanchez C, Knight AM, Hammami B, et al. TRIM46 autoantibody: expanded neurological phenotype and oncological associations (1657). Neurology. 2021;96(15 Supplement). doi:10.1212/WNL.96.15_supplement.1657

T46TC
616448

Tripartite Motif-Containing Protein 46 (TRIM46) IgG, Tissue Immunofluorescence Titer, Spinal Fluid

Clinical Information: Tripartite motif-containing protein 46 (TRIM46) IgG is a marker of an autoimmune neurological disorder commonly associated with underlying malignancy. Patients commonly present with cerebellar ataxia and neoplasms frequently of neuroendocrine lineage.

Useful For: Reporting an end-titer result for tripartite motif-containing protein 46 (TRIM46)-IgG in cerebrospinal fluid specimens Evaluation of an autoimmune/paraneoplastic neurological syndrome among patients presenting with cerebellar ataxia, encephalitis, or encephalomyelitis.

Interpretation: A positive result is consistent with a tripartite motif-containing protein 46 (TRIM46) IgG associated autoimmune disease of the central nervous system. A paraneoplastic cause should be considered.

Reference Values:
Only orderable as a reflex. For more information see:
ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

<1:2

Clinical References: 1. van Coevorden-Hameete MH, van Beuningen SFB, Perrenoud M, et al. Antibodies to TRIM46 are associated with paraneoplastic neurological syndromes. Ann Clin Tran Neurol. 2017;4(9):680-686. doi:10.1002/acn3.396 2. Shams'ili S, de Leeuw B, Hulsenboom E, Jaarsma D, Smitt PS. A new paraneoplastic encephalomyelitis autoantibody reactive with the axon initial segment.

Neurosci Lett. 2009;467(2):169-172. doi:10.1016/j.neulet.2009.10.031 3. Valencia-Sanchez C, Knight AM, Hammami B, et al. TRIM46 autoantibody: expanded neurological phenotype and oncological associations (1657). Neurology. 2021;96(15 Supplement). doi:10.1212/WNL.96.15_supplement.1657

T46IS 616445 Tripartite Motif-Containing Protein 46 (TRIM46) IgG, Tissue Immunofluorescence, Serum

Clinical Information: Tripartite motif-containing protein 46 (TRIM46)-IgG is a marker of an autoimmune neurological disorder commonly associated with underlying malignancy. Patients commonly present with cerebellar ataxia and neoplasms frequently of neuroendocrine lineage.

Useful For: Detecting tripartite motif-containing protein 46 (TRIM46)-IgG in serum specimens Evaluation of an autoimmune/paraneoplastic neurological syndrome among patients presenting with cerebellar ataxia, encephalitis, or encephalomyelitis

Interpretation: A positive result is consistent with a tripartite motif-containing protein 46 (TRIM46)-IgG associated autoimmune disease of the central nervous system. A paraneoplastic cause should be considered.

Reference Values:
Only orderable as part of a profile. For more information see:
ENS2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation,
DMS2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Serum
EPS2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Serum
MDS2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Serum
MAS1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Serum

Negative

Clinical References: 1. van Coevorden-Hameete MH, van Beuningen SFB, Perrenoud M, et al. Antibodies to TRIM46 are associated with paraneoplastic neurological syndromes. Ann Clin Tran Neurol. 2017;4(9):680-686. doi:10.1002/acn3.396 2. Shams'ili S, de Leeuw B, Hulsenboom E, Jaarsma D, Smitt PS. A new paraneoplastic encephalomyelitis autoantibody reactive with the axon initial segment. Neurosci Lett. 2009;467(2):169-172. doi:10.1016/j.neulet.2009.10.031 3. Valencia-Sanchez C, Knight AM, Hammami B, et al. TRIM46 autoantibody: expanded neurological phenotype and oncological associations (1657). Neurology. 2021;96(15 Supplement)

T46IC 616446 Tripartite Motif-Containing Protein 46 (TRIM46) IgG, Tissue Immunofluorescence, Spinal Fluid

Clinical Information: Tripartite motif-containing protein 46 (TRIM46)-IgG is a marker of an autoimmune neurological disorder commonly associated with underlying malignancy. Patients commonly present with cerebellar ataxia and neoplasms frequently of neuroendocrine lineage.

Useful For: Detecting tripartite motif-containing protein 46 (TRIM46)-IgG in cerebrospinal fluid specimens Evaluation of an autoimmune/paraneoplastic neurological syndrome among patients presenting with cerebellar ataxia, encephalitis, or encephalomyelitis

Interpretation: A positive result is consistent with a tripartite motif-containing protein 46 (TRIM46)-IgG associated autoimmune disease of the central nervous system. A paraneoplastic cause

should be considered.

Reference Values:
Only orderable as part of a profile. For more information see:
ENC2 / Encephalopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
DMC2 / Dementia, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
EPC2 / Epilepsy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
MDC2 / Movement Disorder, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid
MAC1 / Myelopathy, Autoimmune/Paraneoplastic Evaluation, Spinal Fluid

Negative

Clinical References: 1. van Coevorden-Hameete MH, van Beuningen SFB, Perrenoud M, et al. Antibodies to TRIM46 are associated with paraneoplastic neurological syndromes. Ann Clin Tran Neurol. 2017;4(9):680-686. doi:10.1002/acn3.396 2. Shams'ili S, de Leeuw B, Hulsenboom E, Jaarsma D, Smitt PS. A new paraneoplastic encephalomyelitis autoantibody reactive with the axon initial segment. Neurosci Lett. 2009;467(2):169-172. doi:10.1016/j.neulet.2009.10.031 3. Valencia-Sanchez C, Knight AM, Hammami B, et al. TRIM46 autoantibody: expanded neurological phenotype and oncological associations (1657). Neurology. 2021;96(15 Supplement). doi:10.1212/WNL.96.15_supplement.1657

FFTRP
91774

Trofile Co-Receptor Tropism Assay

Useful For: Detect HIV-1 coreceptor tropism; determine eligibility for CCR5 antagonist therapy such as maraviroc (Selzentry)

Interpretation: CCR5 Tropic (R5) HIV-1 Virus uses CCR5 to enter CD4+ cells. CXCR4 Tropic (X4) HIV-1 Virus uses CXCR4 to enter CD4+ cells DUAL/MIXED Tropic (D/M) HIV-1 Dual-tropic viruses can use either CCR5 or CXCR4 to enter CD4+ cells. Mixed-tropic populations contain viruses with two or more tropisms. Non-reportable Co-receptor tropism could not be determined by the Trofile assay. Common causes of a non-reportable result are viral load <1,000 copies/mL, reduced viral fitness, or compromised sample collection/handling.

FFTRO
57159

Trofile DNA Co-Receptor Tropism Assay

Useful For:

Interpretation: Trofile DNA Viral Classification CCR5 Tropic (R5) HIV-1: Virus uses CCR5 to enter CD4+ cells. CXCR4 Tropic (X4) HIV-1: Virus uses CXCR4 to enter CD4+ cells. DUAL /MIXED Tropic (D/M) HIV-1: Dual-tropic viruses can use either CXCR4 or CCR5 to enter CD4+ cells. Mixed-tropic populations contain viruses with 2 or more tropisms. Nonreportable: Co-receptor tropism could not be determined. Common causes of nonreportable results are reduced viral fitness or compromised sample handling. Please note that Trofile DNA sample collection and handling instructions differ from Trofile and other Monogram assays. Trofile uses the complete gp160 coding region of the HIV-1 envelope protein ensuring that all of the determinants of tropism are tested. Subtype is determined based on the HIV-1 gp41 envelope region.

WHIPB
87974

Tropheryma whipplei, Molecular Detection, PCR, Blood

Clinical Information: Whipple disease is a chronic, systemic illness that, in the majority of cases,

involves the small intestine and its lymphatic drainage. The disease primarily affects adults of middle age, with a peak incidence in the third and fourth decades of life. Clinical findings may include malabsorption, chronic diarrhea, abdominal pain, arthralgia, fever, and central nervous system symptoms. Pathologic changes associated with Whipple disease are distinctive, with diagnosis dependent on histologic examination of biopsy specimens from involved tissues. Electron microscopic or special high-resolution light microscopic examination of the lamina propria of the small intestine of patients with untreated Whipple disease reveals many rod-shaped bacillary organisms. These tiny bacilli, referred to as Whipple bacilli, measure about 0.25 micrometer long and are seen as periodic acid-Schiff-positive granules within macrophages. These inclusions represent fragments of the cell walls from degenerating bacilli. Culture of Whipple bacilli from biopsy material is laborious, and the organism is very slow growing. Definitive identification of the Whipple-associated bacillus has been difficult because of these limitations. Molecular techniques using polymerase chain reaction and nucleotide sequencing allow classification of this bacillus as an actinomycete not closely related to any other known species, which has been named Tropheryma whipplei.

Useful For: Aiding in the diagnosis of Whipple disease, especially for identifying inconclusive or suspicious cases, using whole blood specimens

Interpretation: A positive result indicates the presence of Tropheryma whipplei DNA. A negative result indicates the absence of detectable T whipplei DNA, but it does not negate the presence of the organism and may occur due to inhibition of polymerase chain reaction, sequence variability underlying primers or probes, or the presence of T whipplei DNA in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. Ramzan NN, Loftus E Jr, Burgart LJ, et al: Diagnosis and monitoring of Whipple disease by polymerase chain reaction. Ann Intern Med. 1997;126:520-527 2. Morgenegg S, Dutly F, Altwegg M: Cloning and sequencing of a part of the heat shock protein 65 gene (hsp65) of "Tropheryma whippleii" and its use for detection of "T whipplei" in clinical specimens by PCR. J Clin Microbiol. 2000;38:2248-2253 3. von Herbay A, Ditton HJ, Schuhmacher F, Maiwald M, : Whipple's disease: staging and monitoring by cytology and polymerase chain reaction analysis of cerebrospinal fluid. Gastroenterology. 1997;113(2):434-441 4. Dolmans RA, Boel CH, Lacle MM, Kusters JG: Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev. 2017 Apr;30(2):529-555. doi: 10.1128/CMR.00033-16

TWRP
80909

Tropheryma whipplei, Molecular Detection, PCR, Varies

Clinical Information: Whipple disease is a chronic, systemic illness that, in most cases, involves the small intestine and its lymphatic drainage. The disease primarily affects adults of middle age, with a peak incidence in the third and fourth decades. Clinical findings may include malabsorption, chronic diarrhea, abdominal pain, arthralgia, fever, and central nervous system symptoms. Pathologic changes associated with Whipple disease are distinctive, with diagnosis dependent on histologic examination of biopsy specimens from involved tissues. Electron microscopic or special high-resolution light microscopic examination of the lamina propria of the small intestine of patients with untreated Whipple disease reveals many rod-shaped bacillary organisms. These tiny bacilli, referred to as Whipple bacilli, measure about 0.25 micrometer long and are seen as periodic acid-Schiff-positive granules within macrophages. These inclusions represent fragments of the cell walls from degenerating bacilli. Culture of Whipple bacilli from biopsy material is laborious and the organism is very slow growing. Definitive identification of the Whipple associated bacillus has been difficult because of these limitations. Molecular techniques using polymerase chain reaction and nucleotide sequencing allowed classification

of this bacillus as an actinomycete not closely related to any other known species, which has been named Tropheryma whipplei.

Useful For: Aiding in the diagnosis of Whipple disease, especially for identifying inconclusive or suspicious cases, using tissue or fluid specimens

Interpretation: A positive result indicates the presence of Tropheryma whipplei DNA. A negative result indicates the absence of detectable T whipplei DNA but does not negate the presence of the organism and may occur due to inhibition of polymerase chain reaction, sequence variability underlying primers or probes, or the presence of T whipplei DNA in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

TROP2
621064

Trophoblast Antigen 2 (TROP2) Immunostain, Semi-Quantitative Immunohistochemistry, Manual

Clinical Information: Trophoblast antigen 2 (TROP2) is overexpressed in many tissues and cancers, including breast and urinary cancer among others. An antibody drug conjugate, sacituzumab govitecan, targets the cell surface protein TROP2. Tumors with high expression of TROP2 are more likely to respond to targeted drug therapy.

Useful For: Identification of breast and urinary cancer, among others

Interpretation: Trophoblast antigen 2 is a membrane protein and immunohistochemical positivity is characterized by a membrane pattern of staining. Results are reported as percent positive cells and intensity of staining. This result should be interpreted in the appropriate clinical context.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Shvartsu A, Bonavida B. Trop2 and its overexpression in cancers: regulation and clinical/therapeutic implications. Genes Cancer. 2015;6(3-4):84-105 2. Bardia A, Mayer I, Diamond J, et al. Efficacy and safety of anti-Trop-2 antibody drug conjugate sacituzumab govitecan (IMMU-132) in heavily pretreated patients with metastatic triple-negative breast cancer. J Clin Oncol. 2017;35:2141-2148 3. Lenart S, Lenart P, Smarda J, Remsik J, Souce K, Benes P. Trop2: Jack of all trades, master of none. Cancers. (Basel). 2020;12(11):3328. doi:10.3390/cancers12113328

TRK
603300

Tropomyosin Receptor Kinase (TRK) Immunostain, Technical Component Only

Clinical Information: Neurotrophic tyrosine receptor kinase (NTRK) is a family of 3 proto-oncogenes including NTRK1, NTRK2, and NTRK3, which encode TRKA, TRKB, and TRKC proteins respectively. Tropomyosin receptor kinase (TRK) immunohistochemistry may be used as a screen for identifying NTRK rearrangements and may be particularly helpful in driver-negative advanced malignancies such as secretory carcinoma, congenital infantile fibrosarcoma, and lipofibromatosis-like neural tumors. Screening for NTRK rearranged tumors is important as patients have been shown to respond to TRK inhibitor therapy.

Useful For: Helpful in the screening for neurotrophic tyrosine receptor kinase (NTRK) rearranged tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Hung YP, Fletcher CDM, Hornick JL. Evaluation of pan-TRK immunohistochemistry in infantile fibrosarcoma, lipofibromatosis-like neural tumour and histological mimics. Histopathology. 2018;73(4):634-644 2. Davis JL, Lockwood CM, Albert CM, Tsuchiya K, Hawkins DS, Rudzinski ER. Infantile NTRK-associated mesenchymal tumors. Pediatr Dev Pathol. 2018;21(1):68-78 3. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 2018;378(8):731-739 4. Hechtman JF, Benayed R, Hyman DM, et al. Pan-Trk immunohistochemistry is an efficient and reliable screen for the detection of NTRK fusions. Am J Surg Pathol. 2017;41(11):1547-1551 5. Agaram NP, Zhang L, Sung YS, et al. Recurrent NTRK1 gene fusions define a novel subset of locally aggressive lipofibromatosis-like neural tumors. Am J Surg Pathol. 2016;40(10):1407-1416 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

HSTNI
614422

Troponin I, High Sensitivity, Plasma

Clinical Information: Troponin is a complex that regulates the contraction of striated muscle. It consists of 3 subunits (C, T, and I) that are located periodically along the thin filament of the myofibrils. Troponin I inhibits actomyosin ATPase. Troponin I is an inhibitory protein and exhibits in 3 isoforms: cardiac muscle, slow-twitch skeletal muscle, and fast-twitch skeletal muscle. The cardiac form of troponin I has 31 amino acid residues on its N-terminal, which allow for specific polyclonal and monoclonal antibody development, as they are not present in the skeletal forms. The cardiac specificity of this isoform improves the accuracy of diagnosis in patients with acute or chronic skeletal muscle injury and possible concomitant myocardial injury. Troponin I is the only troponin isotope present in the myocardium and is not expressed during any developmental stage in skeletal muscle. Troponin I is released into the bloodstream within hours of the onset of symptoms of myocardial infarction or ischemic damage. It can be detected at 3 to 6 hours following onset of chest pain, with peak concentrations at 12 to 16 hours, and remains elevated for 5 to 9 days.

Useful For: Excluding the diagnosis of acute coronary syndromes Explaining troponin T elevations related to skeletal myopathy and/or assay interferences

Interpretation: Elevations in cardiac troponin T (cTnT) can be due to skeletal muscle disease and not cardiac disease in certain circumstances. One way to unmask such elevations is to measure cardiac troponin I (cTnI), which will be normal in that situation. In addition, at times there are interferences that can cause spurious increases or decreases in cTnT values. Conceptually, these same interferences can occur with cTnI but in any given case, the likelihood of having both assays be confounded in that way is highly unusual. Thus, potential false-positive results would be unmasked by a normal cTnI and false-negative results by an elevated value.

Reference Values:
Males > or =18 years: < or =20 ng/L

Females > or =18 years: < or =15 ng/L

Reference values have not been established for patients younger than 18 years old.

Clinical References: Apple FS, Wu AHB, Sandoval Y, et al. Sex-specific 99th percentile upper reference limits for high sensitivity cardiac troponin assays derived using a universal sample bank. Clin Chem. 2020;66(3):434-444

TRPS
65832

Troponin T, 5th Generation, Plasma

Clinical Information: Troponin T is a myofibrillar protein found in striated musculature. There are 2 types of myofilament: a thick filament containing myosin and a thin filament consisting of 3 different proteins, namely actin, tropomyosin, and troponin. Troponin is itself a complex of 3 protein subunits, which are termed troponin T, troponin I, and troponin C: -Troponin T binds the troponin complex to tropomyosin -Troponin I inhibits actomyosin ATPase in relation to the calcium concentration -Troponin C has 4 binding sites for calcium and mediates calcium dependency Troponin T is found in free cytosol and structurally bound protein. The unbound pool of troponin T is the source of early protein release in myocardial damage. Troponin T is released from the structural elements at a later stage, corresponding to the degradation of myofibrils that occurs in irreversible myocardial damage. Troponin T becomes elevated 2 to 4 hours after the onset of myocardial necrosis and can remain elevated for up to 14 days, or even longer on occasion. The most common cause of cardiac injury is myocardial ischemia (ie, acute myocardial infarction). These patients are known to have an adverse short- and long-term prognosis compared to patients with unstable angina and no elevation of troponin T. Many of these patients, especially those with troponin T elevations above 30 ng/L, benefit from an aggressive strategy with anticoagulation and an invasive interventional strategy.

Useful For: Aiding in the exclusion of the diagnosis of acute coronary syndrome in a single plasma specimen Aiding in the diagnosis of acute coronary syndrome Monitoring acute coronary syndromes and estimating prognosis Possible utility in monitoring patients with nonischemic causes of cardiac injury

Interpretation: Values for healthy adults, based upon available literature and clinical guidelines, are 10 ng/L or less for women and 15 ng/L or less for men. For patients who present with suspected acute coronary syndromes, troponin T values greater than the reference interval with a rising (> or =10 ng/L over 2 hours or > or =12 ng/L over 6 hours) pattern are highly suggestive of acute cardiac injury. Decreasing values are indicative of recent cardiac injury. Serial measurement is highly recommended for the diagnosis or exclusion of acute coronary syndromes. Troponin T values greater than the reference interval are associated with adverse events in patients with ischemic heart disease and many other clinical situations. Clinical judgment is necessary to distinguish patients who have ischemic heart disease from those who do not.

Reference Values:
Males: < or =15 ng/L
Females: < or =10 ng/L

Clinical References: 1. Sandoval Y, Jaffe AS: Using High-Sensitivity Cardiac Troponin T for Acute Cardiac Care. Am J Med. 2017 Dec;130(12):1358-1365 2. Reichlin T, Cullen L, Parsonage WA, et al: Two-hour algorithm for triage toward rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Am J Med. 2015 Apr;128(4):369-379 3. Gunsolus IL, Jaffe AS, Sexter A, et al: Sex-specific 99th percentiles derived from the AACC Universal Sample Bank for the Roche Gen 5 cTnT assay: Comorbidities and statistical methods influence derivation of reference limits. Clin Biochem. 2017 Dec;50(18):1073-1077

TROT
82788

Trout, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to trout Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

CRUZI
621062

Trypanosoma cruzi (Chagas) Antibody Panel, Serum

Clinical Information: Chagas disease (American trypanosomiasis) is caused by the protozoan hemoflagellate Trypanosoma cruzi and can lead to acute and chronic clinical manifestations of disease. T cruzi is endemic in many areas of South and Central America. The parasite is usually transmitted by the bite of reduviid (or "kissing") bugs of the genus Triatoma but may also be transmitted by blood transfusion, organ transplantation, food ingestion, and vertically from mother to fetus. The acute febrile stage of disease is frequently undiagnosed and often resolves spontaneously. Diagnosis of acute T cruzi infection is typically confirmed by microscopic identification of trypomastigotes in fresh preparations of anticoagulated blood or buffy coat or by molecular detection. Parasitemia decreases and is undetectable within approximately 90 days of infection. Chronic T cruzi infections are often asymptomatic but may progress to produce disabling and life-threatening cardiac (cardiomegaly, conduction defects) and gastrointestinal (megaesophagus and megacolon) disease. These damaged tissues contain the intracellular amastigote of T cruzi. The parasite is not seen in the blood during the chronic phase. Diagnosis of chronic T cruzi infection relies on serologic detection of antibodies to this organism. However, no single serologic assay is sensitive and specific enough to be relied upon alone. Therefore, per current expert guidelines and the Centers of Disease Control and Prevention, serologic confirmation of chronic T cruzi infection requires positivity on 2 tests utilizing two different methodologies and/or two different T cruzi antigen preparations. When results are discordant, testing by a third assay is recommended to resolve the initial results or, alternatively, repeat testing on a new sample may be required.

Useful For: Diagnosis of chronic Trypanosoma cruzi infection (Chagas disease) using two different methods

Interpretation: CHAGS result CHAGL result Interpretive comment Positive Positive Antibodies to Trypanosoma cruzi (Chagas disease) detected by two separate methods, suggesting current or past infection. Results should be interpreted alongside clinical presentation and exposure history. Positive Negative Antibodies to Trypanosoma cruzi (Chagas disease) detected by one of two assays. Discordant results can be resolved through submission of a new sample for testing or through additional testing at a public health laboratory. Positive Invalid Submission of a new sample is recommended to resolve discordant results. Indeterminate Positive Antibodies to Trypanosoma cruzi (Chagas disease) detected by one of two assays. Discordant results can be resolved through submission of a new sample for testing or through additional testing at a public health laboratory. Indeterminate Negative Submission of a new sample is recommended to resolve discordant results. Indeterminate Invalid Submission of a new sample is recommended to resolve discordant results. Negative Positive Antibodies to Trypanosoma cruzi (Chagas disease) detected by one of two assays. Discordant results can be resolved through submission of a new sample for testing or through additional testing at a public health laboratory. Negative Negative No antibodies to Trypanosoma cruzi (Chagas disease) detected. False negative results may occur in patients tested within 4 weeks of infection. Negative Invalid Submission of a new sample is recommended to resolve discordant results.

Reference Values:
Negative

Reference values apply to all ages.

Clinical References: 1. Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of chagas disease in the United States: a systematic review. JAMA. 2007;298(18):2171-2181 2. Bern C, Messenger LA, Whitman JD, Maguire JH. Chagas disease in the United States: a public health approach. Clin Microbiol Rev. 2019;33(1):e00023-19. doi:10.1128/CMR.00023-19 3. Forsyth CJ, Manne-Goehler J, Bern C, et al. Recommendations for screening and diagnosis of Chagas disease in the United States. J Infect Dis. 2022;225(9):1601-1610. doi:10.1093/infdis/jiab513

CHAGL
622447

Trypanosoma cruzi IgG, Lateral Flow Assay, Serum

Clinical Information: Chagas disease (American trypanosomiasis) is caused by the protozoan hemoflagellate Trypanosoma cruzi and can lead to acute and chronic clinical manifestations of disease. T cruzi is endemic in many areas of South and Central America. The parasite is usually transmitted by the bite of reduviid (or "kissing") bugs of the genus Triatoma but may also be transmitted by blood transfusion, organ transplantation, food ingestion, and vertically from mother to fetus. The acute febrile stage of disease is frequently undiagnosed and often resolves spontaneously. Diagnosis of acute T cruzi infection is typically confirmed by microscopic identification of trypomastigotes in fresh preparations of anticoagulated blood or buffy coat or by molecular detection. Parasitemia decreases and is undetectable within approximately 90 days of infection. Chronic T cruzi infections are often asymptomatic but may progress to produce disabling and life-threatening cardiac (cardiomegaly, conduction defects) and gastrointestinal (megaesophagus and megacolon) disease. These damaged tissues contain the intracellular amastigote of T cruzi. The parasite is not seen in the blood during the chronic phase. Diagnosis of chronic T cruzi infection relies on serologic detection of antibodies to this organism. However, no single serologic assay is sensitive and specific enough to be relied upon alone. Therefore, per current expert guidelines and the Centers of Disease Control and Prevention, serologic confirmation of chronic T cruzi infection requires positivity on 2 tests utilizing two different methodologies and/or two different T cruzi antigen preparations. When results are discordant, testing by a third assay is recommended to resolve the initial results or, alternatively, repeat testing on a new sample may be required.

Useful For: Diagnosis of chronic Trypanosoma cruzi infection (Chagas disease)

Interpretation: CHAGS result CHAGL result Interpretive comment Positive Positive Antibodies to Trypanosoma cruzi (Chagas disease) detected by two separate methods, suggesting current or past infection. Results should be interpreted alongside clinical presentation and exposure history. Positive Negative Antibodies to Trypanosoma cruzi (Chagas disease) detected by one of two assays. Discordant results can be resolved through submission of a new sample for testing or through additional testing at a public health laboratory. Positive Invalid Submission of a new sample is recommended to resolve discordant results. Indeterminate Positive Antibodies to Trypanosoma cruzi (Chagas disease) detected by one of two assays. Discordant results can be resolved through submission of a new sample for testing or through additional testing at a public health laboratory. Indeterminate Negative Submission of a new sample is recommended to resolve discordant results. Indeterminate Invalid Submission of a new sample is recommended to resolve discordant results. Negative Positive Antibodies to Trypanosoma cruzi (Chagas disease) detected by one of two assays. Discordant results can be resolved through submission of a new sample for testing or through additional testing at a public health laboratory. Negative Negative No antibodies to Trypanosoma cruzi (Chagas disease) detected. False negative results may occur in patients tested within 4 weeks of infection. Negative Invalid Submission of a new sample is recommended to resolve discordant results.

Reference Values:
Only orderable as part of a profile. For more information see CRUZI / Trypanosoma cruzi (Chagas) Antibody Panel, Serum.

Negative
Reference values apply to all ages.

Clinical References: 1. Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: a systematic review JAMA. 2007;298(18):2171-2181 2. Bern C, Messenger LA, Whitman JD, Maguire JH. Chagas disease in the United States: A public health approach. Clin Microbiol Rev. 2019;33(1):e00023-19. doi:10.1128/CMR.00023-19 3. Forsyth CJ, Manne-Goehler J, Bern C, et al. Recommendations for screening and diagnosis of Chagas disease in the United States. J Infect Dis. 2022;225(9):1601-1610. doi:10.1093/infdis/jiab513

CHAGS
615244

Trypanosoma cruzi Total Antibody, Enzyme-Linked Immunosorbent Assay, Serum

Clinical Information: Chagas disease (American trypanosomiasis) is caused by the protozoan hemoflagellate Trypanosoma cruzi and can lead to acute and chronic clinical manifestations of disease. T cruzi is endemic in many areas of South and Central America. The parasite is usually transmitted by the bite of reduviid (or "kissing") bugs of the genus Triatoma but may also be transmitted by blood transfusion, organ transplantation, food ingestion, and vertically from mother to fetus. The acute febrile stage of disease is frequently undiagnosed and often resolves spontaneously. Diagnosis of acute T cruzi infection is typically confirmed by microscopic identification of trypomastigotes in fresh preparations of anticoagulated blood or buffy coat or by molecular detection. Parasitemia decreases and is undetectable within approximately 90 days of infection. Chronic T cruzi infections are often asymptomatic but may progress to produce disabling and life-threatening cardiac (cardiomegaly, conduction defects) and gastrointestinal (megaesophagus and megacolon) disease. These damaged tissues contain the intracellular amastigote of T cruzi. The parasite is not seen in the blood during the chronic phase. Diagnosis of chronic T cruzi infection relies on serologic detection of antibodies to this organism. However, no single serologic assay is sensitive and specific enough to be relied upon alone. Therefore, per current expert guidelines and the Centers for Disease Control and Prevention, serologic confirmation of chronic T cruzi infection requires positivity on 2 tests utilizing two different methodologies and/or two different T cruzi antigen preparations. When results are discordant, testing by a third assay is recommended to resolve the initial results or, alternatively, repeat testing on a new sample may be required.

Useful For: Diagnosis of chronic Trypanosoma cruzi infection (Chagas disease)

Interpretation: CHAGS result CHAGL result Interpretive comment Positive Positive Antibodies to Trypanosoma cruzi (Chagas disease) detected by two separate methods, suggesting current or past infection. Results should be interpreted alongside clinical presentation and exposure history. Positive Negative Antibodies to Trypanosoma cruzi (Chagas disease) detected by one of two assays. Discordant results can be resolved through submission of a new sample for testing or through additional testing at a public health laboratory. Positive Invalid Submission of a new sample is recommended to resolve discordant results. Indeterminate Positive Antibodies to Trypanosoma cruzi (Chagas disease) detected by one of two assays. Discordant results can be resolved through submission of a new sample for testing or through additional testing at a public health laboratory. Indeterminate Negative Submission of a new sample is recommended to resolve discordant results. Indeterminate Invalid Submission of a new sample is recommended to resolve discordant results. Negative Positive Antibodies to Trypanosoma cruzi (Chagas disease) detected by one of two assays. Discordant results can be resolved through submission of a new sample for testing or through additional testing at a public health laboratory. Negative Negative No antibodies to Trypanosoma cruzi (Chagas disease) detected. False negative results may occur in patients tested within 4 weeks of infection. Negative Invalid Submission of a new sample is recommended to resolve discordant results.

Reference Values:
Only orderable as part of a profile. For more information see CRUZI / Trypanosoma cruzi (Chagas) Antibody Panel, Serum.

Negative
Reference values apply to all ages.

Clinical References: 1. Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: a systematic review JAMA. 2007;298(18):2171-2181 2. Bern C, Messenger LA, Whitman JD, Maguire JH. Chagas disease in the United States: A public health approach. Clin Microbiol Rev. 2019;33(1):e00023-19. doi:10.1128/CMR.00023-19 3. Forsyth CJ, Manne-Goehler J, Bern C, et al. Recommendations for screening and diagnosis of Chagas disease in the United States. J

CHAGI
622448

Trypanosoma cruzi, Technical Interpretation

Clinical Information: Chagas disease (American trypanosomiasis) is caused by the protozoan hemoflagellate Trypanosoma cruzi and can lead to acute and chronic clinical manifestations of disease. T cruzi is endemic in many areas of South and Central America. The parasite is usually transmitted by the bite of reduviid (or "kissing") bugs of the genus Triatoma but may also be transmitted by blood transfusion, organ transplantation, food ingestion, and vertically from mother to fetus. The acute febrile stage of disease is frequently undiagnosed and often resolves spontaneously. Diagnosis of acute T cruzi infection is typically confirmed by microscopic identification of trypomastigotes in fresh preparations of anticoagulated blood or buffy coat or by molecular detection. Parasitemia decreases and is undetectable within approximately 90 days of infection. Chronic T cruzi infections are often asymptomatic but may progress to produce disabling and life-threatening cardiac (cardiomegaly, conduction defects) and gastrointestinal (megaesophagus and megacolon) disease. These damaged tissues contain the intracellular amastigote of T cruzi. The parasite is not seen in the blood during the chronic phase. Diagnosis of chronic T cruzi infection relies on serologic detection of antibodies to this organism. However, no single serologic assay is sensitive and specific enough to be relied upon alone. Therefore, per current expert guidelines and the Centers of Disease Control and Prevention, serologic confirmation of chronic T cruzi infection requires positivity on 2 tests utilizing two different methodologies and/or two different T cruzi antigen preparations. When results are discordant, testing by a third assay is recommended to resolve the initial results or, alternatively, repeat testing on a new sample may be required.

Useful For: Diagnosis of chronic Trypanosoma cruzi infection (Chagas disease)

Interpretation: CHAGS result CHAGL result Interpretive comment Positive Positive Antibodies to Trypanosoma cruzi (Chagas disease) detected by two separate methods, suggesting current or past infection. Results should be interpreted alongside clinical presentation and exposure history. Positive Negative Antibodies to Trypanosoma cruzi (Chagas disease) detected by one of two assays. Discordant results can be resolved through submission of a new sample for testing or through additional testing at a public health laboratory. Positive Invalid Submission of a new sample is recommended to resolve discordant results. Indeterminate Positive Antibodies to Trypanosoma cruzi (Chagas disease) detected by one of two assays. Discordant results can be resolved through submission of a new sample for testing or through additional testing at a public health laboratory. Indeterminate Negative Submission of a new sample is recommended to resolve discordant results. Indeterminate Invalid Submission of a new sample is recommended to resolve discordant results. Negative Positive Antibodies to Trypanosoma cruzi (Chagas disease) detected by one of two assays. Discordant results can be resolved through submission of a new sample for testing or through additional testing at a public health laboratory. Negative Negative No antibodies to Trypanosoma cruzi (Chagas disease) detected. False negative results may occur in patients tested within 4 weeks of infection. Negative Invalid Submission of a new sample is recommended to resolve discordant results.

Reference Values:
Only orderable as part of a profile. For more information see CRUZI / Trypanosoma cruzi (Chagas) Antibody Panel, Serum.

An interpretive report will be provided.

Clinical References: 1. Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: A Systematic Review. JAMA. 2007;298(18):2171-2181 2. Bern C, Messenger LA, Whitman JD, Maguire JH: Chagas disease in the United States: A public health

approach. Clin Microbiol Rev. 2019;33(1):e00023-19. doi:10.1128/CMR.00023-19 3. Forsyth CJ, Manne-Goehler J, Bern C, et al. Recommendations for screening and diagnosis of Chagas disease in the United States. J Infect Dis. 2022;225(9):1601-1610. doi:10.1093/infdis/jiab513

TRYPN
70572

Trypsin Immunostain, Technical Component Only

Clinical Information: Trypsinogen is an enzyme involved in protein metabolism that is made by the acinar cells of the exocrine pancreas. After secretion into the small intestine, it is cleaved to its active form, trypsin. In normal pancreas, the antibody stains cells within acini. Ductal cells and islet cells are negative. The antibody to trypsin can be useful in classifying carcinomas of the pancreas by identifying cells with acinar differentiation. Carcinomas with ductal or endocrine differentiation will generally be negative.

Useful For: Identifying cells with acinar differentiation in the pancreas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Bohe H, Bohe M, Lindstrom C, et al. Immunohistochemical demonstration of pancreatic secretory trypsin inhibitor in normal and neoplastic colonic mucosa. J Clin Pathol. 1990;43(11):901-904 2. Bohe H, Bohe M, Jonsson P, et al. Quantification of pancreatic secretory trypsin inhibitor in colonic carcinoma and normal adjacent colonic mucosa. J Clin Pathol. 1992;45(12):1066-1069 3. Marchbank T, Chinery R, Hanby AM, et al. Distribution and expression of pancreatic secretory trypsin inhibitor and its possible role in epithelial restitution. Am J Pathol. 1996;148(3):715-722 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TRPTS
70573

Tryptase Immunostain, Technical Component Only

Clinical Information: In normal tissues, antibodies to tryptase stain mast cells with an intense cytoplasmic granular staining pattern. This marker has great utility in supporting a diagnosis of mast cell disease.

Useful For: A marker of mast cells

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Horny H-P, Sotlar K, Stellmacher F, et al. The tryptase positive compact round cell infiltrate of the bone marrow (TROCI-BM): a novel histopathological finding requiring the application of lineage specific markers. J Clin Pathol. 2006;59(3):298-302 2. Irani AMA, Bradford TR, Kepley CL, et al. Detection of MCT and MCTC types of human mast cells by immunohistochemistry using new monoclonal anti-tryptase and anti-chymase antibodies. J Histochem Cytochem.

1989;37:1509-1515 3. Li, CY. Diagnosis of mastocytosis: value of cytochemistry and immunohistochemistry. Leuk Res. 2001;25:537-541 4. Li WV, Kapadia SB, Sonmez-Alpan E, Swerdlow SH. Immunohistochemical characterization of mast cell disease in paraffin sections using tryptase, CD68, myeloperoxidase, lysozyme, and CD20 antibodies. Mod Pathol. 1996;9(10):982-988 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TRYPA
32283

Tryptase, Autopsy, Serum

Clinical Information: Tryptase, a neutral protease, is a dominant protein component of the secretory granules of human mast cells. There are 2 forms of tryptase, designated as alpha and beta, which are encoded by 2 separate genes.(1) Both are expressed as inactive proenzymes. Alpha-protryptase and beta-protryptase are spontaneously released from resting mast cells. The levels of the protrypases reflect the total number of mass cells within the body but are not an indication of mast cell activation. Beta-protryptase is processed to a mature form, which is stored in granules and released as an active tetramer that is bound to heparan or chondroitin sulfate proteoglycans. In contrast, an amino acid change in alpha-protryptase prevents processing to a mature form. Upon mast cell activation, degranulation releases mature tryptase, which is almost exclusively in the form of beta-tryptase. During an anaphylactic episode, mast cell granules release tryptase; measurable amounts are found in blood, generally within 30 to 60 minutes.(2) The levels decline under first-order kinetics with a half-life of approximately 2 hours. Severe anaphylactic reactions can lead to fatal airway, respiratory, and circulatory compromise. Anaphylaxis as a cause of death may be suspected in individuals with a known history of allergy, previous anaphylactic episodes, or based on autopsy evidence including mucous plugging, hyperinflated lungs, and petechial hemorrhages.(3) Measurement of tryptase in postmortem serum samples may be useful in investigating deaths in which anaphylaxis is suspected. However, interpretation of results can be difficult, as the reference value for routine diagnostic testing is not applicable to postmortem samples. A recent study identified a concentration of 53.8 mcg/L for postmortem tryptase, which resulted in a sensitivity of 89% and a specificity of 93% for the identification of anaphylaxis as the cause of death.(4) However, it is unclear how widely applicable this cutoff value is, given the complexities of postmortem specimen collection and biological processes.

Useful For: Evaluation of autopsy cases in which anaphylaxis in the context of allergen exposure or mast cell activation is a suspected cause of death

Interpretation: Increased concentrations of total tryptase may indicate mast cell activation occurring as a result of anaphylaxis or allergen challenge, or it may indicate an increased number of mast cells as seen in patients with mastocytosis. However, no specific cutoff value has been widely validated for autopsy specimens.

Reference Values:
No established reference values

Clinical References: 1. Lyons JJ, Yi T. Mast cell tryptases in allergic inflammation and immediate hypersensitivity. Curr Opin Immunol. 2021;72:94-106. doi:10.10.16/j.coi.2021.04.001 2. Platzgummer S, Bizzaro N, Bilo MB, et al. Recommendations for the use of tryptase in the diagnosis of anaphylaxis and clonal mast cell disorders. Eur Ann Allergy Clin Immunol. 2020;52(2):51-61. doi:10.23822/EurAnnACI.1764-1489.133 3. Garland J, Ondruschka B, Broi UD, et al. Post mortem tryptase: a review of literature on its use, sampling and interpretation in the investigation of fatal anaphylaxis. Forensic Sci Int. 2020;314:110415. doi:10.1016/j.forsciint.2020.110415 4. Tse R, Wong CX, Kesha K, et al. Post mortem tryptase cut-off level for anaphylactic death. Foresnic Sci Int. 2018;284:5-8. doi:10.1016/j.forsciint.2017.12.035

TRYPT
81608

Tryptase, Serum

Clinical Information:

Useful For: Evaluation of individuals with suspected mast cell activation, which may occur as a result of anaphylaxis or allergen challenge Evaluation of patients with suspected mast cell activation syndrome Evaluation of patients with suspected cutaneous or systemic mastocytosis

Interpretation: Transient tryptase concentrations greater than or equal to 11.5 ng/mL may be consistent with mast cell activation in the context of anaphylaxis or allergen challenge; measurement of tryptase in specimens obtained 1 to 6 hours and at least 24 hours after the episode may be useful in demonstrating a return to baseline concentrations. Basal tryptase concentrations greater than or equal to 11.5 mg/mL may be consistent with cutaneous mastocytosis. Basal tryptase concentrations greater than or equal to 20 ng/mL may be consistent with systemic mastocytosis.

Reference Values:
<11.5 ng/mL

Clinical References: 1. Lyons JJ, Yi T. Mast cell tryptases in allergic inflammation and immediate hypersensitivity. Curr Opin Immunol. 2021;72:94-106. doi:10.1016/j.coi.2021.04.001 2. Lyons JJ, Sun G, Stone KD, et al. Mendelian inheritance of elevated serum tryptase associated with atopy and connective tissue abnormalities. J Allergy Clin Immunol. 2014;133(5):1471-1474. doi:10.1016/j.jaci.2013.11.039 3. Platzgummer S, Bizzaro N, Bilo MB, et al. Recommendations for the use of tryptase in the diagnosis of anaphylaxis and clonal mastcell disorders. Eur Ann Allergy Clin Immunol. 2020;52(2):51-61. doi:10.23822/EurAnnACI.1764-1489.133 4. Valent P, Akin C, Bonadonna P, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. J Allergy Clin Immunol Pract. 2019;7(4):1125-1133.e1. doi:10.1016/j.jaip.2019.01.006 5. Valent P, Akin C, Hartmann K, et al. Updated diagnostic criteria and classification of mast cell disorders: A consensus proposal. Hemasphere. 2021;5(11):e646. doi:10.1097/HS9.0000000000000646 6. Valent P, Hoermann G, Bonadonna P, et al. The normal range of baseline tryptase should be 1 to 15 ng/mL and covers healthy individuals with HalphaT. J Allergy Clin Immunol Pract. 2023;11(10):3010-3020. doi:10.1016/j.jaip.2023.08.008

TRYPP
82955

Tryptophan, Plasma

Clinical Information: Amino acids are the basic structural units that comprise proteins and are found throughout the body. Many inborn errors of amino acid metabolism have been identified, including glutaric acidemia type 1, which affect other metabolic activities. Amino acid disorders can manifest at any time in a person's life, but most become evident in infancy or early childhood. These disorders result in the accumulation or the deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the particular amino acid disorder. Tryptophan is an essential amino acid necessary for the synthesis of serotonin, melatonin, and niacin. Low plasma concentrations of tryptophan have been associated with clinical observations of insomnia, anxiety, and depression. Glutaric acidemia type 1 is an autosomal recessive disorder of tryptophan and lysine metabolism caused by a deficiency of glutaryl-CoA dehydrogenase. Early diagnosis and treatment are essential to help prevent encephalopathic crises leading to brain degeneration. These can be provoked by infections, trauma, fever, and fasting. Treatment consists of preventing neurodegeneration through L-carnitine supplementation and strict adherence to an emergency protocol. Dietary protein, particularly lysine and tryptophan, is restricted during the vulnerable period of brain development from 0 to 5 years of age. In addition to other indices of malnutrition, the measurement of plasma concentration of tryptophan is used as an indicator of appropriate dietary therapy.

Useful For: Investigating inadequate tryptophan intake and monitoring dietary treatment

Interpretation: If the result is within the respective age-matched reference range, no interpretation is provided. When an abnormal result is reported, an interpretation may be added, including a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing, if applicable.

Reference Values:
<24 months: 12-103 nmol/mL
2 years-17 years: 21-114 nmol/mL
> or =18 years: 21-108 nmol/mL

Clinical References: 1. Klaessens S, Stroobant V, De Plaen E, Van den Eynde BJ. Systemic tryptophan homeostasis. Front Mol Biosci. 2022;9:897929 2. Larson A, Goodman S. Glutaric acidemia type 1. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2019. Accessed April 22, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK546575/ 3. Goodman SI, Frerman FE. Organic acidemias due to defects in lysine oxidation: 2-ketoadipic acidemia and glutaric acidemia. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill; 2019. Accessed April 22, 2024. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225086303

TRYPU
83823

Tryptophan, Random, Urine

Clinical Information: Amino acids are the basic units that make up proteins and are crucial to virtually all metabolic processes in the body. Tryptophan is an essential amino acid necessary for the synthesis of serotonin, melatonin, and niacin. Hartnup disease is a rare, usually benign, autosomal recessive disorder of renal and intestinal neutral amino acid transport. Reduced intestinal absorption of tryptophan and subsequent loss in the urine lead to a reduction of available tryptophan for the synthesis of niacin. The clinical features associated with Hartnup disease include an erythematous skin rash on exposed surfaces that is identical to the rash seen in pellagra (niacin deficiency) and cerebral ataxia. Biochemically, it is characterized by increased renal excretion of tryptophan and other neutral amino acids. Newborn screening studies reveal that most affected individuals remain asymptomatic, suggesting that clinical expression of symptoms is dependent on additional genetic or environmental factors (ie, multifactorial disease).

Useful For: Aiding in the screening and monitoring of Hartnup disease

Interpretation: If the result is within the respective age-matched reference range, no interpretation is provided. When an abnormal result is reported, an interpretation may be added, including a correlation to available clinical information and recommendations for additional biochemical testing, if applicable.

Reference Values:
<2 months: <241 nmol/mg creatinine
2-35 months: <329 nmol/mg creatinine
3-6 years: <222 nmol/mg creatinine
7-17 years: <218 nmol/mg creatinine
> or =18 years: <140 nmol/mg creatinine

Clinical References: 1. Klaessens S, Stroobant V, De Plaen E, Van den Eynde BJ. Systemic tryptophan homeostasis. Front Mol Biosci. 2022;9:897929 2. Levy HL. Hartnup disorder. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed April 22, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookId=2709&sectionid=225555835

TTF40
602647

TTF41 (SPT24) + p40 Immunostain, Technical Component Only

Clinical Information: Thyroid transcription factor 1 (TTF1) is a nuclear protein (detected by the chromogen 3,3'-diaminobenzidine) expressed in thyroid follicular cells, type II pneumocytes, and a subset of bronchial cells. The p40 antibody recognizes the deltaNp63 isoform of p63 (detected by the chromogen fast red). The predominant localization of p40 is in the basal layer of the stratified squamous and transitional epithelia. Given the relative specificity of TTF1 for cells of thyroid or lung origin, TTF1 is often included in a panel to identify the primary site for carcinomas of unknown origin. The p40 antibody may help to distinguish squamous cell carcinomas from other non-small cell carcinomas.

Useful For: Thyroid transcription factor 1 aids in the classification of carcinomas of unknown origin p40 aids in the classification of carcinomas and lymphomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Reference Values:
This is not an orderable test. Order PATHC / Pathology Consultation. The consultant will determine the need for special stains.

Clinical References: 1. Pelosi G, Fabbri A, Tamborini E, et al. Challenging lung carcinoma with coexistent deltaNp63/p40 and thyroid transcription factor-1 labeling within the same individual tumor cells. J Thorac Oncol. 2015;10(10):1500-1502 2. Whithaus K, Fukuoka J, Prihoda TJ, Jagirdar J. Evaluation of napsin A, cytokeratin 5/6, p63, and thyroid transcription factor 1 in adenocarcinoma versus squamous cell carcinoma of the lung. Arch Pathol Lab Med. 2012;136(2):155-162 3. Sterlacci W, Savic S, Schmid T, et al. Tissue-sparing application of the newly proposed IASLC/ATS/ERS classification of adenocarcinoma of the lung shows practical diagnostic and prognostic impact. Am J Clin Pathol. 2012;137(6):946-956 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

TTRZ
617753

TTR Gene, Full Gene Analysis, Varies

Clinical Information: The systemic amyloidoses include a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. The most common hereditary amyloidosis is familial transthyretin amyloidosis, an autosomal dominant disorder caused by variants in the transthyretin (TTR) gene. The resulting amino acid substitutions lead to a relatively unstable, amyloidogenic TTR protein. Most individuals begin to exhibit clinical symptoms between the third and seventh decades of life. Typically, TTR-associated amyloidosis is progressive over a course of 5 to 15 years, and the most common cause of death is cardiomyopathy. Affected individuals may present with a variety of symptoms, including peripheral neuropathy, blindness, cardiomyopathy, nephropathy, autonomic nervous dysfunction, or bowel dysfunction. It is important to note that this assay does not

detect variants associated with non-TTR forms of familial amyloidosis.

Useful For: Establishing a molecular diagnosis for patients with amyloidosis Identifying variants within TTR known to be associated with amyloidosis, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-424 2. Manganelli F, Fabrizi GM, Luigetti M, Mandich P, Mazzeo A, Pareyson D. Hereditary transthyretin amyloidosis overview. Neurol Sci. 2022:43:595-604. doi:10.1007/s10072-020-04889-2

TSCP
616537

Tuberous Sclerosis Gene Panel, Varies

Clinical Information: Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disorder associated with pathogenic variants in the TSC1 and TSC2 genes. TSC involves multiple organ systems including the skin (angiofibroma, hypomelanotic macule, Shagreen patch), brain (cortical tuber, subependymal nodule and giant cell astrocytoma, seizures including infantile spasms), kidneys (angiomyolipoma), heart (rhabdomyoma), eye (multiple retinal nodular hamartomas) and lungs (lymphangioleiomyomatosis). TSC may also be associated with autism, cognitive impairment, and psychiatric difficulties. Central nervous system tumors are the leading cause of morbidity and mortality. Approximately one-third of individuals with TSC have an affected parent, and two-thirds occur as a result of a de novo disease-causing variant. Although penetrance is complete, TSC is associated with significant inter- and intrafamilial variability in phenotype.

Useful For: Establishing a molecular diagnosis in individuals with features of tuberous sclerosis complex (TSC). Identifying pathogenic variants within the TSC1 and TSC2 genes known to be associated with TSC, allowing for predictive testing of at-risk family members. Prenatal diagnosis in a fetus with ultrasound findings of TSC (eg, cardiac rhabdomyomas)

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. (1). Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424. doi: 10.1038/gim.2015.30 2. Northrup H, Aronow M, Bebin E, et al: Updated

international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. Pediatr Neurol. 2021 Oct;123:50-66. doi: 10.1016/j.pediatrneurol.2021.07.011

RTRP2
614047

Tubular Reabsorption of Phosphorus, Random Urine and Serum

Clinical Information: The tubular reabsorption of phosphate (TRP) is the fraction (or percent) of filtered phosphorus that is reabsorbed by renal tubules. Its measurement is useful when evaluating patients with hypophosphatemia. In general, a reduced TRP in the presence of hypophosphatemia is indicative of a renal defect in phosphate reabsorption. The ratio of the maximum rate of tubular phosphate reabsorption to the glomerular filtration rate (TmP/GFR) is considered the most convenient way to evaluate renal phosphate transport and is referred to as the theoretical renal phosphate threshold. This corresponds to the theoretic lower limit of plasma phosphate below which all filtered phosphate would be reabsorbed. Although direct measurements of parathyroid hormone, which increases renal phosphate excretion, have replaced much of the utility of TmP/GFR measurements, it may still be useful in assessing renal reabsorption of phosphorus in a variety of pathological conditions associated with hypophosphatemia.

Useful For: Assessing renal reabsorption of phosphorus in a variety of pathological conditions associated with hypophosphatemia including hypophosphatemic rickets, tumor-induced osteomalacia, and tumoral calcinosis Adjusting phosphate replacement therapy in severe deficiency states monitoring the renal tubular recovery from acquired Fanconi syndrome

Interpretation: Interpretation of tubular reabsorption of phosphate (TRP) and the maximum rate of TRP to the glomerular filtration rate (TmP/GMR) is dependent upon the clinical situation and should be interpreted in conjunction with the serum phosphorous concentration. TmP/GFR is independent of dietary phosphorus intake, tissue release of phosphorus, and GFR.

Reference Values:

TUBULAR REABSORPTION OF PHOSPHORUS
>80%
(Although, tubular reabsorption of phosphorus levels must be interpreted in light of the prevailing plasma phosphorus and glomerular filtration rate.)

TUBULAR MAXIMUM PHOSPHORUS REABSORPTION/GLOMERULAR FILTRATION RATE (TmP/GFR)
2.6-4.4 mg/dL (0.80-1.35 mmol/L)

PHOSPHORUS (INORGANIC)
Males
1-4 years: 4.3-5.4 mg/dL
5-13 years: 3.7-5.4 mg/dL
14-15 years: 3.5-5.3 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL
Reference values have not been established for patients that are <12 months of age.
Females
1-7 years: 4.3-5.4 mg/dL
8-13 years: 4.0-5.2 mg/dL
14-15 years: 3.5-4.9 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL
Reference values have not been established for patients that are <12 months of age.

PHOSPHORUS, Random Urine
No established reference values

Random urine phosphorus may be interpreted in conjunction with serum phosphorus, using both values to calculate fractional excretion of phosphorus.

The calculation for fractional excretion (FE) of phosphorus (P) is
FE(P)= ([P(urine)XCreat(serum)]/[P(serum)XCreat(urine)]) X 100

CREATININE Serum
Males(1)
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL

Females(1)
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or=16 years: 0.59-1.04 mg/dL

CREATININE, Random Urine
16-326 mg/dL
Reference values have not been established for patients who are less than 18 years of age.

Clinical References: 1. Kulasingam V, Jung BP, Blaustig IM, et al: Pediatric reference intervals for 28 chemistries and immunoassays on the Roche cobas 6000 analyzer--a CALIPER pilot study. Clin Biochem. 2010;43:1045-1050 2. Suki WN, Lederer ED, Rouse D: Renal transport of calcium, magnesium, and phosphate. In: Brenner B, ed: The kidney. 6th ed. WB Saunders Company; 2000:chap 12 3. Bijvoet OL: Relation of plasma phosphate concentration to renal tubular reabsorption of phosphate. Clin Sci. 1969;37:23-36 4. Walton RJ, Bijvoet OL: Nomogram for derivation of renal threshold phosphate Concentration. Lancet. 1975;2:309-310 5. Payne RB: Renal tubular reabsorption of phosphate (TmP/GFR): indications and interpretation. Ann Clin Biochem. 1998;35:201-206 6. Delaney MP, Lamb EJ: Kidney disease. In: Rifai N, Horvath AR, Wittwer CT, eds. Textbook of Clinical Chemistry. 6th ed. Elsevier; 2018:1256-1323

TUNA
82547

Tuna, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to tuna Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

TURKF
82824

Turkey Feathers, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to turkey feathers Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE

antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FGORG
57641

Turkey IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

TURK
82702

Turkey, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend

upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to turkey Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FCTUR
57544

Turmeric (Curcuma longa) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

TRYPI
82848

Tyrophagus putrescentiae, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Tyrophagus putrescentiae Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

TYROS
70577

Tyrosinase (TYROS) Immunostain, Technical Component Only

TYRGP
608033

Tyrosine Disorders Gene Panel, Varies

Clinical Information: Tyrosinemia type 1 (hepatorenal tyrosinemia: HT-1) is an autosomal recessive condition caused by a deficiency of the enzyme fumarylacetoacetate hydrolase (FAH) in the tyrosine degradation pathway. HT-1 primarily affects the liver, kidneys, and peripheral nerves causing severe liver disease, renal tubular dysfunction, and neurologic crises. If left untreated, most patients die of liver failure in the first years of life, and all are at risk of developing hepatocellular carcinoma (HCC). The incidence of HT-1 is approximately 1 in 100,000 live births. Other causes for increased levels of tyrosine in plasma amino acid analysis include tyrosinemia type II, tyrosinemia type III, and hawkinsinuria, although diagnosis for this condition is typically based on the presence of hawkinsin in the urine. Alkaptonuria, another condition in the tyrosine degradation pathway, is characterized by increased plasma and urinary homogentisic acid. Urine turns dark upon standing and alkalinization.

Useful For: Follow up for abnormal biochemical results suggestive of a tyrosine disorder Establishing a molecular diagnosis for patients with tyrosine disorders Identifying variants within genes known to be associated with tyrosine disorders, allowing for predictive testing of at-risk family members

Interpretation:

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Chinsky JM, Singh R, Ficiciolglu C, et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. Genet Med. 2017;19(12). doi:10.1038/gim.2017.101 3. OMIM. Number 203500: Alkaptonuria; AKU. Johns Hopkins University; Updated: March 8,2024. Accessed March 8, 2024. Available at https://omim.org/

TYRBS
607550

Tyrosinemia Follow Up Panel, Blood Spot

Clinical Information: Tyrosinemia type 1 (hepatorenal tyrosinemia, HT-1) is an autosomal recessive condition caused by a deficiency of the enzyme fumarylacetoacetate hydrolase. HT-1 primarily affects the liver, kidneys, and peripheral nerves causing severe liver disease, renal tubular dysfunction, and neurologic crises. If left untreated, most patients die of liver failure in the first years of life, and all are at risk of developing hepatocellular carcinoma (HCC). The incidence of HT-1 is approximately 1 in 100,000 live births. Affected individuals can show a partial response to dietary restriction of phenylalanine and tyrosine, but dietary treatment in conjunction with the administration of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanedione (NTBC; nitisinone), an inhibitor of the proximal tyrosinemia pathway, is very effective when initiated in newborns. Outcome data are promising, and to date, newborn patients treated with NTBC have not developed acute liver disease, neurologic crises, or HCC. According to treatment guidelines established in 2017, monitoring of blood NTBC concentration and succinylacetone (SUAC) levels along with measuring the dietary intake of amino acids, including tyrosine and phenylalanine are part of an individualized surveillance plan for patients with HT-1.(1) Monthly analysis of SUAC, NTBC concentration, and amino acids is suggested for the first year of life with the same compounds being monitored every 3 months to age 5 years and every 6 months thereafter. The analytes encompassed in this assay satisfy the recommendations for diagnosis and monitoring of HT-1. In particular, for NTBC, the current guidelines recommend 40 nmol/mL to 60 nmol/mL plasma concentration, which corresponds to a target range for NTBC in dried blood spots of 17 nmol/mL to 26 nmol/mL based on a blood to plasma conversion factor of 2.34.(2)

Useful For: Monitoring of individuals with tyrosinemia type 1 (HT-1) Diagnosis of HT-1 when used in conjunction with testing for urine organic acids, liver function, alpha-fetoprotein, and molecular genetic analysis of the fumarylacetoacetate hydrolase (FAH) gene

Interpretation: Quantitative results with reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical information.

Reference Values:
TYROSINE:
<4 weeks 40-280 nmol/mL
> or =4 weeks 25-150 nmol/mL

PHENYLALANINE:
27-107 nmol/mL

METHIONINE
11-45 nmol/mL

SUCCINYLACETONE:
< or =1.0 nmol/mL

NITISINONE:
< or =0.5 nmol/mL

Clinical References: 1. Chinsky JM, Singh R, Ficiciolglu C, et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. Genet Med. 2017;19(12). doi:10.1038/gim.2017.101 2. Laeremans H, Turner C, Andersson T, et al. Inter-laboratory analytical improvement of succinylacetone and nitisinone quantification from dried blood spot samples. JIMD Rep. 2020;53(1):90-102 3. Blackburn PR, Hickey RD, Nace RA, et al. Silent tyrosinemia type I without elevated tyrosine or succinylacetone associated with liver cirrhosis and hepatocellular carcinoma. Hum Mutat. 2016;37(10):1097-1105. doi:10.1002/humu.23047 4. Sniderman King L, Trahms C, Scott CR: Tyrosinemia Type I. In: Adam MP, Feldman J, Mirzaa GM, et al, eds: GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated May 25, 2017. Accessed December 26, 2023. Available at: www.ncbi.nlm.nih.gov/books/NBK1515/

TYRSC
610495

Tyrosinemia Follow-Up Panel, Self-Collect, Blood Spot

Clinical Information: Tyrosinemia type 1 (hepatorenal tyrosinemia: HT-1) is an autosomal recessive condition caused by a deficiency of the enzyme fumarylacetoacetate hydrolase. HT-1 primarily affects the liver, kidneys, and peripheral nerves, causing severe liver disease, renal tubular dysfunction, and neurologic crises. If left untreated, most patients die of liver failure in the first years of life, and all are at risk of developing hepatocellular carcinoma (HCC). The incidence of HT-1 is approximately 1 in 100,000 live births. Affected individuals can show a partial response to dietary restriction of phenylalanine and tyrosine, but dietary treatment in conjunction with the administration of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanedione (NTBC; nitisinone), an inhibitor of the proximal tyrosinemia pathway, is very effective when initiated in newborns. Outcome data are promising, and to date, newborn patients treated with NTBC have not developed acute liver disease, neurologic crises, or HCC. According to treatment guidelines established in 2017, monitoring of blood NTBC concentration and succinylacetone (SUAC) levels, along with measuring the dietary intake of amino acids, including tyrosine and phenylalanine, are part of an individualized surveillance plan for patients with HT-1.(1) Monthly analysis of SUAC, NTBC concentration, and amino acids is suggested

for the first year of life with the same compounds being monitored every 3 months to age 5 years and every 6 months thereafter. The analytes encompassed in this assay satisfy the recommendations for diagnosing and monitoring HT-1. In particular, for NTBC, the current guidelines recommend 40 nmol/mL to 60 nmol/mL plasma concentration, which corresponds to a target range for NTBC in dried blood spots of 17 nmol/mL to 26 nmol/mL based on a blood to plasma conversion factor of 2.34.(2) Data from the validation of this assay suggests that NTBC dosing could be individualized while not to exceed DBS levels of 26 nmol/mL.(3)

Useful For: Monitoring of individuals with tyrosinemia type I (hepatorenal tyrosinemia) using a patient-collected specimen

Interpretation: Quantitative results with reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical information.

Reference Values:
TYROSINE
<4 weeks: 40-280 nmol/mL
> or =4 weeks: 25-150 nmol/mL

PHENYLALANINE:
27-107 nmol/mL

METHIONINE
11-45 nmol/mL

SUCCINYLACETONE:
< or =1.0 nmol/mL

NITISINONE:
< or =0.5 nmol/mL

Clinical References:

FSABI 58004 Tysabri (Natalizumab) Immunogenicity

Reference Values:
Negative

UBA1Q 620900 UBA1 Mutation Quantitative Detection, VEXAS syndrome, Droplet Digital PCR, Varies

Clinical Information: VEXAS syndrome is caused by somatic mutations in the UBA1 gene, which is located on the X-chromosome and encodes ubiquitin-activating enzyme E1, an important component in the protein ubiquitylation process. This syndrome, identified in 2020, is characterized by adult-onset rheumatologic and hematologic manifestations. Inflammatory disease can present systemically, as well with more localized findings involving the orbit, skin or ears. Hematologic abnormalities are frequently present, including low blood counts, macrocytic anemia, and characteristic vacuolated myeloid and erythroid precursor cells in the bone marrow.(1) VEXAS syndrome occurs overwhelmingly in male patients, suggesting that biologic females who might acquire a UBA1 mutation may be relatively

protected by the presence of the remaining normal wild type allele.(2) To date, nearly all documented cases of VEXAS syndrome have been caused by seven mutations that occur at three different sites within exon 3 of the UBA1 gene: the intron 2 acceptor splice site and p.Met41 codon region (c.118-122), and the p.Ser56 codon (c.167).(1-4) Importantly, a significant number of VEXAS patients may have predisposition to develop bone marrow failure, clonal hematopoiesis, myelodysplastic syndrome, or other hematologic neoplasms (eg, plasma cell neoplasms).(2-4) Patients with UBA1 mutation and features of bone marrow failure appear to be associated with poor prognosis and may not respond to standard immunosuppressive and hypomethylating agents typically utilized in the treatment of autoinflammatory disorders and myelodysplastic syndrome.(3,4) Testing for these mutations will serve to identify VEXAS syndrome patients who should be considered for alternative therapies or clinical trials.

Useful For: Identification of pathogenic variant(s) in the UBA1 gene in patients presenting with symptoms concerning for or consistent with VEXAS syndrome

Interpretation: The assay is reported as positive or negative. In positive cases, the mutation type and its variant allele fraction (VAF) are reported. VAF%= (mutant copy number)/(mutant copy number + wild-type number) The precision of this quantitative assay is very high but inter-assay variability may occur such that quantitative changes should not be considered significant if 2 single measurements differ by less than 0.5 log (3.16-fold).

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Beck DB, Ferrada MA, Sikora KA, et al. Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. N Engl J Med. 2020;383(27):2628-2638 2. Grayson PC, Patel BA, Young NS. VEXAS syndrome. Blood. 2021;137(26):3591-3594 3. Huang H, Zhang W, Cai W, et al. VEXAS syndrome in myelodysplastic syndrome with autoimmune disorder. Exp Hematol Oncol. 2021;10(1):23 4. Gutierrez-Rodrigues F, Kusne Y, Fernandez J, et al. Spectrum of clonal hematopoiesis in VEXAS syndrome. Blood. 2023;142(3):244-259 5. Koster MJ, Warrington KJ. VEXAS within the spectrum of rheumatologic disease. Semin Hematol. 2021;58(4):218-225 6. Obiorah IE, Patel BA, Groarke EM, et al. Benign and malignant hematologic manifestations in patients with VEXAS syndrome due to somatic mutations in UBA1. Blood Adv. 2021;5(16):3203-3215 7. Oganesyan A, Hakobyan Y, Terrier B, Georgin-Lavialle S, Mekinian A. Looking beyond VEXAS: Coexistence of undifferentiated systemic autoinflammatory disease and myelodysplastic syndrome. Semin Hematol. 2021;58(4):247-253 8. Poulter JA, Savic S. Genetics of somatic auto-inflammatory disorders. Semin Hematol. 2021;58(4):212-217 9. Shaukat F, Hart M, Burns T, Bansal P. UBA1 and DNMT3A mutations in VEXAS syndrome. A case report and literature review. Mod Rheumatol Case Rep. 2022;6(1):134-139. doi:10.1093/mrcr/rxab021 10. Zakine E, Schell B, Battistella M, et al. UBA1 variations in neutrophilic dermatosis skin lesions of patients with VEXAS syndrome. JAMA Dermatol. 2021;157(11):1349-1354

UBIQ
70578

Ubiquitin (UBIQ) Immunostain, Technical Component Only

Clinical Information: Ubiquitin is a polypeptide of approximately 8.5 kDa found in filamentous inclusions and cytosome-related organelles in human idiopathic neurodegenerative diseases, including Alzheimer disease, Pick disease, Lewy body dementia, and Parkinson disease. Ubiquitin is also expressed in Rosenthal fibers in astrocytomas. Ubiquitin protein complexes have also been found in primary lysosome-related granules in mature neutrophils. Ubiquitin labels the periphery of senile plaques and of neurofibrillary tangles in Alzheimer disease, Lewy bodies in Parkinson disease, and Mallory bodies in alcoholic liver disease.

Useful For: Classification of neurodegenerative diseases

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Chu CT, Caruso JL, Cummings TJ, Ervin J, Rosenberg C, Hulette CM. Ubiquitin immunochemistry as a diagnostic aid for community pathologists evaluating patients who have dementia. Mod Pathol. 2000;13(4):420-426 2. Josephs KA, Holton JL, Rossor MN, et al. Frontotemporal lobar degeneration and ubiquitin immunohistochemistry. Neuropathol Appl Neurobiol. 2004;30(4):369-373 3. Katsuse O, Dickson DW. Ubiquitin immunohistochemistry of frontotemporal lobar degeneration differentiates cases with and without motor neuron disease. Alzheimer Dis Assoc Disord. 2005;19 Suppl 1:S37-S43 4. Lennox G, Lowe J, Landon M, Byrne EJ, Mayer RJ, Godwin-Austen RB. Diffuse Lewy body disease: correlative neuropathology using anti-ubiquitin immunocytochemistry. J Neurol Neurosurg Psychiatry. 1989;52(11):1236-1247 5. Mackenzie IR, Feldman HH. Ubiquitin immunohistochemistry suggests classic motor neuron disease, motor neuron disease with dementia, and frontotemporal dementia of the motor neuron disease type represent a clinicopathologic spectrum. J Neuropathol Exp Neurol. 2005;64(8):730-739 6. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

UGTFZ 610064 UDP-Glucuronosyltransferase 1A1 (UGT1A1), Full Gene Sequencing, Varies

Clinical Information: The UGT1A1 gene contains 5 exons and is part of a gene complex located on chromosome 2q37 that encodes several enzymes called uridine diphosphate (UDP)-glucuronosyltransferases. These enzymes perform a chemical reaction called glucuronidation, a major pathway that enhances the elimination of small lipophilic molecules, such as steroids, bilirubin, hormones, and drugs, into water-soluble metabolites that can be excreted from the body. The UGT1A1 enzyme, primarily found in the liver, is responsible for the glucuronidation of bilirubin, converting it from the toxic form of bilirubin (unconjugated bilirubin) to its nontoxic, water-soluble form (conjugated bilirubin). Genetic variants in UGT1A1 may cause reduced or absent UGT1A1 enzymatic activity, resulting in conditions associated with unconjugated hyperbilirubinemia, including Gilbert syndrome and Crigler-Najjar syndrome.(1-4) Gilbert syndrome is the most common hereditary cause of increased bilirubin and is characterized by total serum bilirubin levels of 1 to 6 mg/dL. Gilbert syndrome is generally considered to be an autosomal recessive trait, although autosomal dominant inheritance has been suggested in some cases. Gilbert syndrome is characterized by a 25% to 50% reduction in glucuronidation activity of the UGT1A1 enzyme, along with episodes of mild intermittent jaundice and the absence of liver disease.(1-3) Crigler-Najjar (CN) syndrome is an autosomal recessive disorder caused by more severe reductions in UGT1A1 glucuronidation activity and can be subdivided into type 1 and type 2 (CN1 and CN2). CN1 is the most severe form, with complete absence of enzyme activity and total serum bilirubin levels of 20 to 40 mg/dL. Infants with CN1 present with jaundice shortly after birth that persists thereafter.(1,2,4) CN2 is milder than CN1, with at least partial UGT1A1 activity and total serum bilirubin ranging from 6 to 20 mg/dL.(1,2,4) Phenobarbital, a drug that induces synthesis of a number of hepatic enzymes, is effective in decreasing serum bilirubin levels by approximately 25% in patients with CN2; CN1 does not respond to phenobarbital treatment. If left untreated, the buildup of bilirubin in a newborn can cause bilirubin-induced brain damage, known as kernicterus. In addition to phenobarbital, treatments of CN may include phototherapy, heme oxygenase inhibitors, oral calcium phosphate and carbonate, and liver transplantation.(1,2,4) In addition to the role of UGT1A1 in bilirubin metabolism, this enzyme also plays a role in drug metabolism. UGT1A1 is involved in the metabolism of irinotecan, a

topoisomerase I inhibitor. Irinotecan is a chemotherapy drug used to treat solid tumors, including colon, rectal, and lung cancers. It is a prodrug that forms an active metabolite, SN-38. SN-38 is normally inactivated by conjugation with glucuronic acid followed by biliary excretion into the gastrointestinal tract. If UGT1A1 activity is impaired or deficient, SN-38 fails to become conjugated with glucuronic acid, increasing the concentration of SN-38. This can result in severe neutropenia and diarrhea, which can be life-threatening.(5-8) Additional drugs have also been associated with an increased risk for adverse outcomes in patients with reduced UGT1A1 enzyme activity. The US Food and Drug Administration drug labels for belinostat, nilotinib, pazopanib, and sacituzumab govitecan contain warnings for an increased risk (incidence) of adverse outcomes or increased bilirubin in patients who have UGT1A1 variants associated with reduced activity.(7) The Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment, indicating that patients with homozygous UGT1A1 alleles associated with reduced activity or decreased expression should consider an alternate medication due to a significant risk for developing hyperbilirubinemia (jaundice).(8) Additionally, the concentration of several drugs, including dolutegravir and raltegravir, may be increased in patients with reduced UGT1A1 enzyme activity.(7) In this assay, the UGT1A1 promoter, exons, and exon-intron boundaries are assessed for variants.(5)

Useful For: Establishing a diagnosis of Crigler-Najjar syndrome type I or type II and the trait of Gilbert syndrome Establishing carrier status for Crigler-Najjar syndrome type I or type II Identifying individuals who are at risk of hyperbilirubinemia or who have Gilbert syndrome Identifying individuals who are at increased risk of adverse drug reactions or hyperbilirubinemia when taking drugs that are metabolized by UGT1A1, including atazanavir, belinostat, irinotecan, nilotinib, pazopanib, and sacituzumab govitecan Identifying individuals who may have increased drug levels when taking dolutegravir or raltegravir Follow-up testing for individuals with a suspected UGT1A1 variant, who had negative TA repeat region testing

Interpretation: An interpretive report will be provided that includes assessment of risk for UGT1A1-associated adverse drug reactions as well as interpretation for hyperbilirubinemia syndromes. All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(9) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables. This resource includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
TA Repeat Result: TA6/TA6 (Normal), TA5/TA6 (Heterozygous *36), and TA5/TA5 (Homozygous *36)

Full Gene Sequence Result: No reportable variants were detected in the UGT1A1 gene by sequencing, and No additional reportable variants were detected in the UGT1A1 gene by sequencing.

An interpretive report will be provided.

Clinical References: 1. Skierka JM, Kotzer KE, Lagerstedt SA, O'Kane DJ, Baudhuin LM. UGT1A1 genetic analysis as a diagnostic aid for individuals with unconjugated hyperbilirubinemia. J Pediatr. 2013;162(6):1146-1152.e11522. doi:10.1016/j.jpeds.2012.11.042 2. Moyer AM, Skierka JM, Kotzer KE, Kluge ML, Black JL, Baudhuin LM. Clinical UGT1A1 genetic analysis in pediatric patients: experience of a reference laboratory. Mol Diagn Ther. 2017;21(3):327-335. doi:10.1007/s40291-017-0265-0 3. Thoguluva Chandrasekar V, Faust TW, John S. Gilbert Syndrome. In: StatPearls [Internet]. StatPearls Publishing; Updated February 6, 2023. Accessed June 5, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK470200/ 4. Bhandari J, Thada PK, Yadav D. Crigler Najjar Syndrome. In: StatPearls [Internet]. StatPearls Publishing; Updated February 12, 2024. Accessed June 5, 2024. Available from: www.ncbi.nlm.nih.gov/books/NBK562171/ 5. Goetz MP, McKean HA,

Reid JM, et al. UGT1A1 genotype-guided phase I study of irinotecan, oxaliplatin, and capecitabine. Invest New Drugs. 2013;31(6):1559-1567. doi:10.1007/s10637-013-0034-9 6. Innocenti F, Schilsky RL, Ramirez J, et al. Dose-finding and pharmacokinetic study to optimize the dosing of irinotecan according to the UGT1A1 genotype of patients with cancer. J Clin Oncol. 2014;32(22):2328-2334. doi:10.1200/JCO.2014.55.2307 7. US Food and Drug Administration. Table of Pharmacogenetic Associations. Updated October 26, 2022. Accessed June 5, 2024. Available at www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations 8. Gammal RS, Court MH, Haidar CE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for UGT1A1 and atazanavir prescribing. Clin Pharmacol Ther. 2016;99(4):363-369. doi:10.1002/cpt.269 9. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-424

ULCH
82546

Ulocladium chartarum, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to Ulocladium chartarum Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive

5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

UNIPD
35566

Uniparental Disomy, Varies

Clinical Information: Uniparental disomy (UPD) occurs when a child inherits 2 copies of a chromosome from only one parent and no copies of that chromosome from the other parent. This is typically due to an error in cell division during the formation of egg or sperm cells (meiosis). When an error causing UPD occurs during meiosis I, both chromosome homologs from a single parent are transmitted, resulting in uniparental heterodisomy. When the error causing UPD occurs during meiosis II or as a postzygotic event, and a single parental homolog is transmitted to offspring in duplicate, isodisomy results. Meiotic recombination events within the context of UPD often result in a mixture of regions of heterodisomy and isodisomy. When UPD occurs, the imbalance of maternal versus paternal genetic information for the involved chromosome can be associated with clinical symptoms in the affected child. However, UPD does not always impart an abnormal clinical phenotype. In fact, while isodisomy can result in disease due to a recessive allele, heterodisomy is not expected to result in an abnormal clinical phenotype unless the involved chromosome or chromosomal segment includes imprinted genes. Imprinted genes demonstrate differential expression depending on parent of origin. Disorders that result from UPD of imprinted genes are not due to a defect in the imprinting mechanism itself, but rather they are due to an unbalanced parental contribution of normally imprinted alleles that results in altered expression of imprinted genes. For example, when maternal UPD 15 occurs (2 copies of the maternal chromosome 15 instead of 1 maternal and 1 paternal copy of chromosome 15), it causes Prader-Willi syndrome due to the lack of paternally expressed genes at the imprinted site. UPD has been described for many but not all chromosomes. In addition to the rare cases of autosomal recessive disease that result from isodisomy, clinical syndromes associated with UPD have been described for only a few chromosomes, including chromosomes 6, 7, 11, 14, 15 and 20. UPD cannot be identified by gross cytogenetic analysis and requires molecular DNA-based analysis using multiple polymorphic markers spanning the chromosome of interest. For optimal interpretation of results, specimens from both parents and the child or fetus are recommended. If only one parent specimen is submitted, testing can be performed; however, biparental inheritance and some types of UPD cannot be definitively established. Additionally, the likelihood for uninformative or inconclusive results is higher.

Useful For: Evaluation of patients presenting with mosaicism, confined placental mosaicism, or Robertsonian translocations Evaluation of patients presenting with features of disorders known to be associated with uniparental disomy (eg, Russell-Silver syndrome) Evaluation of disease mechanism in individuals with rare autosomal recessive disease and only one carrier parent

Interpretation: Microsatellite markers are compared between the proband and parental samples for the chromosome of interest. The pattern of the microsatellite markers will be classified as demonstrating uniparental disomy or biparental inheritance when sufficient informative markers are identified.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Del Gaudio D, Shinawi M, Astbury C, et al. Diagnostic testing for uniparental disomy: a points to consider statement from the American College of Medical Genetics and

Genomics (ACMG). Genet Med. 2020;22(7):1133-1141. doi:10.1038/s41436-020-0782-9 2. Kotzot D, Utermann G. Uniparental disomy (UPD) other than 15: phenotypes and bibliography updated. Am J Med Genet. 2005;136(3):287-305. doi:10.1002/ajmg.a.30483 3. Kotzot D. Prenatal testing for uniparental disomy: indications and clinical relevance. Ultrasound Obstet Gynecol. 2008:31(1):100-105. doi: 10.1002/uog.5133 4. Engel E. A fascination with chromosome rescue in uniparental disomy: Mendelian recessive outlaws and imprinting copyrights infringements. Eur J Hum Genet. 2006;14(11):1158-1169. doi:10.1038/sj.ejhg.5201619

FURA
90316

Uranium, Urine

Interpretation: Specimens for elemental testing should be collected in certified metal-free containers. Elevated results for elemental testing may be caused by environmental contamination at the time of specimen collection and should be interpreted accordingly. It is recommended that unexpected elevated results be verified by testing another specimen.

Reference Values:
Reporting limit determined each analysis

Normally: Less than 0.1 mcg/L

UCDP
608020

Urea Cycle Disorders Gene Panel, Varies

Clinical Information: Urea cycle disorders (UCD) are a group of inherited disorders of nitrogen detoxification that result when any of the enzymes in the urea cycle have reduced or absent activity. These disorders include carbamoylphosphate synthetase I deficiency, ornithine transcarbamylase (OTC) deficiency, argininosuccinic acid synthetase deficiency (citrullinemia), argininosuccinic acid lyase deficiency (argininosuccinic aciduria), arginase deficiency, the cofactor producer, N-acetyl glutamate synthetase (NAGS) deficiency, and two amino acid transporters, ornithine translocase deficiency (hyperornithinemia, hyperammonemia, homocitrullinuria syndrome) and citrin deficiency. The role of the urea cycle is to metabolize and clear waste nitrogen, and defects in any of the steps of the pathway can result in an accumulation of toxic ammonia in the nervous system. The urea cycle is also responsible for endogenous production of the amino acids citrulline, ornithine, and arginine. Infants with a complete urea cycle enzyme deficiency typically appear normal at birth, but they present in the neonatal period with lethargy, seizures, hyper- or hypoventilation, and ultimately coma or death, as a result of elevated ammonia levels. Individuals with partial enzyme deficiency may present later in life, typically following an acute illness or other catabolic stressor. Symptoms may be less severe and may appear as episodes of psychosis, lethargy, cyclical vomiting, and behavioral abnormalities. Patients with impaired ornithine metabolism due to ornithine aminotransferase deficiency may present with childhood onset myopia progressing to vision loss in the 4th to 6th decades of life. Patients may or may not have accompanying hyperammonemia but display marked elevations in plasma ornithine. All the UCD are inherited as autosomal recessive disorders, with the exception of OTC deficiency, which is X-linked. UCD may be suspected with elevated ammonia, normal anion gap, and a normal glucose. This comprehensive gene panel is a helpful tool to establish a diagnosis for patients with suggestive clinical and biochemical features given the broad clinical spectrum and genetic heterogeneity of UCD. Molecular genetic testing can help to distinguish among the conditions and allows for diagnostic confirmation. A combination of biochemical tests including quantitative plasma amino acids (AAQP / Amino Acids, Quantitative, Plasma) and urinary orotic acid (OROT / Orotic Acid, Random, Urine) are recommended as the first-tier test to assess patients for UCD. Acute treatment for UCD consists of dialysis and administration of nitrogen scavenger drugs to reduce ammonia concentration. Chronic management typically involves restriction of dietary protein with essential amino acid supplementation. More recently, liver transplantation has been used with success in treating some patients.

Useful For: Follow up for abnormal biochemical results suggestive of a urea cycle disorder (UCD) Establishing a molecular diagnosis for patients with a UCD Identifying variants within genes known to be associated with UCD, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. Brusilow SW, Horwich AL. Urea cycle enzymes. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Accessed March 8, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225084071&bookid=2709&Resultclick=2 3. Haberle J, Burlina A, Chakrapani A, et al. Suggested guidelines for diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis. 2019;1-39. doi:10.1002/jimd.12100 4. Valle D, Simell O. The hyperornithinemias. In: Valle D, Antonarakis S, Ballabio A, Beaudet A, Mitchell GA. eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019. Accessed March 8, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225083672&bookid=2709&Resultclick=2 5. Foshci FG, Morelli MC, Savini S, et al. Urea cycle disorders: A case report of a successful liver transplant and a literature review. World J Gastroenterol. 2015;21(13):4063-4068 6. Ah Mew N, Simpson KL, Gropman AL, et al. Urea cycle disorders overview. In: Adam MP, Everman DB, Mirzaa GM, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated June 22, 2017. Accessed March 8, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1217/

UEBF
606598

Urea Nitrogen, Body Fluid

Clinical Information: Byproducts of nitrogen metabolism are present in high concentration in urine compared to blood and serve as a surrogate marker for the identification of urine leakage into a body compartment. Concentrations of creatinine or urea nitrogen that exceed the concentration found in a concurrent sample of blood are suggestive of the presence of urine.(1) Peritoneal, abdominal, pelvic drain fluids: Disruption of the urinary tract with subsequent leakage of urine into body cavities may be considered as part of the differential diagnosis when body fluid effusions develop of unknown origin.(2) Metabolites such as creatinine or urea that are contained in urine at high concentrations are good candidates to measure in body fluids for this investigation. Elevated concentrations may elicit a more focused radiologic examination to identify possible bladder rupture or perforation or the development of urinary fistula, which are typically corrected by surgical intervention. Peritoneal dialysis fluid: Peritoneal dialysis (PD) is a type of dialysis in which hyperosmotic fluid is passed into the patient's peritoneal cavity for a prescribed dwell time, wherein the peritoneum is employed as the dialysis membrane. The dwell fluid containing waste molecules removed by dialysis is drained and replaced with fresh fluid and the process repeated. Measurements of urea, creatinine, glucose, or other electrolytes in serum, urine, and the peritoneal dialysate fluid, aid in the assessment of peritoneal membrane transport characteristics and serve as markers of dialysis adequacy. Adequacy of PD is important to monitor because patients who maintain a sufficient clearance over time have longer survival.(2) Peritoneal urea clearance volume of distribution or urea (Kt/V) is calculated to measure solute clearance from the daily peritoneal urea clearance (Kt), and the volume of distribution of urea

(V). Adequacy and membrane transport characteristics are calculated by plugging in the appropriate laboratory parameters into software packages used by dialysis centers.

Useful For: Identifying the presence of urine as a cause for accumulation of fluid in a body compartment Assessing adequacy of peritoneal dialysis treatment protocols

Interpretation: Peritoneal and drain fluid concentrations should be compared to serum or plasma. A fluid to serum ratio of greater than 1.0 suggests the specimen may be contaminated with urine.(1) Peritoneal dialysate urea nitrogen concentrations can be used to calculate the adequacy of peritoneal dialysis by monitoring solute clearance over time.(3) All other fluids: Results should be interpreted in conjunction with serum urea nitrogen and other clinical findings.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Manahan KJ, Fanning J. Peritoneal fluid urea nitrogen and creatinine reference values. Obstet Gynecol. 1999;93(5 Pt 1):780-782. doi: 10.1016/s0029-7844(98)00516-x 2. Block DR, Florkowski CM. Body fluids. In: Rafai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier;2018:chap 43 3. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. J Am Soc Nephrol. 1996;7(2):198-207

URAU
607234

Urea, 24 Hour, Urine

Clinical Information: Urea is a low molecular weight substance (60 Da) that is freely filtered by glomeruli, and the majority is excreted into the urine, although variable amounts are reabsorbed along the nephron. It is the major end product of protein metabolism in humans and other mammals. Approximately 50% of urinary solute excretion and 90% to 95% of total nitrogen excretion is composed of urea under normal conditions. Factors that tend to increase urea excretion include increases in glomerular filtration rate, increased dietary protein intake, protein catabolic conditions, and water diuretic states. Factors that reduce urea excretion include low protein intake and conditions that result in low urine output (eg, dehydration).

Useful For: Assessment of protein intake and/or nitrogen balance

Interpretation: Because multiple factors (glomerular filtration rate, dietary protein intake, protein catabolic rate, hydration state, etc.) can independently affect the urinary excretion of urea, all of these factors must be taken into account when interpreting the results.

Reference Values:
> or =18 years: 7-42 g/24 hours
Reference values have not been established for patients who are less than 18 years of age.

Clinical References: 1. Lamb EJ, Jones GRD: Kidney function tests In: Rifai N, Horvath AR, Wittwer CT, eds. Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:498-500 2. Bankir L, Trinh-Trang- Tan MM: Urea and the kidney. In: Brenner BM eds. The Kidney. 6th ed. WB Saunders Company; 2000

URCON
614061

Urea, Random, Urine

Clinical Information: Urea is a low molecular weight substance (60 Da) that is freely filtered by glomeruli, and the majority is excreted into the urine, although variable amounts are reabsorbed along the nephron. It is the major end-product of protein metabolism in humans and other mammals. Approximately 50% of urinary solute excretion and 90% to 95% of total nitrogen excretion is composed of urea under normal conditions. Factors that tend to increase urea excretion include increases in glomerular filtration rate, increased dietary protein intake, protein catabolic conditions, and water diuretic states. Factors that reduce urea excretion include low protein intake and conditions that result in low urine output (eg, dehydration). Urea excretion is a useful marker of protein metabolism. In oliguric patients with a rising creatinine a fractional excretion of urea below 35% is consistent with a prerenal cause, while values above 35% are more consistent with acute kidney injury.(1) The fractional excretion of sodium is also used for this purpose but may be more affected by diuretics. Therefore, the fractional excretion of urea may be particularly useful for patients receiving diuretics.

Useful For: Assessment of kidney failure (prerenal vs acute kidney injury)

Interpretation: Fractional excretion of urea under 35% is consistent with a prerenal cause.

Reference Values:
No established reference values

Random urine urea may be interpreted in conjunction with serum urea, using both values to calculate fractional excretion of urea.

The calculation for fractional excretion (FE) of urea is
FE(U)= ([U(urine)XCreat(serum)]/[U(serum)XCreat(urine)]) X 100

Clinical References: 1. Carvounis CP, Nisar S, Guro-Razuman S: Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure, Kidney Int. 2002 Dec;62(6):2223-2229 2. Lamb EJ, Jones GRD: Kidney function tests. In: Rifai N, Horvath AR, Wittwer CT, eds: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:498-500 3. Bankir L, Trinh-Trang-Tan MM: Urea and the kidney. In: Brenner B, ed: The kidney. 6th ed. WB Saunders Company; 2000

URBRP
65133

Ureaplasma species, Molecular Detection, PCR, Blood

Clinical Information:

Useful For: Rapid, sensitive, and specific identification of Ureaplasma urealyticum and Ureaplasma parvum from whole blood This test is not intended for medicolegal use.

Interpretation: A positive PCR result for the presence of a specific sequence found within the Ureaplasma urealyticum and U parvum ureC gene indicates the presence of U urealyticum or U parvum DNA in the specimen. A negative PCR result indicates the absence of detectable U urealyticum and U parvum DNA in the specimen, but does not rule-out infection as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of U urealyticum or U parvum in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. Bharat A, Cunningham SA, Scott Budinger GR, Kreisel D, et al:

Disseminated Ureaplasma infection as a cause of fatal hyperammonemia in humans. Sci Transl Med 2015;7(284):284re3 2. Stellrecht KA, Woron AM, Mishrik NG, Venezia RA: Comparison of multiplex PCR assay with culture detection of genital mycoplasmas. J Clin Microbiol 2004;42:1528-1533 3. Farrell JJ, Larson JA, Akeson JW, et al: Ureaplasma parvum prosthetic joint infection detected by PCR. J Clin Microbiol 2014;52:2248-2250 4. Waites KB, Taylor-Robinson D: Mycoplasma and Ureaplasma. In: Jorgensen JH, ed. Manual of Clinical Microbiology. 11th ed. ASM Press; 2015:1088-1105 5. Kenny GE: Genital mycoplasmas: Mycoplasma genitalium, Mycoplasma hominis, and Ureaplasma species. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Churchill Livingstone;2020:chap 184

URPRP 65135 Ureaplasma species, Molecular Detection, PCR, Plasma

Clinical Information:

Useful For: Rapid, sensitive, and specific identification of Ureaplasma urealyticum and Ureaplasma parvum from plasma This test is not intended for medicolegal use.

Interpretation: A positive polymerase chain reaction (PCR) result for the presence of a specific sequence found within the Ureaplasma urealyticum and Ureaplasma parvum ureC gene indicates the presence of U urealyticum or U parvum DNA in the specimen. A negative PCR result indicates the absence of detectable U urealyticum and U parvum DNA in the specimen but does not rule out infection as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of U urealyticum or U parvum in quantities below the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. Bharat A, Cunningham SA, Scott Budinger GR, Kreisel D, et al: Disseminated Ureaplasma infection as a cause of fatal hyperammonemia in humans. Sci Transl Med. 2015;7(284):284re3 2. Stellrecht KA, Woron AM, Mishrik NG, Venezia RA: Comparison of multiplex PCR assay with culture detection of genital mycoplasmas. J Clin Microbiol. 2004 Apr;42(4):1528-1533 3. Farrell JJ, Larson JA, Akeson JW, et al: Ureaplasma parvum prosthetic joint infection detected by PCR. J Clin Microbiol. 2014;52:2248-2250 4. Waites KB, Taylor-Robinson D: Mycoplasma and Ureaplasma. In: Jorgensen JH, ed. Manual of Clinical Microbiology. 11th ed. ASM Press; 2015:1088-1105 5. Kenny GE: Genital mycoplasmas: Mycoplasma genitalium, Mycoplasma hominis, and Ureaplasma species. In: Mandell GL ed. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Churchill Livingstone; 2008

URRP 60758 Ureaplasma species, Molecular Detection, PCR, Varies

Clinical Information: Ureaplasma urealyticum and Ureaplasma parvum have been associated with a number of clinically significant infections, although their clinical significance may not always be clear as they are part of the normal genital microbiota. U urealyticum and U parvum have been associated with urethritis and epididymitis. They may cause upper urinary tract infection and have been associated with infected kidney stones. U urealyticum and U parvum may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis. They may also cause neonatal infections, including meningoencephalitis and pneumonia. In addition, U urealyticum and U parvum have been reported to cause unusual infections, such as prosthetic joint infection and infections in transplant recipients. Recently, U urealyticum and U parvum have been found to cause hyperammonemia in lung transplant recipients.(1) In lung transplant recipients with hyperammonemia,

the ideal diagnostic specimen is a lower respiratory specimen (eg, bronchoalveolar lavage fluid), although U urealyticum and U parvum may also be detected in blood. Treatment directed against these organisms has resulted in resolution of hyperammonemia. Culture of Ureaplasma species is laborious, requiring a high degree of technical skill and taking several days. Polymerase chain reaction (PCR) detection is sensitive, specific, and provides same-day results. In addition, PCR allows the differentiation of U urealyticum and U parvum, which is not easily accomplished with culture. The PCR assay has replaced conventional culture for U urealyticum and U parvum at Mayo Clinic Laboratories due to its speed and equivalent performance to culture.

Useful For: Rapid, sensitive, and specific identification of Ureaplasma urealyticum and Ureaplasma parvum from genitourinary, reproductive, bone, spine, joint, and lower respiratory sources This test is not intended for medicolegal use.

Interpretation: A positive polymerase chain reaction (PCR) result for the presence of a specific sequence found within the Ureaplasma urealyticum and Ureaplasma parvum ureC gene indicates the presence of U urealyticum or U parvum DNA in the specimen. A negative PCR result indicates the absence of detectable U urealyticum and U parvum DNA in the specimen but does not rule out infection as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of U urealyticum or U parvum in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References: 1. Bharat A, Cunningham SA, Scott Budinger GR, et al. Disseminated Ureaplasma infection as a cause of fatal hyperammonemia in humans. Sci Transl Med. 2015;7(284):284re3 2. Stellrecht KA, Woron AM, Mishrik NG, Venezia RA. Comparison of multiplex PCR assay with culture detection of genital mycoplasmas. J Clin Microbiol. 2004;42(4):1528-1533 3. Farrell JJ, Larson JA, Akeson JW, et al. Ureaplasma parvum prosthetic joint infection detected by PCR. J Clin Microbiol. 2014;52(6):2248-2250 4. Waites KB, Bebear C: Mycoplasma and Ureaplasma. In: Carroll KC, Pfaller MA, eds. Manual of Clinical Microbiology. 12th ed. ASM Press; 2019;1117-1136 5. Kenny GE. Genital mycoplasmas: Mycoplasma genitalium, Mycoplasma hominis, and Ureaplasma species. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Churchill Livingstone; 2020:chap 184

URCU
614044

Uric Acid, 24 Hour, Urine

Clinical Information: Uric acid is the end-product of purine metabolism. It is freely filtered by the glomeruli and most is reabsorbed by the tubules. There is also active tubular secretion. Increased levels of uric acid in the urine usually accompany increased plasma uric acid levels unless there is a decreased excretion of uric acid by the kidneys. Urine uric acid levels reflect the amount of dietary purines and endogenous nucleic acid breakdown.

Useful For: Assessment and management of patients with kidney stones, particularly uric acid stones

FUABF
75099

Uric Acid, Body Fluid

Reference Values:
Units: mg/dL

URIC
8440

Uric Acid, Serum

Clinical Information: Uric acid is the final product of purine metabolism in humans. Purines, compounds that are vital components of nucleic acids and coenzymes, may be synthesized in the body or they may be obtained by ingesting foods rich in nucleic material (eg, liver, sweetbreads). Approximately 75% of the uric acid excreted is lost in the urine; most of the remainder is secreted into the gastrointestinal tract where it is degraded to allantoin and other compounds by bacterial enzymes. Asymptomatic hyperuricemia is frequently detected through biochemical screening. The major causes of hyperuricemia are increased purine synthesis, inherited metabolic disorder, excess dietary purine intake, increased nucleic acid turnover, malignancy, cytotoxic drugs, and decreased excretion due to chronic renal failure or increased renal reabsorption. Long-term follow-up of these patients is undertaken because many are at risk of developing renal disease; few of these patients ever develop the clinical syndrome of gout. Hypouricemia, often defined as serum urate below 2.0 mg/dL, is much less common than hyperuricemia. It may be secondary to severe hepatocellular disease with reduced purine synthesis, defective renal tubular reabsorption, overtreatment of hyperuricemia with allopurinol, as well as some cancer therapies (eg, 6-mercaptopurine).

Useful For: Diagnosis and treatment of renal failure Monitoring patients receiving cytotoxic drugs and a variety of other disorders, including gout, leukemia, psoriasis, starvation and other wasting conditions

Interpretation: Hyperuricemia is most commonly defined by serum or plasma uric acid concentrations above 8.0 mg/dL in males or above 6.1 mg/dL in females.

Reference Values:

Males
1-10 years: 2.4-5.4 mg/dL
11 years: 2.7-5.9 mg/dL
12 years: 3.1-6.4 mg/dL
13 years: 3.4-6.9 mg/dL
14 years: 3.7-7.4 mg/dL
15 years: 4.0-7.8 mg/dL
> or =16 years: 3.7-8.0 mg/dL
Reference values have not been established for patients who are <12 months of age.

Females
1 year: 2.1-4.9 mg/dL
2 years: 2.1-5.0 mg/dL
3 years: 2.2-5.1 mg/dL
4 years: 2.3-5.2 mg/dL
5 years: 2.3-5.3 mg/dL
6 years: 2.3-5.4 mg/dL
7-8 years: 2.3-5.5 mg/dL
9-10 years: 2.3-5.7 mg/dL
11 years: 2.3-5.8 mg/dL
12 years: 2.3-5.9 mg/dL
> or =13 years: 2.7-6.1 mg/dL
Reference values have not been established for patients who are <12 months of age.

Clinical References: Tietz Textbook of Clinical Chemistry. Chapter 24: Fourth edition, Edited by CA Burtis, ER Ashwood, WS Bruns. WB Saunders Company, Philadelphia, 2006, pp 803-807

RURC1
621395

Uric Acid/Creatinine Ratio, Random, Urine

Clinical Information: Uric acid is the end-product of purine metabolism. It is freely filtered by the glomeruli and most is reabsorbed by the tubules. There is also active tubular secretion. Increased levels of uric acid in the urine usually accompany increased plasma uric acid levels unless there is a decreased excretion of uric acid by the kidneys. Urine uric acid levels reflect the amount of dietary purines and endogenous nucleic acid breakdown. Acute uric acid nephropathy can cause acute renal failure due to uric acid precipitation within tubules. This is most commonly seen in patients with hematologic malignancies (eg, lymphoma, leukemia), often after acute lysis of cells by chemotherapy. Less commonly this may be seen with seizures, treatment of solid tumors, overproduction of uric acid in metabolic disorders such as Lesch-Nyhan syndrome or decreased uric acid reabsorption in the proximal nephron due to tubular disorder (Fanconi syndrome).

Useful For: Differentiation of acute uric acid nephropathy from other causes of acute kidney failure For patients who cannot collect a 24-hour specimen, typically small children, a uric acid to creatinine ratio can be used to approximate 24-hour excretion

Interpretation: Uric acid excretion can be either decreased or increased in response to a variety of pharmacologic agents. Urine uric acid levels are elevated in states of uric acid overproduction such as in leukemia and polycythemia and after intake of food rich in nucleoproteins. A uric acid to creatinine ratio (mg/mg) greater than 1.0 is consistent with acute uric acid nephropathy, whereas values less than 0.75 are consistent with other causes of acute renal failure.(1) A timed 24-hour collection is usually the preferred method for measuring and interpreting this urinary analyte. Random collections normalized to urinary creatinine may be of clinical use in 2 scenarios, however: -When acute renal failure secondary to uric acid is suspected, a uric acid to creatinine ratio (mg/mg) greater than 1.0 is consistent with acute uric acid nephropathy, whereas values less than 0.75 are consistent with other causes of acute renal failure.(1) -In patients who cannot collect a 24-hour specimen, typically small children, a uric acid creatinine ratio can be used to approximate 24-hour excretion. Pediatric Reference Ranges of Uric Acid/Creatinine (mg/mg)(2) Age (year) 5th Percentile 95th Percentile 0-0.5 >1.189 <2.378 0.5-1 >1.040 <2.229 1-2 >0.743 <2.080 2-3 >0.698 <1.932 3-5 >0.594 <1.635 5-7 >0.446 <1.189 7-10 >0.386 <0.832 10-14 >0.297 <0.654 14-17 >0.297 <0.594

Reference Values:
> or =18 years: <0.60 mg/mg creatinine
Reference values have not been established for patients who are younger than 18 years.

Clinical References: 1. Lamb EJ, Jones GRD. Kidney function tests. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:500-503 2. Kelton J, Kelley WN, Holmes EW. A rapid method for the diagnosis of acute uric acid nephropathy. Arch Intern Med. 1978;138(4):612-615 3. Matos V, Van Melle G, Werner D et al. Urinary oxalate and urate to creatinine ratios in a healthy pediatric population. Am J Kidney Dis. 1999; Aug;34(2):e1 4. Newman DJ, Price CP. Renal function and nitrogen metabolites. In: Tietz NW, ed. Textbook of Clinical Chemistry. WB Saunders Company, 1999:1245-1250

U1A1Q 610063 Uridine Diphosphate (UDP) Glucuronosyltransferase 1A1 TA Repeat Genotype, UGT1A1, Varies

Clinical Information: Following primary metabolism by the phase I enzymes (by oxidation, reduction, dealkylation, and cleavage in the intestines and liver), many drugs and their metabolites are further modified for excretion by a group of conjugative, phase II enzymes. One of these phase II enzymes, uridine diphosphate (UDP) glucuronosyltransferase 1A1 (UGT1A1), is responsible for phase II conjugation of certain drugs, like atazanavir, irinotecan, nilotinib, pazopanib, and belinostat. UGT1A1 is additionally responsible for glucuronide conjugation of bilirubin, which renders the bilirubin water soluble and permits excretion of the bilirubin-glucuronide conjugates in urine. Reduced

UGT1A1 gene transcription due to variation in the number of thymine-adenine (TA) repeats in the TATA box of the gene promoter and c.211G>A (*6) results in reduced enzymatic activity and an increased risk for adverse outcomes in response to drugs metabolized by UGT1A1. These variants are also associated with Gilbert syndrome (unconjugated hyperbilirubinemia). The TA repeat number may vary from 5 to 8 TA (TA5-TA8) repeats, with 6 TA (TA6) repeats being the most common allele. TA6 is the reference allele and is considered to have normal UGT1A1 expression. In addition, the rare TA5 repeat (*36: c.-41_-40delTA) has normal or possibly increased UGT1A1 expression. Individuals with TA7 repeat (*28: c.-41_-40dup) or the rare TA8 repeat (TA8 or *37: c.-43_-40dup, which is not distinguished from TA7 with this assay) have decreased expression of UGT1A1. Approximately 10% to 15% of White and African American populations are homozygous for the TA7 repeat (*28/*28). Uridine diphosphate glucuronosyltransferase 1A1 is involved in the metabolism of irinotecan, a chemotherapy drug used to treat solid tumors including colon, rectal, and lung cancers. If UGT1A1 activity is reduced or deficient, the active irinotecan metabolite (SN-38) is less efficiently conjugated with glucuronic acid, which leads to an increased concentration of SN-38. This in turn can result in severe neutropenia and diarrhea, which in some cases can be life-threatening. Individuals who are homozygous for *28 (TA7) have a 50% higher risk of experiencing severe (grade 4 or 5) neutropenia following the administration of irinotecan. Approximately 40% of individuals are heterozygous for the TA7 repeat allele (ie, TA6/TA7 or heterozygous *28). Heterozygous individuals are also at increased risk of grade 4 neutropenia. The drug label for irinotecan indicates that individuals homozygous or heterozygous for TA repeat variants have a higher risk for severe or life-threatening neutropenia. The risk is thought to be greatest in individuals who receive irinotecan once every 3 weeks. Additional drugs have also been associated with an increased risk for adverse outcomes if the patient has reduced UGT1A1 enzyme activity. The US Food and Drug Administration drug labels for atazanavir, nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have reduced activity alleles. Recently, the Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment that indicate patients who are homozygous for a reduced activity (decreased expression) allele should be considered for an alternate medication due to the significant risk for developing hyperbilirubinemia (jaundice).(1) Gilbert syndrome (GS), found in 5% to 10% of the population, is the most common hereditary cause of increased bilirubin and is associated with usually benign, mild hyperbilirubinemia (bilirubin levels are typically around 3 mg/dL). Gilbert syndrome is caused by a 25% to 50% reduced glucuronidation activity of the UGT1A1 enzyme and characterized by episodes of mild intermittent jaundice and the absence of liver disease. Homozygosity for the reduced activity alleles, UGT1A1*6 (c.211G>A) allele, TA7, and TA8, or compound heterozygosity (*6, TA7, or TA8) is consistent with Gilbert syndrome. Heterozygosity for *6, TA7 or TA8 is consistent with carrier status for Gilbert syndrome.

Useful For: Identifying individuals who are at increased risk of adverse drug reactions with drugs that are metabolized by uridine diphosphate glucuronosyltransferase (UGT1A1); especially irinotecan but also atazanavir, nilotinib, pazopanib, and belinostat Identifying individuals with Gilbert syndrome due to the presence of homozygous UGT1A1*6 (c.211G>A, based on NM_000463.2) allele, TA7, homozygous TA8, or compound heterozygous *6, TA7 or TA8 This test is not useful for assessment of Crigler-Najjar syndrome.

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance. Drug-drug interactions must be considered when predicting the UGT1A1 phenotype, especially in individuals heterozygous for the TA7 variant. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
UGT1A1 Phenotype: Normal (extensive) metabolizer

An interpretive report will be provided.

Clinical References: 1. Gammal RS, Court MH, Haidar CE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and atazanavir prescribing. Clin Pharmacol Ther. 2016;99(4):363-369. doi:10.1002/cpt.269 2. Clinical Pharmacogenetics Implementation Consortium (CPIC). CPIC Guideline for Atazanavir and UGT1A1. Updated November 2017. Accessed March 27, 2025. Available at https://cpicpgx.org/guidelines/guideline-for-atazanavir-and-ugt1a1/ 3. Innocenti F, Grimsley C, Das S, et al. Haplotype structure of the UDP-glucuronosyltransferase 1A1 promoter in different ethnic groups [published correction appears in Pharmacogenetics. 2003 Mar;13(3):183]. Pharmacogenetics. 2002;12(9):725-733. doi:10.1097/00008571-200212000-00006 4. Shibata T, Minami Y, Mitsuma A, et al. Association between severe toxicity of nilotinib and UGT1A1 polymorphisms in Japanese patients with chronic myelogenous leukemia. Int J Clin Oncol. 2014;19(2):391-396. doi:1 0.1007/s10147-013-0562-5 5. US Food and Drug Administration: Pharmacogenomic Biomarkers in Drug Labeling. FDA; Updated September 23, 2024. Accessed March 28, 2025. Available at www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling 6. UGT Nomenclature Committee: UGT1A and UGT2B haplotypes and SNPs tables. Canada Research Chair in Pharmacogenomics. June 2005. Accessed March 28, 2025. www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/

GALE
64372

Uridine Diphosphate-Galactose 4' Epimerase, Blood

Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 4 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK), uridine diphosphate galactose-4-epimerase (GALE), and galactose mutarotase (GALM). Epimerase deficiency galactosemia can be categorized into 3 types: generalized, peripheral, and intermediate. Generalized epimerase deficiency galactosemia is rare with less than 10 cases described in the literature and results in profoundly decreased enzyme activity in all tissues, whereas peripheral epimerase deficiency galactosemia results in decreased enzyme activity in red and white blood cells, but normal enzyme activity in all other tissues. This is compared to intermediate epimerase deficiency galactosemia, which results in decreased enzyme activity in red and white blood cells and less than 50% of normal enzyme levels in other tissues. Clinically, infants with generalized epimerase deficiency galactosemia develop symptoms such as liver and kidney dysfunction and mild cataracts when on a normal milk diet, while infants with peripheral or intermediate epimerase deficiency galactosemia do not develop any symptoms. Generalized epimerase deficiency galactosemia is treated by a galactose- and lactose-restricted diet, which can improve or prevent the symptoms of kidney and liver dysfunction and mild cataracts. Despite adequate treatment from an early age, individuals with generalized epimerase deficiency galactosemia remain at increased risk for developmental delay and intellectual disability. Unlike patients with classic galactosemia resulting from a GALT deficiency, female patients with generalized epimerase deficiency galactosemia experience normal puberty and are not at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of epimerase deficiency galactosemia in the United States ranges from approximately 1 in 6700 African American infants to 1 in 70,000 infants of European ancestry. Galactose-1-phosphate (Gal1P) accumulates in the erythrocytes of patients with galactosemia due to either GALT or GALE deficiency or in neonates with GALM deficiency. The quantitative measurement of Gal1P (GAL1P / Galactose-1-Phosphate, Erythrocytes) is useful for monitoring compliance with dietary therapy. Gal1P is thought to be the causative factor for development of liver disease in patients with GALT or GALE deficiency. Because of this, patients should maintain low levels and be monitored on a regular basis. Newborn screening varies from state to state and identifies potentially affected individuals by measuring total galactose (galactose and Gal1P) or determining the activity of the GALT enzyme. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are normal, but an infant has an elevated Gal-1-P, then epimerase deficiency galactosemia should be considered. Molecular analysis of the GALE gene is available; order CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies and specify Gene List ID: IEMCP- MGXGL2. For more information see Galactosemia Testing Algorithm.

Useful For: Diagnosis of uridine diphosphate-galactose 4' epimerase deficiency

Interpretation: Results below 3.5 nmol/h/mg of hemoglobin in properly submitted specimens have different causes from carrier status for a disease-causing variant in the GALE gene (typically reduced uridine diphosphate-galactose 4' epimerase [GALE] activity close to the normal activity range) to generalized epimerase deficiency galactosemia due to biallelic disease-causing variants in the GALE gene that markedly reduce GALE activity. Further differentiation requires additional biochemical and molecular genetic analyses as well as correlation with clinical signs and symptoms. Normal results (> or =3.5 nmol/hour/mg of hemoglobin) are not consistent with galactosemia due to GALE deficiency.

Reference Values:
> or =3.5 nmol/h/mg of hemoglobin

Clinical References: 1. Fridovich-Keil J, Bean L, He M, Schroer R. Epimerase deficiency galactosemia. In: Adam MP, Feldman J, Mirzaa GM,, et al. eds. GeneReviews [Internet]. University of Washington, Seattle; 2011. Updated March 11, 2021. Accessed September 12, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK51671/ 2. Walter JH, Fridovich-Keil JL. Galactosemia. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 12, 2024. Available at https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=%20225081023 3. Timson DJ. Type IV galactosemia. Genet Med. 2019;21(6):1283-1285. doi:10.1038/s41436-018-0359-z 4. Wada Y, Kikuchi A, Arai-Ichinoi N, et al. Biallelic GALM pathogenic variants cause a novel type of galactosemia. Genet Med. 2019;21(6):1286-1294. doi:10.1038/s41436-018-0340-x

UPII
610490

Uroplakin II Immunostain, Technical Component Only

Clinical Information: Uroplakin II (UPII) is a cell membrane protein that forms urothelial plaques on the surface of each urothelial cell and is expressed in the cytoplasm. UPII expression is used in the differentiation between urothelial carcinoma from secondary malignancies involving the urinary tract. UPII also aids in the identification of urothelial origin.

Useful For: Characterization of urothelial carcinoma

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Borhan WM, Cimino-Mathews AM, Montgomery EA, Epstein JI: Immunohistochemical differentiation of plasmacytoid urothelial carcinoma from secondary carcinoma involvement of the bladder. Am J Surg Pathol. 2017 Nov;41(11):1570-1575 2. Leivo MZ, Elson PJ, Tacha DE, Delahunt B, Hansel DE. A combination of p40, GATA-3 and uroplakin II shows utility in the diagnosis and prognosis of muscle-invasive urothelial carcinoma. Pathology. 2016;48(6):543-549. doi:10.1016/j.pathol.2016.05.008 3. Tian W, Guner G, Miyamoto H, et al. Utility of uroplakin II expression as a marker of urothelial carcinoma. Hum Pathol. 2015;46(1):58-64 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

UPGDW
31892

Uroporphyrinogen Decarboxylase, Washed Erythrocytes

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Porphyria cutanea tarda (PCT) is the most common porphyria resulting from inhibition of hepatocyte or erythrocyte uroporphyrinogen decarboxylase (UROD; see The Heme Biosynthetic Pathway). PCT is classified into 3 subtypes. The most frequently encountered is type I, a sporadic or acquired form, typically associated with concomitant disease or other precipitating factors. Patients exhibit normal UROD activity in erythrocytes but decreased hepatic activity. This differs from type II PCT in which patients exhibit approximately 50% activity in both erythrocytes and hepatocytes. Type II accounts for about 20% of cases and is inherited in an autosomal dominant manner with low penetrance. Type III is a rare familial form seen in less than 5% of PCT cases. As in type I, patients with type III PCT have normal UROD activity in erythrocytes with decreased hepatic activity. Type III cases are distinguished from type I by the history of other affected family members. Hepatoerythropoietic porphyria (HEP) is a rare autosomal recessive form of porphyria that typically presents in early childhood. Patients have a severe deficiency of UROD, with activity levels 10% of normal in both hepatocytes and erythrocytes. All forms of PCT and HEP result in accumulation of uroporphyrin and intermediary carboxyl porphyrins in skin, subcutaneous tissues, and the liver. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests, with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma.

Useful For: Diagnosis of porphyria cutanea tarda type II and hepatoerythropoietic porphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated, and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
> or =1.00 RU (normal)
0.80-0.99 RU (indeterminate)
<0.80 RU (indicative of PCT type II)
RU = Relative Units

Clinical References: 1. Tortorelli S, Kloke K, Raymond K. Disorders of porphyrin metabolism. In: Dietzen DJ, Bennett MJ, Wong EDD, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:307-324 2. Nuttall KL, Klee GG. Analytes of hemoglobin metabolism-porphyrins, iron, and bilirubin. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 5th ed. WB Saunders Company; 2001:584-607 3. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-Linked sideroblastic anemia and the porphyrias. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed April 22, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225540906&bookid=2709 4. Singal AK. Porphyria cutanea tarda: Recent update. Mol Genet Metab. 2019;128(3):271-281. doi:10.1016/j.ymgme.2019.01.004

UPGD
8599

Uroporphyrinogen Decarboxylase, Whole Blood

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme

defects in the heme biosynthetic pathway. Porphyria cutanea tarda (PCT) is the most common porphyria resulting from inhibition of hepatocyte or erythrocyte uroporphyrinogen decarboxylase (UROD; see The Heme Biosynthetic Pathway). PCT is classified into 3 subtypes. The most frequently encountered is type I, a sporadic or acquired form, typically associated with concomitant disease or other precipitating factors. Patients exhibit normal UROD activity in erythrocytes but decreased hepatic activity. This differs from type II PCT in which patients exhibit approximately 50% activity in both erythrocytes and hepatocytes. Type II accounts for about 20% of cases and is inherited in an autosomal dominant manner with low penetrance. Type III is a rare familial form seen in less than 5% of PCT cases. As in type I, patients with type III PCT have normal UROD activity in erythrocytes with decreased hepatic activity. Type III cases are distinguished from type I by the history of other affected family members. Hepatoerythropoietic porphyria (HEP) is a rare autosomal recessive form of porphyria that typically presents in early childhood. Patients have a severe deficiency of UROD, with activity levels 10% of normal in both hepatocytes and erythrocytes. All forms of PCT and HEP result in accumulation of uroporphyrin and intermediary carboxyl porphyrins in skin, subcutaneous tissues, and the liver. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests, with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma.

Useful For: Preferred test for the confirmation of a diagnosis of porphyria cutanea tarda type II and hepatoerythropoietic porphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated, and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

Reference Values:
> or =1.00 RU (normal)
0.80-0.99 RU (indeterminate)
<0.80 RU (indicative of PCT type II)
RU = Relative Units

Clinical References: 1. Tortorelli S, Kloke K, Raymond K. Disorders of porphyrin metabolism. In: Dietzen DJ, Bennett MJ, Wong EDD, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:307-324 2. Nuttall KL, Klee GG. Analytes of hemoglobin metabolism-porphyrins, iron, and bilirubin. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 5th ed. WB Saunders Company; 2001:584-607 3. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-Linked sideroblastic anemia and the porphyrias. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed April 22, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225540906&bookid=2709 4. Singal AK. Porphyria cutanea tarda: Recent update. Mol Genet Metab. 2019;128(3):271-281. doi:10.1016/j.ymgme.2019.01.004

UPGC
80288

Uroporphyrinogen III Synthase (Co-Synthase), Erythrocytes

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme

defects in the heme biosynthetic pathway. Congenital erythropoietic porphyria (CEP) is an extremely rare, autosomal recessive porphyria that typically presents in early infancy. Also known as Gunther disease, CEP results from a deficiency of uroporphyrinogen III (co-) synthase (UROIIIS). In most cases, the disorder is suggested during the first few days or weeks of life by pink, violet, or brown urinary staining of diapers. Clinical symptoms include hemolytic anemia, hepatosplenomegaly, skin photosensitivity, scarring and blistering, red or brown dental discoloration (erythrodontia), and hypertrichosis (excess body hair). Growth and cognitive developmental delays are commonly observed in individuals with CEP. A few cases of adult-onset CEP have been reported, typically associated with a myelodysplastic syndrome. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. Molecular confirmatory testing is available on a clinical basis; order CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies; specify UROS Gene List ID: IEMCP-8W4945. For more information see Porphyria (Cutaneous) Testing Algorithm or call 800-533-1710 to discuss testing strategies.

Useful For: Diagnosis of congenital erythropoietic porphyria This test is not useful for diagnosis of acute intermittent porphyria (AIP).

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

Reference Values:
> or =75 Relative Units (normal)

For more information see The Heme Biosynthetic Pathway

Clinical References: 1. Tortorelli S, Kloke K, Raymond K: Disorders of porphyrin metabolism. In: Dietzen DJ, Bennett MJ, Wong EDD, eds. Biochemical and Molecular Basis of Pediatric Disease. 4th ed. AACC Press; 2010:307-324 2. Nuttall KL, Klee GG: Analytes of hemoglobin metabolism-porphyrins, iron, and bilirubin. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 5th ed. WB Saunders Company; 2001:584-607 3. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-Linked sideroblastic anemia and the porphyrias. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019. Accessed September 6, 2024. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225540906&bookid=2709 4. Erwin AL, Desnick RJ. Congenital erythropoietic porphyria: Recent advances. Mol Genet Metab. 2019;128(3):288-297. doi:10.1016/j.ymgme.2018.12.008

FUROC 35328 UroVysion for Detection of Bladder Cancer, Urine

Clinical Information: Cystoscopy and urine cytology have been the primary methods for detecting urothelial carcinoma (UC). Unfortunately, urine cytology has relatively poor sensitivity for the detection of recurrent UC. This is problematic because patients who have undetected recurrent tumors may have tumor progression that places them at increased risk of developing metastatic UC. The UroVysion assay is a fluorescence in situ hybridization (FISH) assay for the detection of recurrent UC. The UroVysion probe set contains probes to the centromeres of chromosomes 3, 7, and 17, and a locus-specific probe to the 9p21 band (site of the P16 tumor suppressor gene). The UroVysion assay detects cells with chromosomal abnormalities consistent with a diagnosis of UC. Studies have shown that the assay has higher sensitivity than urine cytology but similar specificity for the detection of recurrent UC. The UroVysion assay also demonstrates higher specificity than the BTA-stat assay for recurrent UC.

Useful For: Monitoring for tumor recurrence in patients with a history of urothelial carcinoma involving the bladder or upper urinary tract Assessing patients with hematuria for urothelial carcinoma

Interpretation: Lower Tract Samples: Abnormal: any specimen satisfying 1 of the following criteria: -Four or more cells with gains of 2 or more chromosomes -Ten or more cells with a gain of a single chromosome or 10 or more cells with tetrasomic signal patterns (ie, 4 copies for each of the 4 probes) -Homozygous deletion of the 9p21 locus in 20% or more of the cells analyzed For cases that are abnormal, the percentage of abnormal cells and type of chromosomal abnormality (ie, polysomy, trisomy, tetrasomy, or homozygous 9p21 deletion) are indicated in the test report. Negative: -Fewer than 4 cells with gains of 2 or more chromosomes -Fewer than 10 cells with gain of a single chromosome or tetrasomy -Less than 20% of cells with homozygous 9p21 deletion Upper Tract Samples: Abnormal: any upper tract specimen satisfying 1 of the following criteria: -Four or more hypertetrasomy cells with at least 5 copies of 2 or more chromosomes -Ten or more cells with a gain of a single chromosome or 10% or more cells with tetrasomic or near-tetrasomic signal patterns (ie, 4 copies for each of the 4 probes) -Homozygous deletion of the 9p21 locus in 20% or more of the cells analyzed Negative: -Fewer than 4 cells with hypertetrasomy with at least 5 copies of 2 or more chromosomes -Fewer than 10% of cells with tetrasomy -Less than 20% of cells with homozygous 9p21 deletion

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Halling KC, Kipp BR. Bladder cancer detection using FISH (UroVysion assay). Adv Anat Pathol. 2008:15(5):279-286. doi:10.1097/PAP.0b013e3181832320 2. Gayed BA, Seideman C, Lotan Y. Cost-effectiveness of fluorescence in situ hybridization in patients with atypical cytology for the detection of urothelial carcinoma. J Urol. 2013;190(4):1181-1186. doi:10.1016/j.juro.2013.03.117

USPF 58104 USP6 (17p13), Aneurysmal Bone Cyst and Nodular Fasciitis, FISH, Tissue

Clinical Information: Aneurysmal bone cyst (ABC) is a multicystic and expansile bone tumor of uncertain line of differentiation. USP6 rearrangements are detectable in approximately 70% of primary ABC and not in other conditions that may simulate ABC histologically, including giant cell tumor of bone, osteosarcoma, osteoblastoma, brown tumor, cherubism, and vascular neoplasms. Nodular fasciitis (NF) is a self-limited mesenchymal lesion of myofibroblastic differentiation. NF's rapid growth, rich cellularity, and brisk mitotic activity may lead to a misdiagnosis of sarcoma. USP6 rearrangements are detectable in 90% of NF but not in other conditions that may simulate NF, including dermatofibroma, cellular fibrous histiocytoma, fibromatosis, and a large variety of sarcomas.

Useful For: Supporting the diagnosis of aneurysmal bone cyst or nodular fasciitis

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for the USP6 FISH probe (positive result). A positive result is consistent with rearrangement of the USP6 gene locus on 17p13 and supports the diagnosis of aneurysmal bone cyst (ABC) or nodular fasciitis (NF). A negative result is consistent with no rearrangement of the USP6 gene locus on 17p13. However, this result does not exclude the diagnosis of ABC or NF. Rearrangement varies in individual tumors and among different cells in the same tumor.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Oliveira AM, Hsi B, Weremowicz S, et al: USP6 (Tre2) fusion oncogenes in aneurysmal bone cyst. Cancer Res 2004 Mar 15;64(6):1920-1923 2. Oliveira AM, Perez-Atayde AR, Inwards CY, et al: USP6 and CDH11 oncogenes identify the neoplastic cell in primary aneurysmal bone cysts and are absent in so-called secondary aneurysmal bone cysts. Am J Pathol 2004 Nov;165(5):1773-1780 3. Fletcher CDM, Unni KK, Mertens F: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. IARC Press, Lyon, France, 2005, pp 48-49 4. Erickson-Johnson MR, Chou MM, Evers BR, et al: Fusion of Non-Muscle Myosin MYH9 to USP6 Oncogene in Nodular Fasciitis, USCAP Abstract #39, 2011

USTEK
609476

Ustekinumab Quantitation with Antibodies, Serum

Clinical Information: Ustekinumab (UTK) is a fully human IgG1 kappa monoclonal antibody (1) that binds with high affinity to the p40 subunit of human interleukin (IL)12 and IL23 and has been approved for the treatment of patients with moderate to severe Crohn disease (CD), moderate to severe ulcerative colitis (UC), psoriatic arthritis, and plaque psoriasis. The drug prevents IL12 and IL23 bioactivity by binding and neutralizing the shared p40 subunit, preventing interaction with the cell surface receptor protein IL12Rbeta1. Through this mechanism of action, UTK effectively neutralizes IL12 and IL23, proteins that are thought to be associated with gastrointestinal inflammation in CD and UC. In the setting of the inflammatory bowel diseases (IBD), CD and UC, the treatment regimen is started with a single weight-based loading dose of the t-mab administered intravenously (IV), and a maintenance regimen with standard (non-weight based) subcutaneous administration of ustekinumab 8 weeks after induction dose, and every 8 weeks thereafter. There is very little data supporting proactive therapeutic drug monitoring for ustekinumab. This test is most useful in the evaluation of loss of response to therapy. A gradual decrease in efficacy over time following an initial response to biologics is common. In many cases, antibodies generated to the biologic are responsible for treatment failure, as they bind to the drug creating an immunocomplex and clear the drug faster from circulation. For IBD, measurements in nonresponders are indicated at post-induction (week 8) and concentrations of ustekinumab associated with favorable outcomes are greater than 3.5 mcg/mL. In addition, for measurements during maintenance stages of therapy, ustekinumab concentrations greater than or equal to 1 mcg/mL are associated with clinical response and clinical remission. At maintenance stages, ustekinumab concentrations greater than or equal to 4.5 mcg/mL are associated with mucosal healing. In clinical trials, 6% to 12.4% of patients using ustekinumab for psoriasis or psoriatic arthritis developed antibodies-to-ustekinumab (ATU) over time. For IBD, between 2.9% and 4.6% of patients developed ATU when treated with ustekinumab for 1 year.(1) Therefore, it is important to monitor trough concentrations of serum UTK to correlate drug levels with loss of response to therapy. ATU may increase drug clearance in treated patients or neutralize the drug effect, thereby potentially contributing to the loss of response. ATU could also cause adverse events, such as serum sickness and hypersensitivity reactions. Currently, ustekinumab quantitation is performed in conjunction with immunogenicity assessment for ATU.

Useful For: Evaluation of loss of response to therapy Quantification of ustekinumab in human serum Trough level quantitation for evaluation of patients treated with ustekinumab Detection of antibodies to ustekinumab in human serum

Interpretation: Antibodies to ustekinumab (ATU) absent ATU present Ustekinumab quantification <1.0 mcg/mL For nonresponders: Insufficient ustekinumab is present. In the absence of ATU, consider optimizing therapy by increasing the dose or shortening the administration intervals, or by adding an immunomodulator to the therapeutic regimen. For nonresponders: Insufficient ustekinumab is present. Antibodies-to-ustekinumab detected can contribute to faster clearance of ustekinumab and treatment failure. Clinical evaluation is recommended. Ustekinumab quantification > or =1.0 mcg/mL For nonresponders: If the sample was collected at trough ie, immediately before the next infusion, the results could suggest a mechanistic failure of ustekinumab. The provider may consider switching therapeutic regimen outside of the drug class. For nonresponders: If the sample was collected at trough

ie, immediately before the next infusion, the results could suggest a mechanistic failure of ustekinumab. The provider may consider switching therapeutic regimen outside of the drug class.

Reference Values:
USTEKINUMAB QN, S:
Limit of quantitation is 0.3 mcg/mL

In inflammatory bowel disease, at post-induction measurement (week 8), concentrations above 3.5 mcg/mL are associated with good outcomes.

For maintenance stages:
Concentrations > or =1.0 mcg/mL are associated with clinical response and clinical remission
Concentrations > or =4.5 mcg/mL are associated with mucosal healing

USTEKINUMAB AB, S:
Limit of quantitation is 10 AU/mL
Absent: <10 AU/mL
Present: > or =10 AU/mL

Clinical References: 1. Stelara (ustekinumab). Package insert: Prescribing information. Janssen Pharmaceuticals; revised 03/2020 2. Papamichael K, Cheifetz AS, Melmed GY, et al. Appropriate therapeutic drug monitoring of biologic agents for patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2019;17(9):1655-1668.e3

USNU
82388

Ustilago nuda, Mold Grain Rust, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to Ustilago nuda, Mold Grain Rust, IgE Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FNSVG
75140

Vaginitis (VG), NuSwab

Clinical Information: This test is intended to be used as an aid to the diagnosis of bacterial vaginosis (BV) in women with a clinical presentation consistent with this disorder. The BV test utilizes semiquantitative PCR analysis of the three most predictive marker organisms (Atopobium vaginae, BVAB-2, and Megasphaera-1) to generate a total score that correlates directly with the presence or absence of BV. In this test system, samples with a score of 0 to 1 are considered negative for BV, samples with a score of 3 to 6 are positive for BV, and samples with a score of 2 are indeterminate for BV.

Useful For: Used to detect the presence of Candida albicans and Candida glabrata DNA in vaginal samples as an aid to the diagnosis of vulvovaginal candidiasis in symptomatic women. Also used in the diagnosis of Trichomonas vaginalis infections.

Reference Values:
Candida albicans, NAA: Negative
Candida glabrata, NAA: Negative
Trich vag by NAA: Negative

VALPG
37067

Valproic Acid, Free and Total, Serum

Clinical Information: Valproic acid (valproate, Depakote, or Depakene) is an effective medication for absence seizures, generalized tonic-clonic seizures, and partial seizures, when administered alone or in conjunction with other antiepileptic agents. The valproic acid that circulates in blood is 85% to 90% protein-bound under normal circumstances. In uremia or during concomitant therapy with other drugs that are highly protein-bound (such as phenytoin), valproic acid is displaced from protein, resulting in a higher free fraction of the drug circulating in blood. Since neurologic activity and toxicity of valproic acid are directly related to the unbound fraction of drug, adjustment of dosage based on knowledge of the free valproic acid concentration may be useful in the following: concomitant use of highly protein-bound drugs (usually >80% bound), hypoalbuminemia, pregnancy, kidney or liver failure, and in older

adults. In these situations, the total valproic acid concentration in the blood may underestimate the disproportionately higher free valproic acid fraction.

Useful For: Monitoring both total and free valproic acid levels in therapy Assessing compliance Evaluating potential toxicity

Interpretation: The generally acceptable range for total valproic acid used as a reference to guide therapy is 50 to 125 mcg/mL. The corresponding range of free valproic acid concentration for clinical reference is 5 to 25 mcg/mL. Low free valproic acid concentration relative to these ranges may suggest inadequate dosing, whereas a high free valproic acid concentration may be associated with toxic effects. Because the concentration of valproic acid fluctuates considerably depending on the time from last dose, interpretation of the clinical significance of the valproic acid concentration must take into consideration the timing of the blood specimen. For this reason, 2 collections are sometimes made to assess the trough and peak concentrations.

Reference Values:

VALPROIC ACID, TOTAL
Therapeutic: 50 (trough)-125 (peak) mcg/mL
Critical value: > or =151 mcg/mL

VALPROIC ACID, FREE
Therapeutic: 5-25 mcg/mL
Critical value: >30 mcg/mL

Clinical References: 1. Cloyd JC, Fischer JH, Kriel RL, Kraus DM: Valproic acid pharmacokinetics in children: Effects of age and antiepileptic drugs on protein binding and intrinsic clearance. Clin Pharmacol Ther. 1993;53:22-29 2. Wagner ML, Graves NM, Leppik IE, et al: The effect of felbamate on valproic acid disposition. Clin Pharmacol Ther. 1994;56:494-502 3. Dasgupta A, Volk A: Displacement of valproic acid and carbamazepine from protein binding in normal and uremic sera by tolmetin, ibuprofen, and naproxen: presence of inhibitor in uremic serum that blocks valproic acid-naproxen interactions. Ther Drug Monit. 1996;18:284-287 4. Moyer TP: Therapeutic drug monitoring. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 4th ed. WB Saunders Company; 2005:1237-1285 5. Patsalos PN, Spencer EP, Berry DJ: Therapeutic drug monitoring of antiepileptic drugs in epilepsy: A 2018 update. Ther Drug Monit. 2018 Oct;40(5):526-548. doi: 10.1097/FTD.0000000000000546

VALPF
37068

Valproic Acid, Free, Serum

Clinical Information: Valproate (valproate, Depakote, or Depakene) is an effective medication for absence seizures, generalized tonic-clonic seizures, and partial seizures, when administered alone or in conjunction with other antiepileptic agents. The valproic acid that circulates in blood is 85% to 90% protein-bound under normal circumstances. In uremia or during concomitant therapy with other drugs that are highly protein-bound (such as phenytoin), valproic acid is displaced from protein, resulting in a higher free fraction of the drug circulating in blood. Since neurologic activity and toxicity of valproic acid are directly related to the unbound fraction of drug, adjustment of dosage based on knowledge of the free valproic acid concentration may be useful in the following: concomitant use of highly protein-bound drugs (usually >80% bound), hypoalbuminemia, pregnancy, kidney or liver failure, and in older adults. In these situations, the total valproic acid concentration in the blood may underestimate the disproportionately higher free valproic acid fraction.

Useful For: Monitoring free valproic acid in therapy Assessing compliance Evaluating potential toxicity

Interpretation: The generally acceptable range for total valproic acid used as a reference to guide therapy is 50 to 125 mcg/mL. The corresponding range of free valproic acid concentration for clinical reference is 5 to 25 mcg/mL. Low free valproic acid concentration relative to these ranges may suggest inadequate dosing, whereas a high free valproic acid concentration may be associated with toxic effects. Because the concentration of valproic acid fluctuates considerably depending on the time from last dose, interpretation of the clinical significance of the valproic acid concentration must take into consideration the timing of the blood specimen. For this reason, 2 collections are sometimes made to assess the trough and peak concentrations.

Reference Values:
Therapeutic: 5-25 mcg/mL
Critical value: >30 mcg/mL

Clinical References: 1. Cloyd JC, Fischer JH, Kriel RL, Kraus DM: Valproic acid pharmacokinetics in children: Effects of age and antiepileptic drugs on protein binding and intrinsic clearance. Clin Pharmacol Ther. 1993;53:22-29 2. Wagner ML, Graves NM, Leppik IE, et al: The effect of felbamate on valproic acid disposition. Clin Pharmacol Ther. 1994;56:494-502 3. Dasgupta A, Volk A: Displacement of valproic acid and carbamazepine from protein binding in normal and uremic sera by tolmetin, ibuprofen, and naproxen: presence of inhibitor in uremic serum that blocks valproic acid-naproxen interactions. Ther Drug Monit. 1996;18:284-287 4. Patsalos PN, Spencer EP, Berry DJ: Therapeutic drug monitoring of antiepileptic drugs in epilepsy: A 2018 update. Ther Drug Monit. 2018 Oct;40(5):526-548. doi: 10.1097/FTD.0000000000000546

VALPA
37066

Valproic Acid, Total, Serum

Clinical Information: Valproic acid (valproate, Depakote, or Depakene) is an effective medication for absence seizures, generalized tonic-clonic seizures, and partial seizures, when administered alone or in conjunction with other antiepileptic agents. Valproic acid is initially dosed at 15 mg/kg/day, with dosage increases over time to a maximum of 60 mg/kg/day. The volume of distribution of valproic acid is 0.2 L/kg, and its half-life is 10 to 14 hours in adults but is shorter in children. It is approximately 90% protein bound. Hepatic failure and a Reyes-like syndrome associated with administration of valproic acid at therapeutic levels have been reported. Careful monitoring of liver function during the first 6 months of therapy is required. Major side effects such as central nervous system depression, thrombocytopenia, and hepatic dysfunction are likely to be experienced if the peak level is regularly above 125 mcg/mL. Analysis of free valproic acid levels may be useful in delineating the cause of toxicity when the total concentration is not excessive. Valproic acid exhibits substantial effects on the pharmacology of phenytoin, whereas phenytoin exhibits only a limited effect on valproic acid. This is due to the relative abundance of the 2 drugs in the body. Valproic acid is present at a 2- to 3-fold mass excess and a 5- to 7-fold molar excess.

Useful For: Monitoring total valproic acid in therapy Assessing compliance Evaluating potential toxicity

Interpretation: The generally acceptable range for total valproic acid used as a reference to guide therapy is 50 to 125 mcg/mL. Peak levels should not exceed 125 mcg/mL. Because the concentration of valproic acid fluctuates considerably depending on the time from last dose, interpretation of the clinical significance of the valproic acid concentration must take into consideration the timing of the blood specimen. For this reason, 2 collections are sometimes made to assess the trough and peak concentrations.

Reference Values:
Therapeutic: 50 (trough)-125 (peak) mcg/mL

Critical value: > or =151 mcg/mL

Clinical References: 1. Cotariu D, Zaidman JL: Valproic acid and the liver. Clin Chem. 1988 May;34(5):890-897 2. Langman LJ, Bechtel LK, Meier BM, Holstege C: Clinical toxicology. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:832-887 3. Milone MC, Shaw LM: Therapeutic Drug Monitoring. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics. 8th ed. Saunders; 2019:549 4. Patsalos PN, Zugman M, Lake C, James A, Ratnaraj N, Sander JW. Serum protein binding of 25 antiepileptic drugs in a routine clinical setting: a comparison of free non-protein-bound concentrations. Epilepsia. 2017 Jul;58(7):1234-1243. doi: 10.1111/epi.13802

VANPA 37069 Vancomycin, Peak, Serum

Clinical Information: Vancomycin is an antibiotic used to treat infections caused by gram-positive organisms that are resistant to beta-lactam antibiotics, such as methicillin-resistant staphylococci (MRSA), Streptococcus viridans group, penicillin/cephalosporin-resistant Streptococcus pneumoniae, and penicillin/ampicillin-resistant Enterococcus species. The oral formulation, which is not absorbed, is used in the treatment of pseudomembranous colitis caused by Clostridium difficile. Vancomycin is also used when patients are intolerant or allergic to beta-lactam antibiotics. Vancomycin has been associated with nephrotoxicity and ototoxicity, although it appears that many of these reports reflected impurities in early formulations. Monitoring of vancomycin-related nephrotoxicity is recommended only for patients with reduced renal function, those receiving aggressive or prolonged vancomycin regimens, or those at high risk including patients comedicated with other nephrotoxic agents. Trough concentrations are recommended for therapeutic monitoring of vancomycin, preferably acquired at steady-state (just before fourth dose). To avoid development of resistance, vancomycin trough levels should remain above 10.0 mcg/mL. Complicated infections require higher target levels, typically 15.0 to 20.0 mcg/mL. Peak concentrations do not correlate well to efficacy or nephrotoxicity, but may be useful for pharmacokinetic analyses (eg, area under the curve: AUC studies) or for select patients.

Useful For: Monitoring peak levels in selected patients receiving vancomycin therapy

Interpretation: Typical peak levels are between 20.0 and 45.0 mcg/mL. Peak levels are not recommended for monitoring, except in select circumstances such as when performing pharmacokinetic analyses (eg, area under the curve: AUC determination). These levels are consistent with Mayo Clinic Antimicrobial Therapy Guidelines.

Reference Values:
Therapeutic: 20.0-45.0 mcg/mL

Clinical References: 1. Rybak M, Lomaestro B, Rotschafer JC, et al: Therapeutic drug monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2009;66:82-98 2. Estes L, Wilson J: Mayo Clinic Antimicrobial Therapy Quick Guide. Mayo Clinic. 2005. Updated July 29, 2020

VANRA 37071 Vancomycin, Random, Serum

Clinical Information: Vancomycin is an antibiotic used to treat infections caused by gram-positive organisms that are resistant to beta-lactam antibiotics, such as methicillin-resistant staphylococci (MRSA), Streptococcus viridans group, penicillin/cephalosporin-resistant Streptococcus pneumoniae, and penicillin/ampicillin-resistant Enterococcus species. The oral formulation, which is not absorbed, is used

in the treatment of pseudomembranous colitis caused by Clostridium difficile. Vancomycin is also used when patients are intolerant or allergic to beta-lactam antibiotics. Vancomycin has been associated with nephrotoxicity and ototoxicity, although it appears that many of these reports reflected impurities in early formulations. Monitoring of vancomycin-related nephrotoxicity is recommended only for patients with reduced renal function, those receiving aggressive or prolonged vancomycin regimens, or those at high risk including patients comedicated with other nephrotoxic agents. Trough concentrations are recommended for therapeutic monitoring of vancomycin, preferably acquired at steady state (just before fourth dose). To avoid development of resistance, vancomycin trough levels should remain above 10.0 mcg/mL. Complicated infections require higher target levels, typically 15.0 to 20.0 mcg/mL. Peak concentrations do not correlate well to efficacy or nephrotoxicity, but may be useful for pharmacokinetic studies or for select patients. Random levels may be ordered when attempting to determine when to dose vancomycin in patients with renal impairment or those undergoing dialysis.

Useful For: Monitoring adequacy of drug concentration during vancomycin therapy whenever a specimen is submitted or collected without collection timing information

Interpretation: Trough levels correlate better with efficacy than peak levels, with target trough levels of 10.0 and 20.0 mcg/mL, depending on the type of infection. Peak levels are not recommended for monitoring, except in select circumstances such as when performing pharmacokinetic analyses (eg, area under the curve: AUC determinations). Typical peak levels are between 20.0 and 45.0 mcg/mL. These levels are consistent with Mayo Clinic Antimicrobial Therapy Guidelines.

Reference Values:
VANCOMYCIN, TROUGH
Therapeutic: 10.0-20.0 mcg/mL

VANCOMYCIN, PEAK
Therapeutic: 20.0-45.0 mcg/mL

Clinical References: 1. Rybak M, Lomaestro B, Rotschafer JC, et al: Therapeutic drug monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2009;66:82-98 2. Estes L, Wilson J: Mayo Clinic Antimicrobial Therapy Quick Guide. Mayo Clinic. 2005. Updated July 29, 2020

VANTA
37070

Vancomycin, Trough, Serum

Clinical Information: Vancomycin is an antibiotic used to treat infections caused by gram-positive organisms that are resistant to beta-lactam antibiotics, such as methicillin-resistant staphylococci (MRSA), Streptococcus viridans group, penicillin/cephalosporin-resistant Streptococcus pneumoniae, and penicillin/ampicillin-resistant Enterococcus species. The oral formulation, which is not absorbed, is used in the treatment of pseudomembranous colitis caused by Clostridium difficile. Vancomycin is also used when patients are intolerant or allergic to beta-lactam antibiotics. Vancomycin has been associated with nephrotoxicity and ototoxicity, although it appears that many of these reports reflected impurities in early formulations. Monitoring of vancomycin-related nephrotoxicity is recommended only for patients with reduced renal function, those receiving aggressive or prolonged vancomycin regimens, or those at high-risk including patients comedicated with other nephrotoxic agents. Trough concentrations are recommended for therapeutic monitoring of vancomycin, preferably acquired at steady-state (just before fourth dose). To avoid development of resistance, vancomycin trough levels should remain above 10.0 mcg/mL. Complicated infections require higher target levels, typically 15.0 to 20.0 mcg/mL. Peak concentrations do not correlate well to efficacy or nephrotoxicity, but may be useful for pharmacokinetic analyses (eg, area under the curve: AUC studies) or for select patients.

Useful For: Preferred test for monitoring vancomycin therapy Monitoring trough concentrations drawn at steady-state in selected patients receiving vancomycin therapy

Interpretation: Trough levels correlate better with efficacy than peak levels, with target trough levels of 10.0 to 20.0 mcg/mL, depending on the type of infection. These levels are consistent with Mayo Clinic Antimicrobial Therapy Guidelines.

Reference Values:
Therapeutic: 10.0-20.0 mcg/mL

Clinical References: 1. Rybak M, Lomaestro B, Rotschafer JC, et al: Therapeutic drug monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2009;66:82-98 2. Estes L, Wilson J: Mayo Clinic Antimicrobial Therapy Quick Guide. Mayo Clinic. 2005. Updated July 29, 2020

VRERP 84406 Vancomycin-Resistant Enterococcus, Molecular Detection, PCR, Varies

Clinical Information: Vancomycin-resistant enterococci (VRE) are major nosocomial disease-causing bacteria. Patients who are particularly vulnerable to fatal disease from VRE include those with hematologic malignancies and liver transplants. Nosocomial spread of VRE occurs as the result of fecal carriage. Risks for both colonization and infection include prolonged hospitalization, intensive care unit stay, transplantation, hematologic malignancies, and prolonged exposure to antibiotics. The Centers for Disease Control and Prevention provides recommendations to prevent the spread of VRE in institutional settings. These recommendations include isolation of patients experiencing active VRE infection, screening of patients by perianal swab or fecal testing to identify carriers of VRE, and subsequent isolation or cohorting of VRE carriers. Identification and isolation of VRE carriers has been shown to be cost-effective. In Enterococcus faecalis or Enterococcus faecium, vancomycin resistance is usually associated with the presence of vanA or vanB. The presence of these genes is detected by a molecular method in this assay.

Useful For: Identifying carriers of vancomycin-resistant enterococci

Interpretation: Positive test results indicate the presence of either vanA or vanB, which confer vancomycin resistance in Enterococcus faecalis and Enterococcus faecium (and occasionally other organisms). Patients with a positive test result should be placed in isolation or with other vancomycin-resistant enterococci (VRE) carriers according to the institution's infection control practices. A negative result indicates the absence of detectable vanA or vanB DNA but does not rule-out carrier status and may occur due to inhibition of polymerase chain reaction (PCR), sequence variability underlying primers or probes, or the presence of VRE DNA in quantities less than the limit of detection of the assay. In the rare event that PCR testing appears to be negative but there is evidence of PCR inhibition, the result will read "PCR inhibition present." In such cases, a new specimen should be submitted for repeat testing.

Reference Values:
Negative

Clinical References:

FVANG 57669 Vanilla IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

VANIL
82621

Vanilla, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to vanilla Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

VH
9254

Vanillylmandelic Acid and Homovanillic Acid, Random, Urine

Clinical Information: Elevated values of homovanillic acid (HVA), vanillylmandelic acid (VMA), and other catecholamine metabolites (eg, dopamine) may be suggestive of the presence of a catecholamine-secreting tumor (eg, neuroblastoma, pheochromocytoma, or other neural crest tumors). HVA and VMA levels may also be useful in monitoring patients who have been treated as a result of the above-mentioned tumors. HVA levels may also be altered in disorders of catecholamine metabolism: monamine oxidase-A deficiency can cause decreased urinary HVA values, while a deficiency of dopamine beta-hydrolase (the enzyme that converts dopamine to norepinephrine) can cause elevated urinary HVA values.

Useful For: Preferred first test for screening for catecholamine-secreting tumors in a random urine specimen when requesting both homovanillic acid and vanillylmandelic acid Supporting a diagnosis of neuroblastoma Monitoring patients with a treated neuroblastoma

Interpretation: Homovanillic acid (HVA) and vanillylmandelic acid (VMA) concentrations are elevated in more than 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated HVA and VMA values are suggestive of a pheochromocytoma, but they are not diagnostic.

Reference Values:

Vanillylmandelic acid
<1 year: <25.0 mg/g creatinine
1 year: <22.5 mg/g creatinine
2-4 years: <16.0 mg/g creatinine
5-9 years: <12.0 mg/g creatinine
10-14 years: <8.0 mg/g creatinine
> or =15 years: <7.0 mg/g creatinine

Homovanillic acid
<1 year: <35.0 mg/g creatinine
1 year: <30.0 mg/g creatinine
2-4 years: <25.0 mg/g creatinine
5-9 years: <15.0 mg/g creatinine
10-14 years: <9.0 mg/g creatinine
> or =15 years: <8.0 mg/g creatinine

Clinical References: 1. Eisenhofer G. Monoamine-producing tumors. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:765 2. Ormazabal A, Molero-Luis M, Garcia-Cazorla A, Artuch R. Biomarkers for the study of catecholamine and serotonin genetic diseases. In: Garg U, Smith LD, eds. Biomarkers in Inborn Errors of Metabolism: Clinical Aspects and Laboratory Determination. Elsevier; 2017:301-329 3. Strenger V, Kerbl R, Dornbusch HJ, et al. Diagnostic and prognostic impact of urinary catecholamines in neuroblastoma patients. Pediatr Blood Cancer. 2007;48(5):504-509 4. Barco S, Gennai I, Reggiardo G, et al. Urinary homovanillic and vanillylmandelic acid in the diagnosis of neuroblastoma: report from the Italian Cooperative Group for Neuroblastoma. Clin Biochem. 2014;47(9):848-852 5. Matthay KK, Maris JM, Schleiermacher G, et al. Neuroblastoma. Nat Rev Dis Primers. 2016;2:16078. doi:10.1038/nrdp.2016.78

VMA
9454

Vanillylmandelic Acid, 24 Hour, Urine

Clinical Information: Vanillylmandelic acid (VMA) and other catecholamine metabolites (homovanillic acid [HVA] and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). VMA and HVA levels may also be useful in monitoring patients who have been treated as a result of one of the above-mentioned tumors.

Useful For: Screening children for catecholamine-secreting tumors using a 24-hour urine collection when requesting testing for vanillylmandelic acid only Supporting a diagnosis of neuroblastoma Monitoring patients with a treated neuroblastoma

Interpretation: Vanillylmandelic acid and/or homovanillic acid concentrations are elevated in most patients (more than 90%) with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated values are suggestive of a pheochromocytoma, but they are not diagnostic.

Reference Values:
<1 year: <25.0 mg/g creatinine
1 year: <22.5 mg/g creatinine
2-4 years: <16.0 mg/g creatinine
5-9 years: <12.0 mg/g creatinine
10-14 years: <8.0 mg/g creatinine
> or =15 years (adults): <8.0 mg/24 hours

Clinical References: 1. Eisenhofer G. Monoamine-producing tumors. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023: 765-765.e54 2. Hyland K. Disorders of neurotransmitter metabolism. In: Blau N, Duran M, Blaskovics ME, Gibson KM, eds. Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases. Springer; 2003:107-122 3. Ormazabal A. Molero-Luis M. Garcia-Cazorla A. Artuch R. Biomarkers for the study of catecholamine and serotonin genetic diseases. In: Garg U, Smith LD, eds. Biomarkers in Inborn Errors of Metabolism: Clinical Aspects and Laboratory Determination. Elsevier; 2017:301-329 4. Strenger V, Kerbl R, Dornbusch HJ, et al. Diagnostic and prognostic impact of urinary catecholamines in neuroblastoma patients. Pediatr Blood Cancer. 2007;48(5):504-509 5. Barco S, Gennai I, Reggiardo G, et al. Urinary homovanillic and vanillylmandelic acid in the diagnosis of neuroblastoma: report from the Italian Cooperative Group for Neuroblastoma. Clin Biochem. 2014;47(9):848-852 6. Matthay KK, Maris JM, Schleiermacher G, et al. Neuroblastoma. Nat Rev Dis Primers. 2016;2:16078. doi:10.1038/nrdp.2016.78

VMAR
60274

Vanillylmandelic Acid, Random, Urine

Clinical Information: Vanillylmandelic acid (VMA) and other catecholamine metabolites (homovanillic acid [HVA] and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). VMA and HVA levels may also be useful in monitoring patients who have been treated as a result of one of the above-mentioned tumors.

Useful For: Screening children for catecholamine-secreting tumors using a random urine collection when requesting vanillylmandelic acid only Supporting a diagnosis of neuroblastoma Monitoring patients with a treated neuroblastoma

Interpretation: Vanillylmandelic acid (VMA) and/or homovanillic acid concentrations are elevated in more than 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated VMA values are suggestive of a pheochromocytoma, but they are not diagnostic.

Reference Values:
<1 year: <25.0 mg/g creatinine
1 year: <22.5 mg/g creatinine
2-4 years: <16.0 mg/g creatinine
5-9 years: <12.0 mg/g creatinine
10-14 years: <8.0 mg/g creatinine
> or =15 years (adults): <7.0 mg/g creatinine

Clinical References: 1. Eisenhofer G. Monoamine-producing tumors. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:765 2. Hyland K. Disorders of neurotransmitter metabolism. In: Blau N, Duran M, Blaskovics ME, Gibson KM, eds. Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases. Springer; 2003:107-122 3. Ormazabal A. Molero-Luis M. Garcia-Cazorla A. Artuch R. Biomarkers for the study of catecholamine and serotonin genetic diseases. In: Garg U, Smith LD, eds. Biomarkers in Inborn Errors of Metabolism: Clinical Aspects and Laboratory Determination. Elsevier; 2017:301-329 4. Strenger V, Kerbl R, Dornbusch HJ, et al. Diagnostic and prognostic impact of urinary catecholamines in neuroblastoma patients. Pediatr Blood Cancer. 2007;48(5):504-509 5. Barco S, Gennai I, Reggiardo G, et al. Urinary homovanillic and vanillylmandelic acid in the diagnosis of neuroblastoma: report from the Italian Cooperative Group for Neuroblastoma. Clin Biochem. 2014;47(9):848-852 6. Matthay KK, Maris JM, Schleiermacher G, et al. Neuroblastoma. Nat Rev Dis Primers. 2016;2:16078. doi:10.1038/nrdp.2016.78

VZV
70581

Varicella Zoster Virus (VZV) Immunostain, Technical Component Only

Clinical Information: Varicella zoster virus (VZV) is a member of the herpes virus family and is the etiological agent for varicella (chicken pox) and herpes zoster (shingles). The immunostain for VZV uses a cocktail of antibodies that recognizes several glycoproteins, the nucleocapsid protein, and the immediate early protein of the virus.

Useful For: Aids in the identification of varicella zoster virus infection

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Arvin AM: Varicella zoster virus. In: Knipe DM. Howley PM, eds. Fields Virology. Vol 2. 4th ed. Williams and Wilkins; 2001: 2731-2767 2. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus [published correction appears in N Engl J Med 2000 Apr 6;342(14):1063]. N Engl J Med. 2000;342(9):635-645. doi:10.1056/NEJM200003023420906 3. Nikkels AF, Debrus S, Sadzot-Delvaux C, et al. Comparative immunohistochemical study of herpes simplex and varicella-zoster infections. Virchows Arch A Pathol Anat Histopathol. 1993;422(2):121-126 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

VZPG
34944

Varicella-Zoster Antibody, IgG, Serum

Clinical Information: Varicella-zoster virus (VZV), a herpes virus, causes 2 distinct exanthematous (rash-associated) diseases: chickenpox (varicella) and herpes zoster (shingles). Chickenpox is a highly contagious, though typically benign, disease, usually contracted during childhood. Chickenpox is characterized by a dermal vesiculopustular rash that develops in successive crops approximately 10 to 21 days following exposure.(1) Although primary infection with VZV results in immunity and protection from subsequent infection, VZV remains latent within sensory dorsal root ganglia and upon reactivation, manifests as herpes zoster or shingles. During reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash, usually limited to a single dermatome. Shingles is an extremely painful condition typically occurring in older nonimmune adults or those with waning immunity to VZV and in patients with impaired cellular immunity.(2) Individuals at risk for severe complications following primary VZV infection include women who are pregnant, in whom the virus may spread through the placenta to the fetus, causing congenital disease in the infant. Additionally, immunosuppressed patients are at risk for developing severe VZV-related complications, which include cutaneous disseminated disease and visceral organ involvement.(2,3) Serologic screening for IgG-class antibodies to VZV aids in identifying nonimmune individuals.

Useful For: Determination of immune status of individuals to the varicella-zoster virus (VZV) Documentation of previous infection with VZV in an individual without a previous record of immunization to VZV

Interpretation: The reported antibody index (AI) value is for reference only. This is a qualitative test, and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cutoff for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. Positive: AI value of 1.1 or higher: The presence of detectable IgG-class antibodies indicates prior exposure to the varicella-zoster virus (VZV) through infection or immunization. Individuals testing positive are considered immune to varicella-zoster. Equivocal: AI 0.9-1.0 Submit an additional specimen for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: AI of 0.8 or lower The absence of detectable IgG-class antibodies suggests no prior exposure to the VZV or the lack of a specific immune response to immunization.

Reference Values:
Vaccinated: Positive (> or =1.1 antibody index [AI])
Unvaccinated: Negative (< or =0.8 AI)
Reference values apply to all ages.

Clinical References: 1. Yankowitz J, Grose C. Congenital infections. In: Storch GA, ed. Essentials of diagnostic virology. Churchill Livingstone; 2000:187-201 2. Gnann JW, Whitley RJ. Clinical practice. Herpes zoster. N Engl J Med. 2002;347(5):340-346 3. Cvjetkovic D, Jovanovic J, Hrnjakovic-Cvjetkovic I, Brkic S, Bogdanovic M. Reaktivacija herpes zoster infekcije varicela-zoster virusom [Reactivation of herpes zoster infection by varicella-zoster virus]. Med Pregl. 1999;52(3-5):125-128 4. Whitely RJ. Chickenpox and Herpes Zoster (Varicella-Zoster virus). In Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020: 1849-1856

VZGM
61856

Varicella-Zoster Antibody, IgM and IgG, Serum

Clinical Information: Varicella-zoster virus (VZV), a herpesvirus, causes 2 distinct exanthematous (rash-associated) diseases: chickenpox (varicella) and shingles (herpes zoster). Chickenpox is a highly contagious, though typically benign, disease, usually contracted during childhood. Chickenpox is

characterized by a dermal vesiculopustular rash that develops in successive crops approximately 10 to 21 days following exposure.(1) Although primary infection with VZV results in immunity and protection from subsequent infection, VZV remains latent within sensory dorsal root ganglia and upon reactivation, manifests as herpes zoster or shingles. During reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash, usually limited to a single dermatome. Shingles is an extremely painful condition typically occurring in older nonimmune adults or those with waning immunity to VZV and in patients with impaired cellular immunity.(2) Individuals at risk for severe complications following primary VZV infection include women who are pregnant, in whom the virus may spread through the placenta to the fetus causing congenital disease in the infant. Additionally, immunosuppressed patients are at risk for developing severe VZV-related complications, which include cutaneous disseminated disease and visceral organ involvement.(2,3) Serologic screening for IgG-class antibodies to VZV will aid in identifying nonimmune individuals. The presence of IgM-class antibodies to VZV is suggestive of acute or recent infection however results should be correlated with clinical presentation.

Useful For: Laboratory diagnosis of acute and recent infection with varicella-zoster virus (VZV) Determination of immune status of individuals to the VZV Documentation of previous infection with VZV in an individual without a previous record of immunization to VZV

Interpretation: A positive IgG result coupled with a positive IgM result suggests recent infection with varicella-zoster virus (VZV). This result should not be used alone to diagnose VZV infection and should be interpreted in the context of clinical presentation. A positive IgG result coupled with a negative IgM result indicates previous vaccination to or infection with VZV. These individuals are considered to have protective immunity to reinfection. A negative IgG result coupled with a negative IgM result indicates the absence of prior exposure to VZV and nonimmunity. However, a negative result does not rule-out VZV infection. The specimen may have been drawn before the appearance of detectable antibodies. Negative results in suspected early VZV infections should be followed by testing a new serum specimen in 2 to 3 weeks. Equivocal results should be followed up with testing of a new serum specimen within 10 to 14 days.

Reference Values:

IgM
Negative
Reference values apply to all ages.

IgG
Vaccinated: positive (> or =1.1 antibody index [AI])
Unvaccinated: negative (< or =0.8 AI)
Reference values apply to all ages.

Clinical References: 1. Yankowitz J, Grose C: Congenital infections. In: Storch GA, ed. Essentials of diagnostic virology. Churchill Livingstone; 2000:187-201 2. Gnann JW, Whitley RJ. Herpes Zoster. N Engl J Med. 2002;347(5):340-346 3. Cvjetkovic D, Jovanovic J, Hrnjakovic-Cvjetkovic I, Brkic S, Bogdanovic M. Reaktivacija herpes zoster infekcije varicela-zoster virusom [Reactivation of herpes zoster infection by varicella-zoster virus]. Med Pregl. 1999;52(3-5):125-128 4. Whitely RJ: Chickenpox and Herpes Zoster (Varicella-Zoster virus). In Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020: 1849-1856

VZM
80964

Varicella-Zoster Virus (VZV) Antibody, IgM, Serum

Clinical Information: Varicella-zoster virus (VZV), a herpes virus, causes 2 distinct exanthematous (rash-associated) diseases: chickenpox (varicella) and herpes zoster (shingles). Chickenpox is a highly contagious, though typically benign, disease, usually contracted during childhood. Chickenpox is

characterized by a dermal vesiculopustular rash that develops in successive crops approximately 10 to 21 days following exposure.(1) Although primary infection with VZV results in immunity and protection from subsequent infection, VZV remains latent within sensory dorsal root ganglia and upon reactivation, manifests as herpes zoster or shingles. During reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash, usually limited to a single dermatome. Shingles is an extremely painful condition typically occurring in older nonimmune adults or those with waning immunity to VZV and in patients with impaired cellular immunity.(2) Several populations are at risk of suffering unusually severe reactions to VZV infections. The infection in women who are pregnant may spread through the placenta to the fetus causing congenital disease in the infant. Immunocompromised patients in hospitals may contract severe nosocomial infections from others who have active VZV infections and are at risk for developing severe VZV-related complications, which include cutaneous disseminated disease and visceral organ involvement.(2,3) Therefore, serologic screening of direct healthcare providers (physicians, allied healthcare personnel) and individuals in high-risk groups is necessary to avoid uncontrolled spread of infection. While the clinical presentation of VZV infection is generally characteristic, serologic evaluation of patients with atypical and systemic infections is often required. For example, it is extremely important to serologically evaluate patients for the early detection of VZV infections in hospital settings. Nosocomial spread of VZV infection can be life-threatening to immunocompromised patients susceptible to infection.

Useful For: Diagnosing acute-phase infection with varicella-zoster virus

Interpretation: A positive IgM result indicates a recent infection with varicella-zoster virus (VZV). A negative result does not rule out the diagnosis of VZV infection. The specimen may have been drawn before the appearance of detectable antibodies. Negative results in suspected early VZV infection should be followed by testing a new specimen in 2 to 3 weeks.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Yankowitz J, Grose C. Congenital infections. In: Storch GA, ed. Essentials of diagnostic virology. Churchill Livingstone; 2000:187-201 2. Gnann JW Jr, Whitley RJ. Clinical practice. Herpes zoster. N Engl J Med. 2002;347(5):340-346 3. Cvjetkovic D, Jovanovic J, Hrnjakovic-Cvjetkovic I, Brkic S, Bogdanovic M. Reaktivacija herpes zoster infekcije varicela-zoster virusom [Reactivation of herpes zoster infection by varicella-zoster virus]. Med Pregl. 1999;52(3-5):125-128 4. Flamholc L. Neurological complications in herpes zoster. Scand J Infect Dis. 1996;100:35-40 5. Whitely RJ. Chickenpox and Herpes Zoster (Varicella-Zoster virus). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:1849-1856

FVZGC
58045

Varicella-Zoster Virus Antibody, IgG, CSF

Interpretation: The detection of antibodies to varicella-zoster in cerebrospinal fluid may indicate central nervous system infection. However, consideration must be given to possible contamination by blood or transfer of serum antibodies across the blood-brain barrier.

Reference Values:
0.99 S/CO or less: Negative - No significant level of detectable varicella-zoster IgG antibody.

1.00 S/CO or greater: Positive - IgG antibody to varicella-zoster detected, which may indicate a current or past varicella-zoster infection.

LVZV
800168

Varicella-Zoster Virus, Molecular Detection, PCR, Varies

Clinical Information: Varicella-zoster virus (VZV) causes both varicella (chickenpox) and herpes zoster (shingles). VZV produces a generalized vesicular rash on the dermis (chickenpox) in normal children, usually before 10 years of age. After primary infection with VZV, the virus persists in latent form and may emerge clinically (usually in adults 50 years of age and older) to cause a unilateral vesicular eruption, generally in a dermatomal distribution (shingles).

Useful For: Rapid (qualitative) detection of varicella-zoster virus DNA in clinical specimens for laboratory diagnosis of disease due to this virus This test should not be used to screen asymptomatic patients.

Interpretation: Detection of varicella-zoster virus (VZV) DNA in clinical specimens supports the clinical diagnosis of infection due to this virus. VZV DNA is not detected in cerebrospinal fluid from patients without central nervous system disease caused by this virus. This LightCycler polymerase chain reaction assay does not yield positive results with other herpesvirus gene targets (herpes simplex virus, cytomegalovirus, Epstein-Barr virus).

Reference Values:
Negative

Reference values apply to all ages.

Clinical References: 1. Cinque P, Bossolasco S, Vago L, et al. Varicella-zoster virus (VZV) DNA in cerebrospinal fluid of patients infected with human immunodeficiency virus: VZV disease of the central nervous system or subclinical reactivation of VZV infection? Clin Infect Dis. 1997;25(3):634-639 2. Brown M, Scarborough M, Brink N, Manjii H, Miller R. Varicella zoster virus-associated neurological disease in HIV-infected patients. Int J STD AIDS. 2001;12(2):79-83 3. Studahl M, Hagberg L, Rekabdar E, Bergstrom T. Herpesvirus DNA detection in cerebrospinal fluid: differences in clinical presentation between alpha-, beta-, and gamma-herpesviruses. Scand J Infect Dis. 2000;32(3):237-248 4. Iten A, Chatelard P, Vuadens P, et al. Impact of cerebrospinal fluid PCR on the management of HIV-infected patients with varicella-zoster virus infection of the central nervous system. J Neurovirol. 1999;5(2):172-180 5. Sauerbrei A. Varicella-zoster virus infections - antiviral therapy and diagnosis. GMS Infect Dis. 2016;4:Doc01. doi: 10.3205/id000019 6. Sauerbrei A. Diagnosis, antiviral therapy, and prophylaxis of varicella-zoster virus infections. Eur J Clin Microbiol Infect Dis. 2016;35(5):723-734. doi: 10.1007/s10096-016-2605-0

VZVPV
618309

Varicella-Zoster Virus, Molecular Detection, PCR, Varies

Clinical Information: Varicella-zoster virus (VZV) causes both varicella (chickenpox) and herpes zoster (shingles). VZV produces a generalized vesicular rash on the dermis (chickenpox) in normal children, usually before 10 years of age. After primary infection with VZV, the virus persists in latent form and may emerge clinically (usually in adults 50 years of age and older) to cause a unilateral vesicular eruption, generally in a dermatomal distribution (shingles).

Useful For: Rapid (qualitative) detection of varicella-zoster virus DNA in clinical specimens for laboratory diagnosis of disease due to this virus This test should not be used to screen asymptomatic patients.

Interpretation: Detection of varicella-zoster virus (VZV) DNA in clinical specimens supports the clinical diagnosis of infection due to this virus. VZV DNA is not detected in cerebrospinal fluid from patients without central nervous system disease caused by this virus. This LightCycler polymerase chain

reaction assay does not yield positive results with other herpesvirus gene targets (herpes simplex virus, cytomegalovirus, Epstein-Barr virus).

Reference Values:
Negative

Reference values apply to all ages.

Clinical References: 1. Cinque P, Bossolasco S, Vago L, et al. Varicella-zoster virus (VZV) DNA in cerebrospinal fluid of patients infected with human immunodeficiency virus: VZV disease of the central nervous system or subclinical reactivation of VZV infection? Clin Infect Dis. 1997;25(3):634-639 2. Brown M, Scarborough M, Brink N, Manji H, Miller R. Varicella zoster virus-associated neurological disease in HIV-infected patients. Int J STD AIDS. 2001;12(2):79-83 3. Studahl M, Hagberg L, Rekabdar E, Bergstrom T. Herpesvirus DNA detection in cerebrospinal fluid: differences in clinical presentation between alpha-, beta-, and gamma-herpesviruses. Scand J Infect Dis. 2000;32(3):237-248 4. Iten A, Chatelard P, Vuadens P, et al. Impact of cerebrospinal fluid PCR on the management of HIV-infected patients with varicella-zoster virus infection of the central nervous system. J Neurovirol. 1999;5(2):172-180 5. Sauerbrei A. Varicella-zoster virus infections - antiviral therapy and diagnosis. GMS Infect Dis. 2016;4:Doc01. doi:10.3205/id000019 6. Sauerbrei A. Diagnosis, antiviral therapy, and prophylaxis of varicella-zoster virus infections. Eur J Clin Microbiol Infect Dis. 2016;35(5):723-734. doi:10.1007/s10096-016-2605-0

VEGF
63019

Vascular Endothelial Growth Factor, Plasma

Clinical Information: Vascular endothelial growth factor (VEGF) is a critical modulator of angiogenesis (the growth of new blood vessels).(1) In mammals, there are 5 members of the VEGF family, each arising from different genes, with VEGF-A being the most well-studied. VEGF-A promotes angiogenesis by inducing migration of endothelial cells, promoting mitosis of endothelial cells, and upregulating matrix metalloproteinase activity.(2) VEGF-A is regulated by hypoxia, with increased expression when cells detect an environment low in oxygen. Physiologically, VEGF induces new blood vessel formation during embryonic development, after tissue injury, and in response to blocked vessels. VEGF also regulates pathological vessel formation, such as in tumor growth and metastases.(3) Angiogenesis during tumor development is complex, although it is clear that VEGF plays a key role. VEGF also regulates angiogenesis in other disease states including rheumatoid arthritis, osteoarthritis, diabetes, and age-related macular degeneration. In addition, circulating concentrations of VEGF are elevated in patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, a monoclonal plasma cell disorder.(4) Although the pathologic role of VEGF in POEMS is unclear, it is useful as a diagnostic marker and for assessing response to therapy. In addition to the various genes in the VEGF family, VEGFA has multiple splicing variants. VEGFA 165 is the predominant isoform.(2) An internal study has demonstrated that the VEGF assay used by Mayo Clinic Laboratories is specific for the splice variant of VEGF-A 165 and does not detect other isoforms of VEGFA or other VEGF gene products. For more information see Acquired Neuropathy Diagnostic Algorithm.

Useful For: Evaluation of patients with suspected POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, particularly in differentiating from other forms of polyneuropathy and/or monoclonal plasma cell disorders

Interpretation: Elevated concentration of vascular endothelial growth factor (VEGF) may be consistent with a diagnosis of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome. Decreasing concentrations of VEGF over time in a patient with POEMS syndrome may be consistent with a therapeutic response.

Reference Values:
< or =96.2 pg/mL

Clinical References: 1. Apte RS, Chen DS, Ferrara N. VEGF in signaling and disease: Beyond discovery and development. Cell. 2019;176(6):1248-1264 2. Otrock ZK, Makarem JA, Shamseddine AI. Vascular endothelial growth factor family of ligands and receptors: review. Blood Cells Mol Dis. 2007;38(3):258-268 3. Siveen KS, Prabhu K, Krishnankutty R, et al. Vascular endothelial growth factor (VEGF) signaling in tumour vascularization: Potential and challenges. Curr Vasc Pharmacol. 2017;15(4):339-351 4. Brown R, Ginsberg L. POEMS syndrome: clinical update. J Neurol. 2019;266(1):268-277

VIP
8150

Vasoactive Intestinal Polypeptide, Plasma

Clinical Information: Vasoactive intestinal polypeptide (VIP) was originally isolated from porcine small intestine and was recognized by its potent vasodilator activity. This brain/gut hormone has widespread distribution and is present in neuronal cell bodies localized in the central nervous system, digestive, respiratory, and urogenital tracts, and exocrine, thyroid, and adrenal glands. VIP has a wide scope of biological actions. The main effects of VIP include relaxation of smooth muscle (bronchial and vascular dilation), stimulation of gastrointestinal water and electrolyte secretion, and release of pancreatic hormones. Vasoactive intestinal polypeptide-producing tumors are rare; most (90%) are located in the pancreas. Watery diarrhea, hypokalemia, and achlorhydria are key symptoms.

Useful For: Detecting vasoactive intestinal polypeptide-producing tumors in patients with chronic diarrheal diseases

Interpretation: An elevated vasoactive intestinal polypeptide (VIP) may indicate the presence of an enteropancreatic tumor causing hypersecretion of VIP. Vasoactive intestinal polypeptide-producing tumors are unlikely with a 24-hour stool volume below 700 mL.

Reference Values:
<86 pg/mL

Clinical References: 1. Smith SL, Branton SA, Avino AJ, et al. Vasoactive intestinal polypeptide secreting islet cell tumors: a 15-year experience and review of the literature. Surgery. 1998;124(6):1050-1055 2. Ghaferi AA, Chojnacki KA, Long WD, Cameron JL, Yeo CJ. Pancreatic VIPomas: subject review and one institutional experience. J Gastrointest Surg. 2008;12(2):382-393 3. Eisenhofer G, Grebe S, Cheung NK, et al. Monoamine-producing tumors. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:1421 4. Una Cidon E. Vasoactive intestinal peptide secreting tumour: An overview. World J Gastrointest Oncol. 2022;14(4):808-819

VIPI
70580

Vasoactive Intestine Polypeptide (VIP), Technical Component Only

Clinical Information: Excessive vasoactive intestine polypeptide (VIP) production by islet cell tumors has been associated with Verner-Morrison syndrome, also known as pancreatic cholera, in which patients have massive, watery diarrhea. A subset of normal cells in the pancreatic islets express VIP (<1%). Peripheral nerves and ganglion cells also serve as a positive internal control.

Useful For: Aiding in the identification of islet cell tumors

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

VDSFT
621912

VDRL Titer, Spinal Fluid

Clinical Information: Neurosyphilis (NS) caused by the spirochete Treponema pallidum can occur at any stage of syphilis. Currently the Center for Disease Control estimates that approximately 2% of patients with syphilis will develop neuroinvasive syphilis if untreated. Early stages of NS may be asymptomatic or symptomatic, with patients typically exhibiting classic meningitis symptoms. Patients with late-stage NS patients may present with dementia paralytica or tabes dorsalis. Other manifestations of neuroinvasive syphilis include ocular or otologic syphilis, which can occur at any stage, however are more common during early NS. The diagnosis of NS is challenging due to a number of factors, including the lack of consensus on the relevance of abnormal cerebrospinal fluid (CSF) findings in patients who are seropositive for syphilis but neurologically asymptomatic. With respect to diagnostic testing, numerous treponemal and non-treponemal (lipoidal) assays have been evaluated, alongside CSF protein and pleocytosis findings, however direct comparisons of these assays are limited. The Venereal Diseases Research Laboratory (VDRL) assay is currently the only assay with US Food and Drug Administration (FDA) clearance as an aid in the diagnosis of NS, however the sensitivity and specificity of this non-treponemal (lipoidal) assay is highly variable, ranging from 66.7% to 85.7% and 78.2% to 86.7%, respectively. Although no treponemal assay has FDA clearance as an aid for diagnosis of NS, studies evaluating the fluorescent treponemal antibody absorption (FTA-ABS) assay performed in CSF from patients with definitive NS was associated with a sensitivity of 90.9% to 100%. Specificity of this approach ranged from 55% to 100% however, primarily due to the issue of passive diffusion of serum antibodies across the blood-brain barrier. The NS antibody index assay corrects for passive diffusion across an inflamed blood-brain barrier by measuring quantitative levels of anti-T. pallidum antibodies in serum and CSF and normalizing those to total IgG and albumin in both specimen sources. A positive NS antibody index indicates true intrathecal antibody synthesis of antibodies to T. pallidum, which alongside clinical and exposure history can be used to establish a diagnosis of NS. All NS antibody index positive samples are also reflexed for testing by the VDRL assay to acquire a semi-quantitative titer. The NS antibody index should only be ordered in patients who are seropositive for antibodies to T. pallidum in blood, who also present with neurologic manifestations suspicious for NS or who are at risk for asymptomatic NS.

Useful For: Aid in the diagnosis of neuroinvasive syphilis as part of a profile

Interpretation: Negative: No non-treponemal (lipoidal) antibodies to syphilis (T. pallidum) detected. Discordant results between the neurosyphilis antibody index and the VDRL result may be due to increased sensitivity of the antibody index assay. Positive: Results are consistent with neurosyphilis.

Reference Values:
Only orderable as a reflex. For more information see NSAIP / Neurosyphilis IgG Antibody Index with VDRL, Serum and Spinal Fluid.

Negative
Reference values apply to all ages.

Clinical References: 1. Miller JN. Value and limitations of nontreponemal and treponemal tests in

the laboratory diagnosis of syphilis. Clin Obstet Gynecol. 1975;18(1):191-203 2. Radolf JD, Tramont EC, Salazar JC. Syphilis (Treponema pallidum). In Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2865-2892

VDSFQ
802175

VDRL Titer, Spinal Fluid

Clinical Information: The VRDL assay is a nontreponemal serologic test for syphilis that uses a cardiolipin-cholesterol-lecithin antigen to detect reaginic antibodies. The presence of neurosyphilis in untreated patients can be detected by the presence of pleocytosis, elevated protein, and a positive VDRL result.

Useful For: Aiding in the diagnosis of neurosyphilis

Interpretation: A positive VDRL on spinal fluid is highly specific for neurosyphilis.

Reference Values:
Only orderable as a reflex. For more information see VDSF / VDRL, Spinal Fluid.

Negative
Reference values apply to all ages.

Clinical References: 1. Miller JN. Value and limitations of nontreponemal and treponemal tests in the laboratory diagnosis of syphilis. Clin Obstet Gynecol. 1975;18(1):191-203 2. Radolf JD, Tramont EC, Salazar JC. Syphilis (Treponema pallidum). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2865-2892

VDSF
800239

VDRL, Spinal Fluid

Clinical Information: The VDRL assay is a nontreponemal serologic test for syphilis that uses a cardiolipin-cholesterol-lecithin antigen to detect reaginic antibodies. The VDRL test performed on cerebrospinal fluid can be used to diagnose neurosyphilis in patients with a prior history of syphilis infection. The presence of neurosyphilis in untreated patients can be detected by the presence of pleocytosis, elevated protein, and a positive VDRL result.

Useful For: Aiding in the diagnosis of neurosyphilis

Interpretation: A positive VDRL result on spinal fluid is highly specific for neurosyphilis. A single negative VDRL result should not be used to exclude neurosyphilis and repeat testing on a new specimen may be necessary. Positive results will be titered.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Miller JN. Value and limitations of nontreponemal and treponemal tests in the laboratory diagnosis of syphilis. Clin Obstet Gynecol. 1975;18(1):191-203 2. Radolf JD, Tramont EC, Salazar JC. Syphilis (Treponema pallidum). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:2865-2892

VEDOZ
603025

Vedolizumab Quantitation with Antibodies, Serum

Clinical Information: Vedolizumab (Entyvio) is a humanized IgG1 kappa monoclonal antibody directed against integrin alpha-4 beta-7. Blocking the alpha-4 beta-7 integrin results in a gut-selective anti-inflammatory response.(1) The drug is US Food and Drug Administration-approved for the treatment of adult patients with moderately to severely active ulcerative colitis or Crohn disease. The main indication for therapeutic drug monitoring of vedolizumab is in the setting of primary nonresponse or loss-of-response to therapy, also called reactive monitoring.(2-10) Vedolizumab trough concentrations greater than 12 mcg/mL to 15 mcg/mL have been associated with clinical or endoscopic remission.(3,5,11) Proactive monitoring of vedolizumab concentrations has been proposed, but there is not sufficient data to support routine proactive testing at this time. Therapeutic drug monitoring of biologics is usually carried out by measuring the monoclonal antibody therapy concentration and assessing its immunogenicity or the appearance of anti-drug antibodies. Some patients on vedolizumab may develop antibodies to vedolizumab (ATV) over time. In clinical trials, approximately 4% of patients treated with vedolizumab were positive for ATV at any time and 1% or less were persistently positive. Clinically significant ATV impact drug clearance and a positive ATV is associated with lower trough concentrations of vedolizumab.

Useful For: Assessing for primary or secondary loss of response to therapy with vedolizumab An aid to achieving desired serum concentrations of vedolizumab

Interpretation: The limit of quantitation of the test is 2.0 mcg/mL. In a retrospective Mayo Clinic study with 171 patients (62% Crohn disease, 31% ulcerative colitis, and 7% indeterminate colitis), the median vedolizumab trough concentration was 15.3 mcg/mL.(11) Trough (immediately before next infusion) therapeutic concentrations of vedolizumab are expected to be above 15 mcg/mL. Vedolizumab concentration greater than 15 mcg/mL at trough is associated with clinical remission, endoscopic remission, or mucosal healing in inflammatory bowel disease. Clinically significant antibodies-to-vedolizumab impact drug clearance and are associated with low (< or =15 mcg/mL at trough) or undetectable vedolizumab concentration.

Reference Values:

VEDOLIZUMAB QUANTITATION:
Vedolizumab lower limit of quantitation=2.0 mcg/mL

VEDOLIZUMAB ANTIBODIES:
Antibodies to vedolizumab: <9.8 ng/mL

Clinical References: 1. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;22(69)8;369:699-710 2. Williet N, Boschetti G, Fovet M, et al. Association between low trough levels of vedolizumab during induction therapy for inflammatory bowel diseases and need for additional doses within 6 months. Clin Gastroenterol Hepatol. 2017;15(11):1750-1757.e3 3. Dreesen E, Verstockt B, Bian S, et al. Evidence to support monitoring of vedolizumab trough concentrations in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2018;16(12):1937-1946 e8 4. Ungar B, Kopylov U, Yavzori M, et al. Association of vedolizumab level, anti-drug antibodies, and alpha4beta7 occupancy with response in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2018;16(5):697-705.e7 5. Ward MG, Sparrow MP, Roblin X. Therapeutic drug monitoring of vedolizumab in inflammatory bowel disease: Current data and future directions. Therap Adv Gastroenterol. 2018;11:1756284818772786 6. Pouillon L, Rousseau H, Busby-Venner H, et al. Vedolizumab trough levels and histological healing during maintenance therapy in ulcerative colitis. J Crohns Colitis. 2019;13(8):970-975 7. Pouillon L, Vermeire S, Bossuyt P. Vedolizumab trough level monitoring in inflammatory bowel disease: A state-of-the-art overview. BMC Med. 2019;17(1):89 8. Singh S, Dulai PS, Vande Casteele N, et al. Systematic review with meta-analysis: Association between vedolizumab trough concentration and clinical outcomes in patients with inflammatory bowel diseases. Aliment Pharmacol Ther. 2019;50(8):848-857

9. Ungaro RC, Yarur A, Jossen J, et al. Higher trough vedolizumab concentrations during maintenance therapy are associated with corticosteroid-free remission in inflammatory bowel disease. J Crohns Colitis. 2019;13(8):963-969 10. Yarur AJ, Bruss A, Naik S, et al. Vedolizumab concentrations are associated with long-term endoscopic remission in patients with inflammatory bowel diseases. Dig Dis Sci. 2019;64(6):1651-1659 11. Al-Bawardy B, Ramos GP, Willrich MAV, et al. Vedolizumab drug level correlation with clinical remission, biomarker normalization, and mucosal healing in inflammatory bowel disease. Inflamm Bowel Dis. 2019;25(3):580-586

VEDOL
602807

Vedolizumab Quantitation with Reflex to Antibodies, Serum

Clinical Information: Vedolizumab (Entyvio) is a humanized IgG1 kappa monoclonal antibody directed against integrin alpha-4 beta-7. Blocking the alpha-4 beta-7 integrin results in a gut-selective anti-inflammatory response.(1) The drug is US Food and Drug Administration approved for the treatment of adult patients with moderately to severely active ulcerative colitis or Crohn disease. The main indication for therapeutic drug monitoring of vedolizumab is in the setting of primary nonresponse or loss-of-response to therapy, also called reactive monitoring.(2-10) Vedolizumab trough concentrations greater than 12 mcg/mL to 15 mcg/mL have been associated with clinical or endoscopic remission.(3,5,11) Proactive monitoring of vedolizumab concentrations has been proposed, but there is not sufficient data to support routine proactive testing at this time. Therapeutic drug monitoring of biologics is usually carried out by measuring the monoclonal antibody therapy concentration and assessing its immunogenicity or the appearance of anti-drug antibodies. Some patients on vedolizumab may develop antibodies to vedolizumab (ATV) over time. In clinical trials, approximately 4% of patients treated with vedolizumab were positive for ATV at any time and 1% or less were persistently positive. Clinically significant ATV levels, drug clearance, and positive ATV is associated with lower trough concentrations of vedolizumab.

VELV
82917

Velvet Leaf, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to velvet leaf Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FVENE 75577 Venison IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

FBMBL 57975 Venom Bumble Bee (Bombus terrestrus) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 5 6 17.50-49.99 50.00-99.99 >99.99 Very High Positive Very High Positive Very High Positive

Reference Values:
<0.35 kU/L

FHOBG 57714 Venom Honey Bee IgG

Reference Values:
>3.5 mcg/mL

Venom IgG Reference Values: 1.0 – 3.5 mcg/mL Low venom IgG indicating a significant reaction risk. 3.5 – 6.0 mcg/mL Moderate level of venom IgG that may be associated from serious sting reactions (J.Clin.Immun.6:172, 1983) > 6.0 mcg/mL Elevated venom IgG usually associated with protection from serious sting reactions (J.Clin.Immun.6:172, 1983) The interpretative guidelines have been adapted from Golden et al (JACI 1992; 90:386-393). The test method used is the Phadia ImmunoCAP IgG assay which has been recalibrated to correlate with the venom IgG assay referenced

above.

FWFHG
57799

Venom W-F Hornet IgG

Reference Values:
>3.5 mcg/mL

Venom IgG Reference Values: 1.0 – 3.5 mcg/mL Low venom IgG indicating a significant reaction risk. 3.5 – 6.0 mcg/mL Moderate level of venom IgG that may be associated from serious sting reactions (J.Clin.Immun.6:172, 1983) > 6.0 mcg/mL Elevated venom IgG usually associated with protection from serious sting reactions (J.Clin.Immun.6:172, 1983) The interpretative guidelines have been adapted from Golden et al (JACI 1992; 90:386-393). The test method used is the Phadia ImmunoCAP IgG assay which has been recalibrated to correlate with the venom IgG assay referenced above.

VLCZ
35571

Very Long Chain Acyl-CoA Dehydrogenase Deficiency, Full Gene Analysis, Varies

Clinical Information: Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency is an autosomal recessive disorder of mitochondrial fatty acid beta-oxidation. Mitochondrial beta-oxidation plays a major role in energy production and VLCAD catalyzes the first step in the breakdown of fatty acids that are 14 to 20 carbons long. VLCAD deficiency has a reported incidence of approximately 1 in 30,000 births and has a variable age of onset that is generally classified into 3 categories. Individuals with the early-onset type present with cardiomyopathy, hypotonia, and hepatomegaly in the first months of life; sudden death is also frequent. Individuals with the early-childhood onset type typically present with hypoketotic hypoglycemia and hepatomegaly without cardiomyopathy. Individuals with the late-onset type of VLCAD deficiency generally present after childhood with intermittent rhabdomyolysis and muscle dysfunction that often manifests as muscle cramps and exercise intolerance. Review of clinical features and biochemical analysis via plasma acylcarnitines, plasma fatty acid profile, urine organic acids, and fibroblast fatty acid oxidation probe studies are recommended as laboratory evaluations for VLCAD deficiency. Plasma and urine biochemical testing are not reliable for identifying all individuals with VLCAD deficiency or confirming carrier status, as biochemical findings may normalize during periods of good metabolic control. It is uncertain whether skin fibroblast analysis can identify carriers of VLCAD deficiency. The diagnosis is confirmed by molecular testing. Mutations in the ACADVL gene are responsible for VLCAD deficiency. Most mutations are family specific with the exception of the V283A mutation (also reported in the literature as V243A). This mutation is estimated to account for 20% of pathogenic alleles in patients identified by newborn screening. When this test is ordered, results of biochemical assays should be included with the specimen as they are necessary for accurate interpretation of the VLCAD sequence analysis.

Useful For: Confirmation of a diagnosis of very long chain acyl-CoA dehydrogenase (VLCAD) deficiency Carrier screening in cases where there is a family history of VLCAD deficiency, but an affected individual is not available for testing or disease-causing mutations have not been identified

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424 2. Andresen BS, Olpin S, Poorthuis BJ, et al: Clear correlation of genotype with disease phenotype in very-long-chain acyl-CoA dehydrogenase deficiency. Am J Hum Genet 1999;64:479-494 3. Liebig M, Schymik I, Mueller M, et al: Neonatal screening for very long-chain acyl-CoA dehydrogenase deficiency: enzymatic and molecular evaluation of neonates with elevated C14:1-carnitine levels. Pediatrics 2006;118:1065-1069

VHLE
37839

VHL Gene, Erythrocytosis, Mutation Analysis, Varies

Clinical Information: Erythrocytosis (ie, increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera, or secondary, in response to increased serum erythropoietin levels). Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other Epo-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and paraganglioma formation. It is caused by mutations in several genes, including VHL, and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new mutations to arise in an individual. The genes coding for hemoglobin, hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), the erythropoietin receptor (EPOR), and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and VHL can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL typically have normal p50 results. The true prevalence of hereditary erythrocytosis causing mutations is unknown. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum Epo p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased to normal level Normal PHD2/EGLN1 Dominant Normal level Normal BPGM Recessive Normal level Decreased Beta Globin Dominant Normal level to increased Decreased Alpha Globin Dominant Normal level to increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Normal to increased Normal The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate-mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteasomal degradation, which requires prolyl hydroxylation of HIF proline residues. Mutations resulting in altered VHL proteins can lead to familial erythrocytosis, type 2 (ECYT2; OMIM 263400). ECYT2 is a clinically heterogeneous disorder characterized by congenital erythrocytosis with or without high serum EPO levels, venous and arterial thrombosis, and pulmonary hypertension that can manifest as early as infancy but more typically into adulthood. An increased risk for tumors associated with von Hippel-Lindau syndrome, which is also caused by mutations in the VHL gene, has not been observed.

Useful For: Diagnosis of suspected JAK2-negative VHL-related erythrocytosis associated with lifelong sustained increased RBC mass, elevated RBC count, hemoglobin, or hematocrit

Interpretation: Evaluation and categorization of variants is performed using the most recent

published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-423 2. Online Mendelian inheritance in Man-OMIM. Available at http://www.omim.org/entry/263400 3. Bento C, Percy M, Gardie B, et al: Genetic basis of congenital erythrocytosis: mutation update and online databases. Hum Mutat 2014;35(1):15-26 4. Pastore Y, Jedlickova K, Guan Y, et al: Mutations of von Hippel-Lindau tumor-suppressor gene and congenital polycythemia. Am J Hum Genet 2003;73(2):412-419 5. Merchant SH, Oliveira JL, Hoyer JD, et al: Molecular Diagnosis. In Hematopathology. Second edition, Series editor John Goldblum. Edited by ED His. Churchill Livingstone. Hematopathology: A Volume in Foundations in Diagnostic Pathology Series. 2012

VIBC
89658

Vibrio Culture, Feces

Clinical Information: Diarrhea may be caused by a number of agents (eg, bacteria, viruses, parasites, and chemicals), and infection with or exposure to one of these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the physician determine the appropriate testing to be performed. Vibrio cholerae, the causative agent of endemic, epidemic, and pandemic cholera, results in large volumes of rice-water stools due to the production of an enterotoxin. Severe dehydration is of concern in patients without access to adequate medical care. In the United States, Vibrio parahemolyticus is the most common cause of Vibrio disease. V parahemolyticus is associated with the consumption of raw shellfish or fish and results in gastroenteritis with nausea, vomiting, abdominal cramps, low-grade fever, and chills. Usually, rehydration is the only treatment required, although in some cases, antimicrobial therapy is needed.

Useful For: Determining whether Vibrio species may be the cause of diarrhea This test is generally not useful for patients that have been hospitalized for more than 3 days because the yield from these patients' specimens is very low as is the likelihood of identifying a pathogen that has not been detected previously.

VIGA
91089

Vigabatrin (Sabril)

Reference Values:
Units: ug/mL

Therapeutic and toxic ranges have not been established.

Expected serum vigabatrin concentrations in patients receiving recommended daily dosages: 20 – 160 ug/mL

VIM
70579

Vimentin Immunostain, Technical Component Only

Clinical Information: Vimentin is an intermediate filament protein (57 kDa) present in cells of mesenchymal origin. A number of tumors coexpress vimentin and cytokeratin (eg, thyroid carcinomas, pleomorphic adenomas of the salivary glands, and some renal carcinomas). Coexpression of desmin and vimentin has also been reported in a number of soft tissue tumors (eg, rhabdomyosarcomas, leiomyosarcomas, and alveolar soft tissue sarcomas).

Useful For: Identification of cells of mesenchymal origin in normal and neoplastic tissues

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

VIRID
619900

Viral Susceptibility, Defects in Intrinsic and Innate Immunity, Gene Panel, Varies

Clinical Information: Viral infections are common in otherwise healthy individuals, but they may also present clinically due to a primary (genetic) immunodeficiency (ie, inborn error of immunity: IEI). Alternatively, secondary immunodeficiencies may have a similar presentation but result from immunosuppressive medication or illness, such as HIV infection. IEIs may cause a susceptibility to an entire group of pathogens (bacteria, fungi, or viruses), a subset of pathogens (eg, RNA viruses), or can cause susceptibility specific to a single pathogen (eg, Epstein-Barr virus [EBV], human papillomavirus [HPV]). IEIs may also lead to a more severe presentation, including fatal infection caused by a pathogen that usually causes only a mild or non-fatal disease (eg, influenza). This panel targets IEIs that lead to susceptibility to viruses or to a subset of viruses, severe viral pneumonia, or a specific virus. Examples of infections where this gene panel is useful include EBV, skin-tropic beta-HPV, influenza, and SARS-CoV-2. IEIs that lead to systemic immune deficiencies and susceptibility to a large variety of pathogens (eg, T-cell deficiencies) are not included in this panel. EBV is the cause of infectious mononucleosis and persists asymptomatically for life in nearly all adults. It is also associated with the development of T- and B-cell lymphomas, nasopharyngeal and gastric carcinomas, and other malignancies. EBV infection in IEIs can present with fulminant infectious mononucleosis, hemophagocytosis, B-cell proliferative disease (including lymphoma), and hypogammaglobulinemia. Beta-HPVs circulate silently in the general population and cause no visible lesions in most people. Genetic susceptibility to beta-HPVs leads to warts, pityriasis-like lesions, epidermodysplasia verruciformis, and increased risk of non-melanoma skin cancers. Seasonal influenza viruses are common RNA viruses that infect the respiratory tract, causing a benign illness in most infected individuals. Influenza pneumonia or acute respiratory distress syndrome are rare, and the case fatality ratio is less than 1%. Children with severe influenza have been found to carry defects in IRF7, IRF9, STAT1, STAT2, and TLR3. Similarly, the COVID-19 pandemic has revealed that SARS-CoV-2 infection can lead to asymptomatic infection as well as fatal pneumonia. Genetic studies showed that approximately 2 to 3% of cases of severe life-threatening SARS-CoV-2 infection resulted from IEI, mainly genetic defects in the TLR3- or TLR7-dependent type 1 interferon pathway (eg, TLR3, TLR7, IFNAR1/2, STAT2, and IRF7), overlapping with that of severe pneumonia susceptibility in influenza infections.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an inborn error of immunity causing a hereditary form of severe viral susceptibility Establishing a diagnosis of hereditary form of viral susceptibility, allowing for appropriate

management and surveillance for disease features based on the gene and/or variant involved Identifying variants within genes known to be associated with a hereditary form of viral susceptibility, allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

SVISC
610406

Viscosity, Serum

Clinical Information: Viscosity is the property of fluids to resist flow. Hyperviscosity may be manifested by nasal bleeding, blurred vision, headaches, dizziness, nystagmus, deafness, diplopia, ataxia, paresthesias, or congestive heart failure. Funduscopic examination reveals dilation of retinal veins and flame shaped retinal hemorrhages. The most common cause of serum hyperviscosity is the presence of large concentrations of IgM monoclonal proteins, and Waldenstrom macroglobulinemia accounts for 80% to 90% of hyperviscosity cases. Hyperviscosity syndrome can also occur in multiple myeloma patients. Because the ability of a monoclonal protein to cause hyperviscosity is affected by its concentration, molecular weight, and aggregation, sera with concentrations of monoclonal IgM greater than 4 g/dL, IgA greater than 5 g/dL, or IgG greater than 6 g/dL should be tested for hyperviscosity. Serum viscosity and electrophoresis are recommended before and after plasmapheresis in order to correlate viscosity and M-spike with patient symptoms. This correlation may be useful for anticipating the need for repeat plasmapheresis.

Useful For: Detection of increased viscosity Monitoring patients with hyperviscosity syndrome This test is not useful for patients with small concentrations of monoclonal proteins.

Interpretation: Although viscosities greater than 1.5 centipoises (cP) are abnormal, hyperviscosity is rarely present unless the viscosity is greater than 3 cP.

Reference Values:
< or =1.5 centipoises

Clinical References: 1. Gertz MA, Kyle RA: Hyperviscosity syndrome. J Intensive Care Med. 1995;10:128-141 2. Gertz MA: Acute hyperviscosity: syndromes and management. Blood. 2018;132(13):1379-1385 3. Kesmarky G, Kenyeres P, Rabai M, Toth K: Plasma viscosity: a forgotten variable. Clin Hemorheol Microcirc. 2008;39(1-4):243-246 4. Wood AW: Rheology of blood. In: Physiology, Biophysics, and Biomedical Engineering. CRC Press; 2012:217-233

VITAE
605267

Vitamin A and Vitamin E, Serum

Clinical Information: Vitamin A: The level of vitamin A in the plasma or serum is a reflection of the quantities of vitamin A and carotene ingested and absorbed by the intestine (carotene is converted to vitamin A by intestine absorptive cells and hepatocytes). Vitamin A plays an essential role in the function of the retina (adaptation to dim light), is necessary for growth and differentiation of epithelial tissue, and

is required for growth of bone, reproduction, and embryonic development. Together with certain carotenoids, vitamin A enhances immune function, reducing the consequences of some infectious diseases. Degenerative changes in eyes and skin are commonly observed in vitamin A deficiency. Poor adaptation of vision to darkness (night blindness) is an early symptom that may be followed by degenerative changes in the retina. In developing countries, vitamin A deficiency is the principal preventable cause of blindness. Severe or prolonged deficiency leads to dry eye (xerophthalmia), which can result in corneal ulcers, scarring, and blindness. Another important consequence of inadequate intake is acquired immunodeficiency disease, with an increased incidence of death related to infectious diseases. In patients with HIV, vitamin A deficiency is associated with increased disease progression and mortality. Vitamin A in excess can be toxic. In particular, chronic vitamin A intoxication is a concern in normal adults who ingest more than 15 mg per day and in children who ingest more than 6 mg per day of vitamin A over a period of several months. Manifestations are various and include dry skin, cheilosis, glossitis, vomiting, alopecia, bone demineralization and pain, hypercalcemia, lymph node enlargement, hyperlipidemia, amenorrhea, and features of pseudotumor cerebri with increased intracranial pressure and papilledema. Liver fibrosis with portal hypertension and bone demineralization may also result. Congenital malformations, like spontaneous abortions, craniofacial abnormalities, and valvular heart disease have been described in pregnant women taking vitamin A in excess. Consequently, in pregnancy, the daily dose of vitamin A should not exceed 3 mg. Vitamin E (alpha-tocopherol): Vitamin E is the generic term for two different groups of methylated phenol compounds with a chromane alcoholic core linked to poly-carbon chains (tocopherols and tocotrienols). These vitamins are all free radical scavengers, with alpha-tocopherol being the most potent one in humans, as most of the related compounds are not re-secreted by the liver, thus leading to much lower circulating concentrations. Vitamin E deficiency is very rare and mostly seen in patients with extreme malabsorption of fat and in patients with abetalipoproteinemia, a rare inborn error of metabolism. Patients with these conditions may develop peripheral neuropathy, myopathy, retinopathy, and immune deficiency. There is a large body of scientific studies that indicates positive effects on outcomes of various diseases if regular Vitamin E supplementation is provided; however, several trials have shown evidence of increasing bleeding risks at high Vitamin E doses. Therefore, tables of tolerable doses in children and adults have been established, which should not be exceeded. Deficiencies of vitamins A and E may arise from poor nutrition or from intestinal malabsorption. Persons at risk, especially children, include those with bowel disease, pancreatic disease, chronic cholestasis, celiac disease, cystic fibrosis, and intestinal lymphangiectasia. Infantile cholangiopathies that may lead to malabsorption of vitamins A and E include intrahepatic dysplasia and rubella-related embryopathy.

Useful For: Diagnosing vitamin A deficiency and toxicity Evaluating persons with intestinal malabsorption of lipids Monitoring of Vitamin E supplementation/treatment

Interpretation: Vitamin A: The World Health Organization recommends supplementation when vitamin A levels fall below 20.0 mcg/dL. Severe deficiency is indicated at levels less than 10.0 mcg/dL. Vitamin A values above 120.0 mcg/dL suggest hypervitaminosis A and associated toxicity. Vitamin E (alpha-tocopherol): Vitamin E concentrations within the healthy reference population range usually indicate adequate Vitamin A stores. The rare occurrence of low Vitamin A levels might correlate with potential deficiency and investigation of potential fat malabsorptions should be considered. Conversely, Vitamin E concentrations significantly above the upper healthy reference population range might indicate that Vitamin E intake exceeds the tolerable upper daily intake level(s).

Reference Values:

VITAMIN A (RETINOL)
0-6 years: 11.3-64.7 mcg/dL
7-12 years: 12.8-81.2 mcg/dL
13-17 years: 14.4-97.7 mcg/dL
> or =18 years: 32.5-78.0 mcg/dL

VITAMIN E (ALPHA-TOCOPHEROL)

0-17 years: 3.8-18.4 mg/L
> or =18 years: 5.5-17.0 mg/L

Clinical References: 1. Ball GFM. Vitamins: Their role in the human body. Blackwell Publishing; 2004:234-255 2. Ross AC. Vitamin A and carotenoids. In: Shils ME, Shike M, Ross MC, et al, eds. Modern Nutrition in Health and Disease. 10th ed. Lippincott Williams and Wilkins; 2006:351-375 3. Traber MG. Vitamin E. In: Shils ME, Shike M, Ross AC, et al, eds. Modern Nutrition in Health and Disease.10th ed. Lippincott Williams and Wilkins; 2006:434-441 4. Roberts NB, Taylor A, Sodi R. Vitamins and trace elements. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:chap37 5. Sodi R. Vitamins and trace elements. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:417-417.e104.

VITA
42357

Vitamin A, Serum

Clinical Information: The level of vitamin A in the plasma or serum is a reflection of the quantities of vitamin A and carotene (provitamin A) ingested and absorbed by the intestine (carotene is converted to vitamin A by intestinal absorptive cells and hepatocytes). Vitamin A plays an essential role in the function of the retina (adaptation to dim light), is necessary for growth and differentiation of epithelial tissue, and is required for growth of bone, reproduction, and embryonic development. Together with certain carotenoids, vitamin A enhances immune function, reducing the consequences of some infectious diseases. Degenerative changes in eyes and skin are commonly observed in vitamin A deficiency. Poor adaptation of vision to darkness (night blindness) is an early symptom that may be followed by degenerative changes in the retina. In developing countries, vitamin A deficiency is the principal preventable cause of blindness. Severe or prolonged deficiency leads to dry eye (xerophthalmia) that can result in corneal ulcers, scarring, and blindness. Another important consequence of inadequate intake is acquired immunodeficiency disease, where an increased incidence of death is associated with deficient vitamin A levels. Increased susceptibility is associated with vitamin A deficiency. In patients with HIV, vitamin A deficiency is associated with increased disease progression and mortality. Vitamin A in excess can be toxic. In particular, chronic vitamin A intoxication is a concern in normal adults who ingest more than 15 mg per day and children who ingest more than 6 mg per day of vitamin A over a period of several months. Manifestations are various and include dry skin, cheilosis, glossitis, vomiting, alopecia, bone demineralization and pain, hypercalcemia, lymph node enlargement, hyperlipidemia, amenorrhea, and features of pseudotumor cerebri with increased intracranial pressure and papilledema. Liver fibrosis with portal hypertension may also result. Congenital malformations, like spontaneous abortions, craniofacial abnormalities, and valvular heart disease have been described in pregnant women taking vitamin A in excess. Consequently, in pregnancy, the daily dose of vitamin A should not exceed 3 mg.

Useful For: Diagnosing vitamin A deficiency and toxicity Monitoring vitamin A therapy

Interpretation: The World Health Organization recommendations supplementation when vitamin A levels fall below 20.0 mcg/dL. Severe deficiency is indicated at levels less than 10.0 mcg/dL. Vitamin A values above 120.0 mcg/dL suggest hypervitaminosis A and associated toxicity.

Reference Values:
0-6 years: 11.3-64.7 mcg/dL
7-12 years: 12.8-81.2 mcg/dL
13-17 years: 14.4-97.7 mcg/dL
> or =18 years: 32.5-78.0 mcg/dL

Clinical References: 1. Ball GFM. Vitamins: Their role in the human body. Blackwell Publishing; 2004:133-187 2. Ross AC. Vitamin A and carotenoids. In: Shils ME, Shike M, Ross AC, et al, eds.

Modern Nutrition in Health and Disease. 10th ed. Lippincott Williams and Wilkins; 2006:351-375 3. Roberts NB, Taylor A, Sodi R. Vitamins and Trace Elements. In: Rifai N, Horvath AR, Wittwer CT, eds.Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:chap 37 4. Sodi R. Vitamins and trace elements. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:417-417.e104

VITAP
605124

Vitamin A, Serum

Clinical Information: The level of vitamin A in the plasma or serum is a reflection of the quantities of vitamin A and carotene (provitamin A) ingested and absorbed by the intestine (carotene is converted to vitamin A by intestinal absorptive cells and hepatocytes). Vitamin A plays an essential role in the function of the retina (adaptation to dim light), is necessary for growth and differentiation of epithelial tissue, and is required for growth of bone, reproduction, and embryonic development. Together with certain carotenoids, vitamin A enhances immune function, reducing the consequences of some infectious diseases. Degenerative changes in eyes and skin are commonly observed in vitamin A deficiency. Poor adaptation of vision to darkness (night blindness) is an early symptom that may be followed by degenerative changes in the retina. In developing countries, vitamin A deficiency is the principal preventable cause of blindness. Severe or prolonged deficiency leads to dry eye (xerophthalmia) that can result in corneal ulcers, scarring, and blindness. Another important consequence of inadequate intake is acquired immunodeficiency disease, where an increased incidence of death is associated with deficient vitamin A levels. Increased susceptibility is associated with vitamin A deficiency. In patients with HIV, vitamin A deficiency is associated with increased disease progression and mortality. Vitamin A in excess can be toxic. In particular, chronic vitamin A intoxication is a concern in normal adults who ingest more than 15 mg per day and children who ingest more than 6 mg per day of vitamin A over a period of several months. Manifestations are various and include dry skin, cheilosis, glossitis, vomiting, alopecia, bone demineralization and pain, hypercalcemia, lymph node enlargement, hyperlipidemia, amenorrhea, and features of pseudotumor cerebri with increased intracranial pressure and papilledema. Liver fibrosis with portal hypertension may also result. Congenital malformations, like spontaneous abortions, craniofacial abnormalities, and valvular heart disease have been described in pregnant women taking vitamin A in excess. Consequently, in pregnancy, the daily dose of vitamin A should not exceed 3 mg.

Useful For: Diagnosing vitamin A deficiency and toxicity as a part of a profile Monitoring vitamin A therapy

Interpretation: The World Health Organization recommends supplementation when vitamin A levels fall below 20.0 mcg/dL. Severe deficiency is indicated at levels less than 10.0 mcg/dL. Vitamin A values above 120.0 mcg/dL suggest hypervitaminosis A and associated toxicity.

Reference Values:
Only orderable as part of a profile. For more information see VITAE / Vitamin A and Vitamin E, Serum.

0-6 years: 11.3-64.7 mcg/dL
7-12 years: 12.8-81.2 mcg/dL
13-17 years: 14.4-97.7 mcg/dL
> or =18 years: 32.5-78.0 mcg/dL

Clinical References: 1. Ball GFM. Vitamins: Their role in the human body. Blackwell Publishing; 2004:133-187 2. Ross AC. Vitamin A and carotenoids. In: Shils ME, Shike M, Ross AC, et al, eds. Modern Nutrition in Health and Disease. 10th ed. Lippincott Williams and Wilkins; 2006:351-375 3. Roberts NB, Taylor A, Sodi R. Vitamins and trace elements. In: Rifai N, Horvath AR, Wittwer CT, eds.

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FB12
9156

Vitamin B12 and Folate, Serum

Clinical Information: B12: Vitamin B12 (cobalamin) is necessary for hematopoiesis and normal neuronal function. In humans, it is obtained only from animal proteins and requires intrinsic factor (IF) for absorption. The body uses its vitamin B12 stores very economically, reabsorbing vitamin B12 from the ileum and returning it to the liver; very little is excreted. Vitamin B12 deficiency may be due to lack of IF secretion by gastric mucosa (eg, gastrectomy, gastric atrophy) or intestinal malabsorption (eg, ileal resection, small intestinal diseases). Vitamin B12 deficiency frequently causes macrocytic anemia, glossitis, peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. These manifestations may occur in any combination; many patients have the neurologic defects without macrocytic anemia. Pernicious anemia is a macrocytic anemia caused by vitamin B12 deficiency that is due to a lack of IF secretion by gastric mucosa. Serum methylmalonic acid and homocysteine levels are also elevated in vitamin B12 deficiency states. Folate: The term folate refers to all derivatives of folic acid. For practical purposes, serum folate is almost entirely in the form of N-(5)-methyl tetrahydrofolate.(4) Approximately 20% of the folate absorbed daily is derived from dietary sources; the remainder is synthesized by intestinal microorganisms. Serum folate levels typically fall within a few days after dietary folate intake is reduced and may be low in the presence of normal tissue stores. RBC folate levels are less subject to short-term dietary changes. Significant folate deficiency is characteristically associated with macrocytosis and megaloblastic anemia. Lower than normal serum folate also has been reported in patients with neuropsychiatric disorders, in pregnant women whose fetuses have neural tube defects, and in women who have recently had spontaneous abortions.(5) Folate deficiency is most commonly due to insufficient dietary intake and is most frequently encountered in pregnant women or in alcoholics. Other causes of low serum folate concentration include: -Excessive utilization (eg, liver disease, hemolytic disorders, and malignancies) -Rare inborn errors of metabolism (eg, dihydrofolate reductase deficiency, forminotransferase deficiency, 5,10-methylenetetrahydrofolate reductase deficiency, and tetrahydrofolate methyltransferase deficiency)

Useful For: Investigation of macrocytic anemia Workup of deficiencies seen in megaloblastic anemias Investigation of suspected folate deficiency

Interpretation: B12: Concentration of vitamin B12 <180 ng/L may cause megaloblastic anemia and/or peripheral neuropathies. Vitamin B12 concentrations <150 ng/L are considered evidence of vitamin B12 deficiency. Vitamin B12 concentrations between 150 ng/L and 300 ng/L are considered borderline. Follow-up testing for antibodies to intrinsic factor (IF) (IFBA / Intrinsic Factor Blocking Antibody, Serum) is recommended to identify this potential cause of vitamin B12 malabsorption. For specimens without antibodies, follow-up testing of vitamin B12 tissue deficiency by measuring methylmalonic acid (MMA) (MMAS / Methylmalonic Acid [MMA], Quantitative, Serum) and/or homocysteine (HCYSP / Homocysteine, Total, Plasma) may be indicated if the patient is symptomatic. A normal serum concentration of vitamin B12 does not rule out tissue deficiency of vitamin B12. The most sensitive test for vitamin B12 deficiency at the cellular level is the assay for MMA. If clinical symptoms suggest deficiency, measurement of MMA and homocysteine should be considered, even if serum vitamin B12 concentrations are normal. Folate: Serum folate is a relatively nonspecific test.(4) Low serum folate levels may be seen in the absence of deficiency and normal levels may be seen in patients with macrocytic anemia, dementia, neuropsychiatric disorders, and pregnancy disorders. Results <4 mcg/L are suggestive of folate deficiency. The cut-off is based on consensus and was derived from the US NHANES III data.(5) Evaluation of macrocytic anemias commonly requires measurement of the serum concentration of both vitamin B12 and folate; ideally they should be measured at the same point in time. Additional testing with homocysteine and MMA determinations may help distinguish between B12 and folate deficiency states. In folate deficiency, homocysteine levels are elevated and MMA levels are normal. In vitamin B12

deficiency, both homocysteine levels and MMA levels are elevated. For more information, see Vitamin B12 Deficiency Evaluation.

Reference Values:
VITAMIN B12
180-914 ng/L

FOLATE
> or =4.0 mcg/L
<4.0 mcg/L suggests folate deficiency

Clinical References: 1. Babior BM: The megaloblastic anemias. In Hematology. Fifth edition. Edited by WJ Williams, E Beutler, MA Lichtman, et al. New York, McGraw-Hill Book Company, 1995, pp 471-490 2. Shenkin A, Baines M, Fell GS, et al: In Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. Edited by CA Burtis, ER Ashwood, DE Bruns. St. Louis, Elsevier, Inc., 2006, pp 1100-1105 3. Klee GG: Cobalamin and folate evaluation: measurement of methylmalonic acid and homocysteine vs vitamin B12 and folate. Clin Chem 2000 August;46(8 Pt 2):1277-1283 4. Fairbanks VF, Klee GG: Biochemical aspects of hematology. In Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. Philadelphia, WB Saunders Company, 1999, pp 1690-1698 5. George L, Mills JL, Johansson AL, et al: Plasma folate levels and risk of spontaneous abortion. JAMA 2002 October 16;288:1867-1873 6. Benoist BD: Conclusions of a WHO Technical Consultation on folate and vitamin B12 deficiencies. Food and Nutrition Bulletin 2008(volume 29, number 2) S238-S244

B12
9154

Vitamin B12 Assay, Serum

Clinical Information: Vitamin B12 (cobalamin) is necessary for hematopoiesis and normal neuronal function. In humans, it is obtained only from animal proteins and requires intrinsic factor (IF) for absorption. The body uses its vitamin B12 stores very economically, reabsorbing vitamin B12 from the ileum and returning it to the liver; very little is excreted. Vitamin B12 deficiency may be due to lack of IF secretion by gastric mucosa (eg, gastrectomy, gastric atrophy) or intestinal malabsorption (eg, ileal resection, small intestinal diseases). Vitamin B12 deficiency frequently causes macrocytic anemia, glossitis, peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. These manifestations may occur in any combination; many patients have the neurologic defects without macrocytic anemia. Pernicious anemia is a macrocytic anemia caused by vitamin B12 deficiency that is due to a lack of IF secretion by gastric mucosa. Serum methylmalonic acid and homocysteine levels are also elevated in vitamin B12 deficiency states.

Useful For: Investigation of macrocytic anemia Workup of deficiencies seen in megaloblastic anemias

Interpretation: A serum vitamin B12 level less than 180 ng/L may cause megaloblastic anemia and peripheral neuropathies. Vitamin B12 levels less than 150 ng/L are considered evidence of vitamin B12 deficiency. Follow-up with a test for antibodies to intrinsic factor (IFBA / Intrinsic Factor Blocking Antibody, Serum) is recommended to identify this potential cause of vitamin B12 malabsorption. For specimens without antibodies and the patient is symptomatic, follow-up testing for vitamin B12 tissue deficiency may be indicated. Consider analysis of methylmalonic acid (MMAS / Methylmalonic Acid, Quantitative, Serum) and/or homocysteine (HCYSP / Homocysteine, Total, Plasma). Patients with serum vitamin B12 levels between 150 and 400 ng/L are considered borderline deficient and should be evaluated further by functional tests for vitamin B12 deficiency. Plasma homocysteine measurement (HCYSP / Homocysteine, Total, Plasma) is a good screening test where a normal level effectively excludes vitamin B12 and folate deficiency in an asymptomatic patient. However, the test is not

specific, and many situations can cause an increased level. In contrast, an increased serum methylmalonic acid (MMAS / Methylmalonic Acid, Quantitative, Serum) level is more specific for cellular-level B12 deficiency and is not increased by folate deficiency. In patients being evaluated for vitamin B12 deficiency who have intrinsic factor blocking antibodies (IFBA), false elevations of vitamin B12 may occur due to IFBA interference, potentially obscuring a physiological deficiency of vitamin B12. If observed vitamin B12 concentrations are discordant with clinical presentation, measurement of methylmalonic acid (MMAS / Methylmalonic Acid, Quantitative, Serum) should be considered. For more information see Vitamin B12 Deficiency Evaluation.

Reference Values:
180-914 ng/L

Clinical References:

VITB3
604987

Vitamin B3 and Metabolites, Plasma

Clinical Information: Vitamin B3 is the term used for a group of closely related water-soluble pyridine derivatives, primarily derived from tryptophan. Niacin (also known as nicotinic acid) is converted to nicotinamide, which can also be synthesized directly from tryptophan. Nicotinamide serves as the precursor of nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), essential coenzymes for numerous dehydrogenases. Many of these enzymes play a role in energy release from carbohydrates and fats, but numerous other pathways are also NAD/NADP dependent, ranging from intra- and inter-cell signaling, to DNA repair, to fatty acid-, cholesterol- and steroid hormone synthesis, and many other vital biochemical functions. Nicotinuric acid is a major inactive metabolite of niacin and nicotinamide. Vitamin B3 deficiency most severely impacts tissues with high energy requirements or high turnover. Thus, the skin, the gastrointestinal tract, and the brain are primarily affected, but the function of numerous other organ systems, such as bone marrow and heart, might also be impaired. Severe vitamin B3 deficiency manifests as a distinct clinical syndrome, called pellagra, which is clinically characterized by the "3Ds": dermatitis, diarrhea, and dementia; if untreated, it will result in death. The onset of deficiency symptoms is subacute or chronic. The most common cause of vitamin B3 deficiency is inadequate dietary intake of niacin or tryptophan. At-risk populations are older adults, those with limited income, and those who are malnourished or suffer from malabsorption. Malnourished individuals with severe chronic alcoholism are at particularly high risk, as high alcohol intake impairs absorption of niacin and tryptophan as well as further downstream liver metabolism to bioactive of vitamin B3 compounds. Liver disease in general is also a risk factor, as nicotinamide is derived in the liver from tryptophan. This process requires vitamins B6, B2, and iron, so deficiencies of any of these factors might also predispose the individual to vitamin B3 deficiency. Issues that impact the availability of tryptophan for vitamin B3 synthesis can also lead to deficiency. Examples include: -Hartnup disease, a hereditary disorder that reduces tryptophan absorption -Carcinoid syndrome, a gastro-entero-pancreatic neuroendocrine tumor disorder that results in serotonin overproduction, with the majority of available tryptophan being channeled into serotonin synthesis -Various drugs (eg, isoniazid, chloramphenicol, fluorouracil, mercaptopurine) In most cases, vitamin B3 supplementation should result in a cure, even if the deficiency has progressed to the state of pellagra. Vitamin B3 toxicity is much less common than deficiency. Its occurrence is essentially limited to individuals who consume vitamin B3 supplements in extremely excessive doses or to patients who are prescribed niacin for treatment of hypercholesterolemia, as the doses used in this setting are very high. Common symptoms are flushing, itching, dizziness, tachycardia, nausea and vomiting, diarrhea, and gout. Rarely liver damage or stroke has been observed. The onset of symptoms is acute or subacute.

Useful For: Assisting in the diagnosis of suspected vitamin B3 deficiency or toxicity May be useful in determining response to therapy

Interpretation: Nicotinamide concentrations below the established reference range indicate a deficiency. Niacin or nicotinamide concentrations that exceed the upper reference range substantially suggest potential toxicity in patients with excessive supplement intake or under niacin treatment for hypercholesterinemia.

Reference Values:
Nicotinic Acid (Niacin) Cutoff: <5.0 ng/mL
Nicotinamide: 5.0-48.0 ng/mL
Nicotinuric Acid Cutoff: <5.0 ng/mL

Clinical References: 1. Delgado-Sanchez L, Godkar D, Niranjan S: Pellagra. Rekindling of an old flame. Am J Ther. 2008;15(2):173-175. doi: 110.1097/MJT.1090b1013e31815ae31309 2. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA): A Scientific opinion on dietary reference values for niacin. EFSA Journal. 2014;12(7):3759. doi: 10.2903/j.efsa.2014.3759 3. Expert Group on Vitamins and Minerals: Safe Upper Levels for Vitamins and Minerals. Food Standard Agency; 2003:1-361. Accessed April 23, 2024. Available at https://cot.food.gov.uk/sites/default/files/vitmin2003.pdf 4. Fu CS, Swendseid ME, Jacob RA, McKee RW. Biochemical markers for assessment of niacin status in young men: Levels of erythrocyte niacin coenzymes and plasma tryptophan. J Nutr. 1989;119(12):1949-1955 5. Powers HJ. Current knowledge concerning optimum nutritional status of riboflavin, niacin and pyridoxine. Proc Nutr Soc. 1999;58(2):435-440 6. Shah GM, Shah RG, Veillette H, et al. Biochemical assessment of niacin deficiency among carcinoid cancer patients. Am J Gastroenterol. 2005;100(10): 2307-2314. doi: 2310.1111/j.1572-0241.2005.00268.x 7. Sun WP, Zhai MZ, Li D, et al. Comparison of the effects of nicotinic acid and nicotinamide degradation on plasma betaine and choline levels. Clin Nutr. 2017;36(4):1136-1142

FPAB 57394 Vitamin B5 (Pantothenic Acid) Bioassay

Clinical Information: Pantothenic acid, commonly known as vitamin B5, is a water-soluble vitamin. As part of acetyl CoA or an acyl carrier protein, pantothenic acid plays an essential role in metabolic pathways. It functions in the oxidation of both fatty acids and carbohydrates for energy production in the form of A TP. Vitamin B5 also participates in the synthesis of amino acids, fatty acids, ketones, cholesterol, phospholipids, and steroids. Additionally, vitamin B5 contributes to porphyrin and hemoglobin biochemistry and in adrenal function. Pantothenic acid deficiency is exceedingly rare, mostly affecting individuals who are severely malnourished. Those who lack an adequate amount of vitamin B5 may demonstrate symptoms such as paresthesias, muscle weakness, fatigue, nausea, abdominal pains and susceptibility to infection.

Reference Values:

B6PRO 42360 Vitamin B6 Profile (Pyridoxal 5-Phosphate and Pyridoxic Acid), Plasma

Clinical Information: Vitamin B6 is a generic term that refers to the pyridine-based compounds pyridoxine, 4-pyridoxic acid, pyridoxamine, pyridoxal, and their phosphorylated derivatives. Pyridoxal-5'-phosphate (PLP) is the biologically active form and serves as a cofactor for more than 140 different enzyme reactions, representing 4% of all known catalytic activity. Deficiencies can occur in people with mutations of pyridoxal kinase or pyridoxine 5'-phosphate oxidase, as well as in individuals who are pregnant, have kidney disease, are severely malnourished, or have malabsorption. Additionally, deficiencies have been observed with the usage of certain drugs such as isoniazid, penicillamine, benserazide, and carbidopa. Vitamin B6 deficiency is a potential cause of burning mouth syndrome and a possible potentiating factor for carpal tunnel and tarsal tunnel syndromes. Persons who present

chronic, progressive nerve compression disorders may be deficient in vitamin B6 and should be evaluated. Vitamin B6 deficiency is associated with symptoms of scaling of the skin, severe gingivitis, irritability, weakness, depression, dizziness, peripheral neuropathy, and seizures. In the pediatric population, deficiencies have been characterized by diarrhea, anemia, and seizures. Conversely, exceptionally high levels of vitamin B6 can also have toxic effects resulting in sensory and motor neuropathies. Markedly elevated PLP in conjunction with low or normal levels of pyridoxic acid are observed in cases of hypophosphatasia, a disorder caused by loss-of-function mutation(s) of the gene ALPL that encodes the tissue-nonspecific isoenzyme of alkaline phosphatase

Useful For: Determining vitamin B6 status, including in persons who present with progressive nerve compression disorders, such as carpal tunnel and tarsal tunnel syndromes Determining the overall success of a vitamin B6 supplementation program Diagnosis and evaluation of hypophosphatasia Differentiating between hypophosphatasia or dietary supplementation as the likely cause of elevated pyridoxal-5'-phosphate (PLP) levels

Interpretation: Levels for fasting individuals falling in the range of 3 to 30 mcg/L for pyridoxic acid (PA) and 5 to 50 mcg/L for pyridoxal 5-phosphate (PLP) are indicative of adequate nutrition. The following are interpretative guidelines based on PLP and PA results: If PLP is >100 mcg/L and PA is < or =30 mcg/L: -The increased PLP is suggestive of hypophosphatasia. Consider analysis of serum alkaline phosphatase isoenzymes (ALKP / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine) If PLP is >100 mcg/L and PA is 31 to 100 mcg/L or PLP is 81 to 100 mcg/L and PA is < or =30 mcg/L: -The increased PLP is likely related to dietary supplementation; however, a mild expression of hypophosphatasia cannot be excluded. Consider analysis of serum alkaline phosphatase isoenzymes (ALKP / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine). If PLP is 51 to 80 mcg/L or PLP is 81 to 100 mcg/L and PA is >30 mcg/L or PLP is >100 mcg/L and PA is >100 mcg/L: -The elevated PLP is likely due to dietary supplementation.

Reference Values:
PYRIDOXAL 5-PHOSPHATE
5-50 mcg/L

PYRIDOXIC ACID
3-30 mcg/L

Clinical References: 1. Whyte MP, Zhang F, Wenkert D, et al. Hypophosphatasia: Vitamin B6 status of affected children and adults. Bone. 2022;154:116204. doi:10.1016/j.bone.2021.116204 2. Vitamin B6-Fact Sheet for Health Professionals. US Department of Health and Human Services, National Institutes of Health. Office of Dietary Supplements. Updated June 16, 2023. Accessed February 5, 2025. Available at: https://ods.od.nih.gov/factsheets/VitaminB6-HealthProfessional/ 3. Sodi R, Taylor A. Vitamins and trace elements In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics. 8th ed. Elsevier; 2020:466-487 4. Morris MS, Picciano MF, Jacques PF, Selhub J. Plasma pyridoxal 5'-phosphate in the US population: the National Health and Nutrition Examination Survey, 2003-2004. Am J Clin Nutr. 2008;87(5):1446-1454. doi:10.1093/ajcn/87.5.1446

FBIOT
91902

Vitamin B7, H (Biotin)

Clinical Information: Biotin, vitamin B7, or vitamin H, is a water-soluble vitamin. The vitamin plays a role in the transferring of carbon dioxide in the metabolism of fat, carbohydrate and protein by functioning as an enzyme cofactor. It is involved in multiple biochemical reactions including niacin metabolism, amino acid degradation, and the formation of purine, which is an integral part of nucleic

acids. It interacts with histone by the action of biotinyl-transferase. Sometimes the vitamin is used in weight reduction programs. It may be prescribed as a supplement for diabetic patients due to its role in carbohydrate metabolism. Biotin is commonly found in vitamin B complex and many food sources, such as milk, yeast, egg yolk, cereal, and mushrooms. The reference daily intake [RDI of 101.9(c) (8) (IV)] for vitamin B7 is 300 micrograms. Deficiency in the vitamin may result in seborrheic dermatitis, alopecia, myalgia, hyperesthesia, and conjunctivitis. Disorders of biotin metabolism can be acquired or congenital. Biotinidase and holocarboxylase synthethase deficiency are the two better known forms of disorders. The lack of biotin-dependent pyruvate carboxylase, propionyl-CoA carboxylase, methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase can lead to the life-threatening disorder of multiple carboxylase deficiency. Treatment involves a daily dose of approximately 10 mg biotin/day. Irreversible mental or neurological abnormalities may result from delayed clinical intervention.

Reference Values:

Pediatric Normal <12 yrs: 100.0-2460.2 pg/mL
Adults Normal >or=12 yrs: 221.0-3004.0 pg/mL

VITE
42358

Vitamin E, Serum

Clinical Information: Vitamin E is the generic term for two different groups of methylated phenol compounds with a chromane alcoholic core linked to poly-carbon chains (tocopherols and tocotrienols). These vitamins are all free radical scavengers, with a-Tocopherol being the most potent one in humans, as most of the related compounds are not re-secreted by the liver, thus leading to much lower circulating concentrations. Vitamin E deficiency is very rare and mostly seen in patients with extreme malabsorption of fat and in patients with abetalipoproteinemia, a rare inborn error of metabolism. Patients with these conditions may develop peripheral neuropathy, myopathy, retinopathy, and immune deficiency. There is a large body of scientific studies that indicates positive effects on outcomes of various diseases if regular Vitamin E supplementation is provided; however, several trials have shown evidence of increasing bleeding risks at high Vitamin E doses. Therefore, tables of tolerable doses in children and adults have been established, which should not be exceeded.

Useful For: Monitoring of Vitamin E supplementation/treatment Potentially detecting Vitamin E overdoses

Interpretation: Vitamin E concentrations within the healthy reference population range usually indicate adequate Vitamin A stores. The rare occurrence of low Vitamin A levels might correlate with potential deficiency and investigation of potential fat malabsorptions should be considered. Conversely, Vitamin E concentrations significantly above the upper healthy reference population range might indicate that Vitamin E intake exceeds the tolerable upper daily intake level(s).

Reference Values:

0-17 years: 3.8-18.4 mg/L
> or =18 years: 5.5-17.0 mg/L

Clinical References: 1. Ball GFM. Vitamins: Their role in the human body. Oxford, Blackwell Publishing. 2004:234-255 2. Traber MG. Vitamin E. In: Shils ME, Shike M, Ross AC, et al, eds. Modern Nutrition in Health and Disease.10th ed. Lippincott Williams and Wilkins; 2006:434-441 3. Roberts NB, Taylor A, Sodi R. Vitamins and trace elements. In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:chap37 4. Sodi R. Vitamins and trace elements. In: Rifai N, Chiu RWK, Young I, Burnham C-AD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:417-417.e104

VITK1
42364

Vitamin K1, Serum

Clinical Information: Vitamin K1, or phylloquinone, is part of a group of similar fat-soluble vitamins in which the 2-methyl-1,4- naphthoquinone ring is common. Phylloquinone is found in high amounts in leafy green vegetables and some fruits (avocado, kiwi). It is a required cofactor involved in the gamma-carboxylation of glutamate residues of several proteins. Most notably, the inactive forms of the coagulation factors prothrombin (factor II), factors VII, IX, and X, as well as protein S and protein C are converted to their active forms by the transformation of glutamate residues to gamma-carboxyglutamic acid (Gla). Other proteins such as those involved in bone metabolism, cell growth and apoptosis also undergo this Gla transformation. Thus, vitamin K plays a critical role in hemostasis (blood clotting) and acute deficiency is characterized by defective blood coagulation. In neonates, low vitamin K levels in breast milk, inadequate placental transport, and hepatic immaturity leading to insufficient synthesis of coagulation proteins can result in the bleeding disorder hemorrhagic disease of the newborn. To minimize this risk, Vitamin K is commonly administered prophylactically immediately after birth. Other at-risk groups for vitamin K deficiency include those with insufficient dietary intake, malabsorption disorders, cystic fibrosis, cholestasis, and alcoholism, as well as liver and pancreatic disease. Several drugs such as coumarin anticoagulants (ie, warfarin) and antibiotics (ie, cephalosporin) have also been shown to interfere with vitamin K metabolism. High doses of vitamin K have not been shown to produce toxicity. Direct measurement of vitamin K1 by liquid chromatography tandem mass spectrometry has been established as a highly effective strategy to assess status and intake.

Useful For: Assessment of circulating vitamin K1 concentration.

Interpretation: Low vitamin K1 concentrations in the serum are indicative of insufficiency and poor vitamin K1 status.

Reference Values:
<18 years: Not established
> or =18 years: 0.10-2.20 ng/mL

Clinical References: 1. Vitamin K-Fact Sheet for Health Professionals. US Department of Health and Human Services, National Institutes of Health. Office of Dietary Supplements. Updated March 29, 2021. Accessed April 9, 2025. Available at: https://ods.od.nih.gov/factsheets/VitaminK-HealthProfessional/ 2. Zhang Y, Bala V, Mao Z, Chhonker YS, Murry DJ. A concise review of quantification methods for determination of vitamin K in various biological matrices. J Pharm Biomed Anal. 2019;169:133-141. doi:10.1016/j.jpba.2019.03.006 3. Sodi R, Taylor A. Vitamins and trace elements In: Rifai N, Horvath AR, Wittwer CT, eds. Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics. 8th ed. Elsevier; 2020:466-487 4. Booth SL. Vitamin K: food composition and dietary intakes. Food Nutr Res. 2012;56 :10.3402/fnr.v56i0.5505. doi:10.3402/fnr.v56i0.5505 5. Shearer MJ, Newman P. Metabolism and cell biology of vitamin K. Thromb Haemost. 2008;100(4):530-547 6. Mladenka P, Macakova K, Kujovska Krcmova L, et al. Vitamin K - sources, physiological role, kinetics, deficiency, detection, therapeutic use, and toxicity. Nutr Rev. 2022;80(4):677-698. doi:10.1093/nutrit/nuab061 7. Card DJ, Gorska R, Harrington DJ. Laboratory assessment of vitamin K status. J Clin Pathol. 2020;73(2):70-75. doi:10.1136/jclinpath-2019-205997

VLTB
89190

Volatile Screen, Blood

Clinical Information: Volatile substances in blood include ethanol, methanol, isopropanol, and acetone. Acetone is generally elevated in metabolic conditions such as diabetic ketoacidosis. Methanol and isopropanol are highly toxic and result from exogenous ingestion. Ethanol is one of the most widely abused legal substances in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral function as a depressant similar to general anesthetics. This

depression causes most of the typical symptoms, such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment progressively increases. In most jurisdictions in the United States, the per se blood level for being under the influence of alcohol (ethanol) for purposes of driving a motor vehicle is 80 mg/dL (0.08%).

Useful For: Detection and quantitation of acetone, methanol, isopropanol, and ethanol in whole blood Quantification of the concentration of ethanol in blood that correlates with the degree of intoxication Evaluation of toxicity to the measured volatile substances This test is not intended for use in employment-related testing.

Interpretation: Methanol: The presence of methanol indicates exposure that may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure that may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure that may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

Reference Values:

Methanol:
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

Ethanol:
Not detected (Positive results are quantitated.)
Toxic concentration: > or =400 mg/dL

Isopropanol:
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

Acetone:
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

Clinical References: 1. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 2. Mayfield J, Mihic SJ. Ethanol. In: Brunton LL, Knollmann BC. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. McGraw-Hill Education; 2022:chap 27 3. Olson KR, Anderson IB, Benowitz NL, et al. Specific Poisons and Drugs: Diagnosis and Treatment. In: Poisoning and Drug Overdose. 8th ed. McGraw-Hill; 2022:section II

VLTBX
62745

Volatile Screen, Chain of Custody, Blood

Clinical Information: Volatile substances in the blood include ethanol, methanol, isopropanol, and acetone. Acetone is generally elevated in metabolic conditions such as diabetic ketoacidosis. Methanol and isopropanol are highly toxic and result from exogenous ingestion. Ethanol is one of the most widely abused legal substances in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral function as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment progressively increases.

In most jurisdictions in the United States, the per se blood level for being under the influence of alcohol (ethanol) for purposes of driving a motor vehicle is 80 mg/dL (0.08%). Chain of custody is required whenever the results of testing could be used in a court of law. Chain of custody is a record of the disposition of a specimen to document the individuals that collected it, handled it, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detection and quantitation of acetone, methanol, isopropanol, and ethanol in whole blood Quantification of the concentration of ethanol in blood that correlates with the degree of intoxication Evaluation of toxicity to the measured volatile substances This test is not intended for use in employment-related testing. Providing chain-of-custody for when the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: Methanol: The presence of methanol indicates exposure that may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure that may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure that may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

Reference Values:

Methanol:
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

Ethanol:
Not detected (Positive results are quantitated.)
Toxic concentration: > or =400 mg/dL

Isopropanol:
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

Acetone:
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

Clinical References: 1. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 2. Mayfield J, Mihic SJ. Ethanol. In: Brunton LL, Knollmann BC. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. McGraw-Hill Education; 2022:chap 27 3. Olson KR, Anderson IB, Benowitz NL, et al. Specific Poisons and Drugs: Diagnosis and Treatment. In: Poisoning and Drug Overdose. 8th ed. McGraw-Hill; 2022:section II

VLTUX
62746

Volatile Screen, Chain of Custody, Random, Urine

Clinical Information: Urine provides a medium for easy screening for methanol, ethanol, isopropanol, and acetone. Chain of custody is required whenever the results of testing could be used in a

court of law. Chain of custody is a record of the disposition of a specimen to document the individuals that collected it, handled it, and performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting the presence of acetone, methanol, isopropanol, or ethanol in urine with subsequent quantitation Providing chain of custody for when the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was always under the control of personnel involved with testing the specimen; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: Methanol: The presence of methanol indicates exposure that may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure that may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure that may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

Reference Values:

Methanol
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

Ethanol
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL

Isopropanol
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

Acetone
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

Clinical References: 1. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023;chap 43 2. Mayfield J, Mihic SJ. Ethanol. In: Brunton LL, Knollmann BC, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. McGraw-Hill Education; 2012:chap 27 3. Olson KR, Anderson IB, Benowitz NL, et al. Specific Poisons and Drugs: Diagnosis and Treatment. In: Poisoning and Drug Overdose. 8th ed. McGraw-Hill; 2022:section II

VLTU
8826

Volatile Screen, Random, Urine

Clinical Information: Urine provides a medium for easy screening for methanol, ethanol, isopropanol, and acetone.

Useful For: Detecting the presence of acetone, methanol, isopropanol, or ethanol in urine with

subsequent quantitation

Interpretation: Methanol: The presence of methanol indicates exposure that may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure that may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure that may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

Reference Values:

Methanol:
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

Ethanol:
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL

Isopropanol:
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

Acetone:
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

Clinical References: 1. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 2. Mayfield J, Mihic SJ. Ethanol. In: Brunton LL, Knollmann BC. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. McGraw-Hill Education; 2022:chap 27 3. Olson KR, Anderson IB, Benowitz NL, et al. Specific Poisons and Drugs: Diagnosis and Treatment. In: Poisoning and Drug Overdose. 8th ed. McGraw-Hill; 2022:section II

VLTS
8632

Volatile Screen, Serum

Clinical Information: Volatile substances in the blood include ethanol, methanol, isopropanol, and acetone. Methanol and isopropanol are highly toxic; toxicity results from ingestion (exogenous). Acetone is generally elevated in metabolic conditions such as diabetic ketoacidosis (endogenous). It also is a metabolite of isopropanol. Ethanol is one of the most widely abused legal substances in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral function as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment progressively increases. On average, the serum or plasma concentration of the alcohols is 1.2-fold higher than blood concentration. For example, the serum or plasma would contain approximately 0.10 g/dL of ethanol in a blood specimen that contains 0.08 g/dL ethanol. Due to potential variations in the serum to whole blood ratio, serum should not be used in a medico-legal context. However, in the context of medical/clinical assessment, serum or plasma may be

submitted for analysis.

Useful For: Detection and quantitation of acetone, methanol, isopropanol, and ethanol in serum Quantification of the concentration of ethanol in serum correlates with degree of intoxication Evaluation of toxicity to the measured volatile substances

Interpretation: Methanol: The presence of methanol indicates exposure that may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure that may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure that may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

Reference Values:

Methanol:
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

Ethanol:
Not detected (Positive results are quantitated.)
Toxic concentration: > or =400 mg/dL

Isopropanol:
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

Acetone:
Not detected (Positive results are quantitated.)
Toxic concentration: > or =10 mg/dL

Clinical References: 1. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43 2. Mayfield J, Mihic SJ. Ethanol. In: Brunton LL, Knollmann BC. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. McGraw-Hill Education; 2022:chap 27 3. Olson KR, Anderson IB, Benowitz NL, et al. Specific Poisons and Drugs: Diagnosis and Treatment. In: Poisoning and Drug Overdose. 8th ed. McGraw-Hill; 2022:section II

VHLZZ 614589 Von Hippel Lindau Syndrome, VHL, Full Gene Analysis, Varies

Clinical Information: Germline variants in the VHL gene are associated with Von Hippel-Lindau (VHL) syndrome, a rare autosomal dominant hereditary cancer syndrome.(1,2) VHL syndrome is characterized by an increased risk of developing a variety of cancerous and non-cancerous tumors and lesions, including hemangioblastomas of the brain or spinal cord, retinal angiomas, renal, pancreatic and epididymal cysts, pheochromocytomas, pancreatic neuroendocrine tumors, endolymphatic cell tumors, and clear cell renal cell carcinoma.(3) While considered a highly penetrant condition, approximately 20% of VHL syndrome cases are due to new (de novo) disease-causing variants, which, in some cases, result in disease mosaicism.(4) Research has suggested certain combinations of VHL tumors cluster in VHL families, and this may be driven by the type of VHL gene variant present in the family.(4) This observation has led to a phenotype-based classification of VHL syndrome. However, these patterns are not entirely specific and should not necessarily be used for diagnostic or therapeutic purposes. The

National Comprehensive Cancer Network provides recommendations regarding the medical management of individuals with VHL syndrome. Of note, germline variants in the VHL gene are also associated with autosomal recessive hereditary erythrocytosis or polycythemia. Cases of VHL cancer syndrome and erythrocytosis are largely mutually exclusive, although there is some overlap. For information regarding genetic testing for patients suspected to have hereditary erythrocytosis or polycythemia, see HEMP / Hereditary Erythrocytosis Mutations, Whole Blood.

Useful For: Evaluating patients with a personal or family history suggestive of Von Hippel-Lindau (VHL) syndrome Establishing a diagnosis of a VHL allowing for targeted cancer surveillance based on associated risks Identifying genetic variants associated with increased risk for VHL syndrome allowing for predictive testing of at-risk family members

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. OMIM: 193300. Von Hippel-Lindau Syndrome; VHLS. Johns Hopkins University; 1986. Updated June 4, 2020. Accessed September 9, 2024. Available at https://omim.org/entry/193300 2. Beroud C, Collod-Beroud G, Boileau C, Soussi T, Junien C. UMD-VHL mutations database. The Universal Mutation Database (UMD); Accessed July 7, 2021. Available at www.umd.be 3. van Leeuwaarde RS, Ahmad S, Links TP, Giles RH. Von Hippel-Lindau syndrome. In: Adam MP, Everman DB, Mirzaa GM et al, eds. GeneReviews. [Internet]. University of Washington, Seattle; 2000. Updated February 29, 2024. Accessed September 9, 2024. Available at: www.ncbi.nlm.nih.gov/books/NBK1463/ 4. Lonser RR, Glenn GM, McClellan W, et al. von Hippel-Lindau disease. Lancet. 2003;361(9374):2059-2067 5. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

VWD8B
605011

von Willebrand Disease 2N (Subtype Normandy), Plasma

Clinical Information: von Willebrand disease (VWD) is a bleeding disorder due to quantitative or qualitative defects in von Willebrand factor (VWF), which results from disease-causing alterations in the VWF gene. VWD constitutes 1 of the 2 most common bleeding disorders. Most subtypes of VWD are inherited as autosomal dominant traits, although autosomal recessive variants occur. In hemostasis, there are 2 essential roles for VWF. The first is its ability to promote platelet adhesion to damaged vessel walls, and the second is to function as a carrier protein for Factor VIII (FVIII). Thus, noncovalent binding of FVIII to VWF is necessary for normal survival of FVIII in the blood circulation. In patients with severe VWD, the circulating half-life of endogenous or infused FVIII is shorter than expected. Disease-causing alterations within the FVIII binding domain of VWF may result in an isolated 'deficiency' of FVIII associated with a clinically mild to moderate bleeding disorder that may be misdiagnosed as Hemophilia A (HA). Abnormal binding of FVIII to VWF can be detected with a binding assay. Since its initial description in patients from the Normandy region of France, more recent studies suggest that VWD type 2N or Normandy (VWD2N) has been associated with a more severe phenotype among patients who are homozygous for pathogenic alterations within the FVIII binding domain of VWF. In an international survey, FVIII binding defect was detected in 58 out of 1198 (4.8%) patients with mild HA. Other studies confirm these findings and reveal that 1.5% to 16.6% of patients with VWD Type 1 have the FVIII binding defect. The diagnosis of VWD2N has 2 main implications: -Genetic counseling differs

considerably from that for X-linked recessive HA since the inheritance of VWD2N is autosomal recessive. -Optimal treatment or prophylaxis of bleeding requires factor replacement therapy with products containing functional VWF.

Useful For: Diagnosing von Willebrand disease (VWD) type 2N Evaluating patients diagnosed with mild-to-moderate hemophilia A with an autosomal inheritance pattern Evaluating hemophilia A patients with a shortened survival of infused factor VIII (FVIII) (not caused by a specific FVIII inhibitor) Evaluating female patients with low FVIII activity and no prior family history of hemophilia A Evaluating patients with Type 1 or Types 2A, 2B, or 2M VWD with FVIII activity discordantly lower than the von Willebrand factor antigen level

Interpretation: A reduced capacity of a patient's von Willebrand factor (VWF) to bind to recombinant factor VIII (FVIII) is consistent with von Willebrand disease (VWD) type 2N (Normandy). A mild to moderate decrease of the VWF to factor VIII (FVIII) binding ratio suggests the presence of a VWD Type 2N due to heterozygous variants in the FVIII binding domain of VWF. If clinically indicated, DNA sequence analysis of the FVIII binding domain of VWF may provide useful information. Results do not exclude other variants of congenital VWD, eg, type 1, 2A, 2B, or 2M or congenital hemophilia A. Clinical correlation should be made between patient and family bleeding history and results of VWF antigen, factor VIII and VWF activity assays.

Reference Values:
68-106%
Pediatric reference ranges have not been established for this assay but likely achieve adult reference range by 18 years of age.

Clinical References: 1. Veyradier A, Caron C, Ternisien C, et al. Validation of the first commercial ELISA for type 2N von Willebrand's disease diagnosis. Haemophilia. 2011;17(6):944-951. doi:10.1111/j.1365-2516.2011.02499.x 2. Sadler JE. A revised classification of von Willebrand disease. For the Subcommittee on von Willebrand Factor of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis.Thromb Haemost. 1994;71(4):520-525 3. Mazurier C, Gaucher C, Jorieux S, et al. Evidence for a von Willebrand factor defect in factor VIII binding in three members of a family previously misdiagnosed as heamophilia A carriers: consequences for therapy and genetic counselling. Br J Haematol 1990;76(3):372-379. doi:10.1111/j.1365-2141.1990.tb06371.x 4. Schneppenheim R, Budde U, Krey S, et al. Results of a screening for von Willebrand disease type 2N in patients with suspected haemophilia A or von Willebrand disease type 1. Thromb Haemost. 1996;76(4):598-602 5. Seidizadeh O, Peyvandi F, Mannucci PM. Von Willebrand disease type 2N: an update. J Thromb Haemost. 202119(4):909-916. doi:10.1111/jth.15247

AVWPQ
603186

von Willebrand Disease Profile Interpretation

Clinical Information:

Useful For: Interpretation of testing performed as part of a profile for detection of deficiency or abnormality of von Willebrand factor (VWF) and related deficiency of factor VIII coagulant activity Interpretation of testing performed as part of a profile for subtyping von Willebrand disease (VWD) as type 1 (most common), type 2 variants (less common), or type 3 (rare) This test is not useful for detection of hemophilia carriers. This test is not useful for differentiating type 2A versus 2B VWD or platelet-type VWD (pseudo-VWD).

Interpretation: An interpretive report will be provided when testing is complete, noting presence or absence of von Willebrand Disease.

Reference Values:
Only orderable as part of a profile. For more information see AVWPR / von Willebrand Disease Profile, Plasma.

An interpretive report will be provided.

Clinical References: 1. Federici AB, Mannucci PM. Advances in the genetics and treatment of von Willebrand disease. Curr Opin Pediatr. 2002;14(1):23-33 2. Budde U, Schneppenheim R. von Willebrand factor and von Willebrand disease. Rev Clin Exp Hematol. 2001;5(4):335-368 3. Kumar S, Pruthi RK, Nichols WL. Acquired von Willebrand disease. Mayo Clin Proc 2002;77(2):181-187 4. Favaloro EJ and Lippi G. eds. Hemostasis and Thrombosis, Methods and Protocols. Humana Press 2017

AVWPI
603551

von Willebrand Disease Profile Technical Interpretation

Clinical Information: von Willebrand factor (VWF) is synthesized by the endothelial cell and megakaryocyte and is present in these cells, as well as in platelets, subendothelial tissue, and plasma. VWF serves as an adhesive protein important in adhering platelets to subendothelial tissue at the site of vascular injury and for adhering platelets to each other (aggregation). Platelet adhesion and aggregation are essential to form a mechanical hemostatic "plug" and as the focus for interaction of clotting factors and phospholipid required for the formation of the fibrin platelet clot. VWF also stabilizes plasma factor VIII by binding it and protecting it from proteolysis and serves as a carrier protein for that clotting factor. VWF circulates in the blood in 2 distinct compartments. Plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells. Platelet VWF (about 10% of the blood VWF) reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. Plasma VWF circulates normally in multimeric forms with molecular weights ranging from 500,000 to as much as 20,000,000. The high-molecular-weight (HMW) forms of VWF are the most effective components for interaction with platelets. This primary activity of plasma VWF is measured in the laboratory with the VWF activity assay, whereas VWF antigen testing measures the amount of VWF protein, and factor VIII coagulant activity indirectly reflects VWF interaction with factor VIII. VWF multimer analysis visualizes the distribution of VWF multimers and is useful as a reflexive test for subtyping von Willebrand disease (VWD). Levels of factor VIII, VWF antigen, and VWF activity may vary greatly within an individual over time and also with blood type (normal blood type O individuals may have VWF lower than normals of other blood groups). VWF levels (and factor VIII) can be elevated in liver disease, pregnancy, estrogen therapy, inflammation, and after exercise (acute-phase reactant). VWF levels in hemophilia are normal. VWF antigen measurement assesses the mass of plasma VWF protein but does not reflect VWF functions or platelet VWF. The function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma VWF activity. VWD is the most common inherited bleeding disorder, affecting up to 1% of the population. It can also occur as an acquired bleeding disorder. Bleeding symptoms in all types of VWD are primarily mucosal, including epistaxis, menorrhagia, gastrointestinal bleeding, and ease of bruising, but surgical or posttraumatic bleeding can also occur. Subtypes of inherited VWD are: Type 1 VWD: VWF plasma levels (antigen and activity) typically are concordantly reduced in type 1 VWD. Because of this reduction, the level of coagulation factor VIII is often secondarily reduced. Type 1 VWD is the most common VWD variation, representing 70% to 80% of clinical VWD. It is typically inherited in autosomal dominance fashion, although recessively inherited VWD also occurs (eg, type 3 VWD). Clinical severity ranges from mild or minimal to a moderately severe bleeding diathesis and tends to correlate most closely with VWF activity. Severe type 1 disease is also called type 3 VWD, but the distinction between the two may sometimes be difficult. Type 2 VWD: Type 2 VWD variants represent 20% to 30% of clinical VWD, typically autosomal dominant in inheritance. There are 4 subtypes of type 2 VWD: 2A, 2B, 2M, and 2N. Abnormal plasma HMW VWF function and multimeric structure with decreased or absent HMW multimers are characteristic of types 2A and 2B but are normal in type 2M or 2N. VWF activity is decreased in types 2A, 2B, and 2M and typically is discordantly lower than VWF antigen. Type 2N (Normandy) has substantially decreased factor VIII coagulant activity (usually 5%-30% of mean normal),

with normal VWF antigen and activity and normal VWF multimers with clinical manifestation as autosomally inherited mild hemophilia (in contrast to classical X chromosome-linked hemophilia A). Type 2A is the most common of the 4. Type 2B manifests thrombocytopenia, either persistent or transient, and is distinguished from type 2A by abnormally heightened aggregation response of patient platelets and plasma to low dose ristocetin stimulation. Type 2M typically demonstrates hypofunctional VWF with decreased VWF activity discordantly lower than VWF antigen not due to loss of HMW multimers. One variant of type 2M, Vicenza variant VWD, has ultralarge VWF multimers in plasma. Type 3 VWD: VWF is absent or markedly decreased in type 3 VWD (VWF antigen and activity either undetectably low or below 5% to 10% of mean normal), with secondary decrease of factor VIII coagulant activity (5%-30%). VWF multimers may be undetectable or, if present, have a normal distribution. Platelet VWF may also be absent. Acquired VWD: VWD can also occur on an acquired basis by a variety of mechanisms not well understood. Disorders associated with acquired VWD include certain myeloproliferative or lymphoproliferative disorders, plasma cell dyscrasias including monoclonal gammopathy of undetermined significance, autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), and a variety of other diseases. In some cases, no associated disorder is detected. Laboratory testing currently cannot distinguish between congenital and acquired VWD; clinical correlation is required.

Useful For: Technical interpretation of the von Willebrand factor profile test Detection of deficiency or abnormality of von Willebrand factor and related deficiency of factor VIII coagulant activity Subtyping von Willebrand disease (VWD) as type 1 (most common), type 2 variants (less common), or type 3 (rare) This test is not useful for detection of hemophilia carriers. This test is not useful for differentiating type 2A versus 2B VWD or platelet-type VWD (pseudo-VWD).

Interpretation: If the factor VIII, von Willebrand factor (VWF) antigen, VWF activity and VWF activity:VWF antigen ratio results are normal, an interpretive comment will be provided noting no evidence of von Willebrand disease.

Reference Values:
Only orderable as part of a profile. For more information see AVWPR / von Willebrand Disease Profile, Plasma.

An interpretive report will be provided.

Clinical References: 1. Federici AB, Mannucci PM. Advances in the genetics and treatment of von Willebrand disease. Curr Opin Pediatr. 2002;14(1):23-33 2. Budde U, Schneppenheim R. von Willebrand factor and von Willebrand disease. Rev Clin Exp Hematol. 2001;5(4):335-368 3. Kumar S, Pruthi RK, Nichols WL. Acquired von Willebrand disease. Mayo Clin Proc. 2002;77(2):181-187 4. Favaloro EJ, Gosselin RC. eds. Hemostasis and Thrombosis Methods and Protocols. 2nd ed. Humana Press; 2023

AVWPR
603550

von Willebrand Disease Profile, Plasma

Clinical Information: von Willebrand factor (VWF) is synthesized by the endothelial cell and megakaryocyte and is present in these cells, as well as in platelets, subendothelial tissue, and plasma. VWF serves as an adhesive protein important in adhering platelets to subendothelial tissue at the site of vascular injury and for adhering platelets to each other (aggregation). Platelet adhesion and aggregation are essential to form a mechanical hemostatic "plug" and as the focus for interaction of clotting factors and phospholipid required for the formation of the fibrin platelet clot. VWF also stabilizes plasma factor VIII by binding it and protecting it from proteolysis and serves as a carrier protein for that clotting factor. VWF circulates in the blood in 2 distinct compartments. Plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells. Platelet VWF (about 10% of the blood VWF)

reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. Plasma VWF circulates normally in multimeric forms with molecular weights ranging from 500,000 to as much as 20,000,000. The high-molecular-weight (HMW) forms of VWF are the most effective components for interaction with platelets. This primary activity of plasma VWF is measured in the laboratory with the VWF activity assay, whereas VWF antigen testing measures the amount of VWF protein, and factor VIII coagulant activity indirectly reflects VWF interaction with factor VIII. VWF multimer analysis visualizes the distribution of VWF multimers and is useful as a reflexive test for subtyping von Willebrand disease (VWD). Levels of factor VIII, VWF antigen, and VWF activity may vary greatly within an individual over time and also with blood type (normal blood type O individuals may have VWF lower than normal individuals of other blood groups). VWF levels (and factor VIII) can be elevated in liver disease, pregnancy, estrogen therapy, inflammation, and after exercise (acute-phase reactant). VWF levels in hemophilia are normal. VWF antigen measurement assesses the mass of plasma VWF protein but does not reflect VWF functions or platelet VWF. The function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma VWF activity. VWD is the most common inherited bleeding disorder, affecting up to 1% of the population. It can also occur as an acquired bleeding disorder. Bleeding symptoms in all types of VWD are primarily mucosal, including epistaxis, menorrhagia, gastrointestinal bleeding, and ease of bruising, but surgical or posttraumatic bleeding can also occur. Subtypes of inherited VWD are: Type 1 VWD: VWF plasma levels (antigen and activity) typically are concordantly reduced in type 1 VWD. Because of this reduction, the level of coagulation factor VIII is often secondarily reduced. Type 1 VWD is the most common VWD variation, representing 70% to 80% of clinical VWD. It is typically inherited in autosomal dominance fashion, although recessively inherited VWD also occurs (eg, type 3 VWD). Clinical severity ranges from mild or minimal to a moderately severe bleeding diathesis and tends to correlate most closely with VWF activity. Severe type 1 disease is also called type 3 VWD, but the distinction between the two may sometimes be difficult. Type 2 VWD: Type 2 VWD variants represent 20% to 30% of clinical VWD, typically autosomal dominant in inheritance. There are 4 subtypes of type 2 VWD: 2A, 2B, 2M, and 2N. Abnormal plasma HMW VWF function and multimeric structure with decreased or absent HMW multimers are characteristic of types 2A and 2B but are normal in type 2M or 2N. VWF activity is decreased in types 2A, 2B, and 2M and typically is discordantly lower than VWF antigen. Type 2N (Normandy) has substantially decreased factor VIII coagulant activity (usually 5%-30% of mean normal), with normal VWF antigen and activity and normal VWF multimers with clinical manifestation as autosomally inherited mild hemophilia (in contrast to classical X chromosome-linked hemophilia A). Type 2A is the most common of the 4. Type 2B manifests thrombocytopenia, either persistent or transient, and is distinguished from type 2A by abnormally heightened aggregation response of patient platelets and plasma to low dose ristocetin stimulation. Type 2M typically demonstrates hypofunctional VWF with decreased VWF activity discordantly lower than VWF antigen not due to loss of HMW multimers. One variant of type 2M, Vicenza variant VWD, has ultralarge VWF multimers in plasma. Type 3 VWD: VWF is absent or markedly decreased in type 3 VWD (VWF antigen and activity either undetectably low or below 5% to 10% of mean normal, with secondary decrease of factor VIII coagulant activity (5%-30%). VWF multimers may be undetectable or, if present, have a normal distribution. Platelet VWF may also be absent. Acquired VWD: VWD can also occur on an acquired basis by a variety of mechanisms not well understood. Disorders associated with acquired VWD include certain myeloproliferative or lymphoproliferative disorders, plasma cell dyscrasias including monoclonal gammopathy of undetermined significance, autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), and a variety of other diseases. In some cases, no associated disorder is detected. Laboratory testing currently cannot distinguish between congenital and acquired VWD; clinical correlation is required.

Useful For: Detection of deficiency or abnormality of von Willebrand factor (VWF) and related deficiency of factor VIII coagulant activity Subtyping von Willebrand disease (VWD) as type 1 (most common), type 2 variants (less common), or type 3 (rare) This test is not useful for detection of hemophilia carriers.

Interpretation: An interpretive report will be provided when testing is complete.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Federici AB, Mannucci PM. Advances in the genetics and treatment of von Willebrand disease. Curr Opin Pediatr. 2002;14(1):23-33 2. Budde U, Schneppenheim R. von Willebrand factor and von Willebrand disease. Rev Clin Exp Hematol. 2001;5(4):335-368 3. Kumar S, Pruthi RK, Nichols WL. Acquired von Willebrand disease. Mayo Clin Proc. 2002;77(2):181-187 4. Favaloro EJ, Gosselin RC. eds. Hemostasis and Thrombosis Methods and Protocols. 2nd ed. Humana Press; 2023

GNVWD 619201 von Willebrand Disease, VWF and GP1BA Genes, Next-Generation Sequencing, Varies

Clinical Information: von Willebrand disease (VWD) is the most common inherited bleeding disorder, affecting approximately 1% of the population. VWD is a bleeding diathesis that usually involves mucous membranes and skin sites. It is typically of mild to moderate severity, although life-threatening bleeding in the central nervous system or gastrointestinal tract can occur. The most common presenting symptoms in individuals affected by VWD include epistaxis, menorrhagia, bleeding after dental extraction, postoperative bleeding, ecchymoses, bleeding from minor cuts or abrasions, gingival bleeding, and hemarthrosis.(1) While VWD occurs with equal frequency among men and women, symptoms in women are more obvious because of increased bleeding during menstrual periods, pregnancy, and after childbirth. VWD is a result of defects in the concentration, structure, or function of von Willebrand factor (VWF), leading to decreased factor VIII (FVIII) in circulation and/or impaired platelet adhesion and aggregation at the site of vascular injury. The VWF gene encodes for VWF, a protein that protects blood clotting FVIII from degradation in circulation and promotes platelet adhesion and aggregation at the site of vascular injury. In circulation, VWF assembles into linear strings called multimers, the size of which is biologically important; larger multimers being more reactive than smaller multimers. Levels of factor VIII, VWF antigen, and VWF activity may vary greatly within each individual over time and also with blood type (normal type "O" individuals may have VWF lower than normal individuals of other blood groups). VWF levels (and factor VIII) can be elevated in liver disease, pregnancy, estrogen therapy, inflammation, and after exercise (acute-phase reactant). VWF levels in hemophilia are normal. This panel evaluates 2 genes associated with von Willebrand disease and platelet-type von Willebrand disease. Discrimination between these 2 heritable disorders, specifically concerning types 2A and 2B VWD and platelet-type VWD, using genetic analysis can help guide treatment. Genetic testing can also be used to assist in discriminating between type 2N VWD and hemophilia A. Subtyping of VWD using genetic analysis is important for prognosis and in guiding treatment, as well as determining inheritance pattern and risks for family members.(1,2) The risk for developing bleeding associated with these disorders and subtypes varies. The VWF and GP1BA genes have established bleeding risk and expert group guidelines.(1-4) It is recommended that genetic testing be offered to all patients where it may assist in diagnosis and management of von Willebrand disease.(1) Genetic testing is integral to the conclusive diagnosis of platelet-type von Willebrand disease.(5)

Useful For: Evaluating von Willebrand disease and platelet-type von Willebrand disease in patients with a personal or family history suggestive of von Willebrand disease Confirming von Willebrand disease or platelet-type von Willebrand disease diagnoses with the identification of a known or suspected disease-causing alteration in the VWF or GP1BA genes, respectively Determining the disease-causing alterations within the VWF or GP1BA genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of von Willebrand disease or platelet-type von Willebrand disease, respectively Subtyping von Willebrand disease as type 1 (most common), type 2 variants (less common), or type 3 (rare), as well as distinguishing von Willebrand disease from platelet-type von Willebrand disease Identifying the causative alteration for genetic counseling purposes Prognosis and

risk assessment based on the genotype-phenotype correlations Carrier testing for close family members of an individual with a von Willebrand disease or platelet-type von Willebrand disease diagnosis

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

VWACT 602170 von Willebrand Factor Activity, Plasma

Clinical Information: von Willebrand factor (VWF) is a multimeric adhesive glycoprotein that is important for platelet-platelet and platelet-vessel hemostatic interactions. In addition, plasma VWF serves as a carrier protein for coagulation factor VIII, stabilizing its procoagulant activity. VWF circulates in the blood in 2 distinct compartments; plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells and platelet VWF (about 10% of the blood VWF) reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. VWF antigen measurement assesses the mass of plasma VWF protein but does not reflect VWF functions or platelet VWF. The major function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma ristocetin cofactor activity. Patients with congenital severe type 3 von Willebrand disease (VWD) have markedly decreased or immeasurably low VWF antigen in the plasma (and in the platelets), and plasma VWF activity is very low or nondetectable. Patients with types 2A and 2B variants of VWD (with abnormal plasma VWF function and multimeric structure) may have normal or decreased plasma VWF antigen but typically have decreased plasma VWF activity and decreased higher molecular weight VWF multimers in the plasma. Patients with type 2M or type 2N VWD have normal levels of antigen, but either decreased VWF activity not caused by absence of higher molecular weight VWF multimers (type 2M VWD) or decreased factor VIII coagulant activity (type 2N VWD). Patients with type 1 VWD (with decreased but normally functioning plasma VWF) have concordantly decreased plasma VWF antigen and activity. Patients with acquired von Willebrand syndrome may have either normal or decreased plasma VWF antigen and decreased VWF activity. Note: VWF activity measurement is most effective when it is combined with measurement of von Willebrand factor: VWF antigen and factor VIII coagulant activity, preferably as a panel of tests with reflexive testing and interpretive reporting (eg, AVWPR / von Willebrand Disease Profile, Plasma).

Useful For: Diagnosis of von Willebrand disease (VWD) and differentiation of VWD subtypes or differentiation of VWD from hemophilia A Monitoring therapeutic efficacy of treatment with DDAVP (desmopressin) or VWF concentrates in patients with VWD

Interpretation: von Willebrand factor (VWF) activity is reduced in parallel with VWF antigen in von Willebrand disease (VWD), except in types 2A, 2B, and 2M, and some cases of acquired von Willebrand syndrome (AVWS) in which the VWF activity is disproportionately decreased relative to the level of VWF antigen. The VWF activity may be decreased in congenital VWD or AVWS that may be associated with are variety of disorders including monoclonal gammopathies, lymphoproliferative disorders, autoimmune disorders, hypothyroidism, severe aortic stenosis, left ventricular assist device, and arteriovenous malformation. The VWF activity may be increased in association with pregnancy or estrogen use (including oral contraceptives), acute (acute-phase reactant) or chronic inflammation, exercise or stress, liver disease, vasculitis, and thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). Such increases in VWF activity may obscure the laboratory diagnosis of mild

VWD.

Reference Values:
55-200%

Normal, full-term newborn infants may have mildly increased levels which reach adult levels by 90 days postnatal. Healthy, premature infants (30-36 weeks gestation) may have increased levels that reach adult levels by 180 days.

Note: Individuals of blood group "O" may have lower plasma von Willebrand factor (VWF) activity than those of other ABO blood groups, such that apparently normal individuals of blood group "O" may have plasma VWF activity as low as 40% to 50%, whereas the lower limit of the reference range for individuals of other blood groups may be 60% to 70%.

Clinical References: 1. Montgomery RR. Structure and function of von Willebrand factor. In: Colman RW, Hirsh J, Marder VJ, et al, eds. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. 4th ed. Lippincott Williams and Wilkins; 2001:249-274 2. Sadler JE, Lillicrap DL. von Willebrand disease: diagnosis, classification, and treatment. In: Marder VJ, Aird WC, Bennett JS, Schulman S, White II GC, eds. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. 6th ed. Lippincott Williams and Wilkins; 2013:670-683 3. Favaloro EJ and Lippi G. eds. Hemostasis and Thrombosis, Methods and Protocols. 1st ed. Humana Press; 2017 4. Salem RO, Van Cott EM. A new automated screening assay for the diagnosis of von Willebrand Disease. Am J Clin Pathol. 2007;127(5):730-735 5. Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. Humana Press; 2017.

VWAG
9051

von Willebrand Factor Antigen, Plasma

Clinical Information: von Willebrand factor (VWF) is a multimeric adhesive glycoprotein that is important for platelet-platelet and platelet-vessel hemostatic interactions. In addition, plasma VWF serves as a carrier protein for coagulation factor VIII, stabilizing its procoagulant activity. VWF circulates in the blood in 2 distinct compartments; plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells and platelet VWF (about 10% of the blood VWF) reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. VWF antigen measurement assesses the mass of plasma VWF protein but does not reflect VWF functions or platelet VWF. The major function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma ristocetin cofactor activity. Decreased VWF antigen may be seen in: -Congenital von Willebrand disease -Acquired von Willebrand disease that may be associated with monoclonal gammopathies, lymphoproliferative disorders, autoimmune disorders, and hypothyroidism Increased VWF antigen may be seen in association with: -Pregnancy and/or estrogen use -Inflammation (acute-phase reactant) -Exercise or stress -Liver disease -Vasculitis -Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome Note: VWF antigen measurement is most effective when it is combined with measurement of VWF ristocetin cofactor activity and factor VIII coagulant activity, preferably as a panel of tests with reflexive testing and interpretive reporting. Within this context, VWF antigen measurement can be useful for: -Diagnosis of von Willebrand disease (VWD) and differentiation of VWD subtype -Differentiation of VWD from hemophilia A (in conjunction with factor VIII coagulant assay)

Useful For: Diagnosis of von Willebrand disease (VWD) and differentiation of VWD subtype (in conjunction with von Willebrand factor ristocetin cofactor activity and factor VIII coagulant activity) Differentiation of VWD from hemophilia A (in conjunction with factor VIII coagulant assay) Monitoring therapeutic efficacy of treatment with DDAVP (desmopressin) or von Willebrand factor concentrates in patients with VWD

Interpretation: Patients with congenital severe type III von Willebrand disease (VWD) have a markedly decreased or undetectable level of von Willebrand factor (VWF) antigen in the plasma (and in the platelets), in addition to a plasma ristocetin cofactor activity that is either very low or not detectable. Patients with types IIA and IIB variants of VWF (with abnormal plasma VWF function and multimeric structure) may have normal or decreased plasma VWF antigen. However, they typically have decreased plasma ristocetin cofactor activity, along with decreased higher molecular-weight VWF multimers in the plasma. Patients with types IIM or IIN VWD have normal levels of VWF antigen. In spite of this, they either have decreased vWF ristocetin cofactor activity, not caused by absence of higher molecular weight vWF multimers (type IIM VWD), or decreased factor VIII coagulant activity (type IIN VWD) Patients with type I VWD (with decreased but normally functioning plasma VWF) have concordantly decreased plasma VWF antigen and ristocetin cofactor activity. Patients with acquired VWD may have either normal or decreased plasma VWF antigen.

Reference Values:
55-200%
Note: Individuals of blood group "O" may have lower plasma von Willebrand factor (VWF) antigen than those of other ABO blood groups, such that apparently normal individuals of blood group "O" may have plasma VWF antigen as low as 40% to 50%, whereas the lower limit of the reference range for individuals of other blood groups may be 60% to 70%.
Children: Neonates, infants, and children have normal or mildly increased plasma VWF antigen, with respect to the adult reference range.

Clinical References: 1. Sadler JE, Lillicrap DL. von Willebrand disease: Diagnosis, classification, and treatment. In: Marder VJ, Aird WC, Bennett JS, Schulman S, White II GC, eds. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. 6th ed. Lippincott Williams and Wilkins; 2013:670-683 2. Favaloro EJ and Lippi G eds. Hemostasis and Thrombosis, Methods and Protocols. 1st ed. Humana Press; 2017 3. Triplett DA. Laboratory diagnosis of von Willebrand's disease. Mayo Clin Proc. 1991;66(12):832-840 4. Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. Humana Press; 2017

VWFMP 604411 von Willebrand Factor Multimer Analysis, Plasma

Clinical Information: von Willebrand factor (VWF) is a large multimeric plasma glycoprotein that has essential roles in primary hemostasis. Wild-type VWF molecules are series of multimers varying in size from dimers to multimers over 40 subunits (>10-million Daltons). The largest multimers provide multiple binding sites that can interact with both platelet receptors and subendothelial matrix sites of injury and are the most hemostatically active form of VWF. The biological functions of VWF are as follows: 1. VWF is a ligand and mediates platelet adhesion to the subendothelial collagen at the site of vessel wall injury by binding to the platelet receptor glycoprotein (GP)-Ib, V, IX complex and subendothelial collagen. 2. VWF binds and stabilizes procoagulant factor VIII in the circulation. 3. Under conditions of high shear, VWF also mediates platelet-platelet cohesion by binding to the platelet receptor GP-IIb/IIIa (integrin alpha IIb beta3) von Willebrand disease (VWD) is the most common hereditary bleeding disorder that is caused by quantitative or qualitative VWF defect. VWD manifests clinically as easy bruising, mucocutaneous bleeding (eg, epistaxis, menorrhagia), and bleeding after trauma or surgery. VWD has been classified into 3 major types: -Type 1, typically an autosomal dominant disease, is the most common, accounting for approximately 70% of VWD patients. It represents a quantitative deficiency of VWF of variable severity. -Type 2, which is usually an autosomal dominant disease, is characterized by several qualitative abnormalities of VWF. Four subtypes have been identified: 2A, 2B, 2M, and 2N. -Type 3, an autosomal recessive disorder, leads to severe disease with virtually undetectable levels of VWF, as well as very low levels of factor VIII. Acquired von Willebrand syndrome (AVWS) is associated with a number of different disease states and is caused by several different pathophysiological mechanisms, including antibody formation, proteolysis, binding to tumor cells with increased clearance, and decreased synthesis. AVWS is most frequently described in patients with dysproteinemias (including

monoclonal gammopathy of undetermined significance [MGUS], multiple myeloma, and macroglobulinemia), lymphoproliferative disorders, myeloproliferative disorders (eg, essential thrombocythemia), autoimmune diseases (eg, systemic lupus erythematosus), high-shear stress cardiovascular conditions such as severe aortic stenosis, gastrointestinal angiodysplasia, and hypothyroidism.

Useful For: As a reflex component of several coagulation consultation unit codes, when indicated When results of complementary laboratory tests are abnormally low or discordant (eg, F8A / Coagulation Factor VIII Activity Assay, Plasma; VWACT / von Willebrand Factor Activity, Plasma; and VWAG / von Willebrand Factor Antigen, Plasma) To subtype von Willebrand disease (VWD) (primarily identify variants of type 2 VWD) As an aid in determining appropriate treatment

Interpretation: The plasma von Willebrand factor (VWF) multimer analysis is a qualitative visual assessment of the size spectrum and the banding pattern of vWF multimers. This test is used to identify variants of type 2 von Willebrand disease (VWD) that have fewer of the largest multimers, have unusually large multimers, or have qualitatively abnormal "bands" that indicate an abnormal vWF structure.

Reference Values:
Only orderable as part of a coagulation reflex. For more information see:
ALUPP / Lupus Anticoagulant Profile, Plasma
ALBLD / Bleeding Diathesis Profile, Limited, Plasma
AVWPR / von Willebrand Disease Profile, Plasma

An interpretive report will be provided.

Clinical References: 1. Budde U, Schneppenheim R. von Willebrand Factor and von Willebrand Disease. Rev Clin Exp Hematol. 2001;5(4):335-368 2. Ruggeri ZM. Structure and function of von Willebrand Factor: Relationship to von Willebrand's disease. Mayo Clinic Proc. 1991;66(8):847-861 3. Sadler JE. A revised classification of von Willebrand Disease. Thromb Haemost. 1994;71(4):520-525 4. Laffan M, Brown SA, Collins PW, et al. The diagnosis of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors Organization. Haemophilia. 2004;10(3):199-217 5. Mannucci PM. Treatment of von Willebrand's Disease. N Engl J Med 2004;351(7):683-694 6. Pruthi RK, Daniels TM, Heit JA, et al. Plasma von Willebrand factor multimer quantitative analysis by in-gel immunostaining and infrared fluorescent imaging. Thrombo Res. 2010;126(6):543-549 7. Favaloro EJ and Lippi G. eds. Hemostasis and Thrombosis, Methods and Protocols. Humana Press 2017

VWFMS
603851

von Willebrand Factor Multimer Analysis, Plasma

Clinical Information: von Willebrand factor (VWF) is a large multimeric plasma glycoprotein that has essential roles in primary hemostasis. Wild-type VWF molecules are series of multimers varying in size from dimers to multimers over 40 subunits (>10 million Da). The largest multimers provide multiple binding sites that can interact with both platelet receptors and subendothelial matrix sites of injury and are the most hemostatically active form of VWF. The biological functions of VWF are as follows: 1. VWF is a ligand and mediates platelet adhesion to the subendothelial collagen at the site of vessel wall injury by binding to the platelet receptor glycoprotein (GP)-Ib, V, IX complex, and subendothelial collagen 2. VWF binds and stabilizes procoagulant factor VIII in the circulation 3. Under conditions of high shear, VWF also mediates platelet-platelet cohesion by binding to the platelet receptor GP-IIb/IIIa (integrin alpha IIb beta3) von Willebrand disease (VWD) is the most common hereditary bleeding disorder that is caused by quantitative or qualitative VWF defect. VWD manifests clinically as easy bruising, mucocutaneous bleeding (eg, epistaxis, menorrhagia), and bleeding after trauma or surgery. VWD has been classified into 3 major types: -Type 1, typically an autosomal

dominant disease, is the most common, accounting for approximately 70% of VWD patients. It represents a quantitative deficiency of VWF of variable severity. -Type 2, which is usually an autosomal dominant disease, is characterized by several qualitative abnormalities of VWF. Four subtypes have been identified: 2A, 2B, 2M, and 2N. -Type 3, an autosomal recessive disorder, leads to severe disease with virtually undetectable levels of VWF, as well as very low levels of factor VIII. Acquired von Willebrand syndrome (AVWS) is associated with a number of different disease states and is caused by several different pathophysiological mechanisms, including antibody formation, proteolysis, binding to tumor cells with increased clearance, and decreased synthesis. AVWS is most frequently described in patients with dysproteinemias (including monoclonal gammopathy of undetermined significance, multiple myeloma, and macroglobulinemia), lymphoproliferative disorders, myeloproliferative disorders (eg, essential thrombocythemia), autoimmune diseases (eg, systemic lupus erythematosus), high-shear stress cardiovascular conditions such as severe aortic stenosis, gastrointestinal angiodysplasia, and hypothyroidism.

Useful For: Resolving discrepancies when results of complementary laboratory tests (eg, F8A / Coagulation Factor VIII Activity Assay, Plasma; VWACT / von Willebrand Factor Activity, Plasma; and VWAG / von Willebrand Factor Antigen, Plasma) are abnormally low or discordant Subtyping von Willebrand disease (VWD) (primarily identify variants of type 2 VWD) Aiding in determining appropriate treatment Identifying variants of type 2 VWD that have fewer of the largest multimers, have unusually large multimers, or have qualitatively abnormal "bands" that indicate an abnormal von Willebrand factor structure

Interpretation: The plasma von Willebrand factor (VWF) multimer analysis is a qualitative visual assessment of the size spectrum and the banding pattern of VWF multimers.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Budde U, Schneppenheim R. von Willebrand Factor and von Willebrand Disease. Rev Clin Exp Hematol. 2001 Dec;5.(4):335-368 2. Ruggeri ZM. Structure and function of von Willebrand factor: Relationship to von Willebrand's disease. Mayo Clinic Proc. 1991;66(8):847-861 3. Sadler JE. A revised classification of von Willebrand disease. Thromb Haemost. 1994;71:520-525 4. Laffan M, Brown SA, Collins PW, et al. The diagnosis of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors Organization. Haemophilia. 2004;10(3):199-217 5. Mannucci PM. Treatment of von Willebrand's disease. N Engl J Med. 2004;351(7):683-694 6. Pruthi RKl, Daniels TM, Heit JA, et al. Plasma von Willebrand factor multimer quantitative analysis by in-gel immunostaining and infrared fluorescent imaging. Thromb Res. 2010;126(6):543-549 7. Ng C, Motto DG, Di Paola J. Diagnostic approach to von Willebrand disease. Blood. 2015;125(13):2029-2037

VORI
88698

Voriconazole, Serum

Clinical Information: Voriconazole (Vfend) is an antifungal agent approved for treatment of invasive aspergillosis and candidemia/candidiasis, as well as for salvage therapy for infections in patients refractory to, or intolerant of, other antifungal therapy. The drug inhibits the fungal enzyme 14a-sterol demethylase, a critical step in ergosterol biosynthesis. Voriconazole is metabolized in the liver primarily by cytochrome P450 (CYP) 2C19 with CYP2C9 and CYP3A4 having limited roles. The primary metabolite is voriconazole N-oxide, which has no antifungal activity. Drug clearance is primarily dependent on hepatic metabolism. The pharmacokinetics of voriconazole is highly variable and nonlinear, which results in an increased dose leading to a greater than proportional increase in serum concentration. The bioavailability of oral voriconazole is greater than 95%. Approximately 60% of the drug in serum is protein bound. Voriconazole has a volume of distribution of 4.6 L/kg. Most (80%) of the drug is excreted in the urine, exclusively as metabolites. Adverse effects of voriconazole include visual disturbances, skin

rashes, and elevated liver enzyme levels.

Useful For: Monitoring trough levels of voriconazole is suggested for: -Individuals with reduced liver function -Individuals with cytochrome P450 (CYP) 2C19 alterations associated with poor metabolic function -Patients taking other medications that affect CYP2C19 activity -Patients experiencing potential toxicity Monitoring trough levels may be reasonable in patients who are not responding optimally or have drug interactions that may decrease voriconazole levels or to ensure adequate oral absorption

Interpretation: Trough levels above 6 mcg/mL (and especially >10 mcg/mL) have been associated with toxicity in several reports. Trough levels below 1 mcg/mL have been associated with suboptimal response in several reports.

Reference Values:
1.0-5.5 mcg/mL
Trough level (ie, immediately before next dose) monitoring is recommended.

Clinical References: 1. Andes D, Pascual A, Marchetti O: Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother. 2009 Jan;53(1):24-34. doi: 10.1128/AAC.00705-08 2. Hope WW, Billaud EM, Lestner J, Denning DW: Therapeutic drug monitoring for triazoles. Curr Opin Infect Dis. 2008 Dec;21(6):580-586. doi: 10.1097/QCO.0b013e3283184611 3. Wilson JW, Estes LL, eds: Mayo Clinic Antimicrobial Therapy. 2nd ed. Oxford University Press; 2011 4. Donnelly JP, De Pauw BE: Voriconazole-a new therapeutic agent with an extended spectrum of antifungal activity. Clin Microbiol Infect. 2004 Mar;10:107-117 5. Physicians Desk Reference, (PDR) 60th edition. Medical Economics Company, 2006 update to 2008 6. Brunton LL, ed: Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. McGraw-Hill Book Company; 2006 7. Luong ML, Al-Dabbagh M, Groll AH, et al: Utility of voriconazole therapeutic drug monitoring: a meta-analysis. J Antimicrob Chemother. 2016 Jul;71(7):1786-1799. doi: 10.1093/jac/dkw099

FWALP
57561

Wall Eyed Pike (Sander vitreus)(Stizostedium vitreum) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 17.50-49.99 Very High Positive 5 50.00-99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

FWCR1
75573

Walnut Component rJug r 1

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.10 kU/L

FFWNC
75584

Walnut Component rJug r 3

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.10 kU/L

FWALG
57640

Walnut Food (Juglans spp) IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

WALN
82732

Walnut Tree, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to walnut tree Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BLWX
618850

Walnut-Food Components, IgE, Serum

Clinical Information: Allergies to tree nuts are relatively prevalent and can result in severe reactions. The main culprits in tree nut allergies include walnut, almond, pistachio, cashew, pecan, hazelnut, macadamia, Brazil nut, and pine nuts. Tree nut allergy often appears in young children and estimates of prevalence range from 0.1% to greater than 5% of the population, dependent on geographical region. In the case of nut-induced allergic reactions, as with many other foods, symptoms usually present within minutes of ingestion. Over 80% of reactions to tree nuts involve allergy related respiratory symptoms. Tree nut allergies are one of the most dangerous types of allergic reaction with 20% to 40% of cases of related anaphylaxis and 70% to 90% of fatalities attributable to nut exposure (including peanut exposure). Walnut is a relatively common cause of allergic reactions to tree nuts. with an overall population occurrence of 0.7%. Allergy to walnut is often persistent over a lifetime and can be severe. Walnuts can cause sensitization by means of walnut pollens/dust particles in processing industries. Allergy related common symptoms observed are nausea, vomiting, pruritus, abdominal pain urticaria, angioedema, diarrhea, asthma, and anaphylaxis. Walnuts and pecans are related species and there is significant potential for cross-reactively between them. Jug r 1 is a prevalent component protein associated with systemic walnut allergy. In a study observed among patients with systemic allergic reactions to walnuts (n=16), 75% showed IgE binding to Jug r 1 Jug r 1 is the most specific and has the highest positive predictive value for walnut allergic and thus is considered the major component protein for walnut allergy diagnosis. than other walnut food allergenic components. Jug r 1 is the major component considered for diagnosing allergy to walnut. It is a persistent storage protein component (2s albumin), that is both heat and digestion stable. Cross-reactivity of 2S albumins with those of other plant sources, such as black walnut, Brazil nut, pecan, mustard, Corylus (common hazel), and sesame, may occur. Jug r 3 is a lipid transport protein (LTP), that is also a major allergen in walnut. This protein is also resistant to heat/digestion. This component allergen is associated with the risk of severe reactions (food-induced contact urticaria, oral allergy syndrome, gastrointestinal symptoms, and anaphylaxis). Approximately 75% of individuals with walnut allergy show reactivity to this component. Significant association of the presence of IgE antibodies between Jug r 3 (walnut) and Cor a 8 (hazelnut) suggests potential for co-sensitization. Other foods that also contain LTP proteins, such as peach, cherry, hazelnut, almond, and peanut (Ara h 9 component) may also exhibit cross reactivity and co-sensitization to individuals with IgE antibodies against Jug r 3. Positive antibody to total walnut specific testing may be observed with concurrent negative Jug r 1 and Jug r 3 component protein antibody testing may occur

when there is sensitization to other walnut component proteins and/or pollens containing profilins and other proteins.

Useful For: Evaluation of patients with suspected walnut-food allergy to one of 2 walnut-food components

Interpretation: When detectable total walnut-food IgE antibody is present (> or =0.10 IgE kUa/L), additional specific component IgE antibody testing will be performed. If at least one potential specific allergenic walnut-food component IgE is detectable (> or =0.10 IgE kUa/L), an interpretive report will be provided. When the sample is negative for total walnut-food IgE antibody (<0.10 IgE kUa/L), further testing for specific walnut-food component IgE antibodies will not be performed. Negative IgE results for total walnut-food antibody may indicate a lack of sensitization to potential walnut-food allergenic components.

Reference Values:

Only orderable as a reflex. For more information see BLWRF / Walnut-Food, IgE, with Reflex to Walnut-Food Components, IgE, Serum. Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/Equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Salo PM, Arbes SJ Jr, Jaramillo R, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol. 2014;134(2):350-359 2. Waserman S, Watson W. Food allergy. Allergy Asthma Clin Immunol. 2011;7 Suppl 1(Suppl 1):S73. Abrams EM, Sicherer SH. Diagnosis and management of food allergy. CMAJ. 2016;188(15):1087-1093 4. Weinberger T, Sicherer S. Current perspectives on tree nut allergy: a review. J Asthma Allergy. 2018;11:41-51 5. Lomas JM, Jarvinen KM. Managing nut-induced anaphylaxis: challenges and solutions. J Asthma Allergy. 2015;8:115-123 6. Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. J Allergy Clin Immunol. 2008;122(1):145-151 7. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. Pediatrics. 1998;102(1):e6 8. Crespo JF, James JM, Fernandez-Rodriguez C, Rodriguez J. Food allergy: nuts and tree nuts [published correction appears in Br J Nutr. 2008 Feb;99(2):447-8]. Br J Nutr. 2006;96 Suppl 2:S95-S102 9. Yang L, Clements S, Joks R. A retrospective study of peanut and tree nut allergy: Sensitization and correlations with clinical manifestations [published online ahead of print, 2015 Feb 27]. Allergy Rhinol (Providence). 2015;doi:10.2500/ar.20105.6.0108 10. Pastorello EA, Farioli L, Pravettoni V, et al. Lipid transfer protein

and vicilin are important walnut allergens in patients not allergic to pollen. J Allergy Clin Immunol. 2004;114(4):908-914 11. Rosenfeld L, Shreffler W, Bardina L, et al. Walnut allergy in peanut-allergic patients: significance of sequential epitopes of walnut homologous to linear epitopes of Ara h 1, 2 and 3 in relation to clinical reactivity. Int Arch Allergy Immunol. 2012;157(3):238-245 12. Masthoff LJ, Hoff R, Verhoeckx KC, et al. A systematic review of the effect of thermal processing on the allergenicity of tree nuts. Allergy. 2013;68(8):983-993 13. Costa J, Carrapatoso I, Oliveira MB, Mafra I. Walnut allergens: molecular characterization, detection and clinical relevance. Clin Exp Allergy. 2014;44(3):319-341 14. Valcour A, Lidholm J, Borres MP, Hamilton RG. Sensitization profiles to hazelnut allergens across the United States. Ann Allergy Asthma Immunol. 2019;122(1):111-116.e1 15. Asero R, Piantanida M, Pravettoni V. Allergy to LTP: to eat or not to eat sensitizing foods? A follow-up study. Eur Ann Allergy Clin Immunol. 2018;50(4):156-162

BLW
82898

Walnut-Food, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to walnuts Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive

6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BLWRF
618849

Walnut-Food, IgE, with Reflex to Walnut-Food Components, IgE, Serum

Clinical Information:

Useful For: Evaluation of patients with suspected walnut-food allergy

Interpretation: When detectable total walnut-food IgE antibody is present (> or =0.10 IgE kUa/L), additional specific component IgE antibody testing will be performed. If at least one potential specific allergenic walnut-food component IgE is detectable (> or =0.10 IgE kUa/L), an interpretive report will be provided. When the sample is negative for total walnut-food IgE antibody (<0.10 IgE kUa/L), further testing for specific walnut-food component IgE antibodies will not be performed. Negative IgE results for total walnut-food antibody may indicate a lack of sensitization to potential walnut-food allergenic components.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/Equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Salo PM, Arbes SJ Jr, Jaramillo R, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol. 2014;134(2):350-359 2. Waserman S, Watson W. Food allergy. Allergy Asthma Clin Immunol. 2011;7 Suppl 1(Suppl 1):S7 3. Abrams EM, Sicherer SH. Diagnosis and management of food allergy. CMAJ. 2016;188(15):1087-1093 4. Weinberger T, Sicherer S. Current perspectives on tree nut allergy: a review. J Asthma Allergy. 2018;11:41-51 5. Lomas JM, Jarvinen KM. Managing nut-induced anaphylaxis: challenges and solutions. J Asthma Allergy. 2015;8:115-123 6. Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. J Allergy Clin Immunol. 2008;122(1):145-151 7. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic

reactions to peanut and tree nuts in children. Pediatrics. 1998;102(1):e6 8. Crespo JF, James JM, Fernandez-Rodriguez C, Rodriguez J. Food allergy: nuts and tree nuts [published correction appears in Br J Nutr. 2008 Feb;99(2):447-8]. Br J Nutr. 2006;96 Suppl 2:S95-S102 9. Yang L, Clements S, Joks R. A retrospective study of peanut and tree nut allergy: Sensitization and correlations with clinical manifestations [published online ahead of print, 2015 Feb 27]. Allergy Rhinol (Providence). 2015;doi:10.2500/ar.20105.6.0108 10. Pastorello EA, Farioli L, Pravettoni V, et al. Lipid transfer protein and vicilin are important walnut allergens in patients not allergic to pollen. J Allergy Clin Immunol. 2004;114(4):908-914 11. Rosenfeld L, Shreffler W, Bardina L, et al. Walnut allergy in peanut-allergic patients: significance of sequential epitopes of walnut homologous to linear epitopes of Ara h 1, 2 and 3 in relation to clinical reactivity. Int Arch Allergy Immunol. 2012;157(3):238-245 12. Masthoff LJ, Hoff R, Verhoeckx KC, et al. A systematic review of the effect of thermal processing on the allergenicity of tree nuts. Allergy. 2013;68(8):983-993 13. Costa J, Carrapatoso I, Oliveira MB, Mafra I. Walnut allergens: molecular characterization, detection and clinical relevance. Clin Exp Allergy. 2014;44(3):319-341 14. Valcour A, Lidholm J, Borres MP, Hamilton RG. Sensitization profiles to hazelnut allergens across the United States. Ann Allergy Asthma Immunol. 2019;122(1):111-116.e1 15. Asero R, Piantanida M, Pravettoni V. Allergy to LTP: to eat or not to eat sensitizing foods? A follow-up study. Eur Ann Allergy Clin Immunol. 2018;50(4):156-162

WARSQ
610065

Warfarin Response Genotype, Varies

Clinical Information: Warfarin is a Coumarin-based drug commonly utilized in anticoagulation therapy to prevent thrombosis due to inherited and acquired hemostatic disorders. The drug is also used in a number of other medical conditions and treatments including atrial fibrillation and hip replacement surgery. Warfarin acts by interfering with the metabolism of vitamin K, which is necessary for production of key coagulation factors. Warfarin inhibits vitamin K recycling by blocking its metabolism at the vitamin K-epoxide intermediate; thereby decreasing the amount of available vitamin K. Warfarin has a narrow therapeutic window; undermedicating increases the risk for thrombosis and overmedicating increases the risk for cerebrovascular accidents. Warfarin therapy has one of the highest rates of severe adverse drug reactions. Warfarin is dosed using nongenetic factors including gender, weight, and age, and is monitored by coagulation testing in order to maintain the international normalized ratio (INR) within specific limits. However, warfarin metabolism is highly variable and dependent upon genetic factors. Variants within 3 genes and 1 intragenic locus are known to affect the metabolism of warfarin and the dose needed to maintain the correct serum drug level and degree of anticoagulation. The CYP2C9 gene encodes the cytochrome P450 (CYP) 2C9 enzyme that primarily metabolizes the more active isomer of warfarin (S-warfarin) to inactive products. Some CYP2C9 variants result in decreased enzymatic activity and may lead to increases in serum warfarin and overmedicating, driving the INR above the therapeutic target. The second gene, VKORC1 encodes vitamin K epoxide reductase complex subunit-1, a small transmembrane protein of the endoplasmic reticulum that is part of the vitamin K cycle and the target of warfarin therapy.(1) Vitamin K epoxide, a by-product of the carboxylation of blood coagulation factors, is reduced to vitamin K by VKORC1. A VKORC1 promoter variant leads to decreased expression of the gene, resulting in reduced availability of vitamin K. This may cause increases in serum warfarin and overmedicating, driving the INR above the therapeutic target. In addition, there are variations in VKORC1 that lead to warfarin resistance that are tested by this assay. These variations are rare. CYP4F2 metabolizes reduced vitamin K to hydroxyl-vitamin K1, thus removing it from the pathways involved in the activation of clotting factors impacted by warfarin. In individuals who self-identify as being of non-African ancestry, carriers of the CYP4F2*3 (C.1297G>A; rs2108622) variant may need a small (5%-10%) warfarin dosage increase to achieve therapeutic goals. The rs12777823G>A variant is located intragenic in the CYP2C locus on chromosome 10. The A allele has been associated with the need for a 10% to 15% decrease in dose in individuals who self-identify as being of African ancestry. CYP2C9: CYP2C9 metabolizes a wide variety of drugs including warfarin and phenytoin. (Note that if testing is desired for other CYP2C9 substrates, order 2C9QT / Cytochrome P450 2C9 Genotype, Varies. A number of specific CYP2C9 variants result in enzymatic deficiencies. The following information outlines the relationship between

the variants detected in this assay and their effect on the activity of the enzyme (Table 1): Table 1: CYP2C9 allele cDNA nucleotide change (NM_000771.3) Effect on enzyme metabolism *1 None (wild type) Normal activity *2 c.430C>T Reduced activity *3 c.1075A>C No activity *4 c.1076T>C Reduced activity *5 c.1080C>G Reduced activity *6 c.818delA No activity *8 c.449G>A Reduced activity *9 c.752A>G Normal activity *11 c.1003C>T Reduced activity *12 c.1465C>T Reduced activity *13 c.269C>T No activity *14 c.374G>A Reduced activity *15 c.485C>A No activity *16 c.895A>G Reduced activity *17 c.1144C>T Reduced activity *18 c.1190A>C No activity *25 c.353_362del No activity *26 c.389C>G Reduced activity *28 c.641A>T Reduced activity *30 c.1429G>A Reduced activity *33 c.395G>A No activity *35 c.374G>T;c.430C>T No activity VKORC1: The c.-1639 promoter variant is located in the second nucleotide of an E-Box (CANNTG), and its presence disrupts the consensus sequence, reducing promoter activity. In vitro experiments show a 44% higher transcription level of the G versus the A allele.(1) The c.-1639G>A nucleotide change results in decreased gene expression and reduced enzyme activity. This test also determines the genotype for multiple other loci within VKORC1 that have been associated with warfarin resistance. The mechanism by which these variations cause warfarin resistance is not clearly understood. Table 2: Additional Variants Tested Gene/SNV cDNA nucleotide change (VKORC1 NM_024006.5; CYP4F2 NM_001082.4) Effect on enzyme metabolism VKORC1 c.-1639G>A Warfarin sensitivity VKORC1 c.85G>T Warfarin resistance VKORC1 c.106G>T Warfarin resistance VKORC1 c.121G>T Warfarin resistance VKORC1 c.134T>C Warfarin resistance VKORC1 c.172A>G Warfarin resistance VKORC1 c.196G>A Warfarin resistance VKORC1 c.358C>T Warfarin resistance VKORC1 c.383T>G Warfarin resistance CYP4F2*3 c.1297G>A Warfarin resistance rs12777823G>A* N/A Warfarin sensitivity * rs12777823G>A is an intergenic single nucleotide variant (SNV) Warfarin dosing may require adjustment depending on the genotypes identified and the predicted phenotype. Patients who have high warfarin sensitivity may benefit from greatly reduced warfarin dosage or by transitioning to another comparable medication.(2) Similarly, in rare instances, individuals with VKORC1 warfarin resistance variants, may require a higher warfarin dose or may benefit from selection of an alternate medication.

Useful For: Identifying patients who may require warfarin dosing adjustments(3,4) including: -Patients being started on a first prescription for warfarin -Patients who have previously been prescribed warfarin and have required multiple dosing adjustments to maintain the international normalized ratio in the target range -Patients with a history of thrombosis or bleeding when taking warfarin

Interpretation: An interpretive report will be provided that includes assay information, genotype, and an interpretation indicating the patient's predicted warfarin response. The CYP2C9 and CYP4F2 genotypes, with associated star alleles, are assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(5) Individuals without a detectable alteration in CYP2C9 or CYP4F2 will be designated as CYP2C9*1/*1 or CYP4F2*1/*1 For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Individuals who have variants in 1 or more gene tested by this assay may require more frequent monitoring of international normalized ratio (INR) to maintain the INR in the target range. Drug-drug interactions and drug/metabolite inhibition must be considered when prescribing warfarin. Warfarin metabolism may be inhibited through drug-drug interactions, including amiodarone and some statins. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

Reference Values:
An interpretive report will be provided.

Clinical References:

FWARP Warfarin, Plasma
75517

Interpretation: The dosage of warfarin is best adjusted based on the International Normalized Ratio (INR) for prothrombin time. Peak plasma concentrations following single 10 mL doses averaged 0.6 mcg/mL for both R-warfarin and S-warfarin (combined concentration 1.2 mcg/mL). This test is not chiral specific and does not distinguish between the R and S enantiomers of warfarin. The blood to plasma ratio is approximately 0.5.

Reference Values:

Reporting limit determined each analysis.
None Detected mcg/mL

WSPV
82659

Wasp Venom, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to wasp venom Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FWATG
57677

Watermelon IgG

Interpretation:

Reference Values:
Reference ranges have not been established for food-specific IgG tests. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

WMEL
86304

Watermelon, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergy to watermelon Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

WEED1
81882

Weed Panel # 1, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to English plantain, lamb's quarters, mugwort, Russian thistle, and short ragweed allergen Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

WEED2
81883

Weed Panel # 2, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to English plantain, lamb's quarters, mugwort, scale, and Western ragweed allergen Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

WEED3
81884

Weed Panel # 3, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to English plantain, lamb's quarters, red sorrel, and Russian thistle allergen Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists, or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

WEED4
81885

Weed Panel # 4, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to giant ragweed, short ragweed, and Western ragweed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Positive results indicate the possibility of allergic disease induced by one or more allergens present in the multi-allergen cap. Negative results may rule out allergy, except in rare cases of allergic disease induced by exposure to a single allergen. Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

WNVCI
36779

West Nile CSF Interpretation

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds and can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5674 cases of WNV were reported to the Centers for Disease Control and Prevention, among which 2873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. Polymerase chain reaction (PCR) (WNCSF / West Nile Virus, RNA, PCR, Molecular Detection, Spinal Fluid) can detect WNV RNA in specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in spinal fluid and approximately 10% in blood from patients with known WNV infection.

Useful For: Interpretation of testing for a laboratory diagnosis of infection with West Nile virus using spinal fluid specimens Aids in diagnosis of central nervous system infection with West Nile virus

Interpretation: IgM: A positive result is consistent with the acute phase of West Nile virus (WNV) meningitis or encephalitis. In the very early stages of acute WNV infection, IgM may be detectable in spinal fluid (CSF) before it becomes detectable in serum. A negative result may indicate absence of disease. However, specimens collected too early in the acute phase may be negative for IgM-class antibodies to WNV. If WNV central nervous system infection is suspected, a second specimen should be collected in 1 to 2 weeks and tested. IgG: A positive result may indicate recent or past central nervous system (CNS) infection with WNV. Clinical correlation is necessary. This assay is unable to

distinguish between intrathecal antibody synthesis and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. Positive results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

Reference Values:

Only orderable as part of a profile. See WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid.

An interpretive report will be provided.

Clinical References: 1. Petersen LR, Marafin AA. West Nile Virus: a primer for the clinician. Ann Intern Med. 2002;137:173-179 2. Centers for Disease Control and Prevention (CDC). West Nile virus and other arboviral diseases--United States, 2012. MMWR Morb Mortal Wkly Rep. 2013;62(25):513-517 3. Brinton MA. The molecular biology of West Nile Virus: a new invader of the western hemisphere. Ann Rev Microbiol. 2002;56:371-402 4. Habarugira G, Suen WW, Hobson-Peters J, Hall RA, Bielefeldt-Ohmann H. West Nile virus: an update on pathobiology, epidemiology, diagnostics, control and one health implications. Pathogens. 2020;9(7):589

WNVSI
36778

West Nile Serum Interpretation

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds and can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5674 cases of WNV were reported to the Centers for Disease Control and Prevention, among which 2873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. Polymerase chain reaction (PCR) tests (WNVS / West Nile Virus, RNA, PCR, Molecular Detection, Serum) can detect WNV RNA in serum specimens from patients with recent WNV infection (ie, 3 to 5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood from patients with known WNV infection.

Useful For: Interpretation of testing for a laboratory diagnosis of infection with West Nile virus

Interpretation: IgG: The presence of IgG-class antibodies to West Nile virus (WNV) in serum indicates infection with WNV at some time in the past. By 3 weeks postinfection, virtually all infected persons should have developed IgG antibodies to WNV. If acute-phase infection is suspected, serum specimens drawn within approximately 7 days postinfection should be compared with a specimen drawn approximately 14 to 21 days after infection to demonstrate rising IgG antibody levels between the 2 serum specimens. IgM: Presence of specific IgM-class antibodies in a serum specimen is consistent with acute-phase infection with WNV. By the 8th day of illness, most infected persons will have detectable serum IgM antibody to WNV; in most cases it will be detectable for at least 1 to 2 months following disease resolution and, in some cases, will be detectable for 12 months or longer. The absence of IgM antibodies to WNV is consistent with lack of acute-phase infection with this virus. Specimens collected too early in the acute phase (eg, before 8-10 days postinfection) may be negative for IgM-specific antibodies to WNV.

If WNV is suspected, a second specimen collected approximately 14 days postinfection should be tested. In the very early stages of WNV infection, IgM may be detectable in cerebrospinal fluid before it becomes detectable in serum.

Reference Values:

Only orderable as part of a profile. For more information see WNS / West Nile Virus Antibody, IgG and IgM, Serum.

An interpretive report will be provided.

Clinical References: 1. Petersen LR, Marfin AA. West Nile Virus: a primer for the clinician. Ann Intern Med. 2002;137(3):173-179 2. Centers for Disease Control and Prevention (CDC). West Nile virus and other arboviral diseases-United States, 2012. MMWR Morb Mortal Wkly Rep. 2013;62(25):513-517 3. Brinton MA. The molecular biology of West Nile Virus. a new invader of the western hemisphere. Ann Rev Microbiol. 2002;56:371-402 4. Habarugira G, Suen WW, Hobson-Peters J, Hall RA, Bielefeldt-Ohmann H. West Nile virus: an update on pathobiology, epidemiology, diagnostics, control and one health implications. Pathogens. 2020;9(7):589

WNS
36769

West Nile Virus Antibody, IgG and IgM, Serum

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds and can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) In 2012, a total of 5674 cases of WNV were reported to the Centers for Disease Control and Prevention, among which 2873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. Polymerase chain reaction (PCR) tests (WNVS / West Nile Virus, RNA, PCR, Molecular Detection, Serum) can detect WNV RNA in serum specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood from patients with known WNV infection.

Useful For: Laboratory diagnosis of infection with West Nile virus using serum specimens

Interpretation: The presence of IgG-class antibodies to West Nile virus (WNV) in serum indicates infection with WNV at some time in the past. By 3 weeks postinfection, virtually all infected persons should have developed IgG antibodies to WNV. If acute-phase infection is suspected, serum specimens collected within approximately 7 days postinfection should be compared with a specimen collected approximately 14 to 21 days postinfection to demonstrate rising IgG antibody levels between the 2 serum specimens. Presence of specific IgM-class antibodies in a serum specimen is consistent with acute-phase infection with WNV. By the 8th day of illness, most infected persons will have detectable serum IgM antibody to WNV; in most cases it will be detectable for at least 1 to 2 months following disease resolution and, in some cases, will be detectable for 12 months or longer. The absence of IgM antibodies to WNV is consistent with lack of acute-phase infection with this virus. Specimens collected

too early in the acute phase (eg, before 8-10 days postinfection) may be negative for IgM-specific antibodies to WNV. If WNV is suspected, a second specimen collected approximately 14 days postinfection should be tested. In the very early stages of WNV infection, IgM may be detectable in cerebrospinal fluid before it becomes detectable in serum.

Reference Values:
IgG: negative
IgM: negative

Reference values apply to all ages.

Clinical References: 1. Petersen LR, Marfin AA. West Nile Virus: a primer for the clinician. Ann Intern Med. 2002;137:173-179 2. Centers for Disease Control and Prevention (CDC). West Nile virus and other arboviral diseases-United States, 2012. MMWR Morb Mortal Wkly Rep. 2013;62(25):513-517 3. Brinton MA. The molecular biology of West Nile Virus: a new invader of the western hemisphere. Ann Rev Microbiol. 2002;56:371-402 4. Habarugira G, Suen WW, Hobson-Peters J, Hall RA, Bielefeldt-Ohmann H. West Nile Virus: An update on pathobiology, epidemiology, diagnostics, control and "One Health" Implications. Pathogens. 2020;9(7):589

WNC
36772

West Nile Virus Antibody, IgG and IgM, Spinal Fluid

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds and can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) In 2012, a total of 5674 cases of WNV were reported to the Centers for Disease Control and Prevention, among which 2873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. Polymerase chain reaction (PCR) (WNCSF / West Nile Virus, RNA, PCR, Molecular Detection, Spinal Fluid) can detect WNV RNA in specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in spinal fluid and approximately 10% in blood from patients with known WNV infection.

Useful For: Aiding in diagnosis of central nervous system infection with West Nile virus

Interpretation: Presence of specific IgM-class antibodies to West Nile virus (WNV) is consistent with the acute phase of WNV meningitis or encephalitis. In the very early stages of acute WNV infection, IgM may be detectable in spinal fluid (CSF) before it becomes detectable in serum. The absence of IgM antibodies to WNV may indicate absence of disease. However, specimens collected too early in the acute phase may be negative for IgM-class antibodies to WNV. If WNV central nervous system infection is suspected, a second specimen should be collected in 1 to 2 weeks and tested. The presence of IgG-class antibodies to WNV may indicate recent or past central nervous system (CNS) infection with WNV. Clinical correlation is necessary. This assay is unable to distinguish between intrathecal antibody synthesis and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. Positive results should be interpreted with other laboratory and

clinical data prior to a diagnosis of CNS infection.

Reference Values:

IgG: Negative
IgM: Negative

Reference values apply to all ages.

Clinical References:

WNGS
36771

West Nile Virus Antibody, IgG, Serum

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds and can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5674 cases of WNV were reported to the Centers for Disease Control and Prevention, among which 2873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. Polymerase chain reaction (PCR) (WNVS / West Nile Virus, RNA, PCR, Molecular Detection, Serum) can detect WNV RNA in serum specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood from patients with known WNV infection.

Useful For: Detection of IgG antibodies in West Nile virus infections

Interpretation: The presence of IgG-class antibodies to West Nile virus (WNV) in serum indicates infection with WNV at some time in the past. By 3 weeks postinfection, virtually all infected persons should have developed IgG antibodies to WNV. If acute-phase infection is suspected, serum specimens collected within approximately 7 days postinfection should be compared with a specimen collected approximately 14 to 21 days after infection to demonstrate rising IgG antibody levels between the 2 serum specimens.

Reference Values:

Only orderable as part of a profile. For more information see WNS / West Nile Virus Antibody, IgG and IgM, Serum.

Negative
Reference values apply to all ages

Clinical References: 1. Petersen LR, Marfin AA. West Nile Virus: a primer for the clinician. Ann Intern Med. 2002;137(3):173-179 2. Centers for Disease Control and Prevention (CDC). West Nile virus and other arboviral diseases--United States, 2012. MMWR Morb Mortal Wkly Rep. 2013;62(25):513-517 3. Brinton MA. The molecular biology of West Nile Virus. a new invader of the

western hemisphere. Ann Rev Microbiol. 2002;56:371-402 4. Habarugira G, Suen WW, Hobson-Peters J, Hall RA, Bielefeldt-Ohmann H. West Nile virus: An update on pathobiology, epidemiology, diagnostics, control and "one health" implications. Pathogens. 2020;9(7):589

WNGC
36774

West Nile Virus Antibody, IgG, Spinal Fluid

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds and can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5674 cases of WNV were reported to the Centers for Disease Control and Prevention, among which 2873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. Polymerase chain reaction (PCR) (WNCSF / West Nile Virus, RNA, PCR, Molecular Detection, Spinal Fluid) can detect WNV RNA in specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in spinal fluid and approximately 10% in blood, from patients with known WNV infection.

Useful For: Aids in diagnosing recent or past central nervous system West Nile virus infection

Interpretation: A positive result may indicate recent or past central nervous system (CNS) infection with West Nile virus. Clinical correlation is necessary. This assay is unable to distinguish between intrathecal antibody synthesis and serum antibodies introduced into the spinal fluid at the time of lumbar puncture or from a breakdown in the blood-brain barrier. Positive results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

Reference Values:
Only orderable as part of a profile. For more information see WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid.

IgG: Negative
Reference values apply to all ages.

Clinical References:

WNMS
36770

West Nile Virus Antibody, IgM, Serum

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds and can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5674 cases of WNV were reported to the Centers for Disease Control and Prevention, among which 2873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in

death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. Polymerase chain reaction (PCR) tests (WNVS / West Nile Virus, RNA, PCR, Molecular Detection, PCR, Serum) can detect WNV RNA in serum specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood from patients with known WNV infection.

Useful For: Detection of IgM antibodies in West Nile virus infections

Interpretation: Presence of specific IgM-class antibodies in a serum specimen is consistent with acute-phase infection with West Nile virus (WNV). By the 8th day of illness, most infected persons will have detectable serum IgM antibody to WNV; in most cases it will be detectable for at least 1 to 2 months following disease resolution and, in some cases, will be detectable for 12 months or longer. The absence of IgM antibodies to WNV is consistent with lack of acute-phase infection with this virus. Specimens collected too early in the acute phase (eg, before 8-10 days postinfection) may be negative for IgM-specific antibodies to WNV. If WNV is suspected, a second specimen collected approximately 14 days postinfection should be tested. In the very early stages of WNV infection, IgM may be detectable in cerebrospinal fluid before it becomes detectable in serum.

Reference Values:
Only orderable as part of a profile. For more information see WNS / West Nile Virus Antibody, IgG and IgM, Serum.

Negative
Reference values apply to all ages

Clinical References: 1. Petersen LR, Marfin AA. West Nile Virus: a primer for the clinician. Ann Intern Med. 2002;137(3):173-179 2. Centers for Disease Control and Prevention (CDC). West Nile virus and other arboviral diseases--United States, 2012. MMWR Morb Mortal Wkly Rep. 2013;62(25):513-517 3. Brinton MA. The molecular biology of West Nile Virus. a new invader of the western hemisphere. Ann Rev Microbiol. 2002;56:371-402 4. Habarugira G, Suen WW, Hobson-Peters J, Hall RA, Bielefeldt-Ohmann H. West Nile virus: An update on pathobiology, epidemiology, diagnostics, control and "one health" implications. Pathogens. 2020;9(7):589.

WNMC
36773

West Nile Virus Antibody, IgM, Spinal Fluid

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds and can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5674 cases of WNV were reported to the Centers for Disease Control and Prevention, among which 2873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body.

Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. Polymerase chain reaction (PCR) (WNCSF / West Nile Virus, RNA, PCR, Molecular Detection, Spinal Fluid) can detect WNV RNA in specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in spinal fluid and approximately 10% in blood from patients with known WNV infection.

Useful For: Aids in diagnosing central nervous system West Nile virus infections during the acute phase

Interpretation: A positive result is consistent with the acute phase of West Nile virus (WNV) meningitis or encephalitis. In the very early stages of acute WNV infection, IgM may be detectable in spinal fluid before it becomes detectable in serum. A negative result may indicate absence of disease. However, specimens collected too early in the acute phase may be negative for IgM-class antibodies to WNV. If WNV central nervous system infection is suspected, a second specimen should be collected in 1 to 2 weeks and tested.

Reference Values:
Only orderable as part of a profile. For more information see WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid.

IgM: Negative
Reference values apply to all ages.

Clinical References:

WNVBL
608438

West Nile Virus, RNA, PCR, Molecular Detection, Blood

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA virus) that primarily infects birds but occasionally infects horses and humans.(1,2,3) Until the virus was recognized in 1999 in infected birds in New York City, WNV had been detected only in the Eastern hemisphere with a wide distribution in Africa, Asia, the Middle East, and Europe. There are 2 distinct lineages of WNV: lineage 1 has the broadest distribution worldwide, including North America and Europe, whereas lineage 2 is found only in Africa and parts of Europe. Most people who are infected with WNV do not experience symptoms. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including headache, myalgia, and, occasionally, a skin rash on the trunk of the body. About 1 of 150 WNV infections (<1%) results in meningitis or encephalitis. Fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG- and IgM-class antibodies in serum specimens. However, polymerase chain reaction (PCR) testing can be used to detect WNV RNA in serum, whole blood, and urine specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. It may also be useful for patients who are immunocompromised when an antibody response is minimal or absent. Finally, PCR can be useful for supporting a serologic diagnosis, given the known cross-reactivity of WNV serology with other flaviviruses. Studies indicate that whole blood testing by PCR may provide higher sensitivity when testing patients with acute WNV disease (up to 87%) compared to serum, plasma, urine, and cerebrospinal fluid testing.(4) However, viral RNA may be detected for a longer period of time (> or =10 days after symptom onset) in urine than in other sources.(5) Serum testing offers lower sensitivity (26%) but may be used when it is the only specimen type available.

Useful For: Rapid testing for West Nile virus (WNV) RNA (lineage 1 and lineage 2) An adjunctive test to serology for detection of early WNV infection (ie, first few days after symptom onset), with blood specimens potentially providing a greater sensitivity than other sources for WNV RNA detection This test should not be used for screening asymptomatic individuals and should only be used to test patients with signs and symptoms of WNV disease.

Interpretation: A positive result indicates the presence of West Nile virus RNA and is consistent with early infection.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References: 1. Petersen LR, Brault AC, Nasci RS. West Nile virus: review of the literature. JAMA. 2013;310(3):308-315 2. Colpitts TM, Conway MJ, Montgomery RR, Fikrig E. West Nile virus: Biology, transmission, and human infection. Clin Microbiol Rev. 201225(4):635-648 3. Centers for Disease Control and Prevention (CDC): West Nile Virus. CDC; Accessed January 21, 2025. Available at www.cdc.gov/west-nile-virus/?CDC_AAref_Val=https://www.cdc.gov/westnile/healthcareproviders/index.html 4. Lustig Y, Mannasse B, Koren R, et al. Superiority of West Nile virus RNA detection in whole blood for diagnosis of acute infection. J Clin Microbiol. 2016;54(9):2294-2297 5. Barzon L, Pacenti M, Franchin E, et al. Excretion of West Nile virus in urine during acute Infection. J Infect Dis. 2013;208(7):1086-1092

WNVUR 608437 West Nile Virus, RNA, PCR, Molecular Detection, Random, Urine

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA virus) that primarily infects birds but occasionally infects horses and humans.(1,2,3) Until the virus was recognized in 1999 in infected birds in New York City, WNV had been detected only in the Eastern hemisphere, with a wide distribution in Africa, Asia, the Middle East, and Europe. There are 2 distinct lineages of WNV: lineage 1 has the broadest distribution worldwide, including North America and Europe, whereas lineage 2 is found only in Africa and parts of Europe. Most people who are infected with WNV do not experience symptoms. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including headache, myalgia, and, occasionally, a skin rash on the trunk of the body. About 1 of 150 WNV infections (<1%) results in meningitis or encephalitis. Fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG- and IgM-class antibodies in serum specimens. However, polymerase chain reaction (PCR) testing can be used to detect WNV RNA in serum, whole blood, and urine specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. It may also be useful for patients who are immunocompromised when an antibody response is minimal or absent. Finally, PCR can be useful for supporting a serologic diagnosis, given the known cross-reactivity of WNV serology with other flaviviruses. Studies indicate that whole blood testing by PCR may provide higher sensitivity when testing patients with acute WNV disease (up to 87%) compared to serum, plasma, urine, and cerebrospinal fluid testing.(4) However, viral RNA may be detected for a longer period of time (> or =10 days after symptom onset) in urine than in other sources.(5) Serum testing offers lower sensitivity (26%) but may be used when it is the only specimen type available.

Useful For: Rapid testing for West Nile virus (WNV) RNA (lineage 1 and lineage 2) An adjunctive test to serology for detection of early WNV infection (ie, first few days after symptom onset), with urine

specimens potentially retaining WNV RNA longer than other sources This test should not be used for screening asymptomatic individuals and should only be used to test patients with signs and symptoms of WNV disease.

Interpretation: A positive result indicates the presence of West Nile virus RNA and is consistent with early infection.

Reference Values:

Negative

Reference values apply to all ages.

Clinical References: 1. Petersen LR, Brault AC, Nasci RS. West Nile virus: Review of the literature. JAMA. 2013;310(3):308-315 2. Colpitts TM, Conway MJ, Montgomery RR, Fikrig E. West Nile virus: biology, transmission, and human infection. Clin Microbiol Rev. 2012;25(4):635-648 3. Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Disease (NCEZID), Division of Vector-Borne Diseases (DVBD): West Nile Virus: Information for Healthcare Providers. CDC; Reviewed April 25, 2023. Accessed February 6, 2024. Available at www.cdc.gov/westnile/healthcareproviders/index.html 4. Lustig Y, Mannasse B, Koren R, et al. Superiority of West Nile virus RNA detection in whole blood for diagnosis of acute infection. J Clin Microbiol. 2016;54(9):2294-2297 5. Barzon L, Pacenti M, Franchin E, et al. Excretion of West Nile virus in urine during acute infection. J Infect Dis. 2013;208(7):1086-1092

WNVS
608436

West Nile Virus, RNA, PCR, Molecular Detection, Serum

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA virus) that primarily infects birds but occasionally infects horses and humans (1,2,3). Until the virus was recognized in 1999 in infected birds in New York City, WNV had been detected only in the Eastern hemisphere with a wide distribution in Africa, Asia, the Middle East, and Europe. There are 2 distinct lineages of WNV: lineage 1 has the broadest distribution worldwide, including North America and Europe, whereas lineage 2 is found only in Africa and parts of Europe. Most people who are infected with WNV do not experience symptoms. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including headache, myalgia, and, occasionally, a skin rash on the trunk of the body. About 1 of 150 WNV infections (<1%) results in meningitis or encephalitis. Fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG- and IgM-class antibodies in serum specimens. However, polymerase chain reaction (PCR) testing can be used to detect WNV RNA in serum, whole blood, and urine specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. It may also be useful for patients who are immunocompromised when an antibody response is minimal or absent. Finally, PCR can be useful for supporting a serologic diagnosis, given the known cross-reactivity of WNV serology with other flaviviruses. Studies indicate that whole blood testing by PCR may provide higher sensitivity when testing patients with acute WNV disease (up to 87%) compared to serum, plasma, urine, and cerebrospinal fluid testing.(4) However, viral RNA may be detected for a longer period of time (> or =10 days after symptom onset) in urine than in other sources.(5) Serum testing offers lower sensitivity (26%) but may be used when it is the only specimen type available.

Useful For: Rapid testing for West Nile virus (WNV) RNA (lineage 1 and lineage 2) using serum specimens An adjunctive test to serology for detection of early WNV infection (ie, first few days after symptom onset) This test should not be used for screening asymptomatic individuals and should only be used to test patients with signs and symptoms of WNV disease.

Interpretation: A positive result indicates the presence of West Nile virus RNA and is consistent with early infection.

Reference Values:

Negative

Reference values apply to all ages.

Clinical References: 1. Petersen LR, Brault AC, Nasci RS. West Nile virus: review of the literature. JAMA. 2013;310(3):308-315 2. Colpitts TM, Conway MJ, Montgomery RR, Fikrig E. West Nile virus: Biology, transmission, and human infection. Clin Microbiol Rev. 2012;25(4):635-648 3. Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Disease (NCEZID), Division of Vector-Borne Diseases (DVBD): West Nile Virus. CDC; Accessed January 21, 2025. Available at https://www.cdc.gov/west-nile-virus/ 4. Lustig Y, Mannasse B, Koren R, et al. Superiority of West Nile virus RNA detection in whole blood for diagnosis of acute infection. J Clin Microbiol. 2016;54(9):2294-2297 5. Barzon L, Pacenti M, Franchin E, et al. Excretion of West Nile virus in urine during acute Infection. J Infect Dis. 2013;208(7):1086-1092

WNCSF
608435

West Nile Virus, RNA, PCR, Molecular Detection, Spinal Fluid

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA virus) that primarily infects birds but occasionally infects horses and humans.(1,2,3) Until the virus was recognized in 1999 in infected birds in New York City, WNV had been detected only in the Eastern hemisphere with a wide distribution in Africa, Asia, the Middle East, and Europe. There are 2 distinct lineages of WNV: lineage 1 has the broadest distribution worldwide, including North America and Europe, whereas lineage 2 is found only in Africa and parts of Europe. Most people who are infected with WNV do not experience symptoms. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including headache, myalgia, and, occasionally, a skin rash on the trunk of the body. About 1 of 150 WNV infections (<1%) results in meningitis or encephalitis. Fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG- and IgM-class antibodies in serum specimens. However, polymerase chain reaction (PCR) testing can be used to detect WNV RNA in serum, whole blood, and urine specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. It may also be useful for patients who are immunocompromised when an antibody response is minimal or absent. Finally, PCR can be useful for supporting a serologic diagnosis, given the known cross-reactivity of WNV serology with other flaviviruses. Studies indicate that whole blood testing by PCR may provide higher sensitivity when testing patients with acute WNV disease (up to 87%) compared to serum, plasma, urine, and cerebrospinal fluid testing.(4) However, viral RNA may be detected for a longer period of time (> or =10 days after symptom onset) in urine than in other sources.(5) Serum testing offers lower sensitivity (26%) but may be used when it is the only specimen type available.

Useful For: Rapid testing for West Nile virus (WNV) RNA (lineage 1 and lineage 2) using cerebrospinal fluid specimens An adjunctive test to serology for detection of early WNV infection (ie, first few days after symptom onset) This assay should not be used for screening asymptomatic individuals and should only be used to test patients with signs and symptoms of WNV disease.

Interpretation: A positive result indicates the presence of West Nile virus RNA and is consistent with early infection.

Reference Values:

Negative
Reference values apply to all ages.

Clinical References: 1. Petersen LR, Brault AC, Nasci RS. West Nile virus: review of the literature. JAMA. 2013;310(3):308-315 2. Colpitts TM, Conway MJ, Montgomery RR, Fikrig E. West Nile virus: Biology, transmission, and human infection. Clin Microbiol Rev. 2012;25(4):635-648 3. Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Disease (NCEZID), Division of Vector-Borne Diseases (DVBD): West Nile Virus. CDC; Accessed January 21, 2025. Available at https://www.cdc.gov/west-nile-virus/ 4. Lustig Y, Mannasse B, Koren R, et al. Superiority of West Nile virus RNA detection in whole blood for diagnosis of acute infection. J Clin Microbiol. 2016;54(9):2294-2297 5. Barzon L, Pacenti M, Franchin E, et al. Excretion of West Nile virus in urine during acute Infection. J Infect Dis. 2013;208(7):1086-1092

FONS 75448 Western blot for anti-optic nerve autoantibodies in the serum

Reference Values:
A final report will be provided.

WEEPC 83918 Western Equine Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid

Clinical Information: The virus that causes Western equine encephalitis (WEE) is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and, possibly, a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. The onset may be more abrupt in infants and children than for adults. WEE should be suspected in any case of febrile central nervous system (CNS) disease from an endemic area. Infants are highly susceptible to CNS disease, and about 20% of cases are patients under 1 year of age. There is an excess of male patients with WEE clinical encephalitis, averaging about twice the number of infections detected in female patients. After recovery from the acute disease, patients may require several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at a higher risk of permanent brain damage after recovery than adults. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. WEE tends to produce the most severe clinical infections in young persons.

Useful For: Aiding in the diagnosis of Western equine encephalitis using spinal fluid specimens

Interpretation: Detection of organism-specific antibodies in the spinal fluid (CSF) may suggest central nervous system (CNS) infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

Reference Values:
IgG: <1:1

IgM: <1:1
Reference values apply to all ages.

Clinical References: 1. Markoff L: Alphaviruses (Chikungunya, Eastern equine encephalitis). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:1997-20062 2. Piantadosi A, Kanjilal S: Diagnostic approach for arboviral infections in the United States. J Clin Microbiol. 2020;58(12):e01926-19. doi:10.1128/JCM.01926-19

WEEP
83156

Western Equine Encephalitis Antibody, IgG and IgM, Serum

Clinical Information: The virus that causes Western equine encephalitis (WEE) is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. In infants and children, the onset may be more abrupt than for adults. WEE should be suspected in any case of febrile central nervous system (CNS) disease from an endemic area. Infants are highly susceptible to CNS disease and about 20% of cases are patients under 1 year of age. There is an excess of male patients with WEE clinical encephalitis, averaging about twice the number of infections detected in female patients. After recovery from acute disease, patients may require from several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at higher risk of permanent brain damage after recovery than adults. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. WEE tends to produce the most severe clinical infections in young persons.

Useful For: Aiding the diagnosis of Western equine encephalitis using serum specimens

Interpretation: In patients infected with this virus, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Single serum specimen IgG greater than or equal to 1:10 indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicate recent infection. In the United States, it is unusual for any patient to show positive reactions to more than 1 of the arboviral antigens, although Western equine encephalitis (WEE) and Eastern equine encephalitis antigens will show a noticeable cross-reactivity. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age and sex, as well as the occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age: WEE tends to produce the most severe clinical infections in young persons. Infection in male patients is primarily due to working conditions and sports activity taking place where the vector is present.

Reference Values:
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

Clinical References: 1. Gonzalez-Scarano F, Nathanson N: Bunyaviruses. In: Fields BN, Knipe DM, eds. Fields Virology. Vol 1. 2nd ed. Raven Press; 1990:1195-1228 2. Donat JF, Rhodes KH, Groover RV, Smith TF. Etiology and outcome in 42 children with acute nonbacterial meningoencephalitis. Mayo Clin Proc. 1980;55(3):156-160 3. Tsai TF. Arboviruses. In: Murray PR, Baron EJ, Pfaller MA, et al, eds. Manual of Clinical Microbiology. 7th ed. American Society for Microbiology; 1999:1107-1124 4. Calisher CH: Medically important arboviruses of the United States and Canada. Clin Microbiol Rev. 1994 Jan;7(1):89-116 5. Markoff L. Alphaviruses (Chikungunya, Eastern equine encephalitis). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:1997-2006

WRW
82666

Western Ragweed, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to Western ragweed Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FWHTG
57553

Wheat IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

FWHG4
57570

Wheat IgG4

Interpretation: The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 has been studied in response to various oral food immunotherapy treatments but cutoffs have not been established.

Reference Values:
Reference ranges have not been established for food-specific IgG4 tests.

WHT
82686

Wheat, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to wheat Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FWHGY
57577

Whey IgG

Interpretation: The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
Reference ranges have not been established for food-specific IgG tests.

WHEY
82622

Whey, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by

respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to whey Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

ASHW
82730

White Ash, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to white ash Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

BENW
82726

White Bean, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to white bean Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of

allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

WFHV
82658

White Faced Hornet Venom, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to white faced hornet venom Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend

upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

WHIC
82719

White Hickory, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to white hickory Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

WPIN
82729

White Pine, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to white pine Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with

the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

POTA
82710

White Potato, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to white potato Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

FWHFE
57545

Whitefish IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 – 0.34 Equivocal/Borderline 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 High Positive 4 17.50 – 49.99 Very High Positive 5 50.00 – 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

WEGG
610357

Whole Egg, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants). Allergy to egg represents one of the most common causes of food allergy, especially in children. The evaluation for egg-related IgE antibodies can identify up to 95% of individuals at risk for clinical allergic reactions. The most clinically prevalent allergens in egg are found in the egg white, but egg yolk also contains clinically significant specific IgE-binding allergens. The allergenic egg proteins found in egg white include ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3) and lysozyme (Gal d 4). Ovomucoid has been demonstrated to be the most clinically significant egg allergen, in part due to its heat and digestion

resistance. In the yolk, the protein alpha-livetin (Gal d 5) is the major allergen and is involved in bird-egg syndrome. Foods that may contain egg include salad dressings, breads, breaded foods, muffins, cakes, marshmallows, prepared soups and beverages, frostings, ice cream and sherbets, pie fillings, sausages, prepared meats, mayonnaise, coatings and breading for fried foods and other sauces. Sensitization to allergic reaction to inhaled egg-white allergens has been reported in egg-processing workers and bakers. Certain vaccines grown on chick embryos may cause severe allergic reactions in patients when injected. Further development of vaccines, most of which are no longer grown on egg protein, seems to have decreased or even eliminated the risk. There is cross-reactivity between chicken egg white and turkey, duck, goose, and gull egg whites. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease.

Useful For: Establishing a diagnosis of an allergy to whole egg Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Whole egg includes proteins and potential allergens from both egg white and egg yolk. Egg white is generally more allergenic than egg yolk. Clinical reactions to egg are predominantly IgE-mediated immediate reactions characterized by atopic dermatitis, urticarial (hives), angioedema, vomiting, diarrhea, rhinoconjunctivitis, and asthma. Children with atopic dermatitis may have an immediate exacerbation of symptoms or a delayed reaction causing a worsening of their dermatitis 1 to 2 days after exposure to egg. Eosinophilic esophagitis as a result of allergy to egg has been described. Egg white is often responsible for the early development of urticaria and eczema during infancy. In egg yolk, alpha-livetin (Gal d 5) is the major allergen and allergenicity to Gal d 5 is involved in bird-egg syndrome characterized egg intolerance in adults is due to sensitization by inhalation of bird dander. In these cases, there is secondary sensitization or cross-reactivity with serum albumin in egg yolk (Gal d 5) resulting in potential respiratory symptoms including asthma or rhinitis with bird exposure and additional allergic symptoms to egg. Table of Major Egg Allergens Egg white allergen Common name Heat-and Digestion Stability Allergenic activity Gal d 1 Ovomucoid Stable +++ (major allergen) Gal d 2 Ovalbumin Unstable ++ Gal d 3 Ovotransferrin/conalbumin Unstable + Gal d 4 Lysosyme Unstable ++ Egg yolk allergen Gal d 5 Alpha-livetin, serum albumin Partially stable Gal d 6 YGP42, a lipoprotein Stabile Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: 1. Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56 2. Caubet JC, Wang J: Current understanding of egg allergy. Pediatr Clin North Am. 2011;58(2):427-xi. doi: 10.1016/j.pcl.2011.02.014 3. Shin M, Han Y, Ahn K: The influence of the time and temperature of heat treatment on the allergenicity of egg white proteins. Allergy Asthma Immunol Res. 2013 Mar;5(2):96-101. doi: 10.4168/aair.2013.5.2.96.

WESMT
616787

Whole Exome and Mitochondrial Genome Sequencing, Varies

Clinical Information:

Useful For: Serving as a first-tier test to identify a molecular and/or mitochondrial diagnosis in patients with suspected genetic disorders, which can allow for: -Better understanding of the natural history/prognosis -Targeted management (anticipatory guidance, management changes, specific therapies) -Predictive testing of at-risk family members -Testing and exclusion of disease in siblings or other relatives -Recurrence risk assessment Serving as a second-tier test for patients in whom previous genetic testing was negative. Providing a potentially cost-effective alternative to establishing a molecular diagnosis compared to performing multiple independent molecular assays.

Interpretation: Variants of interest are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Separate test reports will be issued for WESDX / Whole Exome Sequencing for Hereditary Disorders, Varies and MITOP / Mitochondrial Full Genome Analysis, Next-Generation Sequencing (NGS), Varies. For whole exome sequencing, variants are reported in one of the following categories: -Likely Causative: variants with a high degree of suspicion for causing the patient's reported clinical features -Possibly Relevant: variants that may be related to the patient's clinical features or variants in genes of uncertain significance (GUS) -Secondary Findings: Medically actionable variants unrelated to the indication for testing (see below for additional information) For mitochondrial variants, the degree of heteroplasmy of each single nucleotide or delin (deletion-insertion) variant, defined as the ratio (percentage) of variant sequence reads to the total number of reads, will also be reported. Large deletions will be reported as either homoplasmic or heteroplasmic, but the degree of heteroplasmy will not be estimated, due to possible preferential amplification of the smaller deletion product by long-range polymerase chain reaction. It is possible that a variant may not be recognized as the underlying cause of disease due to incomplete scientific knowledge about the function of all genes in the human genome and/or the impact of variants in those genes. Secondary Findings: Patients are evaluated for medically actionable secondary findings and these findings are reported in accordance with the ACMG recommendations.(7) Variants in these genes will not be evaluated or reported if the patient selects to opt out of this evaluation, unless they overlap with the patient's reported clinical phenotype. The presence of a variant in family member comparator samples is stated on the patient's (proband's) report unless family members opt out of secondary findings. If the patient (proband) opts out, secondary findings will not be reported for any family member. Variants that are present in family member comparators but absent from the patient (proband) are not evaluated. The absence of a reportable secondary finding does not guarantee that there are no disease-associated or likely disease-associated variants in these genes, as portions of the genes may not be adequately covered by this testing methodology. Exome Reanalysis: Healthcare providers may contact the laboratory at 800-533-1710 to request reanalysis of the patient's exome due to new patient clinical features, advances in genetic knowledge, or changes in testing methodology. A charge may apply for reanalysis. Raw Data Requests: Requests for the raw data obtained from whole exome sequencing should be directed to the laboratory. A separate fee may apply. Raw data will be released for individuals who complete a Mayo Clinic release of information form. If raw data for family member comparators is requested, it will only be released with an accompanying request for the proband's raw data. Contact the laboratory for instructions on completing the release of information form. The laboratory is not responsible for

providing software or other tools needed to visualize, filter, or interpret this data.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Manickam K, McClain MR, Demmer LA, et al: Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomes (ACMG). Genet Med. 2021 Nov;23(11):2029-2037. doi: 10.1038/s41436-021-01242-6 2. ACMG Board of Directors: Points to consider for informed consent for genome/exome sequencing. Genet Med. 2013 Sep;15(9):748-749. doi: 10.1038/gim.2013.94 3. Yang Y, Muzny DM, Xia F, et al: Molecular findings among patients referred for clinical whole-exome sequencing. JAMA. 2014 Nov 12;312(18):1870-1879. doi: 10.1001/jama.2014.14601 4. Lee H, Deignan JL, Dorrani N, et al: Clinical exome sequencing for genetic identification of rare Mendelian disorders. JAMA. 2014 Nov 12;312(18):1880-1887. doi: 10.1001/jama.2014.14604 5. Farwell KD, Shahmirzadi L, El-Khechen D, et al: Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. Genet Med. 2015 Jul;17(7):578-586. doi: 10.1038/gim.2014.154 6. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30 7. Miller DT, Lee K, Gordon AS, et al: Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021Aug;23(8):1391-1398. doi: 10.1038/s41436-021-01171-4

WESDX
616068

Whole Exome Sequencing for Hereditary Disorders, Varies

Clinical Information: This test uses next-generation sequencing technology to assess patients with suspected underlying genetic disorders for single nucleotide and copy number variants within the protein-coding regions (exons and splice junctions) of approximately 20,000 genes simultaneously. Indications for whole exome sequencing include but are not limited to:(1,2) -Patients with one or more congenital anomalies -Patients with developmental delay or intellectual disability with onset prior to age 18 years -Patients with a phenotype and/or family history that strongly suggests an underlying genetic cause, yet genetic tests for that phenotype have failed to arrive at a diagnosis (diagnostic odyssey) -Patients with a phenotype and/or family history that strongly suggests an underlying genetic cause, but the phenotype does not fit with one specific disorder (numerous individual genetic tests would be required for evaluation) -Patients with a suspected genetic disorder that has numerous underlying genetic causes, making analysis of numerous genes simultaneously a more practical approach than single-gene testing (condition is genetically heterogeneous) -Patients with a suspected genetic disorder for which specific molecular genetic testing is not yet available -Patients with an atypical presentation of a genetic disorder It is highly recommended that specimens are also submitted from the patient's biological mother and biological father, which are used for comparison purposes (trio analysis). Based upon published reports, a diagnosis is identified in trio-based whole exome sequencing (WES) in approximately 25% to 37% of cases, with slightly lower diagnostic yield in non-trio WES.(3-5) However, testing for singletons (patient only), duos (patient and one family member to be used as a comparator), and non-traditional trios (patient and two family members to be used as comparators) will also be accepted if both biological parents are unavailable.

Useful For: Serving as a first-tier test to identify a molecular diagnosis in patients with suspected genetic disorders, which can allow for: -Better understanding of the natural history/prognosis -Targeted management (anticipatory guidance, management changes, specific therapies) -Predictive testing of at-risk family members -Testing and exclusion of disease in siblings or other relatives -Recurrence risk

assessment Serving as a second-tier test for patients in whom previous genetic testing was negative Providing a potentially cost-effective alternative to establishing a molecular diagnosis compared to performing multiple independent molecular assays

Interpretation: Variants of interest are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants are reported in one of the following categories: -Likely Causative: variants with a high degree of suspicion for causing the patient's reported clinical features -Possibly Relevant: variants that may be related to the patient's clinical features or variants in genes of uncertain significance (GUS) -Secondary Findings: medically actionable variants unrelated to the indication for testing (see below for additional information) It is possible that a variant may not be recognized as the underlying cause of disease due to incomplete scientific knowledge about the function of all genes in the human genome and/or the impact of variants in those genes. Secondary Findings: Patients are evaluated for medically actionable secondary findings and these findings are reported in accordance with the ACMG recommendations.(7) Variants in these genes will not be evaluated or reported if the patient opts out of this evaluation unless they overlap with the patient's reported clinical features. The presence of a variant in family member comparator samples is stated on the patient's (proband's) report unless family members opt-out of secondary findings. If the patient (proband) opts out, secondary findings will not be reported for any family member. Variants that are present in family member comparators but absent from the patient (proband) are not evaluated. The absence of a reportable secondary finding does not guarantee that there are no disease-causing or likely disease-causing variants in these genes, as portions of the genes may not be adequately covered by this testing methodology. Reanalysis and Raw Data Requests: Patient data is not guaranteed to be stored indefinitely. Requests for reanalysis or release of raw data may not be possible, and a new whole exome sequencing order may be required if the original patient data is no longer available or no longer compatible with current bioinformatics processes or analysis tools. Healthcare providers may contact the laboratory at 800-533-1710 to request reanalysis of the patient's exome due to new patient clinical features, advances in genetic knowledge, or changes in testing methodology. A charge may apply for reanalysis. Requests for the raw data obtained from whole exome sequencing should be directed to the laboratory. A separate fee may apply. Raw data will be released for individuals who complete a Mayo Clinic release of information form. If raw data for family member comparators is requested, it will only be released with an accompanying request for the proband's raw data. Contact the laboratory for instructions on completing the release of information form. The laboratory is not responsible for providing software or other tools needed to visualize, filter, or interpret this data.

Reference Values:

An interpretive report will be provided.

Clinical References: 1. Manickam K, McClain MR, Demmer LA, et al: Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomes (ACMG). Genet Med. 2021 Nov;23(11):2029-2037. doi: 10.1038/s41436-021-01242-6 2. ACMG Board of Directors: Points to consider for informed consent for genome/exome sequencing. Genet Med. 2013;15(9):748-749. doi: 10.1038/gim.2013.94 3. Yang Y, Muzny DM, Xia F, et al: Molecular findings among patients referred for clinical whole-exome sequencing. JAMA. 2014 Nov;312(18):1870-1879. doi: 10.1001/jama.2014.14601 4. Lee H, Deignan JL, Dorrani N, et al: Clinical exome sequencing for genetic identification of rare Mendelian disorders. JAMA. 2014 Nov;312(18):1880-1887. doi: 10.1001/jama.2014.14604 5. Farwell KD, Shahmirzadi L, El-Khechen D, et al: Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. Genet Med. 2015 Jul;17(7):578-586. doi: 10.1038/gim.2014.154 6. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015

May;17(5):405-24. doi: 10.1038/gim.2015.30 7. Miller DT, Lee K, Gordon AS, et al: Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021Aug;23(8):1391-1398. doi: 10.1038/s41436-021-01171-4

WESR
616070

Whole Exome Sequencing Reanalysis, Varies

Clinical Information: Whole exome sequencing utilizes next-generation sequencing to assess patients with suspected underlying genetic disorders for variants within the protein-coding regions (exons and splice junctions) of approximately 20,000 genes simultaneously. Based on a meta-analysis, the diagnostic utility of whole exome sequencing is approximately 36%.(2) In patients who have had negative or inconclusive whole exome sequencing results, reanalysis of whole exome sequencing data has been found to result in a new diagnosis in approximately 15% of cases.(3) For more information see Whole Exome and Genome Sequencing Information and Test Ordering Guide.

Useful For: Identifying a diagnosis or additional variants associated with the phenotype in patients who previously have had a negative or inconclusive whole exome sequencing test Reanalyzing whole exome sequencing data when a patient (proband) presents with new clinical features Reanalyzing whole exome sequencing data to pick up newly discovered gene-disease associations, changes to variant classification, and bioinformatics pipeline upgrades

Interpretation: Variants of interest are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(4) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants are reported in one of the following categories: -Likely Causative: variants with a high degree of suspicion for causing the patient's reported clinical features -Possibly Relevant: variants that may be related to the patient's clinical features or variants in genes of uncertain significance -Secondary Findings: medically actionable variants unrelated to the indication for testing (see below for additional information) It is possible that a variant may not be recognized as the underlying cause of disease due to incomplete scientific knowledge about the function of all genes in the human genome or the impact of variants in those genes. Secondary Findings Patients are evaluated for medically actionable secondary findings and these findings are reported in accordance with the most current ACMG recommendations, including the most up-to-date gene list.(5) Variants in these genes will not be evaluated or reported if the patient opts out of this evaluation unless they overlap with the patient's reported clinical phenotype. The opt in or opt out selection from the original whole exome sequencing test will be maintained unless a new Informed Consent form is returned denoting a change in this selection. If the patient originally opted in to receive secondary findings and a secondary finding was originally reported, the status cannot be changed to opt out. The presence of a variant in family member comparator specimens is stated on the patient's (proband's) report unless family members opt out of secondary findings. If the patient (proband) opts out, secondary findings will not be reported for any family member. Variants that are present in family members comparators but absent from the patient (proband) are not evaluated. The absence of a reportable secondary finding does not guarantee that there are no disease-causing or likely disease-causing variants in these genes, as portions of the genes may not be adequately covered by this testing methodology. Reanalysis and Raw Data Requests Patient data is not guaranteed to be stored indefinitely. Requests for reanalysis or release of raw data may not be possible, and a new whole exome sequencing order may be required if the original patient data is no longer available or no longer compatible with current bioinformatics processes or analysis tools. Requests for the raw data obtained from whole exome sequencing should be directed to the laboratory. A separate fee may apply. Raw data will be released for individuals who complete a Mayo Clinic release of information form. If raw data for family member comparators is requested, it will only be released with an accompanying request for the proband's raw data. Contact the laboratory for instructions on completing the release of information form. The laboratory is not responsible for providing software or other tools needed to visualize, filter, or interpret this data.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Deignan JL, Chung WK, Kearney HM, et al: Points to consider in the reevaluation and reanalysis of genomic test results: A statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2019 June;21(6):1267-1270 2. Clark MM, Stark Z, Farnaes L, et al: Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. NPJ Genom Med. 2018 Jul 9;3:16. doi: 10.1038/s41525-018-0053-8 3. Tan NB, Stapleton R, Stark Z, et al: Evaluating systematic reanalysis of clinical genomic data in rare disease from single center experience and literature review. Mol Genet Genomic Med. 2020;8(11):e1508 4. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424 5. Miller DT, Lee K, Gordon AS, et al: Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021 Aug;23(8):1391-1398. doi: 10.1038/s41436-021-01171-4

WGSDX
614363

Whole Genome Sequencing for Hereditary Disorders, Varies

Clinical Information: Note: Where applicable, verbiage refers to sex assigned at birth. This test uses next-generation sequencing technology to assess the genome of patients with suspected underlying genetic disorders. Indications for whole genome sequencing include, but are not limited to, the following:(1,2) -Patients with one or more congenital anomalies -Patients with developmental delay or intellectual disability with age of onset prior to 18 years -Patients with a phenotype or family history that strongly suggests an underlying genetic cause, yet genetic tests for that phenotype have failed to arrive at a diagnosis (diagnostic odyssey) -Patients with a phenotype or family history that strongly suggests an underlying genetic cause, but the phenotype does not fit with one specific disorder (numerous individual genetic tests would be required for evaluation) -Patients with a suspected genetic disorder that has numerous underlying genetic causes, making analysis of numerous genes simultaneously a more practical approach than single-gene testing (condition is genetically heterogeneous) -Patients with a suspected genetic disorder for which specific molecular genetic testing is not yet available -Patients with an atypical presentation of a genetic disorder It is highly recommended that specimens are also submitted from the patient's biological mother and biological father, which are used for comparison purposes (trio analysis). However, testing for the patient only (singleton), the patient and one first-degree relative (duo), and the patient and two first-degree relatives (nontraditional trios) will also be accepted if the patient's biological mother and biological father are not available for testing. Testing typically includes up to two family member comparators. Contact the laboratory for approval to send the patient and three first-degree relatives (quad). Based upon published reports, a diagnosis is identified by whole genome sequencing (WGS) in up to 44% of cases.(3,4) In comparison to whole exome sequencing (WES), WGS has advantages as it is more comprehensive, detects additional variant types, and includes coverage outside of the exons.(5) WGS has been shown to identify additional diagnoses in patients who previously had WES with negative or inconclusive results.(3,6-8)

Useful For: Serving as a first-tier test to identify a molecular diagnosis in patients with suspected genetic disorders, which can allow for: -Better understanding of the natural history/prognosis -Targeted management (anticipatory guidance, management changes, specific therapies) -Predictive testing of at-risk family members -Testing and exclusion of disease in siblings or other relatives -Recurrence risk assessment Serving as a second-tier test for patients in whom previous genetic testing was negative Providing a potentially cost-effective alternative to establishing a molecular diagnosis compared to performing multiple independent molecular assays(1)

Interpretation: Variants of interest are evaluated according to American College of Medical Genetics and Genomics recommendations.(9,10) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants are reported in one of the following categories: -Likely Causative: Variants with a high degree of suspicion for causing the patient's reported clinical features -Possibly Relevant: Variants that may be related to the patient's clinical features or variants in genes of uncertain significance -Secondary Findings: Medically actionable variants unrelated to the indication for testing (see below for additional information) It is possible that a variant may not be recognized as the underlying cause of disease due to incomplete scientific knowledge about the function of all genes in the human genome and/or the impact of variants in those genes. Secondary Findings: Patients are evaluated for medically actionable secondary findings and these findings are reported in accordance with the American College of Medical Genetics and Genomics recommendations.(11) Variants in these genes will not be evaluated or reported if the patient opts out of this evaluation unless they overlap with the patient's reported clinical features. The presence of a secondary finding in family member comparator samples is stated on the patient's (proband's) report unless family members opt out of secondary findings. If the patient (proband) opts out, secondary findings will not be evaluated or reported in any family member comparators. Secondary findings that are present in family member comparators but absent from the patient (proband) are not evaluated or reported. The absence of a reportable secondary finding does not guarantee that there are no disease-causing or likely disease-causing variants in these genes, as review is limited to known or highly suspected pathogenic findings, and not all regions of these genes are adequately evaluated by this technology. Reanalysis and Raw Data Requests: It is not guaranteed that patient data will be stored indefinitely. Requests for reanalysis or release of raw data may not be possible, and a new whole genome sequencing order may be required if the original patient data is no longer available or no longer compatible with current bioinformatics processes or analysis tools. Healthcare professionals may contact the laboratory at 800-533-1710 to request reanalysis of the patient's genome due to new patient clinical features, advances in genetic knowledge, or changes in testing methodology. A charge may apply for reanalysis. Requests for the raw data obtained from whole genome sequencing should be directed to the laboratory. A separate fee may apply. Raw data will be released for individuals who complete a Mayo Clinic release of information form. If raw data for family member comparators is requested, it will only be released with an accompanying request for the proband's raw data. Contact the laboratory for instructions on completing the release of information form. The laboratory is not responsible for providing software or other tools needed to visualize, filter, or interpret this data.

Reference Values:

An interpretive report will be provided.

Clinical References: 1. Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomes (ACMG). Genet Med. 2021;23(11):2029-2037. doi:10.1038/s41436-021-01242-6 2. ACMG Board of Directors. Points to consider for informed consent for genome/exome sequencing. Genet Med. 2013;15(9):748-749. doi:10.1038/gim.2013.94 3. Lionel AC, Costain G, Monfared N, et al. Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. Genet Med. 2018;20(4):435-443. doi:10.1038/gim.2017.119 4. Lee HF, Chi CS, Tsai CR. Diagnostic yield and treatment impact of whole-genome sequencing in paediatric neurological disorders. Dev Med Child Neurol. 2021;63(8):934-938. doi:10.1111/dmcn.14722 5. Austin-Tse CA, Jobanputra V, Perry DL, et al. Best practices for the interpretation and reporting of clinical whole genome sequencing. NPJ Genom Med. 2022;7(1):27. doi:10.1038/s41525-022-00295-z 6. Splinter K, Adams DR, Bacino CA, et al. Effect of genetic diagnosis on patients with previously undiagnosed disease. N Engl J Med. 2018;379(22):2131-2139. doi:10.1056/NEJMoa1714458 7. Bertoli-Avella AM, Beetz C, Ameziane N, et al. Successful application of genome sequencing in a diagnostic setting: 1007 index cases from a clinically heterogeneous cohort. Eur J Hum Genet. 2021;29(1):141-153. doi:10.1038/s41431-020-00713-9 8. Palmer EE, Sachdev R, Macintosh R, et al. Diagnostic yield of whole genome sequencing after nondiagnostic exome sequencing or gene panel in developmental and epileptic encephalopathies.

Neurology. 2021;96(13):e1770-e1782. doi:10.1212/WNL.0000000000011655 9. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-24. doi:10.1038/gim.2015.30 10. Riggs ER, Andersen EF, Cherry AM, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen) [published correction appears in Genet Med. 2021 Nov;23(11):2230]. Genet Med. 2020;22(2):245-257. doi:10.1038/s41436-019-0686-8 11. Miller DT, Lee K, Gordon AS, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(8):1391-1398. doi:10.1038/s41436-021-01171-4

WGSR
614664

Whole Genome Sequencing Reanalysis, Varies

Clinical Information: Note: Where applicable, verbiage refers to sex assigned at birth. Whole genome sequencing utilizes next-generation sequencing technology to assess the genome of patients with suspected underlying genetic disorders. Based on a meta-analysis, the diagnostic utility of whole genome sequencing is approximately 41%.(2) In patients who have had negative or inconclusive whole genome sequencing results, reanalysis of whole genome sequencing data has been found to result in a new diagnosis in approximately 10% of cases.(3) For more information, see Whole Exome Sequencing (WGS): Questions and Answers for Providers.

Useful For: Identifying a diagnosis or additional variants associated with the phenotype in patients who previously have had a negative or inconclusive whole genome sequencing test Reanalyzing whole genome sequencing data when a patient (proband) presents with new clinical features Reanalyzing whole genome sequencing data to pick up newly discovered gene-disease associations, changes to variant classification, and bioinformatics pipeline upgrades

Interpretation: Variants of interest are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(4,5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants are reported in one of the following categories: -Likely Causative: Variants with a high degree of suspicion for causing the patient's reported clinical features -Possibly Relevant: Variants that may be related to the patient's clinical features or variants in genes of uncertain significance (GUS) -Secondary Findings: Medically actionable variants unrelated to the indication for testing (see below for additional information) It is possible that a variant may not be recognized as the underlying cause of disease due to incomplete scientific knowledge about the function of all genes in the human genome or the impact of variants in those genes. Secondary Findings: Patients are evaluated for medically actionable secondary findings and these findings are reported in accordance with the most current ACMG recommendations, including the most up-to-date gene list.(6) Variants in these genes will not be evaluated or reported if the patient opts out of this evaluation unless they overlap with the patient's reported clinical features. The opt in or opt out selection from the original whole genome sequencing test will be maintained unless a new Informed Consent form is returned denoting a change in this selection. If the patient originally opted in to receive secondary findings and a secondary finding was originally reported, the status cannot be changed to opt out. The presence of a secondary finding in family member comparator samples is stated on the patient's (proband's) report unless family members opt out of secondary findings. If the patient (proband) opts out, secondary findings will not be evaluated or reported in any family member comparators. Secondary findings that are present in family members comparators but absent from the patient (proband) are not evaluated or reported. The absence of a reportable secondary finding does not guarantee that there are no disease-causing or likely disease-causing variants in these genes, as review is limited to known or highly suspected pathogenic findings, and not all regions of these genes are adequately evaluated by this technology. Reanalysis and Raw

Data Requests: It is not guaranteed that patient data will be stored indefinitely. Requests for reanalysis or release of raw data may not be possible, and a new whole genome sequencing order may be required if the original patient data is no longer available or no longer compatible with current bioinformatics processes or analysis tools. Requests for the raw data obtained from whole genome sequencing should be directed to the laboratory. A separate fee may apply. Raw data will be released for individuals who complete a Mayo Clinic release of information form. If raw data for family member comparators is requested, it will only be released with an accompanying request for the proband's raw data. Contact the laboratory for instructions on completing the release of information form. The laboratory is not responsible for providing software or other tools needed to visualize, filter, or interpret this data.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Deignan JL, Chung WK, Kearney HM, et al. Points to consider in the reevaluation and reanalysis of genomic test results: a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2019;21(6):1267-1270 2. Clark MM, Stark Z, Farnaes L, et al. Meta-analysis of the diagnostic and clinical utility of genome and genome sequencing and chromosomal microarray in children with suspected genetic diseases. NPJ Genom Med. 2018;3:16. doi:10.1038/s41525-018-0053-8 3. Costain G, Jobling R, Walker S, et al. Periodic reanalysis of whole-genome sequencing data enhances the diagnostic advantage over standard clinical genetic testing. Eur J Hum Genet. 2018;26(5):740-744. doi:10.1038/s41431-018-0114-6 4. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 5. Riggs ER, Andersen EF, Cherry AM, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen) [published correction appears in Genet Med. 2021 Nov;23(11):2230. Genet Med. 2020;22(2):245-257. doi:10.1038/s41436-019-0686-8 6. Miller DT, Lee K, Gordon AS, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(8):1391-1398. doi:10.1038/s41436-021-01171-4

WRGR
82830

Wild Rye Grass, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to wild rye grass Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of

allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

WILL
82731

Willow, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to willow Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

WT1I
70582

Wilms Tumor (WT-1) Immunostain, Technical Component Only

Clinical Information: Wilms tumor-1 (WT-1) protein is a transcription factor that acts as a tumor suppressor gene. WT-1 is involved in differentiation of certain tissues such as mesothelium and the urogenital system. It is also expressed in Wilms tumor, a kidney tumor found in children. In normal tissues, it is expressed in kidney cells, a subset of hematopoietic cells, Sertoli cells in the testis, granulosa cells in the ovary, and decidual cells of the uterus.

Useful For: Aiding in the identification of Wilms tumor

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Al-Hussaini M, Stockman A, Foster H, McCluggage WG. WT-1 assists in distinguishing ovarian from uterine serous carcinoma and in distinguishing between serous and endometrioid ovarian carcinoma. Histopathology. 2004;44:109-115 2. Hwang H, Quenneville L, Haziji H, Gown AM. Wilms tumor gene product: sensitive and contextually specific marker of serous carcinomas of ovarian surface epithelial origin. Appl Immunohistochem Mol Morphol. 2004;12:122-126 3. Lae ME, Roche PC, Jin L, et al. Desmoplastic small round cell tumor: a clinicopathologic, immunohistochemical, and molecular study of 32 tumors. Am J Surg Pathol. 2002;26(7):823-835 4. Nakatsuka S-I, Oji Y, Horiuchi T, et al: Immunohistochemical detection of WT1 protein in a variety of cancer cells. Mod Pathol

2006;19:804-814 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

WNDZ
619409

Wilson Disease, ATP7B Full Gene Sequencing with Deletion/Duplication, Varies

Clinical Information: Wilson disease (WD) is an autosomal recessive disorder that results from the body's inability to excrete excess copper. Typically, the liver releases excess copper into the bile. Individuals with WD lack the necessary enzyme that facilitates clearance of copper from the liver to bile. As a result, copper accumulates first in the liver and gradually in other organs. The brain, kidneys, bones, and corneas can also be affected. WD affects approximately 1 in 30,000 people worldwide, with a carrier frequency of approximately 1 in 90 individuals. The primary clinical manifestations of WD are hepatic and neurologic. Hepatic disease can be quite variable, ranging from hepatomegaly or other nonspecific symptoms that mimic viral hepatitis to severe liver damage, such as cirrhosis. Neurologic symptoms of WD can include poor fine-motor coordination, ataxia, and dysphagia. Psychiatric manifestations are reported in approximately 20% of individuals with WD. A characteristic ophthalmologic finding is the Kayser-Fleischer ring. Individuals with WD typically begin to show symptoms of liver dysfunction or neurologic disease in the first or second decade of life. If not treated, WD can cause liver failure, severe brain damage, and even death. A variety of laboratory tests are recommended in the initial evaluation for WD. In approximately 95% of cases, serum ceruloplasmin is below normal. Additionally, patients with WD show decreased copper in serum, increased copper in urine, and significantly elevated copper on liver biopsy. While liver biopsy is not recommended as a first-tier screening test for WD, it can be useful to help interpret discrepant biochemical or molecular results. Analyte screening tests should be considered prior to molecular analysis. WD is caused by disease-causing variants in the ATP7B gene. More than 300 disease-causing variants have been identified in the ATP7B gene. Most disease-causing variants are family-specific, with the exception of the H1069Q variant, which accounts for greater than 50% of identified disease alleles in the Northern European population.

Useful For: Confirming the diagnosis of Wilson disease

Interpretation: All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 2. European Association for Study of Liver. EASL Clinical Practice Guidelines. Wilson's disease. J Hepatol. 2012;56(3):671-685 3. Roberts EA, Schilsky ML, American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease: an update. Hepatology. 200847(6):2089-2111 4. Mak CM, Lam CW. Diagnosis of Wilson's disease: a comprehensive review. Crit Rev Clin Lab Sci. 2008;45(3):263-290 5. Bandmann O, Weiss KH, Kaler SG. Wilson's disease and other neurological copper disorders. Lancet Neurol. 2015;14(1):103-113

FWING
57955

Wingscale (Atriplex Canescens) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >=49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

WORM
82680

Wormwood, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to wormwood Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy -To investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

XALDZ 35575 X-Linked Adrenoleukodystrophy, Full Gene Analysis, Varies

Clinical Information: X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disease characterized by magnetic resonance imaging (MRI) findings in the white matter, adrenocortical insufficiency, and abnormal plasma concentrations of very long chain fatty acids. The phenotypic expression of X-ALD varies widely. The phenotypes can be subdivided into 3 main categories: childhood cerebral form, adrenomyeloneuropathy (AMN), and Addison disease only. The childhood cerebral form has onset of symptoms between ages 4 and 8, beginning with attention deficit hyperactivity disorder-like symptoms with progressive cognitive, behavior, vision, hearing, and motor deterioration. AMN usually presents in males in their late twenties as progressive paraparesis, sexual dysfunction, sphincter disturbances, and abnormalities in adrenocortical function. The Addison only phenotype typically presents by age 7.5 with adrenocortical insufficiency without significant neurological involvement. Most of these patients eventually develop AMN. Some female carriers may experience mild AMN symptoms with a later age of onset. The phenotype cannot be predicted by very long chain fatty acids (VLCFA) plasma concentration or by the nature of the genetic variant. The same variant can be associated with each of the known phenotypes. Different phenotypes often occur within a family. POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum testing is the preferred first-tier screening method for X-ALD. This is abnormal in 99% of affected males and 85% of carrier females. Sequencing of the ABCD1 gene is available to confirm the diagnosis of X-ALD, improve carrier detection, and assist with prenatal diagnosis.

Useful For: Confirming a diagnosis of X-linked adrenoleukodystrophy Identifying a variant in the ABCD1 gene

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(2) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Newborn Screening ACT Sheet [Elevated Lysophosphatidylcholine] X-Linked Adrenoleukodystrophy (X-ALD). American College of Medical Genetics and Genomics; 2023. Revised November 2023. Accessed March 25, 2025. Available at www.acmg.net/PDFLibrary/X-ALD-ACT-Sheet.pdf 2. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424 3. Moser HW, Mahmood A, Raymond GV. X-linked adrenoleukodystrophy. Nat Clin Pract Neurol. 2007;3(3):140-151 4. Wang Y, Busin R, Reeves C, et al. X-linked adrenoleukodystrophy: ABCD1 de novo mutations and mosaicism. Mol Genet Metab. 2011;104(1-2):160-166 5. Kemp S, Berger J, Aubourg P: X-linked adrenoleukodystrophy: Clinical, metabolic, genetic and pathophysiological aspects. Biochim Biophys Acta. 2012;1822(9):1465-1474

XHIM 82964 X-Linked Hyper IgM Syndrome, Blood

Clinical Information: CD154 (CD40 ligand: CD40L) is required for the interaction of T cells and

B cells as part of the normal adaptive immune response. Activation of T cells leads to the expression of the CD40L molecule on the cell surface. CD40L binds the CD40 receptor that is constitutively expressed on B cells, monocytes, and macrophages. Interaction of CD40L with CD40 is important in B-cell proliferation, differentiation, and class-switch recombination (isotype class-switching). Patients with X-linked hyper-IgM (XL-HIGM) syndrome have defective CD40L expression on their activated helper CD4 T cells.(1,2) It is the most common class switch recombination defect and accounts for approximately 50% of the patients in this category. It leads to defective B-cell responses and the absence of immunoglobulin class-switching, which are typified by a profound reduction or absence of isotype class-switched memory B cells (CD19+CD27+IgM-IgD-) with low or absent secreted IgG and IgA and normal or elevated serum IgM levels.(1,2) Due to the impairment of T-cell function and macrophage activation, patients with XL-HIGM are particularly prone to opportunistic infections with Pneumocystis jiroveci, Cryptosporidium, and Toxoplasma gondii.(1) A defect in surface expression of CD40L on activated CD4 T cells can be demonstrated using an anti-CD40L antibody and flow cytometry.(3,4) Since certain CD40LG variants can maintain surface protein expression, albeit with loss of function, it is important to also evaluate CD40L-binding capacity to eliminate the possibility of false-negative results. A soluble recombinant, chimeric receptor protein, CD40-uIg, is incorporated into the assay, which assesses CD40L function by determining receptor-binding activity. Approximately 20% of patients with XL-HIGM have activated CD4 T cells with normal surface expression of CD40L but aberrant function.(4) XL-HIGM is a severe primary immunodeficiency that affects male patients, and most patients are diagnosed within a few months to the first year of life. Female patients are typically carriers and asymptomatic. Consequently, this test is only indicated for boys (<10 years) or to identify carriers, women of child-bearing age (<45 years).

Useful For: Screening for X-linked hyper-IgM (XL-HIGM) or CD40L deficiency, primarily in male patients younger than 10 years Ascertaining XL-HIGM carrier status in women of child-bearing age (younger than 45 years)

Interpretation: This is a qualitative assay; CD40L-protein expression and function are reported as present or absent. Absence of CD40L-protein expression and function is consistent with X-linked hyper-IgM (XL-HIGM). In female patients, the presence of 2 populations-normal and abnormal-is consistent with carrier status. Most patients (80%-90%) with XL-HIGM have absent or significantly reduced CD40L expression on their activated CD4 T cells. Patients with normal CD40L expression, but abnormal function, show an absence of binding with soluble chimeric CD40-uIg antibody, substantiating a diagnosis of XL-HIGM. Female patients who are carriers for this disease will show a typical bimodal pattern of CD40L expression, with 50% of the T cells lacking any CD40L expression. In the case of aberrant protein function, a similar profile will be obtained with the CD40-uIg antibody. CD69 is a marker for T-cell activation and serves as a positive control; in the absence of induced CD69 expression on T cells, the presence of XL-HIGM cannot be assessed.

Reference Values:
Present

Clinical References: 1. Etzioni A, Ochs HD. The hyper IgM syndrome-an evolving story. Pediatr Res. 2004:56(4):519-525 2. Durandy A, Peron S, Fischer A. Hyper-IgM syndromes. Curr Opin Rheumatol. 2006;18(4):369-376 3. Lee WI, Torgerson TR, Schumacher MJ, Yel L, Zhu Q, Ochs HD. Molecular analysis of a large cohort of patients with the hyper immunoglobulin M (IgM) syndrome. Blood. 2005;105(5):1881-1890 4. Seyama K, Nonoyama S, Gangsaas I, et al. Mutations of the CD40 ligand gene and its effect on CD40 ligand expression in patients with X-linked hyper IgM syndrome. Blood. 1998;92(7):2421-2434 5. Vargas-Hernandez A, Berron-Ruiz L, Staines-Boone T, et al. Clinical and genetic analysis of patients with X-linked hyper-IgM syndrome. Clin Genet. 2013;83(6):585-587 6. Vavassori V, Mercuri E, Marcovecchio GE, et al. Modeling, optimization, and comparable efficacy of T cell and hematopoietic stem cell gene editing for treating hyper-IgM syndrome. EMBO Mol Med. 2021;13(3):e13545

FCDX3
75843

Xylazine Confirmation (Qualitative), Umbilical Cord, Tissue

Reference Values:
Reporting limit determined each analysis.
Units: ng/g
Only orderable as a reflex test.

YMCRO
35576

Y Chromosome Microdeletions, Molecular Detection, Varies

Clinical Information: Yq microdeletions involving some or all azoospermic factor (AZF) regions, are identified in approximately 3% of infertile men. Yq microdeletions are also the most frequently identified cause of spermatogenic failure in chromosomally normal men with nonobstructive azoospermia (3%-15%) or severe oligospermia (6%-10%). The relative frequency of Yq microdeletions makes the evaluation for them an important aspect of the diagnostic work up in infertile men, especially those with azoospermia or severe oligospermia. Most cases of Yq microdeletions occur de novo, and due to the consequential infertile phenotype, they are typically not transmitted. However, in cases where assisted reproductive technology (eg, testicular sperm extraction followed by intracytoplasmic sperm injection) is used to achieve viable pregnancy, all male offspring born to a microdeletion carrier will carry the deletion and may be infertile. Men testing positive for 1 or more microdeletions who are enrolled in an in vitro fertilization treatment program may wish to consider alternative options to intracytoplasmic sperm injection (eg, donor sperm), and consultation with an experienced reproductive endocrinologist and medical geneticist is recommended. Most Y microdeletions are the result of homologous recombination between repeated sequence blocks. Testing for deletions involves investigating for the presence or absence of markers located within nonpolymorphic regions of the AZF region.

Useful For: Evaluating men with azoospermia, severe oligozoospermia, or otherwise unexplained male factor infertility

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Stahl PJ, Masson P, Mielnik A, Marean MB, Schlegel PN, Paduch DA. A decade of experience emphasizes that testing for Y microdeletions is essential in American men with azoospermia and severe oligozoospermia. Fertil Steril. 2010;94(5):1753-1756 2. Bhasin S. Approach to the infertile man. J Clin Endocrinol Metab. 2007;92(6):1995-2004 3. Fan Y, Silber SJ. Y Chromosome Infertility. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated August 1, 2019. Accessed November 18, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1339/ 4. Kim SY, Kim HJ, Lee BY, Park SY, Lee HS, Seo JT. Y Chromosome Microdeletions in Infertile Men with Non-obstructive Azoospermia and Severe Oligozoospermia. J Reprod Infertil. 2017;18(3):307-315

YFHV
82657

Yellow Faced Hornet Venom, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to

allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to yellow faced hornet venom Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

YJV
82661

Yellow Jacket Venom, IgE, Serum

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from IgE-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with an allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants

and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing a diagnosis of an allergy to yellow jacket venom Defining the allergen responsible for eliciting signs and symptoms Identifying allergens: -Responsible for allergic response and/or anaphylactic episode -To confirm sensitization prior to beginning immunotherapy Testing for IgE antibodies is not useful in patients previously treated with immunotherapy to determine if residual clinical sensitivity exists or in patients in whom the medical management does not depend upon identification of allergen specificity.

Interpretation: Detection of IgE antibodies in serum (class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class	IgE kU/L	Interpretation
0		Negative
0/1	0.10-0.34	Borderline/equivocal
1	0.35-0.69	Equivocal
2	0.70-3.49	Positive
3	3.50-17.4	Positive
4	17.5-49.9	Strongly positive
5	50.0-99.9	Strongly positive
6	> or =100	Strongly positive

Clinical References: Homburger HA, Hamilton RG: Allergic diseases. In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th ed. Elsevier; 2022:chap 56

YERSC
606222

Yersinia Culture, Feces

Clinical Information: Diarrhea may be caused by a number of agents, including bacteria, viruses, parasites, and chemicals; these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the healthcare professional determine the appropriate testing to be performed. Several species of Yersinia that are detected by this test may cause diarrhea. Yersinia enterocolitica is the species most frequently isolated with this test.

Useful For: Determining whether Yersinia species may be the cause of diarrhea Reflexive testing for Yersinia species from nucleic acid amplification test-positive feces This test is generally not useful for patients hospitalized more than 3 days because the yield from specimens from these patients is very low, as is the likelihood of identifying a pathogen that has not been detected previously.

Interpretation: The growth of Yersinia species identifies a potential cause of diarrhea.

Reference Values:
No growth of Yersinia species.

Clinical References:

YAP1 70583 Yes-Associated Protein (YAP) Immunostain, Technical Component Only

Clinical Information: Yes-associated protein (YAP) is a downstream regulatory target in the Hippo signaling pathway that is upregulated in SHH (sonic hedgehog)-associated medulloblastomas and medulloblastomas with activation of the Wnt (wingless-related integration site) signaling pathway and is expressed in lung, placenta, prostate, ovary, and testis.

Useful For: Identification and differentiation of medulloblastomas

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Ellison DW, Dalton J, Kocak M, et al. Medulloblastoma clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. Acta Neuropathol. 2011;121:381-396 2. Northcott PA, Korshunov A, Witt H, et al. Medulloblastoma comprises four distinct molecular variants. J Clin Oncol. 2011;29(11):1408-1414 3. Thompson MC, Fuller C, Hogg TL, et al. Genomics identifies medulloblastoma subgroups that are enriched for specific genetic alterations. J Clin Oncol. 2006;24:1924-1931 4. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

FYOG 57915 Yogurt (Lactobacillus bulgaricus) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

BTB46 605254 ZBTB46 Immunostain, Technical Component Only

Clinical Information: Zinc finger and BTB domain-containing protein 46 (ZBTB46) is a transcription factor expressed by classical dendritic cells and committed dendritic cell precursors. Expression of ZBTB46 differentiates histiocytic disorders such as Langerhans cell histiocytosis, histiocytic sarcoma, and indeterminate cell histiocytosis from Rosai-Dorfman and Erdheim-Chester disease.

Useful For: Identification of dendritic cells and classification of histiocytic disorders

Interpretation: This test does not include pathologist interpretation, only technical performance of the stain. If interpretation is required, order PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References: 1. Reizis B. Classical dendritic cells as a unique immune cell lineage. J Exp Med. 2012 209(6):1053-1056 2. Satpathy AT, Wumesh KC, Albring JC, et al. Zbtb46 expression distinguishes classical dendritic cells and their committed progenitors from other immune lineages. J Exp Med. 2012 209(6):1135-1152 3. Meredith MM, Liu K, Darrasse-Jeze G, et al. Expression of the zinc finger transcription factor zDC (Zbtb46, Btbd4) defines the classical dendritic cell lineage. J Exp Med. 2012 209(6):1156-1165 4. Satpathy AT, Brown RA, Gomulia E, et al. Expression of the transcription factor ZBTB46 distinguishes human histiocytic disorders of classical dendritic cell origin. Mod Path. 2018 31:1479-1486 5. Magaki S, Hojat SA, Wei B, So A, Yong WH. An introduction to the performance of immunohistochemistry. Methods Mol Biol. 2019;1897:289-298. doi:10.1007/978-1-4939-8935-5_25

VZIKM
618559

Zika Virus, IgM Antibody Capture ELISA, Serum

Clinical Information: Zika virus is an RNA virus in the genus Flavivirus and is primarily transmitted through the bite of an infected Aedes species mosquito. Other means of transmission include through transfusion of blood and blood products, sexually through genital secretions, perinatally, vertically from mother to fetus, and potentially through contact with other body secretions such as tears and sweat. Historically, most cases of Zika virus infection have occurred in parts of Africa and South-East Asia. However, Zika virus emerged in South America in early 2015 and is now endemic in over 50 countries in South, Central, and North America, including in several US territories and focal regions of the southern United States. The majority (approximately 80%) of individuals infected with Zika virus are asymptomatic. Among symptomatic patients, fever, headache, retro-orbital pain, conjunctivitis, maculopapular rash, myalgias, and arthralgias are commonly reported. Notably, these symptoms are not distinct and can be seen with other emerging arboviruses, including dengue and chikungunya. Therefore, diagnostic testing for each of these viruses is recommended in patients returning for areas where these viruses cocirculate. Intrauterine or prenatal infection with Zika virus has been causally linked to development of microcephaly, with the greatest risk for fetal abnormality occurring if the infection is acquired during the first trimester. Finally, Zika virus has also been associated with development of Guillain-Barre syndrome. A number of Zika virus serologic and nucleic acid amplification tests have received emergency use authorization through the US Food and Drug Administration. The recommended tests vary by the patient's symptoms, course of illness, and whether the patient is pregnant. The most up-to-date information regarding Centers for Disease Control and Prevention testing guidelines is available at www.cdc.gov/zika/index.html. These guidelines are reflected in Assessment for Zika Virus Infection. Zika virus testing is not recommended for asymptomatic couples attempting conception, given the potential for false-positive and false-negative results. Additionally, it is well established the Zika virus may remain in reproductive fluids, despite negative serologic and molecular test results in blood and urine.

Useful For: Screening for the presence of IgM-class antibodies to Zika virus This test is not intended for medical-legal use. This test is not recommended for asymptomatic couples attempting conception.

Interpretation: See Assessment for Zika Virus Infection for a review of the recommended testing

and interpretation of results. For the most recent Centers for Disease Control and Prevention guidelines for Zika virus testing visit www.cdc.gov/zika/index.html Presumptive Zika Positive: IgM-class antibodies to Zika virus (ZIKV) detected. This is a preliminary result and does not confirm evidence of ZIKV infection. Confirmatory testing may be required as determined by your local health department. False-positive results may occur in patients with other current or prior flavivirus infections (eg, dengue virus). For patients with less than 7 days of symptoms or last possible exposure to ZIKV, reverse transcription polymerase chain reaction (RT-PCR) for ZIKV on serum and urine is recommended. A positive ZIKV RT-PCR result on either specimen is confirmatory for ZIKV infection. Other Flavivirus Positive: Antibodies to a flavivirus, not ZIKV, were detected. Consider targeted testing for IgM-class antibodies to dengue and/or West Nile viruses as appropriate, taking into consideration patient exposure and presentation. Negative: No evidence of IgM-class antibodies to ZIKV. For specimens collected less than 7 days post symptom onset or possible ZIKV exposure, RT-PCR for ZIKV on serum and urine to exclude a false-negative ZIKV IgM result is recommended. For symptomatic patients with travel to dengue endemic areas, testing for IgM antibodies to dengue virus is also recommended.

Reference Values:
Negative

Clinical References: 1. Oduyebo T, Polen KD, Walke HT, et al. Update: Interim guidance for health care providers caring for pregnant women with possible Zika virus exposure-United States (Including U.S. Territories), July 2017. MMWR Morb Mortal Wkly Rep. 2017;66(29):781-793 2. Waggoner JJ, Pinsky BA. Zika virus: Diagnostics for an emerging pandemic threat. J Clin Microbiol. 2016;54(4):860-867 3. Theel ES, Hata DJ. Diagnostic testing for Zika virus: a post outbreak update. J Clin Microbiol. 2018;56(4):e01972-17. doi:10.1128/JCM.01972-17

VZIKU
619431

Zika Virus, PCR, Molecular Detection, Random, Urine

Clinical Information: Zika virus is an RNA virus in the genus Flavivirus and is primarily transmitted through the bite of an infected Aedes species mosquito. Other means of transmission include through transfusion of blood and blood products, sexually through genital secretions, perinatally, vertically from mother to fetus, and, potentially, through contact with other body secretions, such as tears and sweat. Historically, most cases of Zika virus infection have occurred in parts of Africa and Southeast Asia. However, Zika virus emerged in South America in early 2015 and is now endemic in over 50 countries in South, Central, and North America, including in several US territories and focal regions of the southern United States. The majority (approximately 80%) of individuals infected with Zika virus are asymptomatic. Fever, headache, retro-orbital pain, conjunctivitis, maculopapular rash, myalgias and arthralgias are commonly reported among symptomatic patients. Notably, these symptoms are not distinct and can be seen with other emerging arboviruses, including dengue and chikungunya. Therefore, diagnostic testing for each of these viruses is recommended in patients returning form areas where these viruses cocirculate. Intrauterine or prenatal infection with Zika virus has been causally linked to development of microcephaly, with the greatest risk for fetal abnormality occurring if the infection is acquired during the first trimester. Finally, Zika virus has also been associated with development of Guillain-Barre syndrome. A number of Zika virus serologic and nucleic acid amplification tests have received emergency use authorization (EUA) through the US Food and Drug Administration. The recommended tests vary by the patient's symptoms, course of illness, and whether or not the patient is pregnant. For the most up-to-date information regarding the Centers of Disease Control and Prevention testing guidelines visit www.cdc.gov/zika/. These guidelines are reflected in Assessment for Zika Virus Infection. Zika virus testing is not recommended for asymptomatic couples attempting conception, given the potential for false-positive and false-negative results. Additionally, it is well established the Zika virus may remain in reproductive fluids despite negative serologic and molecular test results in blood and urine.

VZIKS
619432

Zika Virus, PCR, Molecular Detection, Serum

Clinical Information: Zika virus is an RNA virus in the genus Flavivirus and is primarily transmitted

through the bite of an infected Aedes species mosquito. Other means of transmission include through transfusion of blood and blood products, sexually through genital secretions, perinatally, vertically from mother to fetus, and, potentially, through contact with other body secretions, such as tears and sweat. Historically, most cases of Zika virus infection have occurred in parts of Africa and Southeast Asia. However, Zika virus emerged in South America in early 2015 and is now endemic in over 50 countries in South, Central, and North America, including in several US territories and focal regions of the southern United States. The majority (approximately 80%) of individuals infected with Zika virus are asymptomatic. Fever, headache, retro-orbital pain, conjunctivitis, maculopapular rash, myalgias, and arthralgias are commonly reported among symptomatic patients. Notably, these symptoms are not distinct and can be seen with other emerging arboviruses, including dengue and chikungunya. Therefore, diagnostic testing for each of these viruses is recommended in patients returning form areas where these viruses cocirculate. Intrauterine or prenatal infection with Zika virus has been causally linked to development of microcephaly, with the greatest risk for fetal abnormality occurring if the infection is acquired during the first trimester. Finally, Zika virus has also been associated with development of Guillain-Barre syndrome. A number of Zika virus serologic and nucleic acid amplification tests have received emergency use authorization through the US Food and Drug Administration. The recommended tests vary by the patient's symptoms, course of illness, and whether or not the patient is pregnant. For the most up-to-date information regarding the Centers of Disease Control and Prevention testing guidelines, visit www.cdc.gov/zika/. These guidelines are reflected in Assessment for Zika Virus Infection. Zika virus testing is not recommended for asymptomatic couples attempting conception, given the potential for false-positive and false-negative results. Additionally, it is well established the Zika virus may remain in reproductive fluids despite negative serologic and molecular test results in blood and urine.

Useful For: Qualitative detection of Zika virus RNA in serum from individuals meeting the Centers of Disease Control and Prevention Zika virus clinical or epidemiologic criteria

Interpretation: A positive test result indicates the presence of Zika virus RNA in the specimen. A negative test result with a positive internal control indicates that Zika virus RNA is not detectable in the specimen. A negative test result with a negative internal control is considered evidence of polymerase chain reaction inhibition or reagent failure. A new specimen should be collected for testing if clinically indicated.

Reference Values:
Negative

Reference values apply to all ages.

Clinical References: 1. Oduyebo T, Igbinosa I, Petersen EE, et al. Update: Interim guidance for health care providers caring for women of reproductive age with possible Zika virus exposure-United States, July 2016. MMWR Morb Mortal Wkly Rep. 2016;65(29):739-744 2. United States Food and Drug Administration. Emergency Use Authorizations (Medical Devices). Updated September 7, 2022. Accessed October 1, 2024. Available at www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm 3. Waggoner JJ, Pinsky BA. Zika Virus: Diagnostics for an emerging pandemic threat. J Clin Microbiol. 2016;54(4):860-867

EZNT8
64926

Zinc Transporter 8 (ZnT8) Antibody, Serum

Clinical Information: Islet cell autoantibodies have been known to be associated with type 1 diabetes mellitus since the 1970s.(1) Since 1988, several autoantigens against which islet antibodies are directed have been identified. These include the insulinoma-associated protein 2 (IA-2), glutamic acid decarboxylase 65 (GAD65), insulin, and, most recently, the zinc transporter ZnT8. Only 4% to 7% of

patients with type 1 diabetes are autoantibody negative, fewer than 10% have only 1 marker, and around 70% have 3 or 4 markers. These findings have been confirmed in multiple specialty laboratories internationally. One or more of these autoantibodies are detected in 93% to 96% of patients with type 1 diabetes, both adults and children. These antibodies are also detectable in relatives of type 1 diabetic patients at risk for developing diabetes, before clinical onset. Because of symptom-onset in adulthood, societal obesity, and initial insulin-independence, some patients with type 1 diabetes are initially diagnosed as having type 2 diabetes,. These patients with either "latent autoimmune diabetes in adulthood" or type 1 diabetes mellitus, may be distinguished from those patients with type 2 diabetes by detection of 1 or more islet autoantibodies, including ZnT8 antibody.(2-5) Patients with gestational diabetes can also be stratified for future diabetes risk by detection of 1 or more islet autoantibodies (including ZnT8 antibody).

Useful For: Clinical distinction of type 1 from type 2 diabetes mellitus Identification of individuals at risk of type 1 diabetes (including high-risk relatives of patients with diabetes, and those with gestational diabetes) Prediction of future need for insulin treatment in adult-onset diabetic patients

Interpretation: Seropositivity for ZnT8 autoantibody (> or =15 IU/mL) is supportive of: -A diagnosis of type 1 diabetes -A high risk for future development of diabetes -A current or future need for insulin therapy in patients with diabetes

Reference Values:
<15.0 U/mL

Clinical References:

ZNU
8591

Zinc, 24 Hour, Urine

Clinical Information: Zinc is an essential element; it is a critical cofactor for carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases, alcohol dehydrogenase, and many other physiologically important proteins. Zinc is a key element required for active wound healing. Zinc depletion occurs because it is either not absorbed from the diet (excess copper or iron interfere with absorption) or lost after absorption. Dietary deficiency may be due to absence (parenteral nutrition), or because the zinc in the diet is bound to fiber and not available for absorption. Once absorbed, the most common route of loss is via exudates from open wounds, such as third-degree burns, or gastrointestinal loss as in colitis. Hepatic cirrhosis also causes excess loss of zinc by enhancing renal excretion. The peptidase, kinase, and phosphorylase enzymes are most sensitive to zinc depletion. Zinc excess is not of major clinical concern. The popular American habit of taking megavitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that zinc interferes with copper absorption, which can lead to hypocupremia.

Useful For: Identifying the cause of abnormal serum zinc concentrations using 24-hour urine specimens

Interpretation: Fecal excretion of zinc is the dominant route of elimination. Renal excretion is a minor, secondary elimination pathway. Normal daily excretion of zinc in the urine is in the range of 20 to 967 mcg/24 h. High urine zinc levels associated with low serum zinc concentrations may be caused by hepatic cirrhosis, neoplastic disease, or increased catabolism. High urine zinc levels associated with normal or elevated serum zinc concentrations indicates a large dietary source, usually in the form of high-dose vitamins. Low urine zinc levels associated with low serum zinc concentrations may be caused by dietary deficiency or loss through exudation common in burn patients and those with gastrointestinal

losses.

Reference Values:
0-17 years: Not established
> or =18 years: 109-1,476 mcg/24 h

Clinical References: 1. Sata F, Araki S, Murata K, Aono H. Behavior of heavy metals in human urine and blood following calcium disodium ethylenediamine tetraacetate injection: observations in heavy metal workers. J Toxicol Environ Health A. 1998;54(3):167-178 2. Afridi HI, Kazi TG, Kazi NG, et al. Evaluation of cadmium, lead, nickel and zinc status in biological samples of smokers and nonsmokers hypertensive patients. J Hum Hypertens. 2010;24(1):34-43 3. Zorbas YG, Kakuris KK, Neofitov IA, Afoninos NI. Zinc utilization in zinc-supplemented and -unsupplemented healthy subjects during and after prolonged hypokinesia. Tr Elem Electro. 2008;25(2):60-68 4. Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

ZN_S
7735

Zinc, Serum

Clinical Information: Zinc is an essential element; it is a critical cofactor for carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases, alcohol dehydrogenase, and many other physiologically important proteins. The peptidases, kinases, and phosphorylases are most sensitive to zinc depletion. Zinc is a key element required for active wound healing. Zinc depletion occurs because it is either not absorbed from the diet (excess copper or iron interfere with absorption) or lost after absorption. Dietary deficiency may be due to absence (parenteral nutrition) or because the zinc in the diet is bound to phytate (fiber) and not available for absorption. Excess copper and iron in the diet (eg, iron supplements) interfere with zinc uptake. Once absorbed, the most common route of loss is via exudates from open wounds or gastrointestinal loss. Zinc depletion occurs in burn patients who lose zinc in the exudates from their burn sites. Hepatic cirrhosis causes excess loss of zinc by enhancing kidney excretion. Other diseases that cause low serum zinc are ulcerative colitis, Crohn disease, regional enteritis, sprue, intestinal bypass, neoplastic disease, and increased catabolism induced by anabolic steroids. The conditions of anorexia and starvation also result in low zinc levels. Zinc excess is not of major clinical concern. The popular American habit of taking mega-vitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that zinc interferes with copper absorption, which can lead to hypocupremia.

Useful For: Detecting zinc deficiency

Interpretation: Normal serum zinc levels are from 66 to 106 mcg/dL in adults. Patients who are burnt and have acrodermatitis may have zinc levels as low as 40 mcg/dL; these patients respond quickly to zinc supplementation. An elevated serum zinc concentration is of minimal clinical interest.

Reference Values:
0-10 years: 60-120 mcg/dL
11-17 years: 66-110 mcg/dL
> or =18 years: 60-106 mcg/dL

Clinical References: 1. Tucker SB, Schroeter AL, Brown PW Jr, McCall JT. Acquired zinc deficiency. Cutaneous manifestations typical of acrodermatitis enteropathica. JAMA. 1976;235(22):2399-2402 2. Skelton JA, Havens PL, Werlin SL. Nutrient deficiencies in tube-fed children. Clin Pediatr. 2006;45(1):37-41 3. Zorbas YG, Kakuris KK, Neofitov IA, Afoninos NI. Zinc

utilization in zinc-supplemented and -unsupplemented healthy subjects during and after prolonged hypokinesis. Tr Elem Electro. 2008;25:60-68 4. Ayling RM, Crook M. Nutrition: Laboratory and clinical aspects. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:457-501

ZNUCR
615259

Zinc/Creatinine Ratio, Random, Urine

Clinical Information: Zinc is an essential element; it is a critical cofactor for carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases, alcohol dehydrogenase, and many other physiologically important proteins. Zinc is a key element required for active wound healing. Zinc depletion occurs because it is either not absorbed from the diet (excess copper or iron interfere with absorption) or lost after absorption. Dietary deficiency may be due to absence (parenteral nutrition) or because the zinc in the diet is bound to fiber and not available for absorption. Once absorbed, the most common route of loss is via exudates from open wounds, such as third-degree burns, or gastrointestinal loss as in colitis. Hepatic cirrhosis also causes excess loss of zinc by enhancing renal excretion. The peptidase, kinase, and phosphorylase enzymes are most sensitive to zinc depletion. Zinc excess is not of major clinical concern. The popular American habit of taking megavitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that zinc interferes with copper absorption, which can lead to hypocupremia.

Useful For: Identifying the cause of abnormal serum zinc concentrations using a random urine specimen

Interpretation: Fecal excretion of zinc is the dominant route of elimination. Renal excretion is a minor, secondary elimination pathway. Normal daily excretion of zinc in the urine is in the range of 89 to 910 mcg/g creatinine. High urine zinc associated with low serum zinc may be caused by hepatic cirrhosis, neoplastic disease, or increased catabolism. High urine zinc with normal or elevated serum zinc indicates a large dietary source, usually in the form of high-dose vitamins. Low urine zinc with low serum zinc may be caused by dietary deficiency or loss through exudation common in burn patients and those with gastrointestinal losses.

Reference Values:
ZINC/CREATININE:
0-17 years: Not established
> or =18 years: 89-910 mcg/g creatinine

CREATITINE:
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years.

Clinical References: 1. Sata F, Araki S, Murata K, Aono H. Behavior of heavy metals in human urine and blood following calcium disodium ethylenediamine tetraacetate injection: observations in heavy metal workers. J Toxicol Environ Health A. 1998;54(3):167-178 2. Afridi HI, Kazi TG, Kazi NG, et al. Evaluation of cadmium, lead, nickel and zinc status in biological samples of smokers and nonsmokers hypertensive patients. J Hum Hypertens. 2010;24(1):34-43 3. Zorbas YG, Kakuris KK, Neofitov IA, Afoninos NI. Zinc utilization in zinc-supplemented and-unsupplemented healthy subjects during and after prolonged hypokinesia. Tr Elem Electro. 2008;25(2):60-68. doi:10.5414/TEP25060 4. Roohani N, Hurrell R, Kelishadi R, Schulin R. Zinc and its importance for human health: An integrative review. J Res Med Sci. 2013;18(2):144-157 5. Rifai N, Chiu RWK, Young I, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 7th ed. Elsevier; 2023

ZNCU
615260

Zinc/Creatinine Ratio, Urine

Clinical Information: Zinc is an essential element; it is a critical cofactor for carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases, alcohol dehydrogenase, and many other physiologically important proteins. Zinc is a key element required for active wound healing. Zinc depletion occurs because it is either not absorbed from the diet (excess copper or iron interfere with absorption) or lost after absorption. Dietary deficiency may be due to absence (parenteral nutrition) or because the zinc in the diet is bound to fiber and not available for absorption. Once absorbed, the most common route of loss is via exudates from open wounds, such as third-degree burns, or gastrointestinal loss as in colitis. Hepatic cirrhosis also causes excess loss of zinc by enhancing renal excretion. The peptidase, kinase, and phosphorylase enzymes are most sensitive to zinc depletion. Zinc excess is not of major clinical concern. The popular American habit of taking megavitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that zinc interferes with copper absorption, which can lead to hypocupremia.

Useful For: Measurement of zinc concentration as a part of identifying the cause of abnormal serum zinc concentrations using a random urine specimen

Interpretation: Fecal excretion of zinc is the dominant route of elimination. Renal excretion is a minor, secondary elimination pathway. Normal daily excretion of zinc in the urine is in the range of 89 to 910 mcg/g creatinine. High urine zinc associated with low serum zinc may be caused by hepatic cirrhosis, neoplastic disease, or increased catabolism. High urine zinc with normal or elevated serum zinc indicates a large dietary source, usually in the form of high-dose vitamins. Low urine zinc with low serum zinc may be caused by dietary deficiency or loss through exudation common in burn patients and those with gastrointestinal losses.

Reference Values:
Only orderable as part of a profile. For more information see ZNUCR / Zinc/Creatinine Ratio, Random, Urine.

0-17 years: Not established
> or =18 years: 89-910 mcg/g creatinine

Clinical References: 1. Sata F, Araki S, Murata K, Aono H. Behaviour of heavy metals in human urine and blood following calcium disodium ethylenediamine tetraacetate injection: observations in heavy metal workers. J Toxicol Environ Health A. 1998;54(3):167-178 2. Afridi HI, Kazi TG, Kazi NG, et al. Evaluation of cadmium, lead, nickel and zinc status in biological samples of smokers and nonsmokers hypertensive patients. J Hum Hypertens. 2010;24(1):34-43 3. Zorbas YG, Kakuris KK, Neofitov IA, Afoninos NI. Zinc utilization in zinc-supplemented and-unsupplemented healthy subjects during and after prolonged hypokinesia. Tr Elem Electro. 2008;25(2):60-68 4. Roohani N, Hurrell R, Kelishadi R, Schulin R. Zinc and its importance for human health: An integrative review. J Res Med Sci. 2013;18(2):144-157 5. Rifai N, Horwath AR, Wittwer CT, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018

FZIP
57107

Ziprasidone (Geodone, Zeldox)

Reference Values:
Units: ng/mL

Expected plasma concentrations in patients taking Recommended Daily Dosages: Up to 220 ng/mL

FZOLP
57738

Zolpidem (Ambien), serum or plasma

Reference Values:
Units: ng/mL

Expected hypnotic zolpidem concentrations in patients taking recommended daily dosages: up to 250 ng/mL.

Toxic range has not been established.

FCDUD
75787

Zolpidem, Umbilical Cord Tissue

Reference Values:
Reporting limit determined each analysis.

Units: ng/g

Only orderable as part of a profile-see FCDSU

ZONI
83685

Zonisamide, Serum

Clinical Information: Zonisamide (Zonegran) is approved as adjunctive therapy for partial seizures refractory to therapy with traditional anticonvulsants. Zonisamide is the pharmacologically active agent; its metabolites are not active. Essentially 100% of the zonisamide dose is absorbed. Approximately 88% of circulating zonisamide is bound to erythrocytes. The relationship between the serum level and dose is not linear because erythrocyte-bound zonisamide is inactive and binding varies with blood concentration. Time to peak zonisamide concentration is 2 to 6 hours; time to peak is delayed by coadministration with food to 4 to 6 hours. Zonisamide is metabolized by N-acetyl transferase (NAT1), cytochrome P450 3A4 (CYP3A4), and uridine diphosphate glucuronosyltransferase (UDPGT). Zonisamide is eliminated in the urine predominantly as the parent drug (35%), N-acetyl zonisamide (15%), and as the glucuronide ester of reduced zonisamide (50%). Coadministration of drugs that affect NAT1, CYP3A4, and UDPGT activity, such as phenytoin and carbamazepine, will decrease zonisamide concentration. A typical zonisamide dose administered to an adult is 400 to 600 mg/day, administered in 2 divided doses. The apparent volume of distribution of zonisamide is 1.5 L/kg. Approximately 40% of the zonisamide circulating in the serum is bound to proteins. Zonisamide protein binding is unaffected by other common anticonvulsant drugs. The elimination half-life from plasma is 50 to 60 hours; the elimination half-life from erythrocytes is over 100 hours. Since zonisamide is cleared predominantly by the kidney, the daily dosage of zonisamide given to patients with a creatinine clearance below 20 mL/min should be reduced.(1,2) Serum level monitoring is recommended for all patients to ensure appropriate dosing because: -Patient response correlates with serum level. -Serum level does not correlate with dose because of concentration-dependent erythrocyte binding. -Elimination is affected by coadministration of drugs that affect NAT1, CYP3A4, and UDPGT. -Kidney function affects elimination. The most common toxicity associated with excessive serum level is drowsiness. Adverse effects not related to serum level include rash, increased serum creatinine and alkaline phosphatase, kidney stone formation, and bruising.

Useful For: Monitoring zonisamide therapy; recommended for all patients to ensure appropriate dosing Assessing medication compliance

Interpretation: Steady-state zonisamide concentration in a trough specimen collected just before next dose correlates with patient response but not with dose. Optimal response to zonisamide occurs when trough zonisamide concentration is in the range of 10 to 40 mcg/mL. Peak serum concentration for

zonisamide occurs 2 to 6 hours after dose, and time to peak is affected by food intake. Because carbamazepine activates glucuronidation, patients taking carbamazepine concomitantly with zonisamide have significantly lower zonisamide concentrations compared to patients on the same dose not receiving carbamazepine.

Reference Values:
10-40 mcg/mL

Clinical References:

FZCCE
57562

Zucchini (Cucurbita spp) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 Positive 4 17.50-49.99 Strong Positive 5 >49.99 Very Strong Positive

Reference Values:
<0.35 kU/L

MULT
35577

Zygosity Testing (Multiple Births), Varies

Clinical Information: Approximately 30% of twins are monozygotic (identical), while 70% are dizygotic (nonidentical or fraternal). Monozygotic twins originate from a single egg and, by definition, have identical DNA markers throughout their genomes. Dizygotic twins, on the other hand, inherit their genetic complement independently from each parent and are no more likely to have genetic material in common than are any other full siblings. Polymorphic DNA markers have been identified. DNA markers are regions of DNA that display normal variability in the type or the number of nucleotide bases at a given location. One class of repetitive DNA that exhibits marked variability is microsatellites. With the use of such markers, it is possible to distinguish one individual from another because of differences detected at these polymorphic loci. Utilizing polymerase chain reaction followed by capillary electrophoresis, the genotypes of a set of twins (triplets, etc) are derived from the analysis of multiple markers. This genotype is compared to those of their parents to determine if the children are mono- or dizygotic. Any differences detected between siblings' microsatellite markers indicate dizygosity. Many disorders are known to occur on a genetic basis though the genes have not been identified for all of them. If one member of a set of twins is diagnosed with a genetic disorder, determination of zygosity, in addition to other testing, may provide additional information regarding risk assessment of unaffected individuals. In addition, zygosity can be useful when evaluating for twin-twin transfusion syndrome during pregnancy or as part of a pre-organ transplant workup for situations where one twin is donating an organ to another twin.

Useful For: Determining genetic risk for an individual whose twin or triplet is affected with a genetic disorder for which a specific genetic test is not available (or such testing is uninformative) Assessment of risks prenatally when one fetus of multiples is known to be affected by a specific disorder Organ or bone marrow transplantation compatibility testing Familial or parental interest

Interpretation: The interpretive report includes an overview of the findings as well as the associated clinical significance

Reference Values:
An interpretive report will be provided.

Clinical References: 1. Appleman Z, Manor M, Magal N, Caspi B, Shohat M, Blickstein I. Prenatal diagnosis of twin zygosity by DNA "fingerprint" analysis. Prenat Diagn. 1994;14(4):307-309 2. Neitzel H, Digweed M, Nurnberg P, et al. Routine applications of DNA fingerprinting with the oligonucleotide probe (CAC)5/(GTG)5. Clin Genet. 1991;39(2):97-103 3. Allen RW, Polesky HF. Parentage and Relationship Testing. In: Leonard DGB, ed. Molecular Pathology in Clinical Practice. 2nd ed. Springer International Publishing; 2016:811-821

P2PHI
608462

[-2]Pro Prostate-Specific Antigen with Prostate Health Index, Serum

Clinical Information: Prostate-specific antigen (PSA) is a glycoprotein produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. In conditions of increase glandular size and tissue damage, PSA is released into circulation. Measurement of serum PSA is useful for determining the extent of prostate cancer and assessing the response to prostate cancer treatment. PSA is also used as a screening tool for prostate cancer detection, although its use in screening has become controversial in recent years. While an elevated serum PSA is associated with prostate cancer, a number of benign conditions, such as benign prostatic hyperplasia (BPH) and prostatitis might lead to elevated serum PSA concentrations. As a consequence, PSA lacks specificity for prostate cancer detection. Several PSA isoforms have been identified that can further increase the specificity of PSA for prostate cancer. In particular, the [-2] form of proPSA (p2PSA) shows improved performance over either total or free PSA for prostate cancer detection on biopsy. The prostate health index (phi) is a formula that combines all 3 PSA forms (total PSA, free PSA, and p2PSA) into a single score. phi is calculated using the following formula: (p2PSA/free PSA) x square root (PSA). In a multicenter study that compared the performance of total PSA, free PSA, p2PSA, and phi in men undergoing prostate biopsy due to a serum PSA concentration between 4 and 10 ng/mL, phi was the best predictor of any prostate cancer, high-grade cancer, and clinically significant cancer. At 95% clinical sensitivity, the clinical specificity of phi was 16.0%, compared to 8.4% for free PSA and 6.5% for total PSA.

Useful For: As an aid in distinguishing prostate cancer from benign prostatic conditions in men aged 50 years and older with total PSA between 4.0 and 10.0 ng/mL and digital rectal examination findings that are not suspicious for cancer.

Interpretation: The prostate health index (phi) may be used to determine the probability of prostate cancer on biopsy in men 50 years of age and older with total prostate-specific antigen (PSA) in the 4.0 to 10.0 ng/mL range. Low phi scores are associated with a lower probability of finding prostate cancer on biopsy, and higher phi scores are associated with an increased probability of finding prostate cancer on biopsy. The choice of an appropriate phi score to be used in guiding clinical decision making may vary for each patient and may depend on other clinical factors or family history. The table below indicates the probability of finding prostate cancer on biopsy when total PSA is in the range of 4.0 to 10.0 ng/mL and may be used as guidance for interpreting the phi score. phi range Probability of cancer 95% Confidence interval 0-26.9 9.8% 5.2%-15.4% 27.0-35.9 16.8% 11.3%-22.2% 36.0-54.9 33.3% 26.8%-39.9% 55.0+ 50.1% 39.8%-61.0%

Reference Values:

Females: Not applicable PROSTATE-SPECIFIC ANTIGEN (PSA) MALES: Age	Reference range
	< or =2.0 ng/mL
40-49 Years	< or =2.5 ng/mL
50-59 Years	< or =3.5 ng/mL
60-69 Years	< or =4.5 ng/mL
70-79 Years	< or =6.5 ng/mL
> or =80 Years	< or =7.2 ng/mL
PERCENT FREE PSA MALES: When total PSA is in the range of 4-10 ng/mL % Free PSA	Probability of cancer
< or =10%	56%
11-15%	28%
16-20%	20%
21-25%	16%
>25%	8%
PROSTATE HEALTH INDEX (phi) MALES: When PSA is in the range of 4-10 ng/mL phi range	Probability of cancer
0-26.9	9.8%
27.0-35.9	16.8%
36.0-54.9	33.3%
> or =55.0	50.1%

Clinical References: 1. Catalona WJ, Partin AW, Sanda MG, et al. A multicenter study of [-2]pro-prostate-specific antigen combined with prostate-specific antigen and free prostate-specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/mL prostate-specific antigen range. J Urology. 2011;185:1650-1655 2. Pecoraro V, Roli L, Plebani M, Trenti T. Clinical utility of the (-2)proPSA and evaluation of the evidence: a systematic review. Clin Chem Lab Med. 2016;54(7):1123-1132. doi:10.1515/cclm-2015-0876 3. Loeb S, Catalona WJ. The Prostate Health Index: a new test for the detection of prostate cancer. Ther Adv Urol. 2014;6(2):74-77 doi:10.1177/1756287213513488